Florida Medicaid

Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria

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Ron DeSantis, Governor
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Introductory Remarks and Abstract

Generally Accepted Professional Medical Standards

The Secretary of the Florida Agency for Health Care Administration requested that the Division of Florida Medicaid review the treatment of gender dysphoria for a coverage determination pursuant to Rule 59G-1.035, Florida Administrative Code (F.A.C.) (See Attachment A for the Secretary's Letter to Deputy Secretary Tom Wallace). The treatment reviewed within this report included "sex reassignment treatment," which refers to medical services used to obtain the primary and/or secondary physical sexual characteristics of a male or female. As a condition of coverage, sex reassignment treatment must be "consistent with generally accepted professional medical standards (GAPMS) and not experimental or investigational" (Rule 59G-1.035, F.A.C., see Attachment B for the complete rule text).

The determination process requires that "the Deputy Secretary for Medicaid will make the final determination as to whether the health service is consistent with GAPMS and not experimental or investigational" (Rule 59G-1.035, F.A.C.). In making that determination, Rule 59G-1.035, F.A.C., identifies several factors for consideration. Among other things, the rule contemplates the consideration of "recommendations or assessments by clinical or technical experts on the subject or field" (Rule 59G-1.035(4)(f), F.A.C.). Accordingly, this report attaches five assessments from subject-matter experts:

- **Attachment C:** Romina Brignardello-Petersen, DDS, MSc, PhD and Wojtek Wiercioch, MSc, PhD: *Effects of Gender Affirming Therapies in People with Gender Dysphoria: Evaluation of the Best Available Evidence*. 16 May 2022.
- **Attachment D:** James Cantor, PhD: *Science of Gender Dysphoria and Transsexualism*. 17 May 2022.
- **Attachment E:** Quentin Van Meter, MD: *Concerns about Affirmation of an Incongruent Gender in a Child or Adolescent*. 17 May 2022.
- **Attachment F:** Patrick Lappert, MD: *Surgical Procedures and Gender Dysphoria*. 17 May 2022.
- **Attachment G:** G. Kevin Donovan, MD: *Medical Experimentation without Informed Consent: An Ethicist's View of Transgender Treatment for Children*. 16 May 2022.

Abstract

Available medical literature provides insufficient evidence that sex reassignment through medical intervention is a safe and effective treatment for gender dysphoria. Studies presenting the benefits to mental health, including those claiming that the services prevent suicide, are either low or very low quality and rely on unreliable methods such as surveys and retrospective analyses, both of which are cross-sectional and highly biased. Rather, the available evidence demonstrates that these treatments cause irreversible physical changes and side effects that can affect long-term health.

Five clinical and technical expert assessments attached to this report recommend against the use of such interventions to treat what is categorized as a mental health disorder (See attachments):

- **Health Care Research:** Brignardello-Petersen and Wiercioch performed a systematic review that graded a multitude of studies. They conclude

that evidence supporting sex reassignment treatments is low or very low quality.

- **Clinical Psychology:** Cantor provided a review of literature on all aspects of the subject, covering therapies, lack of research on suicidality, practice guidelines, and Western European coverage requirements.
- **Plastic Surgery:** Lappert provided an evaluation explaining how surgical interventions are cosmetic with little to no supporting evidence to improve mental health, particularly those altering the chest.
- **Pediatric Endocrinology:** Van Meter explains how children and adolescent brains are in continuous phases of development and how puberty suppression and cross-sex hormones can potentially affect appropriate neural maturation.
- **Bioethics:** Donovan provides additional insight on the bioethics of administering these treatments, asserting that children and adolescents cannot provide truly informed consent.

Following a review of available literature, clinical guidelines, and coverage by other insurers and nations, Florida Medicaid has determined that the research supporting sex reassignment treatment is insufficient to demonstrate efficacy and safety. In addition, numerous studies, including the reports provided by the clinical and technical experts listed above, identify poor methods and the certainty of irreversible physical changes. Considering the weak evidence supporting the use of puberty suppression, cross-sex hormones, and surgical procedures when compared to the stronger research demonstrating the permanent effects they cause, these treatments do not conform to GAPMS and are experimental and investigational.

Health Service Summary

Gender Dysphoria

Frequently used to describe individuals whose gender identity conflicts with their natural-born sex, the term gender dysphoria has a history of evolving definitions during the past decades (Note: This report uses the term "gender" in reference to the construct of male and female identities and the term "sex" when regarding biological characteristics). Prior to the publication of the *Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders* (DSM-V), the American Psychiatric Association (APA) used the diagnosis of gender identity disorder (GID) to describe individuals who sought to transition to the opposite gender. However, behavioral health clinicians sought a revision after determining that using GID created stigma for those who received the diagnosis. This is despite the APA having adopted GID to replace the previous diagnosis of transsexualism for the exact same reason (APA, 2017).[1]

When crafting its new definition and terminology, the APA sought to remove the stigma of classifying as a disorder the questioning of one's gender identity by focusing instead on the psychological distress that such questioning can evoke. This approach argues that individuals seeking behavioral health and transition services are doing so due to experiencing distress and that gender non-conformity by itself is not a mental health issue. This led to the adoption of gender dysphoria in 2013 when the APA released the DSM-V. In addition to using a new term, the APA also differentiated the diagnosis between children and adolescents and adults, listing different characteristics for the two age groups (APA, 2017).

According to the DSM-V, gender dysphoria is defined as "the distress that may accompany the incongruence between one's experienced or expressed gender and one's assigned gender." As for the criteria to receive the diagnosis, the APA issued stricter criteria for children than adolescents and adults. For the former, the APA states that a child must meet six out of eight behavioral characteristics such as having "a strong desire to be of the other gender or an insistence that one is the other gender" or "a strong preference for cross-gender roles in make-believe or fantasy play." The criteria for adults and adolescents are less stringent with individuals only having to meet two out of six characteristics that include "a strong desire to be the other gender" or "a strong desire to be rid of one's primary and/or secondary sexual characteristics." The APA further notes that these criteria can also apply to young adolescents (DSM-V, 2013).

In 2021, the Merck Manual released a slightly different definition for gender dysphoria, citing that the condition "is characterized by a strong, persistent cross-gender identification associated with anxiety, depression, irritability, and often a wish to live as a gender different from the one associated with the

[1] The concept of gender being part of identity and disconnected from biological sex originated during the mid-twentieth century and was publicized by psychologist John W. Money. His research asserted that gender was a complete social construct and separate from biology, meaning that parents and/or caregivers could imprint on a young child (under three years) the identity of a boy or girl. In 1967, Money's theories led to a failed experiment on twin boys where physicians surgically transitioned one to appear as a girl. The twin that underwent sex reassignment never fully identified as a female. However, Money never publicly acknowledged this and reported the experiment as a success. Furthermore, he promoted his conclusions across the scientific community, concealing what actually unfolded. As a result, Money's ideas on gender fluidity served as a basis for performing procedures on children with hermaphroditic features or genital abnormalities. The case reveals how the understanding of a concept (e.g., gender) at any given time can lead to incorrect medical decisions with irreversible consequences (Gaetano, 2015).

sex assigned at birth." Additionally, the Merck Manual further states that "gender dysphoria is a diagnosis requiring specific criteria but is sometimes used more loosely for people in whom symptoms do not reach a clinical threshold" (Merck Manual, 2021). This definition is largely consistent with the DSM-V but does not emphasize the distress component to the same extent.[2]

Like other behavioral health diagnoses classified in the DSM-V, gender dysphoria has the following subtypes:

- **Early-Onset Gender Dysphoria:** This subtype begins during childhood and persists through adolescence into adulthood. It can be interrupted by periods where the individual does not experience gender dysphoria signs and may classify as homosexual (DSM-V, 2013).
- **Late-Onset Gender Dysphoria:** Occurring after puberty or during adulthood, this subtype does not begin until late adolescence and can emerge following no previous signs of gender dysphoria. The APA attributes this partially to individuals who did not want to verbalize their desires to transition (DSM-V, 2013).

Further studies have identified additional subtypes of gender dysphoria. In 2018, Lisa Littman introduced the concept of a rapid-onset subtype. Classified as rapid-onset gender dysphoria (ROGD), it features characteristics such as sudden beginnings during or following puberty. However, it differs from the DSM-V definitions because ROGD is associated with other causes such as social influences (e.g., peer groups, authority figures, and media). In other words, adolescents who had no history of displaying typical gender dysphoria characteristics go through a sudden change in identity following intense exposure to peers and/or media that heavily promotes transgender lifestyles (Littman, 2018). While more long-term studies are needed to confirm whether ROGD is a temporary or long-term condition, Littman's study has initiated discussions regarding potential causes of gender dysphoria as well as introduced a potential subtype.

Additionally, the frequent use of gender dysphoria in clinical and lay discourse has led to a fracturing of the definition. Studies on the topic frequently do not apply the DSM-V's criteria for the diagnosis and overlook certain key features such as distress. In a 2018 review by Zowie Davy and Michael Toze, the authors evaluated 387 articles that examine gender dysphoria and noted stark departures from the APA's definition. They further asserted that the APA intended to "reduce pathologization" by establishing a new definition for gender dysphoria in the DSM-V. This in turn would reduce diagnoses, although as Davy and Toze note, the tendency for the literature to diverge from the APA's definition may result in increased numbers of individuals classified as having gender dysphoria when they do not meet the DSM-V's criteria (Davy and Toze, 2018). This further raises the question of whether individuals are receiving potentially irreversible treatments for the condition when they might not actually have it.

The current usage of gender dysphoria is the result of discussions spanning across decades as demonstrated in the past editions of the DSM. Until 2013, the APA considered having gender identity issues a mental disorder by itself regardless of the presence of psychological distress. That perspective has since shifted to only consider the adverse psychological effects of questioning one's gender as a disorder. In addition, the APA considers gender as part of one's identity, which is not subject to a diagnosis. Whether the APA has shifted its terminology and criteria for gender identity issues due to

[2] Following the release of the Florida Department of Health's guidelines for treating gender dysphoria, Merck removed its definition for "gender dysphoria" from the Merck Manual (Fox News, 2022).

emerging clinical data or cultural changes is another question. In 1994, the APA replaced transsexualism with gender identity disorder as part of the "effort to reduce stigma" (APA, 2017). This raises questions about what influences decisions to revise definitions and criteria; is it social trends or medical evidence?

Behavioral Health Issues Co-Occurring with Gender Dysphoria

Because gender dysphoria pertains directly to the distress experienced by an individual who desires to change gender identities, secondary behavioral health issues can co-occur such as depression and anxiety. If left untreated, these conditions can lead to the inability to function in daily activities, social isolation, and even suicidal ideation. Studies do confirm that adolescents and adults with gender dysphoria report higher levels of anxiety, depression, and poor peer relationships than the general population (Kuper et al, 2019). Other associated conditions include substance abuse, eating disorders, and compulsivity. A significant proportion of individuals with gender dysphoria also have autism spectrum disorder (ASD) (Saleem and Rizvi, 2017). Although the number reporting secondary issues is increased, individuals diagnosed with gender dysphoria do not necessarily constitute the entire population that is gender non-conforming (i.e., does not identify with natal sex), and no information is available breaking down the percentage of those who are non-conforming with gender dysphoria and those who are non-conforming with no distress. Additionally, available research raises questions as to whether the distress is secondary to pre-existing behavioral health disorders and not gender dysphoria. This is evident in the number of adolescents who reported anxiety and depression diagnoses prior to transitioning (Saleem and Rizvi, 2017).

Furthermore, conventional treatments for secondary behavioral health issues are available. These include cognitive behavioral therapy, medication, and inpatient services. The APA reports that treatments for these are highly effective with 80% to 90% of individuals diagnosed with depression responding positively (APA, 2020). In addition, a high percentage of adolescents diagnosed with gender dysphoria had received psychiatric treatment for a prior or co-occurring mental health issue. A 2015 study from Finland by Kaltiala-Heino et al noted that 75% of children seeking sex reassignment services had been treated by a behavioral health professional (Kaltiala-Heino et al, 2015).

Diagnosing Gender Dysphoria

Prior to the publication of the DSM-V, diagnosing individuals experiencing gender identity issues followed a different process. Behavioral health clinicians could assign the diagnosis based on gender non-conformance alone. That has changed since 2013. Today, non-conforming to one's gender is part of personal identity and not a disorder requiring treatment. This change has led professional associations to shift the diagnostic criteria for gender dysphoria to focus on the distress caused by shifting identities (DSM-V, 2013).

For adolescents, the APA identifies "a marked incongruence between one's experienced/expressed gender and natal sex, of at least 6 months' duration" as the core component of gender dysphoria (DSM-V, 2013). What the APA does not elucidate is the threshold for "marked." This raises questions as to whether practitioners exercise uniformity when applying the diagnostic criteria or if they do so subjectively. For example, the WPATH's *Standards of Care for the Health of Transsexual, Transgender, and Gender Non-Conforming People* provides guidance on the processes mental health practitioners should use when assessing for gender dysphoria but offers no benchmarks for meeting diagnostic criteria (WPATH, 2012).

Such processes include evaluating for gender non-conforming behaviors and other co-existing mental disorders like anxiety or depression. This involves not only interviewing the adolescent but also the family in addition to reviewing medical histories. WPATH also asserts that gender dysphoria assessments need to account for peer relationships, academic performance, and provide information of potential treatments. This last component is necessary because it might affect an individual's choices regarding transitioning, particularly if the information does not correspond to the desired outcome (WPATH, 2012).

The diagnosis of gender dysphoria is a relatively recent concept in mental health, being the product of decades of discussion and building upon previous definitions. Instead of treating gender non-conformity as a disorder, behavioral health professionals acknowledge it as part of one's identity and focus on addressing the associated distress. Considering the new criteria, this changes the dynamics of the population who would have qualified for a diagnosis before 2013 and those who would today. Given that desiring to transition into a gender different from natal sex no longer qualifies as a disorder, behavioral health professionals are treating distress and referring adolescents and adults to therapies that are used off-label and pose irreversible effects.

Current Available Treatments for Gender Dysphoria

At present, proposed treatment for gender dysphoria occurs in four stages, beginning with psychological services and ending with sex reassignment surgery. As an individual progresses through each stage, the treatments gradually become more irreversible with surgical changes being permanent. Because of the increasing effects, individuals must have attempted treatment at the previous stage before pursuing the next one (Note: late adolescents and adults have already completed puberty and do not require puberty blockers). Listed in order, the four stages are as follows:

- **Behavioral Health Services:** Psychologists and other mental health professionals are likely the first practitioners individuals with gender dysphoria will encounter. In accordance with clinical guidelines established by the World Professional Association for Transgender Health (WPATH)[3], behavioral health professionals are supposed to "find ways to maximize a person's overall psychological well-being, quality of life, and self-fulfillment." WPATH further discourages services for attempting to change someone's gender identity. Instead, it instructs practitioners to assess for the condition and readiness for puberty blockers or cross-sex hormones while offering guidance to function in a chosen gender. WPATH does assert that the clinicians do need to treat any other underlying mental health issues secondary or co-occurring with gender dysphoria (WPATH, 2012). However, the organization provides conflicting guidance because it also advises practitioners to prescribe cross-sex hormones on demand (Levine, 2018).
- **Puberty Suppression:** Used only on individuals in the earliest stages of puberty (Tanner stage 2), preventing pubertal onset provides additional time to explore gender identities before the physical characteristics of biological sex develop. This treatment is intended to reduce distress and anxiety related to the appearance of adult sexual physical features. To suppress puberty, pediatric endocrinologists inject gonadotropin releasing hormone (Gn-RH) at specific intervals (e.g., 4 weeks or 12 weeks). The Gn-RH suppresses gonadotropin receptors that allow for the

[3] The World Professional Association for Transgender Health asserts that it is a professional organization. However, it functions like an advocacy group by allowing open membership to non-clinicians (WPATH, 2022).

development of primary and secondary adult sexual characteristics. Prior to receiving puberty suppression therapy, individuals must have received a diagnosis of gender dysphoria and have undergone a mental health evaluation (Kyriakou et al, 2020).

- **Cross-Sex Hormones:** For adults and late adolescents (16 years or older), the next treatment phase recommended is taking cross-sex hormones (e.g., testosterone or estrogen) to create secondary sex characteristics. In men transitioning into women, these include breast development and widening around the pelvis. Women who transition into men experience deeper voices, redistribution of fat deposits, and growing facial hair. According to the Endocrine Society, late adolescents who qualify for cross-sex hormones must have a confirmed diagnosis of gender dysphoria from a mental health practitioner with experience treating that population. Some physical changes induced by these hormones are irreversible (Endocrine Society, 2017).
- **Sex Reassignment Surgery:** Sometimes referred to as "gender affirming" surgery, this treatment does not consist of just one procedure but several, depending on the desires of the transitioning individual. Primarily, sex reassignment procedures alter the primary and secondary sexual characteristics. Men transitioning into women (trans-females) undergo a penectomy (removal of the penis), orchiectomy (removal of the testes), and vulvoplasty (creation of female genitals). Other procedures trans-females may undergo include breast augmentation and facial feminization. For women that transition into men (trans-males), procedures include mastectomy (removal of the breasts), hysterectomy (removal of the uterus), oophorectomy (removal of the ovaries), and phalloplasty (creation of male genitals). Because of the complexities involved in phalloplasty, many trans-males do not opt for this procedure and limit themselves to mastectomies. Additionally, the effects of sex reassignment surgery, such as infertility, are permanent (WPATH, 2012).

While some clinical organizations assert that they are the standard of care for gender dysphoria, the U.S. Food and Drug Administration (FDA) currently has not approved any medication as clinically indicated for this condition (Unger, 2018). Although puberty blockers and cross-sex hormones are FDA approved, the FDA did not approve them for treating gender dysphoria, meaning that their use for anything other than the clinical indications listed is off-label (American Academy of Pediatrics, 2014). As for surgical procedures, the FDA does not evaluate or approve them, but it does review all surgical devices (FDA, 2021). In addition, the Endocrine Society concedes that its practice guidelines for sex reassignment treatment does *not* constitute a "standard of care" and that its grades for available services are low or very low (Endocrine Society, 2017).[4]

[4] Disagreement over how to treat gender dysphoria, gender identity disorder, and transsexualism has persisted since sex reassignment surgery first became available in the 1960s. In a 2006 counterargument, Paul McHugh highlights how individuals seeking surgery had other reasons that extended beyond gender identity, including sexual arousal and guilt over homosexuality. In addition, he asserts that undergoing sex reassignment procedures did not improve a patient's overall behavioral health and that providing a "surgical alteration to the body of these unfortunate people was to collaborate with a mental disorder rather than to treat it" (McHugh, 2006).

Literature Review: Introduction

Currently, an abundance of literature and studies on gender dysphoria is available through academic journals, clinical guidelines, and news articles. Similar to other mental health issues, the material addresses a broad range of topics consisting of available treatments, etiology (i.e., causes), risks, benefits, and side effects. Although most stories reported by the media indicate that treatments such as cross-sex hormones and sex reassignment surgery are the most effective, research reveals that numerous questions still exist. These include what are the long-term health effects of taking cross-sex hormones, what are the real causes of gender dysphoria, and how many individuals that transition will eventually want to revert to their natal sex. Additionally, much of the available research is inconclusive regarding the effectiveness of sex reassignment treatments with multiple studies lacking adequate sample sizes and relying on subjective questionnaires. While much of the scientific literature leans in favor of cross-sex hormones and surgery as options for improving the mental health of individuals with gender dysphoria, it does not conclusively demonstrate that the benefits outweigh the risks involved, either short or long-term. What studies do reveal with certainty is that sex reassignment surgery and cross-sex hormones pose permanent effects that can result in infertility, cardiovascular disease, and disfigurement. All of this indicates that further research is necessary to validate available treatments for gender dysphoria. Thus, physicians, who recommend sex reassignment treatment, are not adhering to an evidence-based medicine approach and are following an eminence-based model.

The following literature review addresses the multiple facets of this condition and presents areas of ongoing debate and persisting questions. Beginning with the condition's etiology and continuing with evaluations of puberty blockers, cross-sex hormones, and surgery, the review explains each area separately and in context of gender dysphoria at large. Additionally, the review provides an analysis on available research on mental health outcomes as well as the condition's persistence into adulthood. Taken as a whole, the available studies demonstrate that existing gender dysphoria research is inconclusive and that current treatments are used to achieve cosmetic benefits while posing risky side effects as well as irreversible changes.

Literature Review: Etiology of Gender Dysphoria

What causes gender dysphoria is an ongoing debate among experts in the scientific and behavioral health fields. Currently, the research indicates that diagnosed individuals have higher proportions of autism spectrum disorder (ASD), history of trauma or abuse, fetal hormone imbalances, and co-existing mental illnesses. Also, experts acknowledge that genetics may factor into gender dysphoria. Another potential cause is social factors such as peer and online media influence. At the moment, none of the studies provides a definite cause and offer only correlations and weakly supported hypotheses. In addition, evidence favoring a biological explanation is highly speculative. However, the research does raise questions about whether treatments with permanent effects are warranted in a population with disproportionately high percentages of ASD, behavioral health problems, and trauma.

In a 2017 literature review by Fatima Saleem and Syed Rizvi, the authors examine gender dysphoria's numerous potential causes and the remaining questions requiring further research. In conclusion, the pair indicate that associations exist between the condition and ASD, schizophrenia, childhood abuse, genetics, and endocrine disruption chemicals but that more research is needed to improve understanding of how these underlying issues factor into a diagnosis. Throughout the review, Saleem and Rizvi identify the following as potential contributing elements to the etiology of gender dysphoria:

- **Neuroanatomical Etiology:** During fetal development, the genitals and brain develop during different periods of a pregnancy, the first and second trimesters respectively. Because the processes are separate, misaligned development is possible where the brain may have features belonging to the opposite sex. The authors identify one study where trans-females presented with a "female-like putamen" (structure at the base of the brain) when undergoing magnetic resonance imaging (MRI) scans.[5]
- **Psychiatric Associations:** Saleem and Rizvi identify multiple studies reporting that individuals with gender dysphoria have high rates of anxiety and depressive disorders with results ranging as high as 70% having a mental health diagnosis. In addition, the pair note that schizophrenia may also influence desires to transition. However, the review does not assess whether the mental health conditions are secondary to gender dysphoria.
- **Autism Spectrum Disorder:** Evidence suggests a significant percentage of individuals diagnosed with gender dysphoria also have ASD. The authors note that the available studies only establish a correlation and do not identify mechanisms for causation.
- **Childhood Abuse:** Like the above causes, Saleem and Rizvi note that those with gender dysphoria tended to experience higher rates of child abuse across all categories, including neglect, emotional, physical, and sexual.
- **Endocrine Disruptors:** Although this cause still requires substantial research, it is a valid hypothesis regarding how phthalates found in plastics can create an imbalance of testosterone in fetuses during gestation, which can potentially lead to gender dysphoria. The authors point to one study that makes this suggestion.

[5] Research on neuroanatomical etiology for gender dysphoria remains highly speculative due to limitations of brain imaging (Mayer and McHugh, 2016). In addition, neuroscience demonstrates that exposures to certain environments and stimuli as well as behaviors can affect brain changes (Gu, 2014). Furthermore, available research indicates that male and female brains have different physical characteristics but cannot be placed in separate categories due to extensive overlap of white/grey matter and neural connections (Joel et al, 2015).

Saleem and Rizvi's review reveal that gender dysphoria's etiology can have multiple factors, most of which require treatments and therapies not consisting of cross-sex hormones or surgery. (Saleem and Rizvi, 2017).

Out of the research on the condition's etiology, a large portion focuses on the correlation with ASD. One of the more substantial studies by Van der Miesen et al published in 2018 evaluates 573 adolescents and 807 adults diagnosed with ASD and compares them to 1016 adolescents and 846 adults from the general population. The authors' findings note that adolescents and adults with ASD were approximately 2.5 times more likely to indicate a desire of becoming the opposite sex. Although the methodology used to reach this conclusion consisted of surveys where respondents had a choice of answering "never," "sometimes," or "often," the results correspond with those of similar studies. Van der Miesen et al also indicate that most responses favoring a change in gender responded with "sometimes." Additionally, the authors do not state how many in their sample group actually had a gender dysphoria diagnosis. (Van der Miesen et al, 2018).

Another study by Shumer et al from 2016 utilizes a smaller sample size (39 adolescents) referred to an American hospital's gender clinic. Unlike Van der Miesen et al's research, Shumer et al evaluate subjects with a diagnosis of gender dysphoria for possible signs of ASD or Asperger's syndrome. Their findings revealed that 23% of patients presenting at the clinic would likely have one of the two conditions. Possible explanations for the high percentage are the methods used to gather the data. Shumer et al requested a clinical psychologist to administer the Asperger Syndrome Diagnostic Scale to the parents of the sample patients, four of whom already had an ASD diagnosis. The authors conclude that the evidence to support high incidence of gender dysphoria in individuals with ASD is growing and that further research is needed to determine the specific cause (Shumer et al, 2016).

Research indicating a strong correlation between ASD and gender dysphoria is not the only area where new studies are emerging. Discussions about the effects of prenatal testosterone levels are also becoming more prevalent. One such example is Sadr et al's 2020 study that looks at the lengths of the index and ring fingers (2D:4D) of both left and right hands of 203 individuals diagnosed with gender dysphoria. The authors used this method because prenatal testosterone levels can affect the length ratios of 2D:4D. By comparing the ratios of a group with gender dysphoria to a cohort from the general population, Sadr et al could assess for any significant difference. Their results indicated a difference in trans-females who presented with more feminized hands. For trans-males, the difference was less pronounced. The results for both groups were slight, and the meta-analysis that accompanies the study notes no statistically significant differences in multiple groups from across cultures. However, Sadr et al further assert that the evidence strongly suggests elevated prenatal testosterone levels in girls and reduced amounts in boys may contribute to gender dysphoria, requiring additional research (Sadr et al, 2020).

In addition to biological factors and correlations with ASD, researchers are exploring psychological and social factors to assess their role in gender dysphoria etiology. This literature examines a range of potential causative agents, including child abuse, trauma, and peer group influences. One such study by Kozlowska et al from 2021 explores patterns in children with high-risk attachment issues who also had gender dysphoria. The authors wanted to assess whether past incidents of abuse, loss, or trauma are associated with higher rates of persons desiring to transition. As a basis, Kozlowska et al cite John Bowlby's research on childhood brain development, noting that the process is not linear and depends

heavily on lived experiences. The study further acknowledges that biological factors combined with life events serve as the foundation for the next developmental phase and that early poor-quality attachment issues increase the risk for psychological disorders in adolescence and adulthood. Such disorders include mood and affective disorders, suicidal ideations, and self-harm. Kozlowska et al also cite other studies that indicate a high correlation between gender dysphoria and "adverse childhood events" and further assert that the condition "needs to be conceptualized in the context of the child's lived experience, and the many different ways in which lived experience is biologically embedded to shape the developing brain and to steer each child along their developmental pathway" (Kozlowska et al, 2021).

For their study, Kozlowska et al recruited 70 children diagnosed with gender dysphoria and completed family assessments going back three generations. This in-depth level was necessary to ascertain any and all events that could affect a child's developmental phases. Additionally, the researchers individually assessed the diagnosed children. To establish comparisons, Kozlowska et al performed assessments on a non-clinical group and a mixed-psychiatric group. Their results demonstrate that children with gender dysphoria have significantly higher rates of attachment issues as well as increased reports of "adverse childhood events" such as trauma (e.g., domestic violence and physical abuse). Furthermore, the authors indicate that a high proportion of families reported "instability, conflict, parental psychiatric disorder, financial stress, maltreatment events, and relational ruptures." These results led Kozlowska et al to conclude that gender dysphoria can be "associated with developmental pathways – reflected in at-risk patterns of attachment and high rates of unresolved loss and trauma – that are shaped by disruptions to family stability and cohesion." The study also cites that treatment requires "a comprehensive biopsychosocial assessment with the child and family, followed by therapeutic interventions that address, insofar as possible, the breadth of factors that are interconnected with each particular child's presentation" (Kozlowska et al, 2021).

This recent study raises questions regarding the medical necessity of gender dysphoria treatments such as puberty blockers and cross-sex hormones for adolescents. If high percentages of children diagnosed with gender dysphoria also have histories of trauma and attachment issues, should conventional behavioral health services be utilized without proposing treatments that pose irreversible effects? Would that approach not provide additional time to address underlying issues before introducing therapies that pose permanent effects (i.e., the watchful waiting approach)?

Aside from the notion that childhood abuse and adversity can potentially cause gender dysphoria, other possible explanations such as social factors (e.g., peer influences and media) may be contributing factors. Research on rapid onset gender dysphoria (ROGD) links this phenomenon to peer and social elements. In an analysis utilizing parent surveys, Lisa Littman asserts that the rapid rise of ROGD is not associated with the traditional patterns of gender dysphoria onset (i.e., evidence of an individual's gravitation to the opposite sex documented over multiple years) but rather exposure to "social and peer contagion." Littman uses this term in the context of definitions cited in academic literature, stating that "social contagion is the spread of affect or behaviors through a population" and that "peer contagion is the process where an individual and peer mutually influence each other in a way that promotes emotions and behaviors that can potentially undermine their own development or harm others." Examples of the latter's negative effects include depression, eating disorders, and substance abuse. What prompted this study is a sudden increase of parents reporting their daughters declaring themselves to be transgender without any previous signs of gender dysphoria. Littman also indicates

that these parents cite that their daughters became immersed in peer groups and social media that emphasized transgender lifestyles (Littman, 2018).

In addition to identifying characteristics of ROGD, the study examines social media content that provides information to adolescents regarding how to obtain cross-sex hormones through deception of physicians, parents, and behavioral health professionals. Such guidance includes coaching on how to fit a description to correspond to the DSM-V and pressures to implement treatment during youth to avoid a potential lifetime of unhappiness in an undesirable body. Littman further states that "online content may encourage vulnerable individuals to believe that non-specific symptoms and vague feelings should be interpreted as gender dysphoria." The study also notes that none of the individuals assessed using the parental surveys qualified for a formal diagnosis using the DSM-V criteria (Littman, 2018).

The survey responses revealed similar data to Kozlowska et al's study with 62.5% of the adolescents having a mental health or neurodevelopmental disorder. Furthermore, the responses indicate a rapid desire to bypass behavioral health options and pursue cross-sex hormones. 28.1% of parents surveyed stated that their adolescents did not want psychiatric treatments. One parent even reported that their daughter stopped taking prescribed anti-depressants and sought advice only from a gender therapist. Littman's research further reveals that 21.2% of parents responded that their adolescent received a prescription for puberty blockers or cross-sex hormones at their first visit (Littman, 2018). These responses indicate that practitioners do not uniformly follow clinical guidelines when making diagnoses or prescribing treatment.

In the discussion, Littman proposes two hypotheses for the appearance of ROGD. The first states that social and peer contagion is one of the primary causes, and the second asserts that ROGD is a "maladaptive coping mechanism" for adolescents dealing with emotional and social issues. While the surveyed parents did not report early signs of gender dysphoria, a majority noted that their daughters had difficulty in handling negative emotions. Littman concludes that ROGD is distinct from gender dysphoria as described in the DSM-V and that further research is needed to assess whether the condition is short or long-term (Littman, 2018). What the study does not explore, but raises the question, is what proportion of those being treated for gender dysphoria are adolescents with ROGD.

Littman's study along with the others reveal that the causes of gender dysphoria are still a mystery and could have multiple biological and social elements. Because of this ongoing uncertainty, treatments that pose irreversible effects should not be utilized to address what is still categorized as a mental health issue. That allows adequate opportunity for individuals to receive treatment for co-existing mental disorders, establish their gender dysphoria diagnoses, and understand how cross-sex hormones and surgery will alter the appearance of their bodies as well as long-term health.

Literature Review: Desistance of Gender Dysphoria and Puberty Suppression

The World Professional Association for Transgender Health (WPATH) and the Endocrine Society both endorse the use of gonadotropin releasing hormones (Gn-RH) to suppress puberty in young adolescents who have gender dysphoria. Both organizations state that the treatment is safe and fully reversible. In addition, they state that delaying pubertal onset can provide extra time for adolescents to explore the gender in which they choose to live. The associations further state that puberty suppression is necessary to prevent the development of primary and secondary sexual characteristics that can inhibit successful transitions into adulthood (WPATH, 2012; Endocrine Society, 2017). Of the two groups, WPATH offers clinical criteria an individual should meet to qualify for puberty suppression such as addressing psychological co-morbidities and assessing whether gender dysphoria has intensified (WPATH, 2012).

Neither organization explains that the majority of young adolescents who exhibit signs of gender dysphoria eventually desist and conform to their natal sex and that the puberty suppression can have side effects. Both organizations neglect to mention that using Gn-RH for gender dysphoria by altering the appearance is not an FDA-approved clinical indication. Furthermore, the research used to justify puberty suppression is low or very-low quality and little information is available on long-term effects (Hruz, 2019). Additionally, in his assessment, Quentin Van Meter explained that physical differences between central precocious puberty and natural onset puberty demonstrate that Gn-RH does not have permanent adverse effects for those treated for the former but can for the latter such as insufficient bone-mineral density and neural development (Van Meter, 2022). Also, as recently as May 17, 2022, during a U.S. Senate Committee on Appropriations hearing, Lawrence Tabak, acting director of the National Institutes of Health, responded to Senator Marco Rubio, acknowledging that no long-term studies are available evaluating the effects of puberty blockers when used for gender dysphoria (U.S. Senate Committee on Appropriations, 2022).

Currently, some studies provide weak support for this treatment but leave too many questions as to its effectiveness and medical necessity, especially considering how many children decide against transitioning. In addition, puberty blockers halt development of primary and secondary sexual characteristics and deny opportunities for adolescents to adapt and become comfortable with their natal sex. Instead, puberty blockers can serve as a potential "gateway drug" for cross-sex hormones by denying them the experience of physically maturing (Laidlaw et al, 2018).

A 2013 study by Steensma et al offers data on the percentage of children who opt not to transition after experiencing gender dysphoria. The authors follow 127 adolescents (mean age of 15 during the evaluation period) for four years who had been referred to a Dutch gender dysphoria clinic. Out of this cohort, 47 (37%; 23 boys and 24 girls) continued experiencing the condition and applied for sex reassignment treatment. The other 80 adolescents never returned to the clinic. Because this clinic was the only one that treated gender dysphoria in the Netherlands, Steensma et al assumed that those who did not return no longer desired transitioning. The study indicates one of the key predictors for persisting gender dysphoria was the age of first presentation. Older adolescents that started going to the clinic were more likely to persist, while younger adolescents tended not to follow through. Steensma et al provide further insight into other predicting factors, particularly on how each individual views his or her gender identity. The authors note that adolescents who "wished they were the other sex" were more likely to become desisters and that those who "believed that they were the other sex" persisted

and later sought sex reassignment treatment (Steensma et al, 2013). While the study focuses on factors that contribute to the condition's persistence or desistance, it raises the question as to whether puberty suppression is necessary when age plays such an important role regarding the decision to transition.

WPATH and the Endocrine Society state that the primary reason for initiating pubertal suppression is not to treat a physical condition but to improve the mental health of adolescents with gender dysphoria. However, available research does not yield definitive results that this method is effective at addressing a mental health issue. The "gold standard" for medical studies is the randomized-controlled trial (RCT). Because RCTs utilize large sample sizes, have blind testing groups (i.e, placebos), and use objective controls, they can offer concrete conclusions and shape the array of established treatments. In addition, RCTs require comparisons between cohort outcomes and ensure that participants are randomly assigned to each group. These measures further reduce the potential for bias and subjectivity (Hariton and Locascio, 2018).

Presently, no RCTs that evaluate puberty suppression as a method to treat gender dysphoria are available. Instead, the limited number of published studies on the topic utilize small sample sizes and subjective methods (Hruz, 2019). A 2015 article by Costa et al is one such example. The study asserts that "psychological support and puberty suppression were both associated with an improved global psychological functioning in gender dysphoric adolescents." To reach this conclusion, the authors selected 201 children diagnosed with the condition and divided them into two groups, one to receive psychological support only and the other to get puberty blockers in addition to psychological support. Costa et al did not create a third group that lacked a gender dysphoria diagnosis to serve as a control. To assess whether puberty suppression is an effective treatment, the authors administered two self-assessments (Utrect Gender Dysphoria Scale and Children's Global Assessment Scale)[6] to the groups at 6-month intervals during a 12-month period. Because the study relies heavily on self-assessments, the conclusions are likely biased and invalid. Another problem that is also present and common throughout articles supporting puberty suppression is the short-term period of the study. Costa et al's conclusions may not be the same if additional follow-ups occurred three or five years later (Costa et al, 2015). This further raises the question whether low-quality studies like Costa et al's should serve as the basis for clinical guidelines advising clinicians to prescribe drugs for off-label purposes.

Aside from questionable research, information regarding the full physical effects of puberty suppression is incomplete. In a 2020 consensus parameter prepared by Chen et al, 44 experts in neurodevelopment, gender development, and puberty/adolescence reached a conclusion stating that "the effects of pubertal suppression warrant further study." The basis for this was that the "full consequences (both beneficial and adverse) of suppressing endogenous puberty are not yet understood." The participating experts emphasized that the treatment's impact on neurodevelopment in adolescents remains unknown. Chen et al explain that puberty-related hormones play a role in brain development as documented in animal studies and that stopping these hormones also prevents neurodevelopment in addition to sexual maturation. The authors further raise the question whether normal brain development resumes as if it had not been interrupted when puberty suppression ceases. Because this

[6] Behavioral health practitioners use the Children's Global Assessment Scale (CGAS) to measure child functioning during the evaluation process to determine diagnoses. Available evidence indicates that the CGAS is not effective for evaluating children who experienced trauma and presented with mental health symptoms (Blake et al, 2006).

question remains unanswered, it casts doubt on the veracity of organizations' assertions that puberty suppression is "fully reversible" (Chen et al, 2020).

In addition to the unanswered questions and low-quality research, puberty suppression causes side effects, some of which have the potential to be permanent. According to a 2019 literature review by De Sanctis et al, most side effects associated with Gn-RH are mild, consisting mostly of irritation around injection sites. However, clinicians have linked the drug to long-term conditions such as polycystic ovarian syndrome, obesity, hypertension, and reduced bone mineral density. While reports of these events are low and the authors indicate that Gn-RH is safe for treating central precocious puberty (Note: De Sanctis et al do not consider gender dysphoria in their analysis), the review raises questions about whether off-label use to treat a psychological condition is worth the risks (De Sanctis et al, 2019).

Furthermore, De Sanctis et al cite studies noting increased obesity rates in girls who take Gn-RH but that more research is needed to gauge the consistency. Additionally, the authors note that evidence is strong regarding reduced bone mineral density during puberty suppression but indicate that the literature suggests it is reversible following treatment (De Sanctis et al, 2019). While research leans toward the reversibility of effects on bone mineral density, the quantity of studies available on this subject are limited. Also, no long-term research has been completed on how puberty suppression affects bone growth. This is significant because puberty is when bone mass accumulates the most (Kyriakou et al, 2020). One example of a complication involving bone growth and Gn-RH is slipped capital femoral epiphysis. This condition occurs when the head of the femur (i.e., thighbone) can slip out of the pelvis, which can eventually lead to osteonecrosis (i.e., bone death) of the femoral head. Although the complication is rare, its link to puberty suppression indicates that the "lack of adequate sex hormone exposure" could be a cause (De Sanctis et al, 2019).

The current literature on puberty suppression indicates that using it to treat gender dysphoria is off-label, poses potentially permanent side effects, and has questionable mental health benefits. The limited research and lack of FDA approval for that clinical indication prompt questions about whether medications with physically altering effects should be used to treat a problem that most adolescents who experience it will later overcome by conforming to their natal sex. Additional evidence is required to establish puberty suppression as a standard treatment for gender dysphoria.

Literature Review: Cross-Sex Hormones as a Treatment for Gender Dysphoria

Currently, the debate surrounding the use of cross-sex hormones to treat gender dysphoria revolves around their ability to improve mental health without causing irreversible effects. It is not about whether taking cross-sex hormones can alter someone's appearance. The evidence demonstrating the effectiveness of cross-sex hormones in achieving the secondary sexual characteristics of the opposite sex is abundant. Also, the overall scientific consensus concludes that individuals who take cross-sex hormones will reduce the primary sexual function of his or her natal sex organs. What researchers continue evaluating are the short and long-term effects on mental health, impacts on overall physical health, and how the changes affect the ability to detransition. Of these, benefits to mental health overshadow the other discussions. Prescribers of cross-sex hormones focus so heavily on behavioral health outcomes that they de-emphasize that these drugs cause permanent physical changes and side effects that can lead to premature death (Hruz, 2020). Some clinical guidelines such as WPATH's do not even indicate that some of the changes are irreversible.

Like puberty suppression, the Endocrine Society and WPATH provide guidance on administering cross-sex hormones to individuals with gender dysphoria. Both organizations state that this treatment should not be administered without a confirmed diagnosis of gender dysphoria and only after a full psychosocial assessment. In addition, behavioral health practitioners must ensure that any mental comorbidities are not affecting the individual's desire to transition. WPATH and the Endocrine Society further state that clinicians should administer hormone replacements such as testosterone and Estradiol (estrogen) in gradual phases, where the dose increases over several months. For trans-females, the organizations state that progesterone (anti-androgen) is also necessary to block the effects of naturally produced testosterone (WPATH, 2012; Endocrine Society, 2017). When taking cross-sex hormones, trans-males need increased doses for the first six months. After that, the testosterone's effects are the same on lower doses. Once started, individuals cannot stop taking hormones unless they desire to detransition (Unger, 2016).

Although the two groups provide similar guidance, they vary on statements that can have significant impact on long-term outcomes, particularly regarding age. According to WPATH's standards, 16 years is the general age for initiating cross-sex hormones, but the organization acknowledges that the treatment can occur for younger individuals depending on circumstances (WPATH, 2012). This differs from the Endocrine Society, which states no specific age for appropriateness and explains the disagreements in assigning a number. The group highlights that most adolescents have attained sufficient competence by age 16 but may not have developed adequate abilities to assess risk (Endocrine Society, 2017). This raises the question whether adolescents can make sound decisions regarding their long-term health. Additionally, the varying guidance raises an issue with WPATH not only using age 16 as a standard but also indicating that younger adolescents are capable of making that choice.

WPATH's guidance also does not stress the irreversible nature of cross-sex hormones, citing the treatment as "partially reversible" and not indicating which changes are permanent. Furthermore, parts of WPATH's information are misleading and directly conflict with guidance issued by clinics and other sources. One such example consists of WPATH stating that "hormone therapy *may* (emphasis added) lead to irreversible changes." This statement is misleading in light of existing research, which indicates that multiple physical changes are permanent. In addition, WPATH claims that certain effects of cross-

sex hormones such as clitoral enlargement can last one to two years when it is actually irreversible (UCSF, 2020). WPATH also does not explain the risks to male fertility, noting that lowered sperm count or sterility is "variable." The University of California at San Francisco (UCSF) provides starkly different information by stating that trans-females should expect to become sterile within a few months of starting cross-sex hormones. UCSF also advises trans-females to consult a sperm bank if they may want to father children after transitioning (WPATH, 2012; UCSF, 2020). Below is a chart that outlines the effects of cross-sex hormones and identifies which ones are reversible or permanent.

Physical Changes Effectuated by Cross-Sex Hormones	
Physical Changes in Trans-Males (Female-to-Male Transitions)	
Physical Change	**Reversible or Irreversible**
Oily Skin or Acne	Reversible
Facial and Body Hair Growth	Irreversible
Male-Pattern Baldness	Irreversible
Increased Muscle Mass	Reversible
Body Fat Redistribution	Reversible
Ceasing of Menstruation	Reversible
Enlarged Clitoris	Irreversible
Vaginal Atrophy	Reversible
Deepening of Voice	Irreversible
Physical Changes in Trans-Females (Male-to-Female Transitions)	
Body Fat Redistribution	Reversible
Decreased Muscle Mass	Reversible
Skin Softening or Decrease in Oiliness	Reversible
Lower Libido	Reversible
Fewer Spontaneous Erections	Reversible
Male Sexual Dysfunction	Possibly Irreversible
Breast Growth	Irreversible
Decrease in Testicular Size	Reversible
Decrease in Sperm Production or Infertility	Likely Irreversible
Slower Facial and Body Hair Growth	Reversible

Sources: UCSF, 2020; WPATH, 2012; Endocrine Society, 2017[7]

The above chart demonstrates that trans-males and trans-females experience different effects from cross-sex hormones that can cause myriad issues in later life. For example, trans-males who opt to detransition may face challenges related to permanent disfigurement (e.g., facial hair and deepened voices). Trans-females, on the other hand, may not endure the same issues pertaining to visible physical changes but might become despondent over being unable to reproduce. This can occur regardless of whether the transitioning individual is satisfied with sex reassignment. Given that the clinical guidelines do not provide uniform information on the permanent effects of cross-sex hormones, clinicians are unable to make sound recommendations to patients. This treatment can supposedly alleviate symptoms

[7] This chart consists of conclusions regarding physical changes made by three different clinical organizations. If one organization determined that a physical change was irreversible, that was sufficient to meet the criteria to be listed as "irreversible" in the chart.

of distress. However, cross-sex hormones' permanent effects also have the potential to cause psychological issues.

Arguments favoring cross-sex hormones assert that the desired physical changes can alleviate mental health issues in individuals with gender dysphoria but do not consider that hormones used in this manner, like puberty blockers, are off-label. While the FDA has approved estrogen and testosterone for specific clinical indications (e.g., hypogonadism), it has not cleared these drugs for treating gender dysphoria. Additionally, these arguments do not acknowledge that the U.S. Drug Enforcement Administration (DEA) lists testosterone as a Schedule III controlled substance, meaning that it has a high probability of abuse (DEA, 2022). Furthermore, evidence of psychological benefit from cross-sex hormones is low-quality and relies heavily on self-assessments taken from small sample groups (Hruz, 2020).

A 2019 study by Kuper et al seeks to demonstrate that adolescents desiring cross-sex hormones have elevated rates of depression, anxiety, and challenges with peer relationships. To make their findings, the authors provided questionnaires to 149 adolescents who presented at a gender clinic in Dallas, Texas and concluded that half of the sample group experienced increased psychological issues. One problem with the study is that it relies on parent or self-assessments such as the Youth-Self Report, Body-Image Scale, and the Child Behavior Checklist. While these assessments have strong reliability, the sample is cross-sectional, consisting of gender dysphoric individuals who presented for an initial visit at the clinic. Also, Kuper et al do not directly link these psychological symptoms to gender dysphoria but rather insinuate a strong connection. Without an analysis of the longitudinal histories of the participants, the study cannot demonstrate whether gender dysphoria was a direct cause of the psychological issues, which could possibly result from trauma, abuse, or family dysfunction. Kuper et al's study only presents weak correlation between adolescents who report symptoms of distress and gender dysphoria. While the authors do not claim that the participants' psychological problems caused the condition, they fail to explicitly state that no demonstrable relationship exists and explain that their findings are "broadly consistent with the previous literature" (Kuper et al, 2019).

Additionally, a more comprehensive literature review from 2019 by Nguyen et al evaluates the effect of cross-sex hormones on mental health outcomes. Although the authors argue that the evidence supports the treatment, they do note that available studies use "uncontrolled observational methods" and "rely on self-report." The review also asserts that "future research should focus on applying more robust study designs with large sample sizes, such as controlled prospective cohort studies using clinician-administered ratings and longitudinal designs with appropriately matched control groups." All of these are characteristics of RCTs. While Nguyen et al highlight flaws in the studies in their conclusion, they do not emphasize them in their analysis, opting to focus primarily on results. Another problem with the studies selected for the review is the short-term periods for evaluation. Out of 11 studies Nguyen et al discuss, only one tracks its participants for 24 months. The others only follow their cohorts for 6 or 12 months (Nguyen et al, 2019). Without long-term data to support assertions that cross-sex hormones substantially improve the mental health of individuals with gender dysphoria, the review cannot make definitive conclusions on the treatment's benefits.

Basing their stances on this low-quality evidence, clinical associations such as the American Academy of Pediatrics (AAP) and the American Psychology Association endorse the use of cross-sex hormones as treatments for gender dysphoria. In particular, the AAP discourages use of the term "transition" and

asserts that medical treatments used to obtain secondary characteristics of the opposite sex are "gender affirming." This decision mirrors the DSM-V's interpretation of gender being part of identity. The AAP further states that taking cross-sex hormones is an "affirmation and acceptance of who they (i.e., patient) have always been" (AAP, 2018). The American Psychological Association also takes a similar stance in its *Resolution on Gender Identity Change Efforts* by asserting that medical treatments such as puberty suppression, cross-sex hormones, and surgery improve mental health and quality of life and reinforce the notion that transitioning and seeking sex reassignment therapies do not constitute a psychological disorder (American Psychological Association, 2021). Stances like these can substantially influence practitioners and their treatment recommendations. Given that low-quality evidence serves as the basis for supportive positions, this raises questions about whether clinicians can make informed decisions for their patients that will promote the best outcomes.

James Cantor published a critique in 2020 of the AAP's endorsement of "gender affirming" treatments, arguing that the organization did not base its recommendations on established medical evidence. He asserts that the AAP's position is based on research that does not support intervention but rather supports "watchful waiting" because most transgender youths desist and identify as their natal sex during puberty. Cantor further argues that the AAP not only disregards evidence but also cites "gender affirming" interventions as the only effective method. To conclude, he states the organization is "advocating for something far in excess of mainstream practice and medical consensus" (Cantor, 2020).

Given those evidentiary problems, those who rely on the AAP's endorsement as a basis for "gender affirming" treatments are practicing eminence-based medicine as opposed to evidence-based medicine. Eminence-based medicine refers to clinical decisions made by relying on the opinions of prominent health organizations rather than relying on critical appraisals of scientific evidence (Nhi Le, 2016). While it is true that the AAP has more knowledge than a lay person and a degree of credibility in the medical community, the opinions of such organizations are not valid unless they are based on quality evidence.

Research on sex reassignment also does not adequately address the reasons for and prevalence of detransitioning. Although no definite numbers are available regarding the percentage of transgender people who decide to detransition, research indicates that roughly 8% decide to return to their natal sex. The reasons range from treatment side effects to more self-exploration that provided insight on individuals' gender dysphoria. In a 2020 study by Lisa Littman, 101 people who had detransitioned provided their basis for doing so. Out of the sample group, 96% had taken cross-sex hormones and 33% had sex reassignment surgery. The average age for transitioning was 22 years, and the mean duration for the transition was 4 years. This indicates that even allowing additional time beyond the recommended age of 16 years can still lead to regrets. The study also raises the question as to whether individuals who transitioned at 16 or younger wanted to detransition in greater numbers. The author further offers reasons why these individuals sought cross-sex hormones and surgery, which include having endured trauma (mental or sexual), homophobia (challenged to accept oneself as a homosexual), peer and media influences, and misogyny (applicable only to trans-males). To obtain the results, the participants responded to a survey that asked about their backgrounds (e.g., reasons for transitioning, mental health comorbidities), and motivations for detransitioning. Littman noted that half of the women (former trans-males) had a mental health disorder and/or had experienced trauma within a year of deciding to transition. Men (former trans-females) reported much lower numbers of behavioral health issues and trauma after de-transitioning. Additionally, 77% of men surveyed identified as the opposite gender prior to transition, whereas just 58% of women had (Littman, 2020).

Of the reasons cited for detransitioning, the majority (60%) noted that they became more comfortable with their natal sex. Other reasons included concerns over complications from the treatments, primarily cross-sex hormones, and lack of improved mental health. Other less-cited explanations include concerns about workplace discrimination and worsening physical health. The study also notes that approximately 36% of participants experienced worse mental health symptoms. Based on the findings, Littman concludes that more research is needed in tracking the transgender population to obtain accurate percentages of those who decide to detransition and that men and women reported varying reasons for deciding to transition and later return to their natal sex. The author notes that higher rates of trauma and peer group influences might have contributed to women's decisions, which Littman attributes partially to rapid onset gender dysphoria (Littman, 2020). What the study also indicates is that cross-sex hormones are not a validated treatment for gender dysphoria. Nearly all of the participants had taken them and decided against maintaining the physical changes. Given that the majority of surveyed detransitioners cited that they were comfortable with their biological sex, the study indicates that gender dysphoria is not necessarily a lifelong issue. This necessarily raises doubts about whether cross-hormones, which cause permanent physical damage, is justified.

In addition to the psychological factors, cross-sex hormones pose significant long-term health risks to transitioning individuals. Currently, little information is available given that researchers have not had adequate time to study the effects in this population. However, use of hormones for other conditions has yielded data on how these drugs can affect the body and the cardiovascular system in particular. Because of the high dosages required to achieve physical change and the need to continuously take the drugs, cross-sex hormones can potentially harm quality of life and reduce life expectancy for transitioning individuals. According to Dutra et al, trans-females are three times more likely to die from a cardiovascular event than the general population. In their 2019 literature review, Dutra et al examined the results of over 50 studies evaluating the effects of cross-sex hormones on not only transgender individuals but those with menopause and other endocrine disorders, all of which indicate that use of estrogen or testosterone can increase risks for cardiovascular disease. Throughout their review, Dutra et al cite examples of trans-females having higher triglyceride levels after 24 months of cross-sex hormones and how researchers halted a study on estrogen due to an increase in heart attacks among participants. Another article the authors reference indicates a higher risk for thromboembolisms (i.e., blood clots) in trans-females. For trans-males, Dutra et al explain that research shows significant increased risk for hypertension, high cholesterol, obesity, and heart attacks. One study noted that trans-males have a four times greater risk of heart attack compared to women identifying as their natal sex. Dutra et al conclude that most transgender individuals are younger than 50 and that more studies are needed as this population ages. They do note that available studies indicate that cross-sex hormones pose dangers to long-term cardiovascular health (Dutra et al, 2019).

In sum, the literature reveals that the evidence for cross-sex hormones as a treatment for gender dysphoria is weak and insufficient. Between the permanent effects, off-label use, and consequences to long-term health, cross-sex hormones are a risky option that does not promise a cure but does guarantee irreversible changes to both male and female bodies. Additionally, the inadequate studies serving as the basis for recommendations by clinical associations can lead to providers making poorly informed decisions for their patients. Research asserting that taking cross-sex hormones improves mental health is subjective and short-term. More studies that utilize large sample sizes and appropriate

methods is required before the medical profession should consider cross-sex hormones as one of gender dysphoria's standard treatments.

Literature Review: Sex Reassignment Surgery

The final phase of treatment for gender dysphoria is sex reassignment surgery. This method consists of multiple procedures to alter the appearance of the body to resemble an individual's desired gender. Some procedures apply to the genitals (genital procedures) while others affect facial features and vocal cords (non-genital procedures). While the surgery creates aesthetical aspects, it does not fully transform someone into the opposite biological sex. Transgender persons who undergo the procedures must continue taking cross-sex hormones to maintain secondary sexual characteristics. Additionally, all physical changes are irreversible, and the success rate of a surgery varies depending on the procedure and the population. For example, surgeries for trans-females have much better results than those for trans-males. Complications such as post-operative infections can also arise with the urinary tract system. However, sex reassignment surgery supposedly can provide drastic, if not complete, relief from gender dysphoria (Endocrine Society, 2017). The following is a list of procedures (both genital and non-genital) for trans-females and trans-males that create physical features of the desired sex.

Procedures for Trans-Females

- **Genital Surgeries:** These consist of penectomy (removal of the penis), orchiectomy (removal of the testicles), vaginoplasty (construction of a neo-vagina), clitoroplasty (construction of a clitoris), and vulvoplasty (construction of a vulva and labia). To perform, a surgeon begins by deconstructing the penis and removing the testicles. The penile shaft and glans are repurposed to serve as a neo-vagina and artificial clitoris (Note: These are not actual female genitalia but tissue constructed to resemble female anatomy). If the shaft tissue is insufficient, the surgeon may opt to use a portion of intestine to build a neo-vagina. The scrotum serves as material for fashioning a vulva and labia. In addition to constructing female genitalia, the surgeon reroutes the urethra to align with the neo-vagina. Genital surgeries for trans-females result in permanent sterility (Bizic et al, 2014).
- **Chest Surgery:** To attain full breasts, trans-females can undergo enlargement. The procedure is similar to breast augmentation for women where a surgeon places implants underneath breast tissue. Prior to surgery, trans-females need to take cross-sex hormones for roughly 24 months to increase breast size to get maximum benefit from the procedure (Endocrine Society, 2017).
- **Cosmetic and Voice Surgeries:** Designed to create feminine facial features, fat deposits, and vocal sounds, these procedures are secondary to genital procedures and intended to alter trans-females' appearances to better integrate into society as a member of the desired gender (WPATH, 2012).

Procedures for Trans-Males

- **Mastectomy:** This is the most performed sex reassignment surgery on trans-males because cross-sex hormones and chest-binding garments are often insufficient at diminishing breasts. To remove this secondary sexual characteristic, trans-males can undergo a mastectomy where a surgeon removes breast tissue subcutaneously (i.e., under the skin) and reconstructs the nipples to appear masculine. The procedure can result in significant scarring (Monstrey et al, 2011).
- **Genital Surgeries:** Unlike the procedures for trans-females, genital surgeries for trans-males are more complex and have lower success rates. Consisting of hysterectomy, oophorectomy

(removal of the ovaries), vaginectomy (removal of the vagina), phalloplasty (construction of a penis), and scrotoplasty (construction of prosthetic testicles), a team of surgeons must manufacture a penis using skin from the patient (taken from an appendage) while removing the vagina and creating an extended urethra. The functionality of the artificial penis can vary based on how extensive the construction was. Attaining erections requires additional surgery to implant a prosthesis, and the ability to urinate while standing is often not achieved. Genital procedures for trans-males result in irreversible sterility (Monstrey et al, 2011).

- **Cosmetic Surgeries:** Similar to trans-females, these procedures create masculine facial features, fat deposits, and artificial pectoral muscles. They aid trans-males with socially integrating as their desired gender. Surgery to deepen voices is also available but rarely performed (WPATH, 2012).

Because sex reassignment surgery is irreversible, the criteria for receiving these procedures is the strictest of all gender dysphoria treatments. WPATH and the Endocrine Society suggest rigorous reviews of patient history and prior use of other therapies before approving. Furthermore, the two organizations recommend that only adults (18 years old) undergo sex reassignment surgery.[8] WPATH and the Endocrine Society also recommend ensuring a strongly documented diagnosis of gender dysphoria, addressing all medical and mental health issues, and at least 12 months of cross-sex hormones for genital surgeries. Although the organizations agree on most criteria, they differ on whether hormones should be taken prior to mastectomies. WPATH asserts that hormones should not be a requirement, whereas the Endocrine Society advises up to 2 years of cross-sex hormones before undergoing the procedure (WPATH, 2012; Endocrine Society, 2017). What this indicates is that trans-males might undergo breast removal without having first pursued all options if their clinician adheres to WPATH's guidelines, which can lead to possible regret over irreversible effects.

As with cross-sex hormones, sex reassignment surgery's irreversible physical changes can potentially show marked mental health improvements and prevent suicidality in people diagnosed with gender dysphoria. In April 2022, the chair of the University of Florida's pediatric endocrinology department, Dr. Michael Haller, advocated for the benefits of "gender affirming" treatments (WUSF, 2020). However, the available evidence calls such statements into question. Recent research assessing both cross-sex hormones and sex reassignment surgery indicate that the effects on "long-term mental health are largely unknown." In studies regarding the benefits of surgery, the results have the same weaknesses as the research for the effectiveness of cross-sex hormones. These include small sample sizes, self-report surveys, and short evaluation periods, all of which are insufficient to justify recommendations for irreversible treatments (Bränström et al, 2020).

Two studies conducted in Sweden provide insight on the effectiveness of sex reassignment surgery in improving the behavioral health of transgender persons. Because Sweden has a nationalized health system that collects data on all residents, this country can serve as a resource to assess service utilization and inpatient admissions. Both studies, one by Dhejne et al from 2011 and another by Bränström et al published in 2020, assessed individuals who had received sex reassignment surgery and examined outcomes over several decades. Dhejne et al's findings indicate that sex reassignment

[8] Although practice guidelines indicate the minimum age to undergo sex reassignment surgery is 18, available evidence demonstrates that mastectomies have been performed on adolescent girls as young as 13 who experience "chest dysphoria" (Olson-Kennedy et al, 2018).

procedures do not reduce suicidality. The authors explained that individuals who underwent sex reassignment surgery were still more likely to attempt or commit suicide than those in the general population. This study is unique because it monitored the subjects over a long period of time. Dhejne et al note that the transgender persons tracked for the study did not show an elevated suicide risk until ten years after surgery (Dhejne et al, 2011). Given that a high proportion of research follows sex reassignment patients for much shorter timeframes, this evidence indicates that surgery might have little to no effect in preventing suicides in gender dysphoric individuals over the long run.

In addition to having an increased suicide risk, Dhejne et al discuss how individuals who underwent sex reassignment procedures also had higher mortality due to cardiovascular disease. The authors do not list the specific causes but establish the correlation. Given that cross-sex hormones can damage the heart, the increased risk could be related to the drugs and not the surgery. Furthermore, the study explains that the tracked population had higher rates of psychiatric inpatient admissions following sex reassignment. Dhejne et al established this by examining the rates of psychiatric hospitalizations in these individuals prior to surgery and noted higher utilization in the years following the procedures. These results are in comparison to the Swedish population at large. While the study contradicts other research emphasizing improvements in mental health issues, it has its limitations. For example, the sample size is small. Dhejne et al identified only 324 individuals who had undergone sex reassignment surgery between 1973 and 2003. In addition, the authors noted that while the tracked population had increased suicide risks when compared to individuals identifying as their natal sex, the rates could have been much higher if the procedures were not available (Dhejne et al 2011). What this study postulates is that sex reassignment surgery does not necessarily serve as a "cure" to the distress resulting from gender dysphoria and that ongoing behavioral health care may still be required even after a complete transition.

Bränström et al's study evaluating the Swedish population used a larger sample (1,018 individuals who had received sex reassignment surgery) but tracked them for just a ten-year period (2005 to 2015).[9] Unlike Dhejne et al, the authors did not track suicides and focused primarily on mood or anxiety disorder treatment utilization. Their results indicate that transgender persons who had undergone surgery utilized psychiatric outpatient services at lower rates and were prescribed medications for behavioral health issues at an annual decrease rate of 8%. Bränström et al also did not limit comparisons to Sweden's overall population and factored in transgender persons who take cross-sex hormones but have not elected to have surgery. Those results still presented a decrease in outpatient mental health services. However, Bränström et al note that individuals only on cross-sex hormones showed no significant reduction in that category, which calls into question claims regarding effectiveness of cross-sex hormones in ameliorating behavioral issues.

The Bränström et al study prompted numerous responses questioning its methodology. The study lacked a prospective cohort or RCT design, and it did not track all participants for a full ten-year period (Van Mol et al, 2020). These criticisms resulted in a retraction, asserting that Bränström et al's conclusions were "too strong" and that further analysis by the authors revealed that the new "results demonstrated no advantage of surgery in relation to subsequent mood or anxiety disorder-related

[9] Although Bränström et al claim to follow individuals for a ten-year period, peer reviews of the research revealed that this was not the case, noting the authors had varying periods of tracking, ranging from one to ten years (Van Mol et al, 2020).

health care visits or prescriptions or hospitalizations following suicide attempts in that comparison" (Kalin, 2020).

There are multiple explanations for why the Bränström et al study reached different results than the Dhejne et al study. For starters, Bränström et al tracked a larger sample group over a later period (2005 to 2015 as opposed to 1973 to 2003) during which gender dysphoria underwent a dramatic shift in definition. Also, Dhejne et al did not see elevated suicides until after ten years, raising the question as to whether sex reassignment surgery has temporary benefits on mental health rather than long-term or permanent benefits. Like the other Swedish study, Bränström et al's findings are a correlation and do not specifically state that the procedures cause reduced psychiatric service utilization (Bränström et al, 2020).

A 2014 study by Hess et al in Germany evaluated satisfaction with sex reassignment procedures by attempting to survey 254 trans-females on their quality of life, appearance, and functionality as women. Out of the participants selected, only 119 (47%) returned completed questionnaires, which Hess et al indicate is problematic because dissatisfied trans-females might not have wanted to provide input. The results from the collected responses noted that 65.7% of participants reported satisfaction with their lives following surgery and that 90.2% indicated that the procedures fulfilled their expectations for life as women. While these results led Hess et al to conclude that sex reassignment surgery generally benefits individuals with gender dysphoria, the information is limited and raises questions (Hess et al, 2014). Such questions include whether the participants had mental health issues before or after surgery and did their satisfaction wane over time. Hess et al only sent out one questionnaire and not several to ascertain consistency over multiple years. Questions like these raise doubts about the validity of the study. Although Hess et al's research is just one study, numerous others utilize the same subjective methods to reach their conclusions (Hruz, 2018).

In his assessment, Patrick Lappert contributes additional insight on the appropriate clinical indications for mastectomies, noting that removal of breast tissue is necessary following the diagnosis of breast cancer or as a prophylactic against that disease. He cites that this basis is verifiable through definitive laboratory testing and imaging, making it an objective diagnosis, whereas gender dysphoria has no such empirical methods to assess and depends heavily on the patient's perspective. Also, Lappert notes that trans-males who make such decisions are doing so on the idea that the procedure will reduce their dysphoria and suicide risk. However, they are making an irreversible choice based on anticipated outcomes supported only by weak evidence, and thus cannot provide informed consent (Lappert, 2022).

The literature is inconclusive on whether sex reassignment surgery can improve mental health for gender dysphoric individuals. Higher quality research is needed to validate this method as an effective treatment. This includes studies that obtain detailed participant histories (e.g., behavioral diagnoses) and track participants for longer periods of time. These are necessary to evaluate the full effects of treatments that cause irreversible physical changes. In addition, sex reassignment procedures can result in severe complications such as infections in trans-females and urethral blockage in trans-males. Health issues related to natal sex can also persist. For example, trans-males who undergo mastectomy can still develop breast cancer and should receive the same recommended screenings (Trum et al, 2015). Until more definitive evidence becomes available, sex reassignment surgery should not qualify as a standard treatment for gender dysphoria.

Literature Review: Quality of Available Evidence and Bioethical Questions

Quality of Available Evidence

Clinical organizations that have endorsed puberty suppression, cross-sex hormones, and sex reassignment surgery frequently state that these treatments have the potential to save lives by preventing suicide and suicidal ideation. The evidence, however, does not support these conclusions. James Cantor notes that actual suicides (defined as killing oneself) are low, occur at higher rates for men, and that interpretations of available research indicate a blurring of numbers between those with gender dysphoria and homosexuals (Cantor, 2022). Although information exists that contradicts certain arguments, media outlets continue to report stories emphasizing the "lifesaving" potential of sex reassignment treatment. A May 2022 story by NBC announced survey results under the headline "Almost half of LGBTQ youths 'seriously considered suicide in the past year'" (NBC, 2022). This is a significant claim that can have a sensational effect on patients and providers alike, but how strong is the evidence supporting it? Almost all of the data backing this assertion are based on surveys and cross-studies, which tend to yield low-quality results (Hruz, 2018). In addition, how many gender dysphoric individuals are seeing stories in the media and not questioning the narrative? Because research on the effectiveness of treatments is ongoing, a debate persists regarding their use in the adolescent and young-adult populations, and much of it is due to the low-quality studies serving as evidence.

In their assessment, Romina Brignardello-Petersen and Wojtek Wiercioch examined the quality of 61 articles published between 2020 and 2022 (Note: See Attachment A for the full study). They identified research on the effectiveness of puberty blockers, cross-sex hormones, and sex reassignment surgery and assigned a grade (high, moderate, low, or very low) in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Out of the articles reviewed, all with a few exceptions received grades of low or very low quality when demonstrating outcomes regarding improvements in mental health and overall satisfaction with transitioning. For puberty blockers, Brignardello-Petersen and Wiercioch identified low quality evidence for alleviating gender dysphoria and very low quality for reducing suicidal ideation. The authors also had nearly identical findings for cross-sex hormones. However, they noted moderate quality evidence for the likelihood of cardiovascular side effects. Regarding surgery, Brignardello-Petersen and Wiercioch graded articles that examined overall satisfaction and complication rates. None of the studies received grades higher than low quality. These findings led the authors to conclude that "there is great uncertainty about the effects" of sex reassignment treatments and that the "evidence alone is not sufficient to support" using such treatments. Among the studies graded was one the U.S. Department of Health and Human Services cited in its information on "gender affirming" treatments. The authors noted this research had a "critical risk of bias" and was of low quality (Brignardello-Petersen and Wiercioch, 2022).

For his part, James Cantor provided a review of available literature, which addresses studies on etiology, desistance, effectiveness of puberty blockers and cross-sex hormones, suicidal behaviors, and clinical association and international guidelines. Throughout his analysis, Cantor cites weak evidence, poor methodologies (e.g., retrospective versus prospective studies), and lack of professional endorsements in research that indicates the benefits of sex reassignment treatment. Additionally, he notes that improvements in the behavioral health of adolescents who take cross-sex hormones can be attributed to the counseling they receive concurrently and that suicidality is not likely to result from gender

dysphoria but from co-occurring mental disorders. The reasoning behind the third point is based on the blending of suicide and suicidality, which are two distinct concepts. The former refers specifically to killing oneself, and the second regards ideation and threats in attempts to receive help. Cantor specifically notes that actual suicides are highly unlikely among gender dysphoric individuals, particularly trans-males. His other conclusions indicate that young children who experience gender identity issues will most likely desist by puberty, that multiple phenomena can cause the condition, and that Western European health services are not recommending medical intervention for minors. The basis for these statements is the paucity of high to moderate quality evidence on the effectiveness of sex reassignment treatments and numerous studies demonstrating desistance (Cantor, 2022).

Despite the need for stronger studies that provide definitive conclusions, many practitioners stand by the recommendations of the AAP, Endocrine Society, and WPATH. This is evident in a letter submitted to the *Tampa Bay Times*, which was a rebuttal to the Florida Department of Health's (DOH) guidance on treatment for gender dysphoria (Note: The guidance recommends against using puberty blockers, cross-sex hormones, or surgery for minors) (DOH, 2022). The authors, led by six professors at the University of Florida's College of Medicine, state that recommendations by clinical organizations are based on "careful deliberation and examination of the evidence by experts." However, evaluations of these studies show otherwise. Not only does the available research use cross-sectional methods such as surveys, but it provides insufficient evidence based on momentary snapshots regarding mental health benefits. These weak studies are the foundation for the clinical organizations' guidelines that the University of Florida professors tout as a gold standard. In addition, the letter's authors state that DOH's guidance is based on a "non-representative sample of small studies and reviews, editorials, opinion pieces, and commentary" (Tampa Bay Times, 2022). That statement misses the point when it comes to evidence demonstrating whether treatments with irreversible effects are beneficial because the burden of proof is on those advocating for this treatment, not on those acknowledging the need for further research. This raises the question concerning how much academic rigor these professors are applying to practice guidelines released by clinical organizations and whether they also apply the same level of rigor to novel treatments for other conditions (e.g., drugs, medical devices).

Another example of a lack of rigor is a 2019 article by Herman et al from the University of California at Los Angeles (UCLA) that evaluated responses to a 2015 national survey on transgender individuals and suicide. Unlike other studies, this one utilized a large cohort with 28,000 participants from across the U.S. responding. However, the researchers used no screening criteria and did not randomly select individuals. In addition, responses consisted entirely of self-reports with no supporting evidence to even prove a diagnosis of gender dysphoria. Although Herman et al conclude that the U.S. transgender population is at higher risk for suicidal behaviors, the authors' supporting evidence is subjective and serves as a weak basis. Additionally, the survey results do not establish gender dysphoria as a direct cause of suicide or suicidal ideation. The questions required participants to respond about their overall physical and mental health. Out of those that indicated "poor" health, 77.7% reported suicidal thoughts or attempts during the previous year, whereas just 29.1% of participants in "excellent" health had. These percentages indicate that causes beyond gender dysphoria could be affecting suicidal behaviors. Other reasons cited include rejection by family or religious organizations and discrimination. The authors also acknowledge that their findings are broad, not nationally representative, and should serve as a basis for pursuing future research (Herman et al, 2019).

Yet another example is a study published in 2022 by Olson et al tracks 300 young children that identify as transgender over a 5-year period, and asserts low probabilities for detransitioning, while supporting interventions such as puberty blockers. The authors found that children (median age of 8 years) who identified as a gender that differed from their natal sex were unlikely to desist at a rate of 94% and conclude that "transgender youth who socially transitioned at early ages" will continue "to identify that way." While this appears to contradict earlier studies that demonstrate most young adolescents who change gender identities return to their "assigned gender at birth," the authors note differences and limitations with the results. For example, Olson et al notes that they did not verify whether the participants met the DSM-V's diagnostic criteria for gender dysphoria and that the children's families supported the decisions to transition. Instead, the authors relied on a child's chosen pronouns to classify as transgender. Also, Olson et al acknowledged that roughly 66% of the sample was biologically male. This is particularly significant considering that the majority of transitioning adolescents in recent years were natal females. Another issue with the study includes the median age at the end of follow-up (13 years), which is when boys begin puberty. Furthermore, the authors cite that the participants received strong parental support regarding the transitions, which constitutes positive reinforcement (Olson et al, 2022). Other research demonstrates that such feedback on social transitioning from parents and peers can prevent desistance following pubertal onset (Zucker, 2019). Despite these limitations, the New York Times announced the study's publication under the headline "Few Transgender Children Change Their Minds After 5 Years" (New York Times, 2022). Such a title can add to the public's perception that gender dysphoria requires early medical intervention to address.

Bioethical Questions

The irreversible physical changes and potential side effects of sex reassignment treatment raise significant ethical questions. These questions concern multiple bioethical principles including patient autonomy, informed consent, and beneficence. In a 2019 article, Michael Laidlaw, Michelle Cretella, and Kevin Donovan argue that prescribing puberty blockers or cross-sex hormones on the basis that they will alleviate psychological symptoms should not be the standard of care for children with gender dysphoria. Additionally, the three authors assert that such treatments "constitute an unmonitored, experimental intervention in children without sufficient evidence of efficacy or safety." The primary ethical question Laidlaw, Cretella, and Donovan pose is whether pushing physical transitioning, particularly without parental consent, violates fully informed consent (Laidlaw et al, 2019).

In accordance with principles of bioethics, several factors must be present to obtain informed consent from a patient. These consist of being able to understand and comprehend the service and potential risks, receiving complete disclosure from the physician, and voluntarily providing consent. Bioethicists generally do not afford the ability of giving informed consent to children who lack the competence to make decisions that pose permanent consequences (Varkey, 2021). Laidlaw, Cretella, and Donovan reinforce this point regarding sex reassignment treatment when they state that "children and adolescents have neither the cognitive nor the emotional maturity to comprehend the consequences of receiving a treatment for which the end result is sterility and organs devoid of sexual function" (Laidlaw et al, 2019). This further raises the question whether clinicians who make such treatment recommendations are providing full disclosure about the irreversible effects and truly obtaining informed consent.

Another issue is the conflict between consumerism and the practitioner's ability to provide appropriate care. Consumerism refers to patients learning about treatments through media/marketing and requesting their health care provider to prescribe it, regardless of medical necessity. Considering that social media is rife with individuals promoting "gender affirmative" drugs and surgeries, children are making self-assessments based on feelings they may not understand and that can lead to deep regret in the future (Littman, 2018). This can contribute to patients applying pressure on their doctors to prescribe medications not proven safe or effective for the condition. Consumerism can also affect bioethical compliance because it constrains clinicians from using their full "knowledge and skills to benefit the patient," which is "tantamount to a form of patient abandonment and therefore is ethically indefensible" (Varkey, 2021).

In his assessment, G. Kevin Donovan explains the bioethical challenges related to sex reassignment treatment, emphasizing the lack of informed consent when administering these services. He asserts that gender dysphoria is largely a self-diagnosis practitioners cannot verify with empirical tests (e.g., labs and imaging) and that providing such treatments is experimental. Because of the lack of consent and off-label use of puberty blockers and cross-sex hormones, Donovan raises the question as to how "experienced and ethical physicians so mislead others or be so misled themselves?" He further attributes this phenomenon to societal and peer pressures that influence self-diagnosis and confirm decisions to transition. As a result, these pressures lead to individuals wanting puberty blockers, cross-sex hormones, and surgery. Donovan goes on to identify several news stories where embracing sex reassignment treatment is a "cult-like" behavior. To conclude, he links these factors back to the failure to obtain informed consent from transgender patients and how that violates basic bioethical principles (Donovan, 2022).

Coverage Policies of the U.S. and Western Europe

U.S. Federal Level Coverage Policies

Medicare: In 2016, the Centers for Medicare and Medicaid Services (CMS) published a decision memo announcing that Medicare Administrative Contractors (MACs) can evaluate sex reassignment surgery coverage on a "case-by-case" basis. [10] CMS specifically noted that the decision memo is not a National Coverage Determination and that "no national policy will be put in place for the Medicare program" (CMS, 2016). This memo was the result of CMS reviewing over 500 studies, reports, and articles to the validity of the procedures. Following its evaluation, CMS determined that "the quality and strength of evidence were low due to mostly observational study designs with no comparison groups, subjective endpoints, potential confounding . . . small sample sizes, lack of validated assessment tools, and considerable (number of participants in the studies) lost to follow up." In 2017, CMS reinforced this position with a policy transmittal that repeated the 2016 memo's criteria (CMS, 2017).

The basis for Medicare's decision is that the "clinical evidence is inconclusive" and that "robust" studies are "needed to ensure that patients achieve improved health outcomes." In its review of available literature, CMS sought to answer whether there is "sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria." After evaluating 33 studies that met inclusion criteria, CMS's review concludes that "not enough high-quality evidence" is available "to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria and whether patients most likely to benefit from these types of surgical intervention can be identified prospectively." Additionally, out of the 33 studies, just 6 provided "useful information" on the procedures' effectiveness, revealing that their authors "assessed quality of life before and after surgery using validated (albeit non-specific) psychometric studies" that "did not demonstrate clinically significant changes or differences in psychometric test results" following sex reassignment surgery (CMS, 2016).

U.S. Department of Defense – Tricare: Tricare does not cover sex reassignment surgery, but it will cover psychological services such as counseling for individuals diagnosed with gender dysphoria and cross-sex hormones when medically necessary (Tricare, 2022).[11]

U.S. Department of Veterans Affairs: The U.S. Department of Veterans Affairs (VA) does not cover sex reassignment surgery, although it will reimburse for cross-sex hormones and pre- and post-operative care related to transitioning. Because the VA only provides services to veterans of the U.S. armed forces, it cannot offer sex reassignment treatment to children (VA, 2020).[12]

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[10] The Centers for Medicare and Medicaid Services is part of the U.S. Department of Health and Human Services. Its primary functions are to administer the entire Medicare system and oversee federal compliance of state Medicaid programs. In addition, CMS sets reimbursement rates and coverage criteria for the Medicare program.
[11] Tricare is the insurance program that covers members of the U.S. armed forces and their families. This includes children of all ages.
[12] The U.S. Department of Veterans Affairs oversees the Veterans Health Administration (VHA), which consists of over 1,000 hospitals, clinics, and long-term care facilities. As the largest health care network in the U.S., the VHA provides services to veterans of the U.S. armed forces.

State-Level Coverage Policies

Florida: In April 2022, DOH issued guidance for the treatment of gender dysphoria, recommending that minors not receive puberty blockers, cross-sex hormones, or sex reassignment surgery. [13] The justification offered for recommending against these treatments is that available evidence is low-quality and that European countries also have similar guidelines. Accordingly, DOH provided the following guidelines:

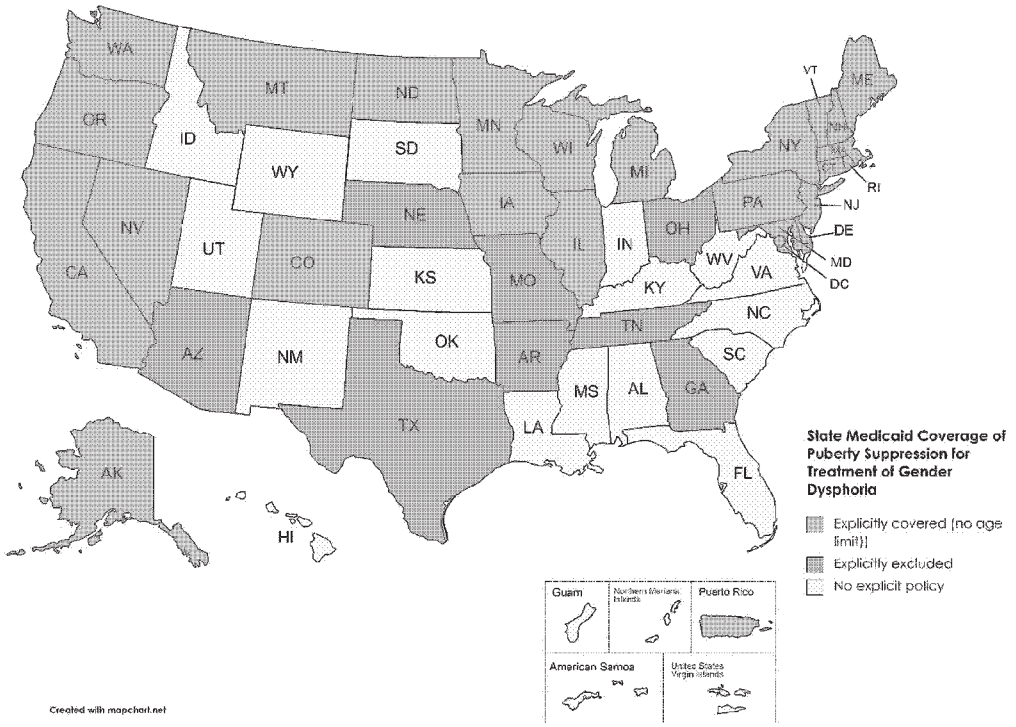
- "Social gender transition should not be a treatment option for children or adolescents."
- "Anyone under 18 should not be prescribed puberty blockers or hormone therapy."
- "Gender reassignment surgery should not be a treatment option for children or adolescents."
- "Children and adolescents should be provided social support by peers and family and seek counseling from a licensed provider."

In a separate fact sheet released simultaneously with the guidance, DOH further asserts that the evidence cited by the federal government cannot establish sex reassignment treatment's ability to improve mental health (DOH, 2022).

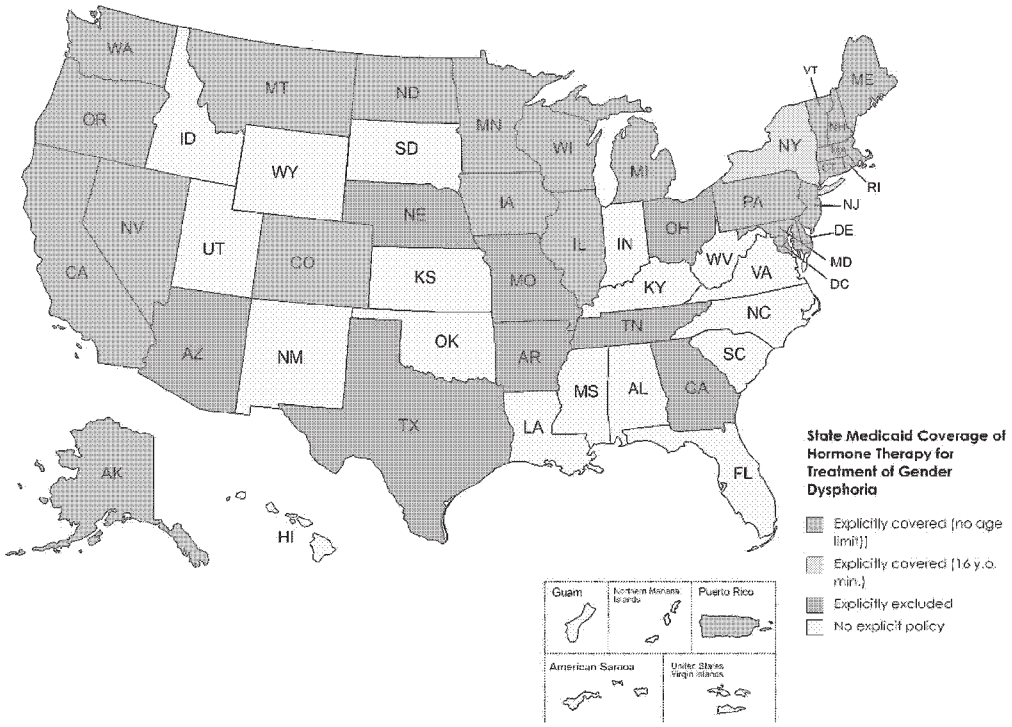
State Medicaid Programs: Because individual states differ in health services offered, Medicaid programs vary in their coverage of sex reassignment treatments. The following maps identify states that cover sex reassignment treatments, states that have no policy, and states that do not cover such treatments.

[13] Unlike the federal government, the State of Florida delegates responsibilities for Medicaid and health care services to five separate agencies (Agency for Health Care Administration, Department of Health, Department of Children and Families, Department of Elder Affairs, and Agency for Persons with Disabilities). Each agency has its own separate head (secretary or surgeon general), which reports directly to the Executive Office of the Governor. As Florida's public health agency, DOH oversees all county health departments, medical professional boards, and numerous health and welfare programs (e.g., Early Steps and Women, Infants, and Children). Because it oversees the boards, DOH has authority to release practice guidelines.

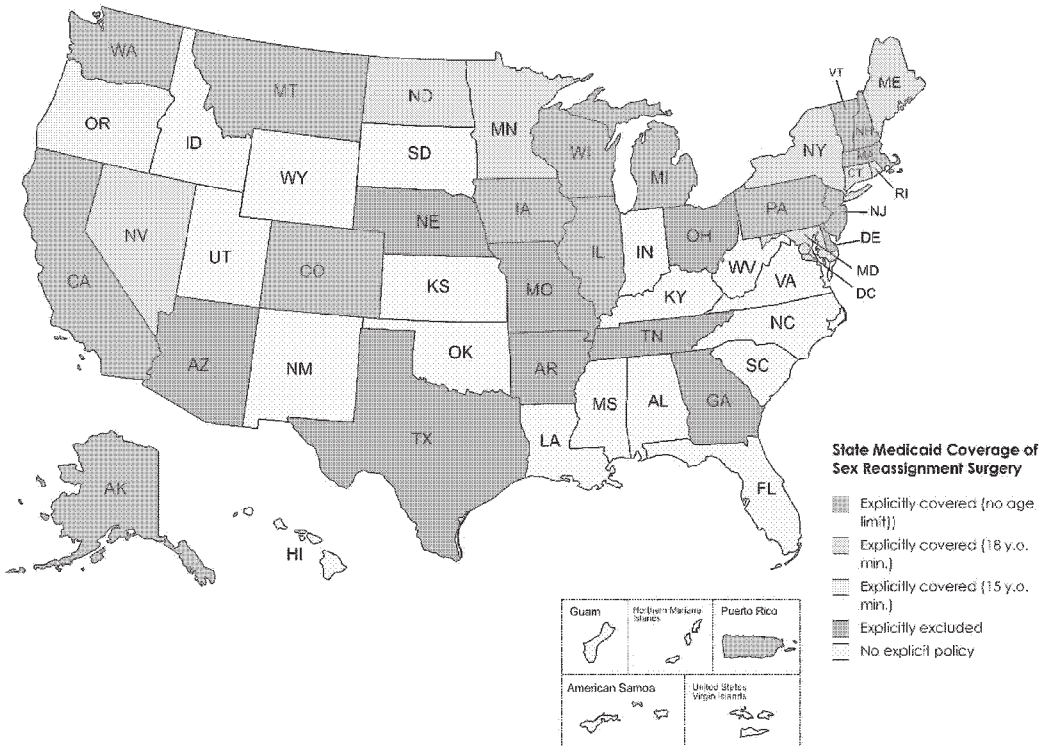
State Medicaid programs with coverage decisions regarding puberty blockers:



State Medicaid programs with coverage decisions regarding cross-sex hormones:



State Medicaid programs with coverage decisions regarding sex reassignment surgery:



Western Europe

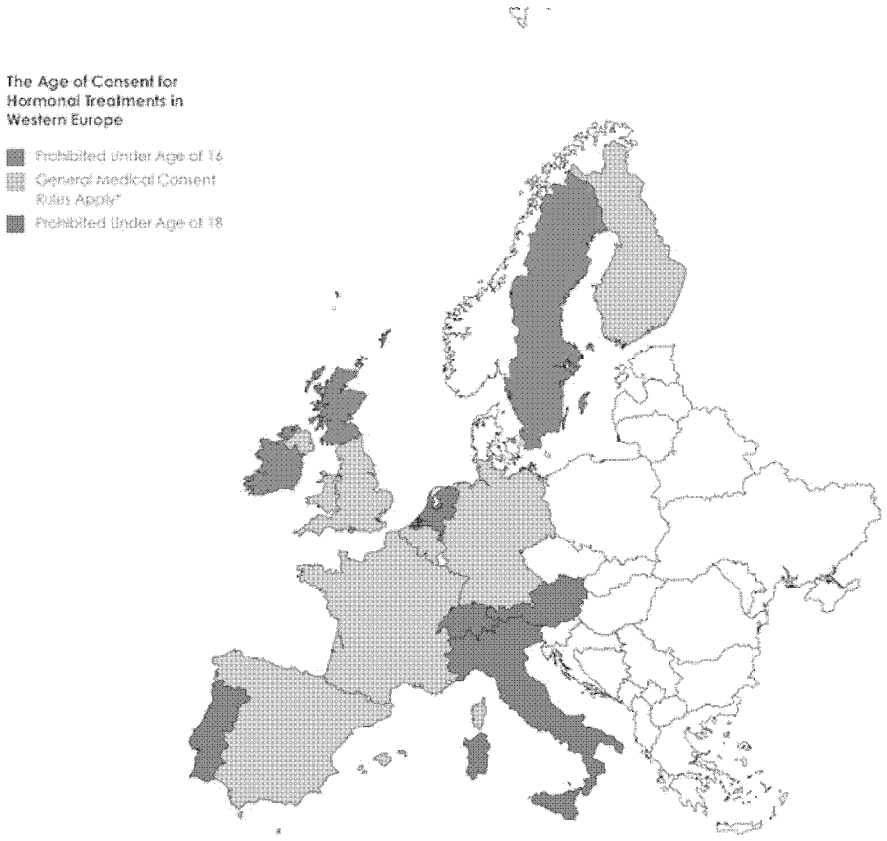
Scandinavian countries such as Sweden and Finland have released new guidelines on sex reassignment treatment for children. In 2022, the Swedish National Board of Health stated that "the risks of hormonal interventions for gender dysphoric youth outweigh the potential benefits." With the exception of youths who exhibited "classic" signs of gender identity issues, adolescents who present with the condition will receive behavioral health services and gender-exploratory therapy (Society for Evidence Based Gender Medicine, 2022).

In Finland, the Palveluvalikoima issued guidelines in 2020 stating that sex reassignment in minors "is an experimental practice" and that "no irreversible treatment should be initiated." The guidelines further assert that youths diagnosed with gender dysphoria often have co-occurring psychiatric disorders that must be stabilized prior to prescribing any cross-sex hormones or undergoing sex reassignment surgery (Palveluvalikoima, 2020).

The United Kingdom (U.K.) is also reassessing the use of irreversible treatments for gender dysphoria due the long-term effects on mental and physical health. In 2022, an independent interim report commissioned by the U.K.'s National Health Service (NHS) indicates that additional research and systematic changes are necessary to ensure the safe treatment of gender dysphoric youths. These include reinforcing the diagnosis process to assess all areas of physical and behavioral health, additional training for pediatric endocrinologists, and informing parents about the uncertainties regarding puberty blockers. The interim report is serving as a benchmark until the research is completed for final guidelines (The Cass Report, 2022).

Like state Medicaid programs, health systems across Western Europe also vary in their coverage of sex reassignment treatment.

Western European nations' requirements for cross-sex hormones:



In this context, the age requirement for access to any medical treatment without consent of parents or of a public authority. This age may range from 16 to 18 years depending on each country's laws.

Western European nations' requirements for sex reassignment surgery:

In this context, the age requirement for access to any medical treatment without consent of parents or of a public authority. This age may range from 16 to 18 years depending on each country's laws.

Generally Accepted Professional Medical Standards Recommendation

This report does not recommend sex reassignment treatment as a health service that is consistent with generally accepted professional medical standards. Available evidence indicates that the services are not proven safe or effective treatments for gender dysphoria.

Rationale

The available medical literature provides insufficient evidence that sex reassignment through medical intervention is a safe and effective treatment for gender dysphoria. As this report demonstrates, the evidence favoring "gender affirming" treatments, including evidence regarding suicidality, is either low or very low quality:

- **Puberty Blockers:** Evidence does not prove that puberty blockers are safe for treatment of gender dysphoria. Evidence that they improve mental health and reduce suicidality is low or very low quality.
- **Cross-Sex Hormones:** Evidence suggesting that cross-sex hormones provide benefits to mental health and prevents suicidality is low or very low quality. Rather, evidence shows that cross-sex hormones cause multiple irreversible physical consequences as well as infertility.
- **Sex Reassignment Surgery:** Evidence of improvement in mental health and reduction in suicidality is low or very low quality. Sex reassignment surgery results in irreversible physical changes, including sterility.

While clinical organizations like the AAP endorse the above treatments, none of those organizations relies on high quality evidence. Their eminence in the medical community alone does not validate their views in the absence of quality, supporting evidence. To the contrary, the evidence shows that the above treatments pose irreversible consequences, exacerbate or fail to alleviate existing mental health conditions, and cause infertility or sterility. Given the current state of the evidence, the above treatments do not conform to GAPMS and are experimental and investigational.

__✓__ **Concur** ____ **Do not Concur**

Comments:

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_____ 6/2/22

Deputy Secretary for Medicaid (or designee) *Date*

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Attachments

Attachment A: Secretary for the Florida Agency for Health Care Administration's Letter to Deputy Secretary Thomas Wallace. 20 April 2022.

Attachment B: Complete text of Rule 59G-1.035, F.A.C.

Attachment C: Romina Brignardello-Petersen, DDS, MSc, PhD and Wojtek Wiercioch, MSc, PhD: *Effects of Gender Affirming Therapies in People with Gender Dysphoria: Evaluation of the Best Available Evidence*. 16 May 2022.

Attachment D: James Cantor, PhD: *Science of Gender Dysphoria and Transsexualism*. 17 May 2022.

Attachment E: Quentin Van Meter, MD: *Concerns about Affirmation of an Incongruent Gender in a Child or Adolescent*. 17 May 2022.

Attachment F: Patrick Lappert, MD: *Surgical Procedures and Gender Dysphoria*. 17 May 2022.

Attachment G: G. Kevin Donovan, MD: *Medical Experimentation without Informed Consent: An Ethicist's View of Transgender Treatment for Children*. 16 May 2022.

ATTACHMENT A

RON DESANTIS
GOVERNOR

SIMONE MARSTILLER
SECRETARY

April 20, 2022

Tom Wallace
Deputy Secretary for Medicaid
Agency for Health Care Administration
2727 Mahan Drive
Tallahassee, FL 32308

Dear Deputy Secretary Wallace:

On April 20, 2022, the Florida Department of Health released guidance on the treatment of gender dysphoria for children and adolescents.[1] The Florida Medicaid program does not have a policy on whether to cover such treatments for Medicaid recipients diagnosed with gender dysphoria. Please determine, under the process described in Florida Administrative Code Rule 59G-1035, whether such treatments are consistent with generally accepted professional medical standards and not experimental or investigational. Pursuant to Rule 59G-1035(5), I look forward to receiving your final determination.

Sincerely,

Simone Marstiller
Secretary

[1] *See* https://www.floridahealth.gov/newsroom/2022/04/20220420-gender-dysphoria-press-release.pr.html (last visited Apr. 20, 2022).

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59G-1.050 General Medicaid Policy.

(1) Purpose. This rule specifies requirements that apply to all providers rendering Florida Medicaid services to recipients.

(2) Billing the Recipient. Providers must inform a recipient of his or her responsibility to pay for services that are not covered by Florida Medicaid, and document in the recipient's file that the recipient was informed of his or her liability, prior to rendering each service.

(a) Providers may seek reimbursement from a recipient under the following circumstances:

1. The recipient is not eligible for Florida Medicaid on the date of service.

2. The service rendered is not covered by Florida Medicaid, if the provider seeks reimbursement from all patients for the specific service.

3. The provider verifies that the recipient has exceeded the Florida Medicaid coverage.

4. The recipient is enrolled in a Florida Medicaid managed care plan (plan) and is informed that:

a. The plan denies authorization for the service.

b. The treating provider is not in the plan's provider network (with the exception of emergency services).

(b) Providers may not seek reimbursement from recipients for missed appointments.

(c) Providers may not seek reimbursement from the recipient if the provider fails to bill Florida Medicaid correctly and in a timely manner. Providers who submit a claim to Florida Medicaid for reimbursement of a covered service whether the claim has been approved, partially approved, or denied, may not:

1. Seek reimbursement from the recipient, the recipient's relatives, or any person, or persons, acting as the recipient's designated representative.

2. File a lien against the recipient, the recipient's parent, legal guardian, or estate.

3. Apply money received from any non-Florida Medicaid source to charges related to a claim paid by Florida Medicaid (also known as "balance billing").

4. Turn a recipient's overdue account over to a collection agency, except in circumstances as specified in paragraph (2)(a), above.

(3) Cost of Doing Business. Florida Medicaid does not reimburse for time spent completing and submitting Florida Medicaid claims or time spent responding to an audit.

(4) Emergency Medicaid For Aliens. Florida Medicaid covers emergency services provided to aliens who meet all Florida Medicaid eligibility requirements except for citizenship or alien status, as follows:

(a) Eligibility is only authorized for the duration of the emergency.

(b) Florida Medicaid does not cover continuous or episodic services after the emergency has been alleviated.

(c) Providers must submit documentation establishing the emergency nature of the service with the claim for reimbursement. Exceptions are labor, delivery, and dialysis services, which are considered emergencies and are payable without documentation when the emergency indicator is entered on the claim form.

(5) Free Choice of Providers. Recipients may obtain services from any qualified Florida Medicaid provider that agrees to provide the services in accordance with Title 42, Code of Federal Regulations (CFR), section 431.51, except:

(a) Allowable restrictions specified in section 1915(a) of the Social Security Act.

(b) When the recipient is enrolled in a Florida Medicaid managed care program. Managed care plans may not restrict enrollee choice for a family planning provider and must cover family planning services regardless of whether the provider is in the managed care plan's provider network.

(6) Inmates of a Public Institution. Florida Medicaid does not cover services provided to individuals residing in public institutions as defined in 42 CFR 435.1009 and Section 409.9025, F.S. These individuals include those residing in correctional and holding facilities for prisoners who meet either of the following:

(a) Have been arrested or detained pending disposition of charges.

(b) Held under court order as material witnesses or juveniles.

(7) Gender Dysphoria.

(a) Florida Medicaid does not cover the following services for the treatment of gender dysphoria:

1. Puberty blockers;

2. Hormones and hormone antagonists;

3. Sex reassignment surgeries; and

4. Any other procedures that alter primary or secondary sexual characteristics.

(b) For the purpose of determining medical necessity, including Early and Periodic Screening, Diagnosis, and Treatment (EPSDT), the services listed in subparagraph (7)(a) do not meet the definition of medical necessity in accordance with Rule 59G-1.010, F.A.C.

(8) Out-of-State Services.

(a) Emergency. Florida Medicaid covers emergency services provided out-of-state without a referral, or authorization, when the recipient's health will be endangered if the care and services are postponed until returning to Florida.

(b) Non-Emergency. Florida Medicaid covers services performed out-of-state, in accordance with the service-specific coverage policy, when both of the following are met:

1. The recipient's primary care or specialist physician refers the recipient for services.

2. Services are prior authorized by the Florida Medicaid quality improvement organization in accordance with Florida Medicaid's Authorization Requirements Policy, as incorporated by reference in Rule 59G-1.053, F.A.C.

(c) Florida Medicaid does not cover services for recipients living out-of-state who are enrolled under the Title-IV-E Florida foster or adoption subsidy.

(9) Payment in Full. Providers must accept payment from Florida Medicaid as payment in full, except for Florida Medicaid copayments and coinsurance. For information on copayment requirements and exemptions, refer to Florida Medicaid's General Policies on copayment and coinsurance.

(10) Recipients or Providers that are Out of the Country. Florida Medicaid does not cover services provided to recipients when they are outside of the United States (U.S.), or for services rendered by providers who are not in the U.S.

(11) Refusal of Services.

(a) Providers may not refuse to provide a covered Florida Medicaid service to a recipient solely because the recipient's eligibility does not display in the Florida Medicaid Management Information System, if the recipient has a valid temporary proof of eligibility from the Department of Children and Families, or proof of presumptive eligibility.

(b) Right to Refuse Services. Providers may limit the number of Florida Medicaid recipients the provider serves, and accept or reject recipients in accordance with the policies of the facility or practice, except as follows:

1. A hospital may not refuse to provide emergency services in accordance with the 1986 Emergency Medical Treatment and Active Labor Act.

2. Providers may not deny services to recipients based solely upon race, creed, color, national origin, disabling condition, or disability, in accordance with federal anti-discrimination laws.

(12) Solicitation (Patient Brokering). Providers may not knowingly solicit, offer, pay, or receive any payment, including any kickback, bribe, or rebate, directly or indirectly, overtly or covertly, in cash or in kind, in return for referring an individual to a person for furnishing, or arranging for the furnishing of, any item or service for which payment may be made, in whole or in part, under the Florida Medicaid program, or in return for obtaining, purchasing, leasing, ordering, or arranging for, or recommending, obtaining, purchasing, leasing, or ordering any goods, facility, item, or service, for which payment may be made, in whole or in part, under the Florida Medicaid program.

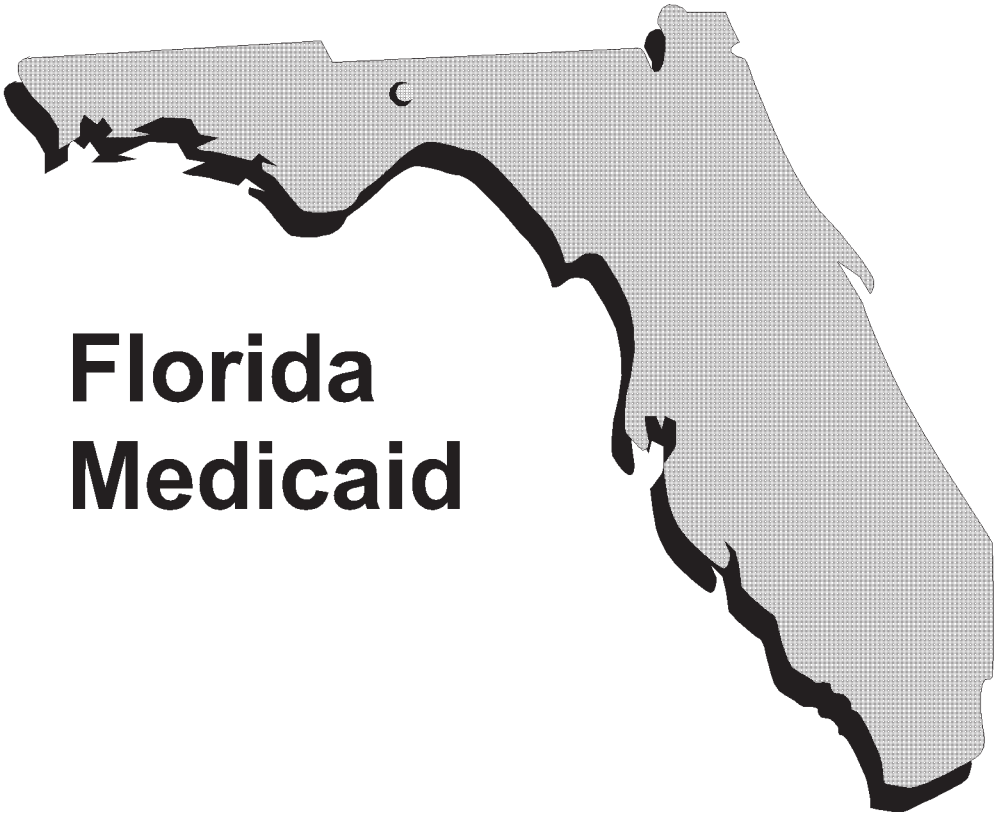
Rulemaking Authority 409.919, 409.961 FS. Law Implemented 409.902, 409.9025, 409.973 FS. History–New 3-11-18, Amended 8-21-22.

59G-1.010 Definitions.

(1) This rule applies to all providers rendering Florida Medicaid services to recipients.

(2) All providers must be in compliance with the provisions of the Florida Medicaid Definitions Policy, August 2017, incorporated by reference. The policy is available on the Agency for Health Care Administration's website at http://ahca.myflorida.com/Medicaid/review/index.shtml, and at http://www.flrules.org/Gateway/reference.asp?No=Ref-08567.

Rulemaking Authority 409.919, 409.961 FS. Law Implemented 409.901-.920, 409.973 FS. History–New 4-29-93, Formerly 10P-1.010, Amended 6-24-98, 4-16-06, 9-18-17.



Florida Medicaid

Definitions Policy

Agency for Health Care Administration

August 2017

August 2017

Pl. Trial Ex. 022

1.0 Introduction

This policy contains definitions of commonly used terms that are applicable to all sections of Rule Division 59G, Florida Administrative Code (F.A.C.), unless specifically stated otherwise in a service-specific coverage policy or rule.

This policy is intended for use by all providers that render services to Florida Medicaid recipients. This policy must be used in conjunction with Florida Medicaid's general policies and any applicable service-specific and claim reimbursement policies with which providers must comply.

All Florida Medicaid policies are promulgated in Rule Division 59G, F.A.C. Coverage policies are available on the Agency for Health Care Administration's (AHCA) Web site at http://ahca.myflorida.com/Medicaid/review/index.shtml.

2.0 Definitions

2.1 Abuse

As defined in section 409.913, Florida Statutes (F.S.).

2.2 Activities of Daily Living (ADLs)

ADLs include:

- Bathing
- Dressing
- Eating (oral feedings and fluid intake)
- Maintaining continence (examples include taking care of a catheter or colostomy bag or changing a disposable incontinence product when the recipient is unable to control bowel or bladder functions)
- Toileting
- Transferring

2.3 Adjudicate

Make an official decision regarding a claim submitted to AHCA, or its designee, for payment.

2.4 Adult Health Screening

Medical examination furnished to assess the health status of recipients age 21 years and older in order to detect and prevent disease, disability and other adverse health conditions or their progression.

2.5 Agency (AHCA)

The Florida Agency for Health Care Administration.

2.6 Applicant, Provider

Individual, group, or organization that has submitted a written application to become a Florida Medicaid provider to AHCA, or its designee, but has not yet received final action.

2.7 Applicant, Recipient

Individual who has submittted an application for Florida Medicaid to the Florida Department of Children and Families, but has not received a final action, including an individual whose application was submitted through a representative or a person acting on his or her behalf.

2.8 Attending Physician

Doctor of medicine or osteopathy licensed in accordance with Chapter 458 or 459, F.S., and who is identified as having primary responsibility for a recipient's medical care.

2.9 Audit

Examination of records supporting amounts reported in an annual cost report, to determine the accuracy and propriety of the report; or, an analysis of documentation supporting a

provider's Florida Medicaid claims during a period of time, to determine whether payments were accurate.

2.10 Authorization
Approval to deliver Florida Medicaid covered services.

2.11 Authorized Representative
As defined in Title 42, Code of Federal Regulations (CFR), section 435.923.

2.12 Beneficiaries
Persons receiving medical benefits under Medicare.

2.13 Billing Agent
Florida Medicaid-enrolled entity that offers claims submission services to providers.

2.14 Business Records
Documents related to the administrative or commercial activities of a provider.

2.15 Calendar Year
The period of days beginning on January 1 and ending on December 31.

2.16 Cap
See Service Limit.

2.17 Care Plan
See Plan of Care or Plan of Treatment.

2.18 Caregiver
Person(s) attending to the needs of another person, who is physically or mentally impaired, injured, incapacitated, or a child unable to care for him or herself.

2.19 Case Management
A process that assesses, plans, implements, coordinates, monitors, and evaluates the options and services required to meet a recipient's or an enrollee's heath needs using communications and all available resources to promote quality outcomes. Proper care coordination/case management occurs across a continuum of care, addressing the ongoing individual needs of a recipient or an enrolllee rather than being restricted to a single practice setting.

2.20 Case Manager
Individual who furnishes case management services directly to or on behalf of a recipient, on an individual basis.

2.21 Centers for Medicare and Medicaid Services (CMS)
Federal agency within the United States Department of Health and Human Services (DHHS) that administers the Medicare program and works in partnership with state governments to administer Medicaid, the Children's Health Insurance Program (CHIP), and health insurance portability standards.

2.22 Clean Claim
A claim completed in accordance with Florida Medicaid billing guidelines, accompanied by all documentation required by federal or state law or state administrative rule for payment, and which may be processed and adjudicated without obtaining additional information from the provider or from a third-party, including a claim that originated in AHCA's claim system. It does not include a claim from a provider who is under investigation for fraud, abuse, or violation of state or federal Medicaid laws, rules, regulations, policies, or directives, or a claim under review for medical necessity.

2.23 Clearinghouse
Third-party entity that transmits claims created by a provider.

2.24 Coinsurance
The amount that a Medicare beneficiary (or other third-party) pays to a provider for furnishing medical or allied care, goods, or services.

2.25 Consultation
Opinion rendered by a health professional at the request of another health professional.

2.26 Contractor
Any entity under contract with AHCA including all employees, subcontractors, agents, volunteers, and anyone acting on behalf of, in the interest of, or for a contractor.

2.27 Controlling Interest
As defined in 42 CFR 455.101.

2.28 Copayment
The amount a recipient is required to pay a provider for furnishing Florida Medicaid covered services.

2.29 Corrective Action Plan (CAP)
Written plan of action developed by the cited entity to correct cited deficiencies in compliance with federal or state regulations, rules, or policies.

2.30 Cost-based Reimbursement
Reimbursement based on the provider's actual costs for rendering Florida Medicaid covered services to recipients.

2.31 Coverage Policy
A policy document that contains coverage information about a Florida Medicaid service (also known as a Handbook).

2.32 Covered Services
Medical and allied care, goods, services, or procedures that are reimbursable by Florida Medicaid.

2.33 Current Procedural Terminology (CPT®) codes
Systematic listing and coding of procedures and services published yearly by the American Medical Association. CPT® is a registered trademark of the American Medical Association.

2.34 Date of Service (DOS)
Date the provider furnished a Florida Medicaid covered service to a recipient, unless otherwise specified.

2.35 Diagnosis and Procedure Codes
The most current edition of the International Classification of Diseases, which is a method of classifying written descriptions of diseases, injuries, conditions, and procedures using alphabetic and numeric designations or codes.

2.36 Diagnosis-Related Groups (DRG)
A payment method which involves classifying inpatient stays and determining a price based on a combination of the classification and the hospital where the services were performed.

2.37 Disclosing Entity
As defined in 42 CFR 455.101.

2.38 Disenrollment
The discontinuance of an enrollee's membership in a managed care plan or of an enrollee's participation in a federally-approved waiver program.

2.39 Dually Eligible Recipient
Any person who is eligible to receive benefits under the Florida Title XIX Medicaid program, and the federal Title XVIII Medicare program.

2.40 Electronic Data Exchange Vendor
Any third-party entity that transmits Health Insurance Portability and Accountability Act (HIPAA) covered transactions on behalf of an enrolled provider.

2.41 Eligible Person
See Recipient.

2.42 Emergency Care, Emergency Medical Services, or Emergency Services
Medical screening, examination, and evaluation by a physician or, if applicable, by other appropriate personnel under the supervision of a physician, to determine whether an emergency medical condition exists; and if it does, the care, treatment, or surgery for a covered service by a physician necessary to relieve or eliminate the emergency medical condition, within the service capability of a hospital.

2.43 Enrollee
Recipient who is a member of a managed care plan.

2.44 Established Patient
Recipient who has received professional medical or allied care, goods, or services from the provider within the past three years.

2.45 Examination
The evaluation of a recipient by a health care practitioner during the process inherent to the diagnosis and treatment of any disease, complaint, or disorder.

2.46 Experimental or Experimental and Clinically Unproven or Investigational
Related to drugs, devices, medical treatments, or procedures when:

- The drug or device cannot be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and approval for marketing has not been given at the time the drug or device is furnished.
- Reliable evidence shows the drug, device, medical treatment, or procedure is the subject of on-going phase I, II or III clinical trials, or under study to determine its maximum tolerated dose, toxicity, safety, or efficacy as compared with the standard means of treatment or diagnosis.
- Reliable evidence shows the consensus among experts regarding the drug, device, medical treatment, or procedure is that further studies or clinical trials are necessary to determine its maximum tolerated dose, toxicity, safety, or efficacy as compared with the standard means of treatment or diagnosis.
- The drug or device is used for a purpose that is not approved by the FDA.

2.47 Explanation of Medicaid or Medicare Benefits (EOB or EOMB)
Statement mailed to a recipient, beneficiary, or provider explaining the payment of his or her claim.

2.48 Fair Hearing
As defined in Rule 59G-1.100, F.A.C.

2.49 Fee-for-Service
Method of reimbursement for Florida Medicaid covered services based on fees set by AHCA for defined care, goods, or services.

2.50 Fee-For-Service Delivery System
The mode by which providers who are enrolled in Florida Medicaid receive reimbursement for Florida Medicaid covered services rendered to recipients who are not enrolled in a managed care plan.

2.51 Felony
As defined in section 775.08, F.S.

2.52 Fiscal Year
July 1 through June 30.

2.53 Florida Medicaid Management Information System (FMMIS)
Computer system used to process Florida Medicaid claims and encounter transactions to produce management information relating to the Florida Medicaid program.

2.54 Global Reimbursement
Method of payment wherein the provider is paid one fee for a service that consists of multiple procedure codes rendered on the same date of service or over a specified time period.

2.55 Goods
Appliances, equipment, supplies, or other items normally or usually recognized by medical professionals as medically necessary in the treatment of or rehabilitation from the covered illness or injury, including drugs and durable medical equipment.

2.56 Grievance
As defined in 42 CFR 438.400.

2.57 Group or Group Practice
Two or more health care practitioners who practice at a common location, whether or not they share common facilities, supporting staff, or equipment, whose organization possesses a common federal employer identification number (FEIN).

2.58 Healthcare Common Procedure Coding System (HCPCS)
Common procedure coding system administered by the Centers for Medicare and Medicaid Services that is used by health care providers to identify the services performed.

2.59 Health Insurance Portability and Accountability Act (HIPAA)
Federal law that protects health insurance coverage for workers and their families when they change or lose their jobs. The federal laws include the HIPAA Privacy Rule, the HIPAA Security Rule, and the HIPAA Breach Notification Rule, to protect the privacy of an individual's health information; set national standards for the security of protected health information sent electronically; and to require notification following a breach of unsecured protected health information.

2.60 Home and Community-based Services Waiver
Specific program and set of Florida Medicaid covered services authorized under section 1915(c) of the federal Social Security Act designed to assist recipients in receiving services in their home and the community and to avoid institutionalization.

2.61 Independent
Not under common control or governance, direct or indirect ownership.

2.62 Indirect Ownership Interest
As defined in 42 CFR 455.101.

2.63 Inpatient
Recipient who has been admitted to a hospital for hospital services with the expectation of remaining at least overnight and occupying a bed even though the recipient may be discharged or transferred to another hospital and may not use the hospital bed overnight.

2.64 Instrumental Activities of Daily Living (IADLs)
IADLs include:

- Grocery shopping
- Laundry
- Light housework
- Meal preparation
- Medication management
- Money management
- Personal hygiene
- Transportation
- Using the telephone to take care of essential tasks (examples include paying bills and setting up medical appointments)

2.65 Insurer
Entity authorized to furnish health care or health care insurance coverage.

2.66 Internal Control Number (ICN)
Thirteen digit number assigned to each claim when it is received by the fiscal agent for processing.

2.67 Investigation
Activities to determine if issues of non-compliance exist with the laws, rules, or policies governing Florida Medicaid, and other laws wherein AHCA has authority.

2.68 Leave Days
When a recipient is absent from the provider's setting overnight for an allowable reason.

2.69 Legal Representative
As defined in section 409.901, F.S.

2.70 Level of Care
A determination of clinical eligibility for a Florida Medicaid program or waiver.

2.71 Licensed
Facility, equipment, system(s), or an individual that has formally met and is registered in accordance with all applicable federal, state, county, and local requirements, and has authorization from the applicable competent authority to perform an act which, without such authorization, would be illegal.

2.72 Locum Tenens Provider
Provider who substitutes on a temporary basis for another provider while the permanent provider is indisposed and must enroll in Florida Medicaid as an individual treating provider before services may be reimbursed.

2.73 Long-term Care Plan
Managed care plan that provides services in accordance with section 409.98, F.S., for the long-term care program of the Statewide Medicaid Managed Care program.

2.74 Managed Care Plan
As defined in section 409.962, F.S.

2.75 Managed Medical Assistance Plan
Managed care plan that provides services in accordance with section 409.973, F.S., for the medical assistance program of the Statewide Medicaid Managed Care program.

2.76 Managing employee
General manager, business manager, administrator, director, or other person who exercises operational or managerial control of a provider, or who directly or indirectly conducts the day-to-day operations of a provider.

2.77 Medicaid Agency
As defined in section 409.901(1), F.S. In Florida, the Medicaid agency is AHCA.

2.78 Medicaid Fraud Control Unit (MFCU)
Unit in the Office of the Attorney General of Florida designated to investigate and prosecute fraud involving providers that intentionally defraud the state's Medicaid program through fraudulent billing.

2.79 Medicaid Identification Card (ID)
Card furnished to recipients that is used by providers to verify eligibility.

2.80 Medicaid-related Records
Records that relate to the provider's business or profession and to a recipient. Medicaid-related records also include records related to non-Medicaid customers, clients, or patients, to the extent that the documentation is shown by AHCA to determine a provider's entitlement to payments under the Florida Medicaid program.

2.81 Medical Assistance
Any provision of, payment for, or liability for medical or allied care, goods, or services by Florida Medicaid to, or on behalf of, any recipient.

2.82 Medical Records
Documents corresponding to Florida Medicaid covered services furnished in any place of service.

2.83 Medically Necessary or Medical Necessity
The medical or allied care, goods, or services furnished or ordered must meet the following conditions:

- Be necessary to protect life, to prevent significant illness or significant disability, or to alleviate severe pain
- Be individualized, specific, and consistent with symptoms or confirmed diagnosis of the illness or injury under treatment, and not in excess of the patient's needs
- Be consistent with generally accepted professional medical standards as determined by the Medicaid program, and not experimental or investigational
- Be reflective of the level of service that can be safely furnished, and for which no equally effective and more conservative or less costly treatment is available statewide
- Be furnished in a manner not primarily intended for the convenience of the recipient, the recipient's caretaker, or the provider

The fact that a provider has prescribed, recommended, or approved medical or allied care, goods, or services does not, in itself, make such care, goods or services medically necessary or a medical necessity or a covered service.

Medically necessary or medical necessity for inpatient hospital services requires that those services furnished in a hospital on an inpatient basis could not, consistent with the provisions of appropriate medical care, be effectively furnished more economically on an outpatient basis or in an inpatient facility of a different type.

2.84 Medically Needy
Florida Medicaid coverage group (also referred to as share-of-cost) that includes individuals who would qualify for Medicaid, except that their income or resources exceed Florida Medicaid's income or resource limits.

2.85 Medicare
Medical assistance program authorized by Title XVIII of the federal Social Security Act, 42 U.S.C. section 1395 et seq., and regulations thereunder.

2.86 Multidisciplinary Team
Group consisting of representatives from all professional disciplines involved in the care of an individual and participating in the development and implementation of an individual medical, nursing, rehabilitative, or active treatment plan to achieve a unified and integrated program for meeting the individual's needs.

2.87 National Provider Identifier (NPI)
Unique identification number for covered health care providers. Covered health care providers and all health plans and health care clearinghouses use the NPIs in the administrative and financial transactions adopted under HIPAA. The NPI is a ten-position, intelligence-free numeric identifier (ten-digit number).

2.88 New Patient
Recipient who has not received any professional medical or allied care, goods, or services from the provider or the provider group within the past three years.

2.89 Newborn
Infant from birth through the first four weeks of life.

2.90 Nursing Home
"Nursing home facility," as defined in section 400.021, F.S.

2.91 Officer
High-ranking person in a given corporation (business entity); normally appointed by the board of directors.

2.92 Optional Coverage Groups
Groups of individuals who may, at the option of the Florida legislature, be covered by Florida Medicaid in accordance with the provisions of federal law and Chapter 409, F.S.

2.93 Overpayment
As defined in section 409.913, F.S.

2.94 Ownership Interest
As defined in 42 CFR 455.101.

2.95 Palliative Care
An approach that improves the quality of life of patients and their families who are facing problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification, assessment, and treatment of pain and other problems, physical, psychosocial, and spiritual.

2.96 Patient Responsibility
The portion of a recipient's monthly income, as determined by the Department of Children and Families, that the recipient is responsible to pay to the nursing facility, intermediate care facility for individuals with intellectual disabilities, hospice, or toward home and community-based services.

2.97 Person(s)
Natural persons, corporations, partnerships, associations, clinics, groups, and all other similar entities.

2.98 Personal Needs Allowance
Portion of a recipient's monthly income that he or she is allowed to keep to pay for incidental expenses when residing in a residential or institutional setting.

2.99 Physical Examination
Personal, face-to-face contact with a recipient by a licensed physician or by another licensed medical professional under the supervision of a physician, for the purpose of diagnosis and treatment of medical disorders.

2.100 Place of Service (POS)
Physical location where a provider renders Florida Medicaid covered services to, or for, a recipient.

2.101 Plan of Care (POC) or Plan of Treatment
Individualized written program for a recipient developed by health care professionals based on the need for medical care established by the attending physician and designed to meet the medical, health, and/or rehabilitation needs of a recipient.

2.102 Post Authorization
Approval for Florida Medicaid covered services after the services have been rendered to a recipient.

2.103 Primary Care
Comprehensive, coordinated, and readily-accessible medical care, furnished at the recipient's first point of contact with the health care system, including health promotion and maintenance, treatment of illness and injury, early detection of disease, and referral to specialists when appropriate.

2.104 Principal
Any officer, director, billing agent, managing employee, or affiliated person, or any partner or shareholder who has an ownership interest equal to five percent or more in the provider.

2.105 Procedure Code
Number that Florida Medicaid uses to identify the procedures that providers render to recipients.

2.106 Provider
The term used to describe any entity, facility, person, or group that is enrolled to furnish services under the Florida Medicaid program.

2.107 Provider Agreement or Provider Agreement Contract
Contract between AHCA and a provider for the furnishing of Florida Medicaid covered services to recipients.

2.108 Quality Improvement Organization (QIO) or QIO-like Entity
Entity designated through the Centers for Medicare and Medicaid Services to perform utilization review services and to monitor the appropriateness of care provided to individuals through a state Medicaid program.

2.109 Rate
The reimbursement amount specified on the applicable Florida Medicaid fee schedule, posted on AHCA's Web site for cost-based services, or the mutually agreed upon amount between AHCA and the provider, for a Florida Medicaid service.

2.110 Recipient
Individual determined to be eligible for Florida Medicaid covered services by the Department of Children and Families or the Social Security Administration, and who is enrolled in the Florida Medicaid program.

2.111 Records
See Business Records, Medicaid-related Records, and Medical Records.

2.112 Recoupment
Process by which AHCA recovers an overpayment or inappropriate payment from a Florida Medicaid provider.

2.113 Reliable Evidence
Published reports and articles in the authoritative medical and scientific literature; the written protocol or protocols used by the facility or the protocol(s) of another facility studying substantially the same drug device or medical treatment or procedure; or the written informed consent used by the treating facility or by another facility studying substantially the same drug device or medical treatment or procedure.

2.114 Resident
Individual who resides in a facility as defined in section 400.021, F.S.

2.115 Risk or Underwriting Risk
Potential for loss that is assumed by a contractor and that may arise because the cost of providing care, goods, or services may exceed the capitation or other payment made by AHCA to the contractor under terms of the contract.

2.116 Routine
Medications, treatments, care, goods, or services furnished in accordance with an established or predetermined schedule, and performed for recipients whose medical needs are stabilized or chronic.

2.117 Screen, Screening, or Screening Services
Assessment of a recipient's physical or mental condition to determine the need for further evaluation or services.

2.118 Self-audit
Review of claims a provider conducts on its own to ensure compliance with Florida Medicaid rules.

2.119 Service(s)
Any diagnostic or treatment procedure(s) or other medical or allied care claimed to have been furnished to a recipient and listed in an itemized claim for payment; or, in the case of a claim based on costs, any entry in the cost report, books of account, or other documents supporting such claim.

2.120 Service Limit or Service Limitation
Maximum amount, duration, or scope of a Florida Medicaid covered service.

2.121 Specialty Plan
As defined in section 409.962, F.S.

2.122 Statewide Medicaid Managed Care
A service delivery system created in Part IV, Chapter 409, F.S. consisting of the:

- Long-term care program as described in section 409.978, F.S.
- Managed medical assistance program as described in section 409.971, F.S.

2.123 Subcontract
Written agreement entered into by a contractor for provision of services on its behalf.

2.124 Subcontractor
Any person or entity to which a provider or contractor has contracted or delegated some of its management functions or its responsibilities for providing medical or allied care, goods, or services; or its claiming or claims preparation or processing functions, or responsibilities.

2.125 Suspension
Exclusion of a provider by AHCA from further participation in the Florida Medicaid program for a specific period of one year or less, after which the provider must apply for reenrollment in order to participate in the Florida Medicaid program.

2.126 Swing Bed
Bed in a rural hospital licensed pursuant to Chapter 395, F.S., that can also be used for skilled or intermediate nursing care services.

2.127 Termination
Exclusion by AHCA of a provider from further participation in the Florida Medicaid program for a period of one year to twenty years.

2.128 Therapeutic Leave
A non-medical visit outside the facility used for overnight visits with family or friends.

2.129 Third-party Payment
Performance of a duty, promise, or obligation, or discharge of a debt or liability, by the delivery, provision, or transfer of third-party benefits for medical or allied care, goods, or services.

2.130 Treating Provider
Individual provider who personally renders Florida Medicaid covered services, or assumes responsibility for rendering Florida Medicaid covered services, through personal supervision, on behalf of a Florida Medicaid group provider.

2.131 Treatment Plan
See Plan of Care (POC).

2.132 Treatment Services
Corrective, therapeutic, or restorative services furnished as a result of a diagnosis identified during a screening.

2.133 Vendor
Individual or entity that engages in the business of selling care, goods, services, or commodities.

2.134 Visit
Face-to-face contact between a health care practitioner and a recipient that takes place at a center, office, home, or other place of service.

2.135 Void
Negation of an original payment.

59G-1.035 Determining Generally Accepted Professional Medical Standards.

(1) Definitions.

(a) Generally accepted professional medical standards – Standards based on reliable scientific evidence published in peer-reviewed scientific literature generally recognized by the relevant medical community or practitioner specialty associations' recommendations.

(b) Health service(s) – Diagnostic tests, therapeutic procedures, or medical devices or technologies.

(c) Relevant – Having a significant and demonstrable bearing on the matter at hand.

(2) Pursuant to the criteria set forth in subparagraph 59G-1.010(166)(a)3., Florida Administrative Code (F.A.C.), the Agency for Health Care Administration (hereafter referred to as Agency) will determine when health services are consistent with generally accepted professional medical standards and are not experimental or investigational.

(3) Health services that are covered under the Florida Medicaid program are described in the respective coverage and limitations handbooks, policies, and fee schedules, which are incorporated by reference in the F.A.C. The public may request a health service be considered for coverage under the Florida Medicaid program by submitting a written request via e-mail to HealthServiceResearch@ahca.myflorida.com. The request must include the name, a brief description, and any additional information that supports coverage of the health service, including sources of reliable evidence as defined in paragraph 59G-1.010(84)(b), F.A.C.

(4) To determine whether the health service is consistent with generally accepted medical standards, the Agency shall consider the following factors:

(a) Evidence-based clinical practice guidelines.

(b) Published reports and articles in the authoritative medical and scientific literature related to the health service (published in peer-reviewed scientific literature generally recognized by the relevant medical community or practitioner specialty associations).

(c) Effectiveness of the health service in improving the individual's prognosis or health outcomes.

(d) Utilization trends.

(e) Coverage policies by other creditable insurance payor sources.

(f) Recommendations or assessments by clinical or technical experts on the subject or field.

(5) Based upon the information collected, a report with recommendations will be submitted to the Deputy Secretary for Medicaid (or designee) for review. The Deputy Secretary for Medicaid (or designee) will make a final determination as to whether the health service is consistent with generally accepted professional medical standards and not experimental or investigational.

(6) In order for the health service to be covered under the Florida Medicaid program, it must also meet all other medical necessity criteria as defined in subsection 59G-1.010(166), F.A.C., and funded through the General Appropriations Act or Chapter 216, F.S.

Rulemaking Authority 409.919 FS. Law Implemented 409.902, 409.906, 409.912, 409.913 FS. History–New 2-26-14, Amended 9-28-15.

AHCA Automated Prior Authorizations and Bypass Lists 01-2023

Automated PA:

Edit	Drugs	Steps
Anti-epileptic Drugs (AED) Auto PA Automated PA approval satisfies L=Auto PA and Non-PDL drug logic Brand and Generic PDL products will bypass the logic Products coded as REMS/RDDS drug will bypass the logic	**Anticonvulsants List A** **Generic Name** / **Brand Name** / **Drug Code** Brivaracetam / Briviact / HSN = 043088 Cenobamate / Xcopri / HSN =-046241 Clobazam / Sympazan / GSN = 078861, 078862, 078863 Diazepam / Valtoco / GSN = 080630, 080631, 080632, 080633 Eslicarbazepine / Aptiom / HSN = 036675 Perampanel / Fycompa / HSN = 039628 Ethotoin / Peganone / HSN = 001880 Methsuximide / Celontin* / HSN = 001890 Midazolam / Nayzilam / GSN = 079754 Oxcarbazepine / Oxtellar XR / GSN = 070190, 070191, 070192 Rufinamide / Banzel / GSN = 063076, 063077 **Anticonvulsants List B** **Generic Name** / **Brand Name** / **Drug Code** Carbamazepine / Tegretol, Tegretol XR, Carbatrol, Epitol, Equetro / HSN = 001893 Clobazam / Onfi / GSN = 017026, 020647, 027400, 071282 Clonazepam / Klonopin / HSN = 001894 Diazepam / Diastat / GSN = 034015, 034016, 034017, 034018, 034019, 059781, 059782 Divalproex Sodium / Depakote/Depakote Sprinkle/Depakote ER / HSN = 001884 Ethosuximide / Zarontin / HSN = 001891 (excluding GSN 004555- Zarontin solution) Felbamate / Felbatol / HSN = 008186 Gabapentin / Neurontin, Gralise ER / HSN = 008831 excluding GSN 063753 (powder)	**Incoming drug within Anticonvulsant drug list A** **Step 1:** Look back 730 days in the patient's medical history for a seizure diagnosis (see approvable ICD-10s below). If found, approve. If not found, deny for NCPDP 75/2462 with additional message "Recip doesn't have Req Diagnosis on file for this Medication. **Incoming drug within Anticonvulsant drug list B** **Step 1:** Look back 730 days in the patient's medical history for a seizure diagnosis (see approvable ICD-10s below). If found, proceed to step 2. If not found, deny for NCPDP 75/2462 with additional message "Recip doesn't have Req Diagnosis on file for this Medication. **Step 2:** Look back 365 days in the patient's medical history for a paid claim of the same drug HICL (may be different strength, brand or generic). If found, approve. If not found, deny for NCPDP 75/2462 with additional message "Recip doesn't have reqd Drug use Supporting this Medication." **Approvable Seizure Diagnosis ICD-10 Codes** **ICD-10-CM Code** / **Description** ICD 10: G25.3 / Myoclonus ICD 10 Disease Group: G80 / Cerebral Palsy ICD 10 Disease Group: G40 / Epilepsy ICD 10 Disease Group: G45, G46 / Transient cerebral ischemic attacks and related syndromes ICD 10 Disease Block: I60-I69 / Vascular syndromes of brain in Cerebrovascular diseases Cerebrovascular Disease ICD 10: G90.1ICD 10 Disease Block: Q00-Q07 / Familial dysautonomia [Riley –Day] Congenital Malformations of the brain, spinal cord, nervous system ICD 10 Disease Group: R56.00 / Convulsions, not elsewhere classified ICD 10 Disease Group: S06 / Intracranial Injury ICD 10: T74.12XA T74.12XD T74.12XS T74.4XXA / Child physical abuse, confirmed/suspected, initial encounter Shaken infant syndrome, initial encounter

Pl. Trial Ex. 024

Edit	Drugs			Steps	
	Lacosamide	Vimpat	HSN = 035872 excluding GSN 064437 (vial)	T74.4XXD T74.4XXS T76.12XA T76.12XD T76.12XS	
	Lamotrigine	Lamictal/ODT/XR/XR Starter Dose Pack, Subvenite	HSN = 007378 (excluding GSNs 065170, 065171 065172 - Lamictal ODT Start Kt)	ICD 10 Disease Group: F07 F48	Personality change due to known physiological condition and non-psychotic mental disorders
	Levetiracetam	Keppra, Roweepra	HSN = 020952 (excluding GSNs 074071, 074072 - Elepsia XR, 075619, 075620, 075621, 075622 - Spritam)	ICD 10 Disease Block: F70-F79	Intellectual Disabilities
	Mephobarbital	Mebaral	HSN = 001895	ICD 10: S09.8XXA S09.8XXD S09.8XXS S09.90XD S09.90XS	Other/unspecified injuries of the head, initial encounter
	Oxcarbazepine	Trileptal	HSN = 011735 (excluding GSNs 070190, 070191, 070192 – Oxtellar XR)		
	Phenobarbital	Luminal	HSN = 001561 excluding GSN = 003584 (powder)		
	Phenytoin Sodium ER	Dilantin	HSN = 001877 (excluding GSNs 049445, 049444 – Phenytek caps)		
	Phenytoin Infatab	Dilantin /Phenytoin	HSN = 001879 (excluding GSN 004531 - Dilantin Infatab)		
	Primidone	Mysoline	HSN = 001886 excluding GSN = 058477 (powder)		
	Rufinamide	Banzel suspension	GSN = 067131		
	Tiagabine	Gabitril	HSN = 015773		
	Topiramate	Topamax/Topiragen	HSN = 011060 excluding GSNs 064519 (powder), 071344, 071346, 071347 (Trokendi XR), 072123, 072124, 072125, 072126, 072127 (Qudexy XR) and 082803 (Eprontia solution)		
	Valproic Acid	Depakene	HSN = 001883 excluding GSNs = 064275, 064276, 013477 (Stavzor) and 051616 (Liquid)		

Incoming drug within Anticonvulsant drug list C

Step 1: Look back 730 days in the patient's medical history for a seizure diagnosis (see approvable ICD-10s above). If found, approve. If not found, proceed to step 2.

Step 2: Look back 730 days in the patient's medical history for a Tuberous sclerosis diagnosis (see approvable ICD-10s below). If found, approve. If not found, deny for NCPDP 75/2462 with additional message "Recip doesn't have Req Diagnosis on file for this medication."

Approvable Tuberous Sclerosis Diagnosis ICD-10 Codes	
ICD-10-CM Code	**Description**
ICD 10: Q85.1	Tuberous Sclerosis

Incoming drug within Anticonvulsant drug list D

Step 1: If incoming claim is for a medication on <Anticonvulsants List D> look back 365 days within claims history for a medication on <Anticonvulsants List D>. If found, CLAIM PAYS; Otherwise PROCEED TO STEP 2. (AG and quantity limitations still apply)

Step 2: Look back 730 days in the patient's medical history for a seizure diagnosis (see approvable ICD-10s above). If found, approve. If not found, proceed to step 3.

Step 3: Look back 730 days in the patient's medical history for a migraine diagnosis (see approvable ICD-10s below). If found, go to Step 4. If not found, deny for NCPDP 75/2462 with

Edit	Drugs	Steps

Valproic Sodium	Depakene syrup	HSN = 001882 excluding GSNs = 031533 (vials) and 057977 (powder)
Vigabatrin	Sabril Tablets, Sabril Powder Pack, Vigadrone	HSN = 007377
Zonisamide	Zonegran	HSN = 021140

Anticonvulsants List C		
Generic Name	**Brand Name**	**Drug Code**
Cannabidiol	Epidiolex	HSN = 045006

Generic Name	Brand Name	Drug Code
Topiramate ER	Qudexy XR/ Trokendi XR	GSN = 072123, 072124, 072125, 072126, 072127, 071343, 071344, 071346, 071347

Medication	**Drug Code**
Amitriptyline	HSN = 001643
Divalproex Sodium/ Valproic Acid	HSN = 001882, 001883, 001884
Propranolol	HSN = 002101 (excluding vial GSN = 043103)
Timolol	GSN = 005142, 005140, 005141
Topiramate	HSN = 011060

additional message "Recip doesn't have Req Diagnosis on file for this Medication."

Step 4: Look back 365 days in the patient's medical history for two paid claims from the < Migraine Prophylaxis List>. If found, approve. If not found, deny for NCPDP 75/2462 with additional message "Recip doesn't have req'd Drug use Supporting this Medication.

ICD-10-CM Code	Description
G43.5	Persistent migraine aura without cerebral infarction
G43.50	Persistent migraine aura without cerebral infarction, not intractable
G43.501	Persistent migraine aura without cerebral infarction, not intractable with status migrainosus
G43.509	Persistent migraine aura without cerebral infarction, not intractable without status migrainosus
G43.51	Persistent migraine aura without cerebral infarction, intractable
G43.511	Persistent migraine aura without cerebral infarction, intractable with status migrainosus
G43.519	Persistent migraine aura without cerebral infarction, intractable without status migrainosus
G43.6	Persistent migraine aura with cerebral infarction
G43.60	Persistent migraine aura with cerebral infarction, not intractable

<table>
<tr><th>Edit</th><th>Drugs</th><th colspan="2">Steps</th></tr>
<tr><td></td><td></td><td colspan="2"><table>
<tr><td>G43.601</td><td>Persistent migraine aura with cerebral infarction, not intractable with status migrainosus</td></tr>
<tr><td>G43.609</td><td>Persistent migraine aura with cerebral infarction, not intractable without status migrainosus</td></tr>
<tr><td>G43.61</td><td>Persistent migraine aura with cerebral infarction, intractable</td></tr>
<tr><td>G43.611</td><td>Persistent migraine aura with cerebral infarction, intractable with status migrainosus</td></tr>
<tr><td>G43.619</td><td>Persistent migraine aura with cerebral infarction, intractable without status migrainosus</td></tr>
<tr><td>G43.7</td><td>Chronic migraine without aura</td></tr>
<tr><td>G43.70</td><td>Chronic migraine without aura, not intractable</td></tr>
<tr><td>G43.701</td><td>Chronic migraine without aura, not intractable with status migrainosus</td></tr>
<tr><td>G43.709</td><td>Chronic migraine without aura, not intractable without status migrainosus</td></tr>
<tr><td>G43.71</td><td>Chronic migraine without aura, intractable</td></tr>
<tr><td>G43.711</td><td>Chronic migraine without aura, intractable with status migrainosus</td></tr>
<tr><td>G43.719</td><td>Chronic migraine without aura, intractable without status migrainosus</td></tr>
</table></td></tr>
<tr><td>Dose Optimization v3.4
Approval will NOT override Non-PDL edit</td><td><table>
<tr><th colspan="2">Dose Optimization Drug List</th></tr>
<tr><th>Drug Code</th><th>Description</th></tr>
<tr><td>HICL = 000094</td><td>Terazosin (Hytrin)</td></tr>
</table></td><td colspan="2">Step 1: For all drugs in the Dose Optimization Drug List: if the quantity per day on the incoming claim is >= 1.8 and <= 2.2 or >=3.8, proceed to Step 2; otherwise claim pays without PA.
Step 2: If the incoming claim is for Valsartan (HSN 012204) or</td></tr>
</table>

Edit	Drugs		Steps
	GSN = 000301, 022649, 000304, 022651		Ramipril (HSN 006080) then proceed to Step 3; otherwise deny claim for NCPDP 76.
	HICL = 000132 GSN = 017266, 000393, 000390, 000391	Lisinopril (Zestril/Prinivil)	**Step 3:** If claim is for Valsartan (HSN 012204) or Ramipril (HSN 006080), look back in history 720 days for the following ICD-9s (indicate heart failure): 4–8.xx - 428.9x. If ICD-9 found and quantity per day <3.8 claim pays; otherwise claim denies for NCPDP 76.
	HICL = 000181 30 mg GSN = 021059	Nifedipine SR (Procardia XL/Adalat CC)	
	HICL = 002793 10 mg GSN = 016310, 050555, 20 mg GSN = 006460, 050556	Lovastatin Sustained Release (Altoprev)	

Dose Optimization Drug List *(continued)*

Drug Code	Description
HICL = 002793 10 mg GSN = 016310, 050555, 20 mg GSN = 006460,050556	Lovastatin Immediate Release (Mevacor, Generic)
HICL = 006031 GSN = 015584, 015585, 015586, 044421	Doxazosin (Cardura)
HICL = 006080 GSN = 015939, 015940, 015941	Ramipril (Altace)*
HICL = 006106 GSN = 016017, 016018	Fosinopril (Monopril)
HICL = 006205 5 mg GSN = 016295, 2.5 mg GSN = 021743	Felodipine (Plendil)
HICL = 006227 10 mg GSN = 016366, 20 mg GSN = 016367, 40 mg GSN = 020741	Pravastatin (Pravachol)
HICL = 006312 5 mg GSN = 016576, 10 mg GSN = 016577, 20 mg GSN = 016578, 40 mg GSN = 016579	Simvastatin (Zocor)
HICL = 006494 2.5 mg GSN = 016925, 5 mg GSN = 016926	Amlodipine (Norvasc)
HICL = 006544 GSN = 024484, 053980	Cetirizine (Zyrtec)
HICL = 007842 GSN = 019187	Zolpidem (Ambien)
HICL = 008268 10 mg GSN = 024498, 20 mg GSN = 024499	Nisoldipine (Sular)
HICL = 008946 20 mg GSN = 021694, 40 mg GSN = 021695	Fluvastatin (Lescol)
HICL = 008991 GSN = 026376, 026377	Trandolapril (Mavik)
HICL = 008993 GSN = 030106, 049296, 051653	Lansoprazole (Prevacid)
HICL = 009829 GSN = 023381, 023382	Losartan (Cozaar)

Edit	Drugs	Steps

HICL = 009934 GSN = 023591	Moexipril (Univasc) – brand formulation only
HICL = 011505 GSN = 054009, 046450, 047453	Mirtazapine (Remeron)
HICL = 012204 GSN = 050805, 048401, 029208, 048400	Valsartan (Diovan)*
HICL = 012259 GSN = 029335, 059039	Donepezil (Aricept)

Dose Optimization Drug List *(continued)*

Drug Code	Description
HICL = 013911 GSN = 041337, 033722	Perindopril (Aceon)
HICL = 015576 GSN = 034470, 034468	Irbesartan (Avapro)
HICL = 018839 GSN = 047126, 040910	Telmisartan (Micardis)
HICL = 021607 GSN = 047525, 062245	Esomeprazole (Nexium)
HICL = 022008 GSN = 039545	Pantoprazole (Protonix)
HICL = 023490 GSN = 050289	Olmesartan (Benicar)
HICL = 025009 10 mg GSN = 051784, 20 mg GSN = 051785, 40 mg GSN = 051786	Rosuvastatin (Crestor)
HICL = 026791 GSN = 058484	Eszopiclone (Lunesta)
HICL =016913 GSN = 037015, 037016, 037017	Candesartan (Atacand)

Lidocaine Adhesive Edit

Automated PA approval does not satisfy Non-PDL edit

Lidocaine Adhesive List

Generic Name	Brand Name	Drug Code
Lidocaine	Lidoderm Adh Patch	GSN = 043256 and generic drug name code = 1 or 2
Lidocaine	ZTlido Adh Patch	GSN = 078210 and generic drug name code = 1 or 2

Other Neuropathic Pain List

Generic Name	Brand Name	Drug Code
Amitriptyline	Elavil	HICL=001643

Step 1: If incoming drug is for <Lidocaine Adhesive List>, look back 730 days in the patient's medical history for a diagnosis of herpes zoster or post herpetic neuralgia <ICD 10 codes listed below> if found: CLAIM PAYS. Otherwise, proceed to Step 2.

Approvable Herpes Zoster or Post Herpetic Neuralgia Diagnosis ICD-10 Disease Groups

B01, B02	Herpes zoster or Post herpetic neuralgia

Step 2: Look back in patient's drug therapy 365 days for 1or more fills of amitriptyline, gabapentin, pregabalin, Savella, duloxetine, Qutenza, or Nucynta/ER <Other Neuropathic Pain List>, if found: CLAIM PAYS. Otherwise, DENY for NCPDP EC 75 PRIOR AUTHORIZATION REQURIED with supplemental messaging: "missing prerequisite drug therapy."

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td>
<table>
<tr><td>Gabapentin</td><td>Neurontin, Gralise</td><td>HICL = 008831</td></tr>
<tr><td>Pregabalin</td><td>Lyrica</td><td>HICL = 026470</td></tr>
<tr><td>Duloxetine</td><td>Cymbalta</td><td>HICL = 026521</td></tr>
<tr><td>Milnacipran</td><td>Savella</td><td>HICL = 021229</td></tr>
<tr><td>Capsaicin</td><td>Qutenza</td><td>HICL = 036916</td></tr>
<tr><td>Tapentadol</td><td>Nucynta/ER</td><td>HICL = 036411</td></tr>
</table>
</td><td></td></tr>
<tr><td>OxyContin

Automated PA approval satisfies Non-PDL edit</td><td>
<table>
<tr><th>Drug Code = GSN</th><th>Generic Name</th></tr>
<tr><td>24504</td><td>Oxycontin 10mg Tablets</td></tr>
<tr><td>24505</td><td>Oxycontin 20mg Tablets</td></tr>
<tr><td>24506</td><td>Oxycontin 40mg Tablets</td></tr>
<tr><td>25702</td><td>Oxycontin 80mg Tablets</td></tr>
<tr><td>63515</td><td>Oxycontin 15mg Tablets</td></tr>
<tr><td>63516</td><td>Oxycontin 30mg Tablets</td></tr>
<tr><td>63517</td><td>Oxycontin 60mg Tablets</td></tr>
<tr><td>72862</td><td>Oxycontin 10mg Tablets</td></tr>
<tr><td>72863</td><td>Oxycontin 15mg Tablets</td></tr>
<tr><td>72864</td><td>Oxycontin 20mg Tablets</td></tr>
<tr><td>72865</td><td>Oxycontin 30mg Tablets</td></tr>
<tr><td>72866</td><td>Oxycontin 40mg Tablets</td></tr>
<tr><td>72867</td><td>Oxycontin 60mg Tablets</td></tr>
<tr><td>72868</td><td>Oxycontin 80mg Tablets</td></tr>
</table>
</td><td>Step 1: If incoming claim is for OxyContin (and generics if available) GSNs: 24504 (10mg), 63515 (15mg), 24505 (20mg), 63516 (30mg), 24506 (40mg), 63517 (60mg), 25702 (80mg), 072862 (10 mg) 072863 (15mg) 072864 (20 mg), 072865 (30mg), 072866 (40mg), 072867 (60mg), 072868 (80mg), is patient >/= 11 years of age?

• If yes, proceed to step 2. If no, deny for age (NCPDP EC 75).

Step 2: Look back in drug history for 30 days for a different strength of oxycodone CR (GSNs: 24504 (10mg), 63515 (15mg), 24505 (20mg), 63516 (30mg), 24506 (40mg), 63517 (60mg), 25702 (80mg), 072862 (10 mg) 072863 (15mg) 072864 (20 mg), 072865 (30mg), 072866 (40mg), 072867 (60mg), 072868 (80mg)

• If not found, proceed to step 3. If found, deny for therapeutic duplication which requires a PA (NCPDP EC 75)

Step 3: Look back in medical claims history 730 days for ICD 10 Disease Block C00-C14, C15-C26, C30-C39, C40-C41, C43-C44, C45-C49, C50, C51-C58, C60-C63, C64-C68, C69-C72, C73-C75, C76-C80, C7A, C7B, C81-C96, D00-D09, D10-D36, D37-D48, D3A, D49, OR Disease Group D56, D57, D58 (sickle cell disease), ICD 10 – K31.7, K63.5, Q85.00, Q85.01, Q85.02 (cancer) OR an LTC indicator or Patient Residence 03 on the claim.

• If found, proceed to step 7. If not found, proceed to step 4.

Step 4: Look back in drug history 365 days for any drug in HICL 011043 (Fusilev) or any drug in HIC3s V1W, V3C, V3I, V3L, Q5N, V1A, V1B, V1C, V1D, V1E, V1F, V1J, V1K, V1M, V1N, V1O, V1Q, V1R, V1T, V1U, V1V, V1X, V3A, V3D, V3E, V3F, V3H, V1I, V3M, Z2G, Z2W (antineoplastics) EXCLUDING HSN 006025 (Alferon), 006068 (Actimmune), GSN 031099 (Aldara), GSN 066038, 068613 (Zyclara), GSN 036872, 045266 (Oral methotrexate)
• If found, proceed to step 7. If not found proceed to step 5.</td></tr>
</table>

Edit	Drugs	Steps
		Step 5: Look back in drug history 90 days for a fill of OxyContin (GSNs: 24504 (10mg), 63515 (15mg), 24505 (20mg), 63516 (30mg), 24506 (40mg), 63517 (60mg), 25702 (80mg), 072862 (10 mg) 072863 (15mg) 072864 (20 mg), 072865 (30mg), 072866 (40mg), 072867 (60mg), 072868 (80mg) • If found, proceed to step 6. If not found, deny for missing prerequisite drug therapy NCPDP EC 75 **Step 6:** Look back in medical claims history 365 days for ICD 10 Disease Group D55.0, D55.1, G11.0, G11.2, G11.3, G11.8, G12.9 G12.0, G12.9, G12.1, G12.8, G12.21, G12.21, G95.0, G95.19, G95.11, G32.0, G99.2, G95.89, G95.81, G95.9, G95.29, G95.20, G90.50, G90.519, G90.511, G90.512, G90.513 , G90.521, G90.522, G90.523, G90.529, G90.59, G35 ,G36.0, G37.0, G37.5, , G37.3, , G73.3, G37.3, G37.1, G37.2, G37.8, G36.1, G36.8, G37.9, G36.9, , G82.50, , G82.20, G04.1, G82.21, G82.22, G83.0, G83.10, , G83.20, ,G83.30,G83.31, G83.32,G83.33, G83.34, G83.4 (G83.5), , G83.81, G83.82 G83.83, G83.84, G83.89, G83.9, G54.6, G54.7, , G60.0, G60.2 G61.0, , G63, , M47.12, M47.011, M47.012, M47.013, M47.014, M47.015, M47.016, M47.019, M47.021, M47.022, M47.029, M47.11, M47.13 , M47.14, M47.15 M47.16, M48.20, M48.21, M48.22, M48.23, M48.24, M48.25, M48.26, M48.27, M48.10, M48.11, M48.12, M48.13, M48.14, M48.15, M48.16, M48.17, M48.18, M48.19, M48.9, M25.78, M47.10, M50.20, M50.21, M50.22, M50.23, M51.26, M51.27, M51.24, M51.25, M51.9, M51.34, M51.35, , M51.36, M51.37, M51.36, M51.37, M51.34, M51.35, M51.9, , M50.00, M50.01, M50.02, M50.03, , M51.04, M51.05, ,M51.06, M96.1, M96.1, , M96.1, , M96.1, M46.40, M51.9, M46.48, M46.49, , M50.80, M50.90, M46.41, M46.42, M46.43, M50.81, M50.82, M50.83, M50.91, M50.92, M50.93, , M46.45, M51.84, M51.85, M46.44, M46.47, M51.86, M51.87, M46.46, M48.02, M48.01, M48.03, M99.20, M99.21, M99.30, M99.31, M99.40, M99.41, M99.50, M99.51, M99.60, M99.61, M99.70, M99.71, M54.12, M54.13, M50.10, M50.11, M50.12, M50.13, M54.11, M54.02, M54.00, M54.01, M67.88, M48.00, M48.04, M48.05, M99.22, M99.32, M99.42, M99.52, M99.62, M99.72, M48.06, M99.43, M99.53, M99.63, M99.73, M48.07, M99.23, M99.33, M48.06, M48.08, M99.34, M99.35, M99.36, M99.37, M99.38, M99.39, M99.44, M99.45, M99.46, M99.47, M99.48, M99.49, M99.55, M99.56, M99.57, M99.58, M99.59, M99.64, M99.65, M99.66, M99.67, M99.68, M99.69, M99.74, M99.75, M99.76, M99.77, M99.78, M99.79, M99.24, M99.25, M99.26, M99.27, M99.28, M99.29, M54.14, M54.15, M54.16, M54.17, M51.14, M51.15, M51.16, M51.17, M89.00, M89.011, M89.012, M89.019, M89.021, M89.022, M89.029, M89.031, M89.032, M89.039, M89.041, M89.042, M89.049, M89.051, M89.052, M89.059, M89.061, M89.062, M89.069, M89.071, M89.072, M89.079, M89.08, M89.09 • If found, proceed to step 7. If not found, deny for missing approvable diagnosis NCPDP EC 75

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>Step 7: If incoming claim is for OxyContin 10mg, 15mg, 20mg, 30mg, 40mg, or 60mg (see GSNs above) proceed to step 8. If incoming claim is for OxyContin 80mg (see GSN above), proceed to step 9.

Step 8 If incoming claim is for OxyContin 10mg, 15mg, 20mg, 30mg, 40mg, or 60mg (see GSN above) and quantity does not exceed 2 tablets per day (60 tablets per 30 days) across all strengths
• If YES, claim passes and pays. If no, claim denies for plan limitations exceeded NCPDP EC 76

Step 9: If incoming claim is for OxyContin 80mg (see GSN above) and quantity does not exceed 4 tablets per day (120 tablets per 30 days)
• If YES, claim passes and pays. If no, claim denies for plan limitation exceeded NCPDP EC 76</td></tr>
<tr><td>HIV Therapy Auto PA

Automated PA approval satisfies L=Auto PA drug logic

Brand and Generic PDL products will bypass the logic

*Automated PA approval will NOT override R = Non-PDL edit and will not satisfy the automation logic</td><td>
<table>
<tr><th colspan="4">HIV Therapy List</th></tr>
<tr><th>HIC3</th><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>W0H</td><td>Darunavir/ Cobicistat/ Emtricitabine/ Tenofovir Alafenamide</td><td>Symtuza</td><td>HSN=044568</td></tr>
<tr><td rowspan="2">W0I</td><td>Cabotegravir/ Rilpivirine</td><td>Cabenuva</td><td>HSN=046258</td></tr>
<tr><td>Dolutegravir/ Rilpivirine</td><td>Juluca</td><td>HSN=044647</td></tr>
<tr><td>W0K</td><td>Dolutegravir/ Lamivudine</td><td>Dovato</td><td>HSN=045679</td></tr>
<tr><td rowspan="5">W5C</td><td>Atazanavir</td><td>Reyataz powder pckt, caps*</td><td>HSN=025390</td></tr>
<tr><td>Atazanavir Sulfate/

Cobicistat</td><td>Evotaz</td><td>HSN=041722</td></tr>
<tr><td>Fosamprenavir</td><td>Lexiva susp, tabs*</td><td>HSN=025662</td></tr>
<tr><td>Indinavir</td><td>Crixivan</td><td>HSN=010683</td></tr>
<tr><td>Nelfinavir</td><td>Viracept</td><td>HSN=010858</td></tr>
</table>
</td><td>Step 1: If the incoming claim is from the HIV therapy list with PA code = L (excluding HSNs/HIC3s listed below) and the recipient is </= 1 year old or the claim is submitted with a day supply of < 34 days with New/refill code = zero and Refills Authorized = 0: NO PA REQUIRED. Otherwise, PROCEED TO STEP 2.

<table>
<tr><td>HSN 033888</td><td>Atripla</td></tr>
<tr><td>HIC3 W5X</td><td>Biktarvy/ Genvoya/ Stribild</td></tr>
<tr><td>HSN 046258</td><td>Cabenuva</td></tr>
<tr><td>HSN 044797</td><td>Cimduo/ Temixys</td></tr>
<tr><td>HSN 037822</td><td>Complera</td></tr>
<tr><td>HSN 045195</td><td>Delstrigo</td></tr>
<tr><td>HSN 045679</td><td>Dovato</td></tr>
<tr><td>HSN 037628</td><td>Edurant</td></tr>
<tr><td>HSN 041722</td><td>Evotaz</td></tr>
<tr><td>HSN 044647</td><td>Juluca</td></tr>
<tr><td>HSN 043121</td><td>Odefsey</td></tr>
<tr><td>HSN 045216</td><td>Pifeltro</td></tr>
<tr><td>HSN 041531</td><td>Prezcobix</td></tr>
<tr><td>HSN 046684</td><td>Rukobia</td></tr>
</table>
</td></tr>
</table>

Edit	Drugs				Steps
		Ritonavir*	Norvir	HSN=010412	
		Saquinavir	Invirase	HSN=010232	
	W5J	Abacavir	Ziagen*	HSN=018857	
		Didanosine DR	Videx EC	HSN=006510	
		Emtricitabine	Emtriva soln, caps*	HSN=025426	
		Lamivudine	Epivir*	HSN=010215	
		Stavudine	Zerit	HSN=009060	
		Zidovudine	Retrovir vial, caps, syrup*	HSN=004185	
	W5K	Doravirine	Pifeltro	HSN=045216	
		Efavirenz	Sustiva*	HSN=018748	
		Etravirine	Intelence	HSN=035342	
		Nevirapine	Viramune*	HSN=011592	
		Rilpivirine	Edurant	HSN=037628	
	W5L	Abacavir Sulfate/ Lamivudine	Epzicom*	HSN=026524	
		Abacavir/ Lamivudine/ Zidovudine	Trizivir*	HSN=021800	
		Lamivudine/ Zidovudine	Combivir*	HSN=014014	
	W5M	Lopinavir/ Ritonavir	Kaletra tabs, soln*	HSN=021582	
	W5O	Emtricitabine/ Tenofovir Alafenamide	Descovy	HSN=026515	
		Emtricitabine/ Tenofovir disoproxil fumarate	Truvada*	HSN=043241	
		Lamivudine/ Tenofovir df	Temixys Cimduo	HSN=044797	
	W5P	Darunavir	Prezista	HSN=033842	
		Darunavir/ Cobicistat	Prezcobix	HSN=041531	

HSN 044568	Symtuza
HSN 044763	Symfi/ Symfi Lo
HIC3 W5Z	Triumeq/Triumeq PD
HSN 044791	Trogarzo
HSN 040834	Vitekta

Step 2: If the incoming claim is from the HIV therapy list look back in medical claims history 730 days for ICD -10 B20, Z21, B97.35, ICD-9 098.7, 098.71, 098.711, 098.712, 098.713, 098.719, 098.72, 098.73: IF FOUND, PROCEED TO STEP 3. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75), M/I Diagnosis Code (supplemental message).

Step 3: If the incoming claim is <Edurant>, PROCEED TO STEP 4. If the incoming claim is for <Cabenuva>, <Juluca>, <Rukobia>, OR <Trogarzo> PROCEED TO STEP 5. Otherwise, CLAIM PAYS.

Step 4: If the incoming claim is <Edurant> and the patient drug history does not contain a fill from the HIV Therapy list for greater than 5 days old but less than 365 days old OR if there is a previous history of itself in the past 365 days: CLAIM PAYS. If not found DENY for PRIOR AUTHORIZATION REQUIRED (75), Patient is not treatment naïve (supplemental message).

Step 5: If the incoming claim is <Cabenuva> look back 365 days in patient drug history for a total of at least 3 fills from the HIV Therapy list OR a previous history of itself in the past 365 days. If found CLAIM PAYS. If not found Deny for PRIOR AUTHORIZATION REQUIRED (75), *Missing Prerequisite drug therapy* (supplemental message). **

If the incoming claim is <Juluca>, <Rukobia> OR <Trogarzo> look back 365 days in patient drug history for a total of at least 6 fills from the HIV Therapy list OR a previous history of itself in the past 365 days. If found CLAIM PAYS. If not found Deny for PRIOR AUTHORIZATION REQUIRED (75), Missing Prerequisite Drug Therapy (supplemental message).

** The Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents recommends viral suppression for at least 3 months. The full recommendation can be found here.

Note: This automation does **NOT** override existing age or quantity limits.

Edit	Drugs				Steps
		Tipranavir caps	Aptivus	HSN=033003	
		Tipranavir soln	Aptivus	HSN=035849	
	W5Q	Doravirine/ Lamivudine/ Tenofo df	Delstrigo	HSN=045195	
		Efavirenz/ Emtricita/Tenofo df	Atripla*	HSN=033888	
		Efavirenz/ Lamivudine/ Tenofo df	Symfi Lo* Symfi*	HSN=044763	
		Emtricita/ Rilpivirine/Tenofo df	Complera	HSN=037822	
		Emtricita/ Rilpivirine/ Tenofo Ala	Odefsey	HSN=043121	
	W5U	Cabotegravir	Vocabria*	HSN=046411	
		Dolutegravir	Tivicay	HSN=040533	
		Raltegravir	Isentress	HSN=035072	
	W5X	Bictegrav/ Emtricita/ Tenofo Ala	Biktarvy	HSN=044765	
		Elviteg/Cob/ Emtricita/ Tenofo df	Stribild	HSN=039543	
		Elviteg/Cob/ Emtricita/ Tenofo Ala	Genvoya	HSN=042778	
	W5Z	Abacavir/ Dolutegravir/ Lamivudine	Triumeq/ Triumeq PD	HSN=041355	
	W0J	Ibalizumab	Trogarzo	HSN=044791	
	W50	Fostemsavir	Rukobia	HSN=046684	
	*blue font indicates manufacturer obsolete				

Drug Name	Age Limit (Min Age)	Quantity Limitation
Apretude	12	7 (vials) per year
Atripla	12	1 per day
Biktarvy	3	1 per day
Cabenuva	12	6 (mL's) per month
Cimduo	12	1 per day
Complera	12	1 per day
Delstrigo	12	1 per day
Dovato	18	1 per day
Edurant	12	1 per day
Evotaz	12	1 per day
Genvoya	6	1 per day
Juluca	18	1 per day
Odefsey	12	1 per day
Pifeltro	12	1 per day
Prezcobix	12	1 per day
Rukobia	18	2 per day
Stribild	12	1 per day
Symfi, Symfi Lo	12	1 per day
Symtuza	12	1 per day
Temixys	12	1 per day
Triumeq	6	1 per day
Triumeq PD	1	6 per day
Vitekta	18	1 per day
Vocabria	12	1 per day

Pneumococcal vaccine	HICL	Drug Name	Step 1: If the incoming claim is for Pneumovax, look back in claims history 730 days for paid claim of Prevnar 13: If found, DENY for PRIOR AUTHORIZATION REQUIRED (75) with add'l message "Therapeutic duplication of this medication not allowed."
	004212	Pneumovax	
	036856	Prevnar 13	

AHCA Automated Prior Authorizations and Bypass Lists 01-2023

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>Step 2: If the incoming claim is for Prevnar 13, look back in claims history 730 days for paid claim of Pneumovax: If found, DENY for PRIOR AUTHORIZATION REQUIRED (75) with add'l message "Therapeutic duplication of this medication not allowed."</td></tr>
<tr><td>Hepatitis C
Auto PA

Automated PA approval satisfies L = Auto PA drug logic

*Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic</td><td>
<table>
<tr><th colspan="2">Hepatitis Therapy List A</th></tr>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Daklinza</td><td>HSN = 041377</td></tr>
<tr><td>Epclusa</td><td>HSN = 043561</td></tr>
<tr><td>Harvoni</td><td>HSN = 041457</td></tr>
<tr><td>Mavyret</td><td>HSN = 044453</td></tr>
<tr><td>Olysio</td><td>HSN = 040771</td></tr>
<tr><td>Sovaldi</td><td>HSN = 040795</td></tr>
<tr><td>Technivie</td><td>HSN = 041734</td></tr>
<tr><td>Viekira XR/Pak</td><td>HSN = 041644</td></tr>
<tr><td>Vosevi</td><td>HSN = 044428</td></tr>
<tr><td>Zepatier</td><td>HSN = 043030</td></tr>
</table>
<table>
<tr><th colspan="2">Hepatitis Therapy List B</th></tr>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Pegasys</td><td>HSN = 024035</td></tr>
<tr><td>PenIntron</td><td>HSN = 021367 Excluding GSNs 067283, 067284, 067285-Sylatron</td></tr>
<tr><td>Copegus
Moderiba
Ribapak</td><td>HSN = 004184
Excluding GSN
009631-Virazole</td></tr>
</table>
</td><td>
Step 1: Is incoming claim from the < Hepatitis Therapy List B> with Prior Authorization = L-AutoPA? If True, Go to Step 2. If False, Stop.

Step2: Look back 730 days in medical claims history for ICD-10 Disease Group B17, B18, B19 (Hepatitis C) excluding ICD 10 B17.0, B17.2, B19.1, B19.10, B19.11 (Hepatitis B & E). IF FOUND, PROCEED TO STEP 4. Otherwise, PROCEED TO STEP 3.

Step 3: Look back 730 days in medical claims history for ICD-10 J12.1, B97.4 (RSV), Disease Group B16, ICD 10 B19.10, B19.11 (Hepatitis B), Disease Group C43, D03 (Malignant Melanoma). IF FOUND, APPROVE. Otherwise, DENY for NCPDP EC 75/31008 with supplemental message: M/I Diagnosis Code

Step 4: Look back in drug history 30 days for any drug in < Hepatitis Therapy List A>. IF FOUND, APPROVE. Otherwise DENY for NCPDP EC 75/31006 with supplemental message: Missing Prerequisite drug therapy

<table>
<tr><th colspan="2">Approvable Hepatitis C Diagnosis ICD-10 Disease Groups</th></tr>
<tr><td>B17, B18, B19 (excluding ICD-10 B17.0, B17.2, B19.1, B19.10, B19.11)</td><td>Hepatitis C</td></tr>
</table>
<table>
<tr><th colspan="2">Approvable Hepatitis B Diagnosis ICD-10 Disease Groups</th></tr>
<tr><td>B16</td><td>Hepatitis B</td></tr>
<tr><td>C43, D03</td><td>Malignant Melanoma</td></tr>
</table>
<table>
<tr><th colspan="2">Approvable Hepatitis B Diagnosis ICD-10 CM Codes</th></tr>
<tr><td>J12.1, B97.4</td><td>RSV-respiratory syncytial virus</td></tr>
<tr><td>B19.10, B19.11</td><td>Hepatitis B</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td>Ribasphere/Rebetol

Ribatab</td><td></td></tr>
<tr><td>Tobramycin nebulizer solution
Auto PA

Automated PA approval satisfies L=Auto PA drug logic

*Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic</td><td>
<table>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>Tobramycin 300mg/4ml Ampule*</td><td>Bethkis 300mg/4ml Ampule</td><td>GSN = 064682</td></tr>
<tr><td>Tobramycin Pak 300mg/5ml*</td><td>Kitabis Pak 300mg/5ml</td><td>GSN = 073201</td></tr>
<tr><td>Tobramycin 300mg/5ml Ampule</td><td>Tobi 300mg/5ml Solution*</td><td>GSN = 037042</td></tr>
</table>
</td><td>Step 1: If the incoming claim is for Tobramycin ampule (GSN 037042), Bethkis Ampules (GSN 064682) or Kitabis Pak (GSN 073201) with Prior Authorization = L-AutoPA, Go to Step 2.

Step 2: Look back in the medical claims history 730 days for ICD 10 Disease Group E84 (Cystic Fibrosis). If found, NO PA REQUIRED. Otherwise, Deny for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code”

Note: This edit does NOT override quantity limits

<table>
<tr><th colspan="2">Approvable ICD-10 Disease Groups</th></tr>
<tr><td>E84</td><td>Cystic fibrosis</td></tr>
</table>
</td></tr>
<tr><td>Gaucher Therapy Automation

Automated PA approval satisfies L=Auto PA drug edit

Automated PA approval will NOT override R=Non-PDL edit</td><td>
<table>
<tr><th colspan="2">Gauchers Therapy List</th></tr>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>*Cerdelga</td><td>HSN = 041346</td></tr>
<tr><td>*Cerezyme</td><td>HSN = 009022</td></tr>
<tr><td>Elelyso</td><td>HSN = 039837</td></tr>
<tr><td>*Vpriv</td><td>HSN = 036874</td></tr>
<tr><td>Zavesca</td><td>HSN = 025098</td></tr>
</table>
*Denotes: R-Non PDL agents and non-preferred agents will NOT satisfy the automation logic
</td><td>Step 1: If the incoming claim is for a product from the <Gauchers Therapy List>, look back in the medical claims history 730 days for ICD 10 Disease Group E75 (Lipidoses-Gaucher’s). If found, NO PA REQUIRED. Otherwise, Deny for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code).”

<table>
<tr><th colspan="2">Quantity Limitation</th></tr>
<tr><td>Cerdelga</td><td>2 capsules per day</td></tr>
<tr><td>Cerezyme</td><td>22 vials per 27 days</td></tr>
<tr><td>Elelyso</td><td>82 vials per 25 days</td></tr>
<tr><td>Vpriv</td><td>41 vials per 25 days</td></tr>
<tr><td>Zavesca</td><td>3 capsules per day</td></tr>
</table>
</td></tr>
</table>

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<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th colspan="2">Approvable ICD-10 Disease Groups</th></tr>
<tr><td>E75</td><td>Lipidoses-Gaucher's</td></tr>
</table>
</td></tr>
<tr><td>Hereditary Angioedema Auto PA

Automated PA approval satisfies L = Auto PA drug edit

Automated PA approval will NOT override R = Non-PDL edit</td><td>
<table>
<tr><th colspan="3">HAE Drug List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>Icatibant</td><td>Firazyr
*Sajazir</td><td>HICL = 035962</td></tr>
<tr><td>C1 Esterase Inhibitor</td><td>Berinert
*Cinryze
*Haegarda</td><td>HICL = 018568</td></tr>
<tr><td>C1 Esterase Inhibitor, Recombinant</td><td>*Ruconest</td><td>HICL = 037766</td></tr>
<tr><td>Ecallantide</td><td>*Kalbitor</td><td>HICL = 036797</td></tr>
<tr><td>Lanadelumab-FLYO</td><td>*Takhzyro</td><td>HICL = 045177</td></tr>
<tr><td>Berotralstat</td><td>*Orladeyo</td><td>HICL = 047016</td></tr>
</table>
*Denotes: R-Non PDL agents and non-preferred agents will NOT satisfy the automation logic
</td><td>
Step 1: If incoming drug in <HAE Drug List> and prior authorization code = L, look back 365 days in the patient's health conditions for an ICD-10 = D84.1 (Hereditary Angioedema) if found, NO PA REQUIRED. Otherwise, deny for PRIOR AUTHORIZATION REQUIRED NCPDP EC 75 with supplemental message: "RECEPIENT DOESN'T HAVE REQ DIAGNOSIS ON FILE."
Note: The following quantity limits apply:
<table>
<tr><th colspan="2">Quantity Limits</th></tr>
<tr><td>Firazyr</td><td>9 mls per 28 days</td></tr>
<tr><td>Berinert</td><td>16 vials per 28 days</td></tr>
<tr><td>Cinryze</td><td>20 vials per 30 days</td></tr>
<tr><td>Haegarda</td><td>22 vials per 30 days (3000 unit vials)
33 vials per 30 days (2000 unit vials)</td></tr>
<tr><td>Ruconest</td><td>2 vials per day</td></tr>
</table>
<table>
<tr><th colspan="2">Approvable ICD-10 CM Code</th></tr>
<tr><td>D84.1</td><td>Hereditary Angioedema</td></tr>
</table>
</td></tr>
<tr><td>Step Therapy for Trintellix

Automated PA approval satisfies L=Auto PA drug edit

Automated PA approval will NOT override R = Non-PDL edit</td><td>
<table>
<tr><th colspan="3">Trintellix List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>vortioxetine hydrobromide</td><td>Trintellix</td><td>HICL = 040637</td></tr>
</table>
<table>
<tr><th colspan="3">SSRI List</th></tr>
<tr><td>Citalopram hydrobromide</td><td>Celexa</td><td>HICL= 010321 and generic drug name = 1</td></tr>
<tr><td>Escitalopram oxalate</td><td>Lexapro</td><td>HICL =024022 and generic drug name = 1</td></tr>
<tr><td>Fluoxetine HCL</td><td>Prozac</td><td>HICL = 001655 (excluding GSN 046219, 046216, 065296 –Sarafem) and generic drug name = 1</td></tr>
<tr><td>Paroxetine/ER HCL</td><td>Paxil, Paxil CR</td><td>HICL =007344and generic drug name = 1</td></tr>
<tr><td>Paroxetine Mesylate</td><td>Pexeva</td><td>HICL =025796 (excluding GSN 071167 – Brisdelle) and generic drug name = 1</td></tr>
<tr><td>Sertraline HCL</td><td>Zoloft</td><td>HICL = 006324 and</td></tr>
</table>
</td><td>
Step 1: If the incoming claim is for Trintellix <Trintellix List>, look back in the medical claims history 730 days for ICD 10 Disease Group: F32 (major depressive disorder – single episode), 296.3, ICD 10 Disease Group: F33 (major depressive disorder – recurrent episodes). If found, proceed to step 2. Otherwise, Deny for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message: "M/I Diagnosis Code."
Step 2: If incoming claim is for Trintellix <Trintellix List>, look back 180 days in patient's drug history for a claim in <Trintellix List>, If found: CLAIM PAYS. Otherwise, Proceed to Step 3.
Step 3: If incoming drug is for Trintellix <Trintellix List>, look back 180 days in the patient's drug history for 1 claim of a generic SSRI <SSRI> list and a day supply ≥ 24. If found, proceed to step 4. Otherwise, deny for NCPDP EC 75 with supplemental message: "missing prerequisite drug therapy."
Step 4: If incoming drug is for Trintellix <Trintellix List>, look back 180 days in the patient's drug history for 1 claim of other generic antidepressant <other
</td></tr>
</table>

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Edit	Drugs	Steps

		generic drug name code = 1

Other Antidepressants List		
Generic Name	**Brand Name**	**Drug Code**
Bupropion Hydrobromide ER	Aplenzin	HICL = 036156 and generic drug name code = 1
Bupropion HCL/SR/XL	Wellbutrin /SR/XL, Budeprion SR/XL	HICL = 001653 (excluding GSN 031439-Buproban/ Zyban) and generic drug name code = 1
Nefazodone HCL	Serzone	HICL = 009612 and generic drug name code = 1
Vilazodone	Viibryd	HICL = 037597 and generic drug name code = 1
Antipsychotic/Antidepressant Combinations		
Amitriptyline/ chlordiazepoxide	Limbitrol	HICL = 001656 and generic drug name code = 1
Amitriptyline/ perphenazine	Etrafon, Triavil	HICL = 013819 and generic drug name code = 1
Olanzapine/ fluoxetine	Symbyax	HICL = 025800 and generic drug name code = 1
Heterocyclics		
Amoxapine	N/A	HICL = 001648 and generic drug name code = 1
Maprotiline HCL	Ludiomil	HICL = 001651 and generic drug name code = 1
Mirtazapine	Remeron	HICL = 011505 and generic drug name code = 1
Trazodone HCL/ER	Desyrel, Oleptro ER	HICL = 001652 and generic drug name code = 1

MAOIs		
Isocarboxazid	Marplan	HICL = 001638 and generic drug name code = 1

antidepressant list> and a day supply ≥24. If found: **CLAIM PAYS**. Otherwise, deny for NCPDP EC 75 with supplemental message: *"missing prerequisite drug therapy."*

**Quantity and age limitations are not a part of the automated prior authorization. (Max quantity = 1 per day; Minimum age = 18 years)

Note:

The meds below do not have an FDA indication for depression thus were omitted from the automation:

MAOIs			
Generic Name	**Brand Name**	**Drug Code**	**FDA approved Indication**
Rasagiline Mesylate	Azilect	HICL = 032911	Parkinson's disease
SSRIs			
Fluvoxamine maleate CR	Luvox CR	HICL = 006338	Obsessive Compulsive Disorder (OCD), social phobia (social anxiety disorder)
Fluoxetine	Sarafem Rapiflux	GSN: 46216 46219	Premenstrual dysphoric disorder (PMDD)
Paroxetine mesylate	Brisdelle	GSN 71167	Hot Flashes
TCAs			
Clomipramine HCL	Anafranil	HICL = 004744	OCD

Approvable ICD-10 Disease Groups	
F32	Major depressive disorder- single episode
F33	Major depressive disorder-recurrent episodes

Edit	Drugs			Steps
	Phenelzine sulfate	Nardil	HICL = 001639 and generic drug name code = 1	
	Tranylcypromine sulfate	Parnate	HICL = 001640 and generic drug name code = 1	
	Selegiline HCL	Emsam	HICL = 033510 and generic drug name code = 1	
	SNRIs			
	Desvenlafaxine ER	Khedezla	HSN = 040202 and generic drug name code = 1	
	Desvenlafaxine succinate ER	Pristiq ER	HSN = 035420 and generic drug name code = 1	
	Desvenlafaxine fumarate	N/A	HSN = 040692 and generic drug name code = 1	
	Duloxetine HCL DR	Cymbalta	HICL = 026521 and generic drug name code = 1	
	Levomilnacipran	Fetzima	HICL = 040632 and generic drug name code = 1	
	Venlafaxine/ ER HCL	Effexor, Effexor XR	HICL = 008847 and generic drug name code = 1	
	TCAs			
	Amitriptyline HCL	Elavil	HICL = 001643 and generic drug name code = 1	
	Desipramine HCL	Norpramin	HICL = 001645 and generic drug name code = 1	
	Doxepin HCL	Silenor, Sinequan	HICL = 001650 (excluding GSN 021715-Prudoxin/Zonalon cream) and generic drug name code = 1	
	Imipramine HCL	Tofranil	HICL = 001641 and generic drug name code = 1	
	Imipramine pamoate	Tofranil PM	HICL = 001642 and generic drug name code = 1	
	Nortriptyline HCL	Aventyl, Pamelor	HICL = 001644 **and generic drug name code = 1**	
	Protriptyline HCL	Vivactil	HICL = 001646 **and generic drug name code = 1**	
	Trimipramine maleate	Surmontil	HICL = 001649 **and generic drug name code = 1**	

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<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td>**Please note: Blue font indicates product is no longer available</td><td></td></tr>
<tr><td>Tybost Automation
Automated PA approval satisfies L=Auto PA drug edit
Automated PA approval will NOT override R = Non-PDL edit</td><td>
<table>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Tybost</td><td>HSN= 041076</td></tr>
</table>
</td><td>Step 1: If the incoming claim is for <Tybost> look back in the patient's drug history 40 days for a claim of <HSN 033842 - Prezista> or <HSN 025390 -Reyataz>. IF FOUND, PROCEED TO STEP 2. Otherwise, DENY for NCPDP EC 75 with supplemental message: "missing prerequisite drug therapy."
Step 2: If the incoming claim is for <Tybost> and the quantity on the incoming claim is less than or equal to 1 tablet per day: NO PA REQUIRED. Otherwise, DENY for PLAN LIMITATIONS EXCEEDED (76).</td></tr>
<tr><td>Dual RAS Blockade DUR edit</td><td>
<table>
<tr><th colspan="3">RAS Inhibitors List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>HICL</th></tr>
<tr><td colspan="3">Angiotensin Converting Enzyme Inhibitors (ACE)</td></tr>
<tr><td>benazepril</td><td>Lotensin</td><td>006113</td></tr>
<tr><td>benazepril</td><td>Lotensin HCT</td><td>008962</td></tr>
<tr><td>benazepril</td><td>Lotrel</td><td>010041</td></tr>
<tr><td>captopril</td><td>Capoten</td><td>000128</td></tr>
<tr><td>captopril</td><td>Capozide</td><td>000127</td></tr>
<tr><td>Enalapril</td><td>Vasotec / Epaned</td><td>000130</td></tr>
<tr><td>Enalapril</td><td>Vaseretic</td><td>000129</td></tr>
<tr><td>fosinopril</td><td>Monopril</td><td>006106</td></tr>
<tr><td>fosinopril</td><td>Monopril HCTZ</td><td>018610</td></tr>
<tr><td>Lisinopril</td><td>Prinivil, Zestril</td><td>000132</td></tr>
<tr><td>lisinopril</td><td>Prinzide, Zestoretic</td><td>000131</td></tr>
<tr><td>moexipril</td><td>Univasc</td><td>009934</td></tr>
<tr><td>moexipril</td><td>Uniretic</td><td>014293</td></tr>
<tr><td>perindopril</td><td>Aceon</td><td>013911</td></tr>
<tr><td>perindopril</td><td>Prestalia</td><td>036967</td></tr>
<tr><td>quinapril</td><td>Accupril</td><td>007631</td></tr>
<tr><td>quinapril</td><td>Accuretic/Quinaretic</td><td>007826</td></tr>
<tr><td>ramipril</td><td>Altace</td><td>006080</td></tr>
<tr><td>trandolapril</td><td>Mavik</td><td>008991</td></tr>
<tr><td>trandolapril</td><td>Tarka</td><td>012230</td></tr>
</table>
<table>
<tr><th colspan="3">RAS Inhibitors List (continued)</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>HICL</th></tr>
<tr><td colspan="3">Angiotensin Receptor Blockers (ARB)</td></tr>
<tr><td>azilsartan</td><td>Edarbi</td><td>037444</td></tr>
</table>
</td><td>Automation Logic:
Step 1: If incoming claim from <RAS Inhibitor List> look back 100 days for fill from <RAS Inhibitor List> excluding itself, that has a day supply >/=84. If found, claim rejects NCPDP 76 with additional message "TD of Angiotensin drug. Review & submit appropriate DUR cd." If not found, proceed to Step #2.
Step 2: If incoming claim from <RAS Inhibitor List> look back 30 days for fill from <RAS Inhibitor List> excluding itself. If found, claim rejects NCPDP 76 with additional message "TD of Angiotensin drug. Review & submit appropriate DUR cd." If not found, claim pays.
Limitation:
Allow 2 pharmacy level overrides in 180 days for claims that deny out of the RAS Inhibitor AutoPA. Pharmacy must submit DUR Reason For Service Code: TD-Therapeutic Duplication for pharmacy level override. Deny the third, and subsequent attempts of a pharmacy level overrides (within a rolling 180 days) NCPDP 75 PA required with additional message "PA Req'd.Max:2 Angiotensin TD ovr/180 dys. FaxPA877-614-1078"</td></tr>
</table>

Edit	Drugs			Steps
	azilsartan	Edarbyclor	038370	
	candesartan	Atacand	016913	
	candesartan	Atacand HCT	021280	
	eprosartan	Teveten	016920	
	eprosartan	Teveten HCT	024744	
	irbesartan	Avalide	018963	
	irbesartan	Avapro	015576	
	losartan	Cozaar	009829	
	losartan	Hyzaar	009863	
	olmesartan	Benicar	023490	
	olmesartan	Benicar HCT	025446	
	olmesartan	Azor	035042	
	olmesartan	Tribenzor	037089	
	telmisartan	Micardis	018839	
	telmisartan	Micardis HCT	021873	
	telmisartan	Twynsta	036697	
	valsartan	Diovan	012204	
	valsartan	Diovan HCT	017084	
	valsartan	Exforge	034433	
	valsartan	Exforge HCT	036305	
	valsartan	Entresto	042256	
	Direct Renin Inhibitors (DRI)			
	aliskiren	Tekturna	034493	
	aliskiren	Tekturna HCT	035338	
	aliskiren	Tekamlo	037135	
	aliskiren	Amturnide	037333	

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr>
<td>Dual PPI Blockade DUR edit</td>
<td>
<table>
<tr><th colspan="3">Proton Pump Inhibitors List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>HICL</th></tr>
<tr><td colspan="3">and generic drug name code = 1 or 2
and Route of Admin = Oral</td></tr>
<tr><td>rabeprazole</td><td>Aciphex</td><td>018847</td></tr>
<tr><td>dexlansoprazole</td><td>Dexilant</td><td>036085</td></tr>
<tr><td>esomeprazole</td><td>Nexium</td><td>021607</td></tr>
<tr><td>lansoprazole</td><td>Prevacid</td><td>008993
025742</td></tr>
<tr><td>omeprazole</td><td>Prilosec</td><td>011115
004673</td></tr>
<tr><td>pantoprazole</td><td>Protonix</td><td>022008</td></tr>
<tr><td>omeprazole/ sodium bicarbonate</td><td>Zegerid</td><td>033512</td></tr>
</table>
</td>
<td>
Automation Logic:

Step 1: If incoming claim from <PPI List> and route of administration = oral, look back 30 days for a fill from <PPI List> , excluding itself. If found, claim rejects 76 with additional message “TD Proton Pump Inhibitor; Review & submit appropriate DUR cd”. If not found, claim pays.

Limitation:

Allow 1 pharmacy level override in 180 days for claims that deny out of the PPI AutoPA. Pharmacy must submit DUR Reason For Service Code: TD-Therapeutic Duplication for pharmacy level override. Deny the second, and subsequent attempts of a pharmacy level overrides (within a rolling 180 days) NCPDP 75 PA required with additional message “PA Req’d.Max:1 ProtonPumpInhib TD ovr/180dys.FaxPA877-614-1078

Max Fill Limit:

For incoming claims from <PPI List> and route of administration = oral and a day supply >/= 28, create a maximum fill limit = 6 fills per 365 days across the HSNs. The 7th attempted fill will reject 76 – Plan limitations exceeded with additional message “PPI Therapy not indicated for chronic use”. Excluding recipients with a diagnosis, within 730 days, of Zollinger-Ellison syndrome, Barrett’s esophagus, gastric malignancy, cystic fibrosis or history of gastric bypass as listed below:

<table>
<tr><th>ICD-10 CM Code</th><th>Description</th></tr>
<tr><td>PCS Code:

0D9600Z
0D960ZZ
0D9630Z
0D963ZZ
0D9640Z
0D964ZZ
0D967ZZ
0D968ZZ
0DC60ZZ
0DC63ZZ
0DC64ZZ
0DH602Z
0DH603Z
0DH63UZ
0DH64UZ</td><td>Drainage of Stomach with Drainage Device, Open Approach, Percutaneous Approach, Percutaneous Endoscopic Approach
Drainage of Stomach, Open Approach, Percutaneous Approach ,Percutaneous Endoscopic Approach, Via Natural or Artificial Opening, Via Natural or Artificial Opening Endoscopic
Extirpation of Matter from Stomach, Open Approach, Percutaneous Approach, Percutaneous Endoscopic Approach
Insertion of Monitoring Device into Stomach, Open Approach
Insertion of Infusion Device into Stomach, Open Approach, Percutaneous Endoscopic Approach</td></tr>
<tr><td>0D1607A
0D160JA
0D160KA
0D160ZA</td><td>Bypass Stomach to Cutaneous with Autologous Tissue Substitute, Open Approach, Percutaneous Endoscopic Approach, Via Natural or Artificial</td></tr>
</table>
</td>
</tr>
</table>

Edit	Drugs	Steps	
		0DH90UZ 0DH93UZ 0DH94UZ 0DH97UZ 0DH98UZ 0DHA0UZ 0DHA7UZ	Intestine, Open Approach, Percutaneous Approach, percutaneous Endoscopic Approach, Via Natural or Artificial Opening, Via Natural or Artificial Opening Endoscopic Insertion of Feeding Device into Duodenum, Open Approach, Percutaneous Approach, percutaneous Endoscopic Approach, Via Natural or Artificial Opening, Via Natural or Artificial Opening Endoscopic
		0D9670Z	Drainage of Stomach with Drainage Device, Via Natural or Artificial Opening
		0D9670Z	Drainage of Stomach with Drainage Device, Via Natural or Artificial Opening Endoscopic
		K22.70 K22.710 K22.711 K22.719	Barrett's esophagus without dysplasia Barrett's esophagus with low grade dysplasia Barrett's esophagus with high grade dysplasia Barrett's esophagus unspecified
		Z98.84	Bariatric surgeries
		Z98.0	Gastric Bypass
		ICD 10 Disease group: C15	Malignant Neoplasm of esophagus
		ICD 10 Disease group: C16	Malignant Neoplasm of stomach
		E16.4	Abnormality of secretion of Gastrin
		ICD-10 Disease Group E84	Cystic Fibrosis
		K31.84	Gastroparesis
		K94.20 K94.21 K94.22 K94.23 K94.29	Gastrostomy complication unspecified Gastrostomy hemorrhage Gastrostomy infection Gastrostomy malfunction Other complications of gastrostomy

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>K94.10
K94.11
K94.12
K94.13
K94.19</td><td>Enterostomy Complication, Unspecified
Enterostomy Hemorrhage
Enterostomy Infection
Enterostomy Malfunction
Other Complications of Enterostomy</td></tr>
<tr><td>Z93.1</td><td>Gastrostomy Status</td></tr>
<tr><td>Z93.4</td><td>Other artificial openings of gastrointestinal tract status</td></tr>
<tr><td>Z43.1</td><td>Encounter for Attention to Gastrostomy</td></tr>
<tr><td>Z43.4</td><td>Encounter for attention to other artificial openings of digestive tract</td></tr>
</table>
</td></tr>
<tr><td>Duration Edit SMR (Skeletal Muscle Relaxants)</td><td>
<table>
<tr><th colspan="3">SMR List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>Baclofen*</td><td>N/A</td><td>HICL = 001949</td></tr>
<tr><td>Chlorzoxazone</td><td>Lorzone</td><td>HICL = 001941</td></tr>
<tr><td>Cyclobenzaprine</td><td>Flexeril/ Amrix/ Fexmid</td><td>HICL = 001950</td></tr>
<tr><td>Orphenadrine</td><td>N/A</td><td>HICL = 001906</td></tr>
<tr><td>Metaxalone</td><td>Skelaxin</td><td>HICL = 001945</td></tr>
<tr><td>Methocarbamol</td><td>Robaxin</td><td>HICL = 001938</td></tr>
<tr><td>Tizanidine*</td><td>Zanaflex</td><td>HICL = 011582</td></tr>
<tr><td colspan="3">and Route of Admin = oral and day supply >/= 30</td></tr>
</table>
</td><td>6 fills every 365 days
*EXCLUDING drugs in HSN 001949 (Baclofen) or HSN 001949 (Zanaflex) that have a diagnosis listed below, in history, within the past 730 days:
<table>
<tr><th>ICD-10 CM Code</th><th>Description</th></tr>
<tr><td>ICD 10 Disease Group: G11, ICD 10: G32.81</td><td>Hereditary Ataxia</td></tr>
<tr><td>ICD 10: G12.20, G12.21, G12.22, G12.29, G12.8</td><td>Motor Neuron disease: Other spinal muscle atrophis and related syndromes</td></tr>
<tr><td>ICD 10: I69.053, I69.051, I69.052, I69.053, I69.054, I69.059, I69.151, I69.152, I69.153, I69.154, I69.159, I69.251, I69.252, I69.253, I69.254, I69.259, I69.351, I69.352, I69.353, I69.354, I69.359, I69.851, I69.852, I69.853, I69.854, I69.859, I69.951, I69.952, I69.953, I69.954, I69.959</td><td>Hemiplegia and hemiparesis following unspecified cerebrovascular disease</td></tr>
<tr><td>ICD 10: I69.031, I69.032, I69.033, I69.034, I69.039, I69.131, I69.132, I69.133, I69.134, I69.139, I69.231, I69.232, I69.233, I69.234, I69.239, I69.331, I69.332, I69.333, I69.334, I69.339, I69.831, I69.832, I69.833, I69.834, I69.839, I69.931, I69.932, I69.933, I69.934, I69.939</td><td>Monoplegia of upper limb following unspecified cerebrovascular disease</td></tr>
<tr><td>ICD 10:
I69.041, I69.042, I69.043, I69.044, I69.049, I69.141,</td><td>Monoplegia of lower limb following unspecified cerebrovascular disease</td></tr>
</table>
</td></tr>
</table>

Edit	Drugs	Steps	
		I69.142, I69.143, I69.144, I69.149, I69.241, I69.242, I69.243, I69.244, I69.249, I69.341, I69.342, I69.343, I69.344, I69.349, I69.841, I69.842, I69.843, I69.844, I69.849, I69.949, I69.941, I69.942, I69.943, I69.944, I69.949	
		ICD 10: I69.061, I69.062, I69.063, I69.064, I69.065, I69.069, I69.161, I69.162, I69.163, I69.164, I69.165, I69.169, I69.261, I69.262, I69.263, I69.264, I69.265, I69.269, I69.361, I69.362, I69.363, I69.364, I69.365, I69.369, I69.861, I69.862, I69.863, I69.864, I64.865, I69.869, I69.961, I69.962, I69.963, I69.964, I69.965, I69.969	Other paralytic syndrome following unspecified cerebrovascular disease
		ICD 10: I69.00, I69.10, I69.20, I69.30, I69.80, I69.90	Unspecified sequelae of unspecified cerebrovascular disease
		ICD 10: G35	Multiple sclerosis
		ICD 10 Disease Groups: G36, G37	Other demyelinating diseases of central nervous system
		ICD 10 Disease Group: G81	Hemiplegia/Hemiparesis
		ICD 10 Disease Group: G80	Cerebral Palsy
		ICD 10 Disease Group: G82, G83	Paraplegia (parapaesis) and quadriplegia (quadriparesis) Other paralytic syndromes
		ICD 10: R53.2	Functional Quadriplegia
		ICD 10: R29.0	Tetany
		ICD 10: S14.101A, S14.102A, S14.103A, S14.104A, S14.105A, S14.106A, S14.107A, S14.108A, S14.109A, S14.111A, S14.112A, S14.113A, S14.114A, S14.115A, S14.116A, S14.117A, S14.118A, S14.119A, S14.121A, S14.122A, S14.123A, S14.124A, S14.125A, S14.126A, S14.127A, S14.128A, S14.129A, S14.131A, S14.132A, S14.133A, S14.134A, S14.135A, S14.136A, S14.137A, S14.138A, S14.139A, S14.141A, S14.142A,	Spinal Cord Injury without evidence of spinal bone injury

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>S14.143A, S14.144A,
S14.145A, S14.146A,
S14.147A, S14.148A,
S14.149A, S14.0XXA,
S14.151A, S14.152A,
S14.153A, S14.154A,
S14.155A, S14.156A,
S14.157A, S14.158A,
S14.159A, S24.101A,
S24.102A, S24.103A,
S24.104A, S24.109A,
S24.111A, S24.112A,
S24.113A, S24.114A, 24. 119A,
S24.131A, S24.132A,
S24.133A, S24.134A,
S24.139A, S24.141A,
S24.142A, S24.143A,
S24.144A, S24.149A,
S24.151A, S24.152A,
S24.153A, S24.154A,
S24.159A, S24.0XXA,
S34.01XA, S34.101A,
S34.102A, S34.103A,
S34.104A, S34.105A,
S34.109A, S34.111A,
S34.112A, S34.113A,
S34.114A, S34.115A,
S34.119A, S34.121A,
S34.122A, S34.123A,
S34.124A, S34.125A,
S34.129A, S34.131A,
S34.132A, S34.139A,
S34.02XA, S34.3XXA</td></tr>
<tr><td>Hypertonic Solution
Automated PA approval satisfies L=Auto PA drug edit and non OBRA-rebateable status</td><td><table><tr><th colspan="2">Hypertonic Solution</th></tr><tr><th>Drug Name</th><th>GSN</th></tr><tr><td>Sodium Chloride 3%, vial neb soln</td><td>000588</td></tr><tr><td>Sodium Chloride 7% vial neb soln</td><td>062746</td></tr><tr><td>Hyper-Sal 7% neb solution</td><td></td></tr><tr><td>Pulmosal 7% neb solution</td><td></td></tr><tr><td>Sodium Chloride 10% vial neb sol</td><td>000587</td></tr><tr><td>Hyper-Sal 3.5% neb solution</td><td>068364</td></tr></table></td><td>Step 1: If the incoming claim is from the <Hypertonic solution list>, look back in the medical claims history 730 days for ICD 10 Disease Group E84 (Cystic Fibrosis). If found, NO PA REQUIRED. Otherwise, Deny for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code.”

<table><tr><th colspan="2">Approvable ICD 10-CM Disease Group</th></tr><tr><td>E84</td><td>Cystic fibrosis</td></tr></table></td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td><table><tr><td>Nebusal 6% neb solution</td><td>067053</td></tr></table></td><td></td></tr>
<tr><td>Alpha Antitrypsin deficiency (AAT deficiency) Automation

Automated PA approval satisfies L=Auto PA drug edit

Automated PA approval will NOT override R = Non-PDL edit</td><td><table><tr><th colspan="3">AAT Deficiency Drug List</th></tr><tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr><tr><td rowspan="4">Alpha-1 Proteinase inhibitor</td><td>Aralast
Aralast NP</td><td rowspan="4">HSN = 004529</td></tr><tr><td>Glassia</td></tr><tr><td>Prolastin C</td></tr><tr><td>Zemaira</td></tr></table></td><td>Step 1: If incoming drug in <AAT deficiency List> and prior authorization code = L, look back 730 days in the patient's health conditions for an ICD-10 = E88.01 (Alpha-antitrypsin deficiency) if found, NO PA REQUIRED. Otherwise, deny for PRIOR AUTHORIZATION REQUIRED NCPDP EC 75 with supplemental message: "RECEPIENT DOESN'T HAVE REQ DIAGNOSIS ON FILE."

<table><tr><th colspan="2">Approvable ICD-10 CM Code</th></tr><tr><td>E88.01</td><td>Alpha Antitrypsin deficiency (AAT) or Alpha -1 Antitrypsin deficiency</td></tr></table></td></tr>
<tr><td>Fabrazyme Automation

Automated PA approval satisfies L=Auto PA drug edit

Automated PA approval will NOT override R = Non-PDL edit</td><td><table><tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr><tr><td>Agalsidase Beta</td><td>Fabrazyme</td><td>HSN = 024861</td></tr></table></td><td>Step 1: If incoming claims is for <HSN 024861> and prior authorization code = L, look back 730 days in the patient's health conditions for an ICD-10 = E75.21 (Fabry –Anderson disease) if found, NO PA REQUIRED. Otherwise, deny for PRIOR AUTHORIZATION REQUIRED NCPDP EC 75 with supplemental message: "RECEPIENT DOESN'T HAVE REQ DIAGNOSIS ON FILE."

<table><tr><th colspan="2">Approvable ICD-10 CM Code</th></tr><tr><td>E75.21</td><td>Fabry (Anderson) disease</td></tr></table></td></tr>
<tr><td>Pulmozyme

Automated PA approval satisfies L=Auto PA drug edit

Automated PA approval will NOT override R = Non-PDL edit</td><td><table><tr><th>Drug Name</th><th>Drug Code</th></tr><tr><td>Pulmozyme 1mg/mL</td><td>HSN=008832</td></tr></table></td><td>Step 1: Step 1: If the incoming claim is for Pulmozyme (HSN 008832) look back in medical claims history 730 days for any of the following ICD codes: ICD-10 Disease Group E84 (Cystic Fibrosis). If found, NO PA REQUIRED.
Otherwise, deny for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message "M/I Diagnosis Code

<table><tr><th colspan="2">Approvable ICD 10-CM Disease Group</th></tr><tr><td>E84</td><td>Cystic fibrosis</td></tr></table></td></tr>
<tr><td>Long Acting Opioid Polypharmacy</td><td><table><tr><th colspan="2"><Long Acting Opioid List></th></tr><tr><th>Drug Name</th><th>Drug Code</th></tr><tr><td>Buprenorphine (Belbuca)</td><td>GSNs = 075050, 075051, 075052, 075053, 075054, 075055, 075056</td></tr><tr><td>Fentanyl (Duragesic)</td><td>GSNs = 015880, 015881, 015882, 015883, 059102, 073524, 073525, 073532</td></tr></table></td><td>Step 1: If incoming claim is from <Long Acting Opioid List> look back 30 days for a fill from <Long Acting Opioid List (different HSN)>, excluding itself. If found, Proceed to STEP 2: If not CLAIM PAYS

Step 2: Look back in medical claims history 365 days for ICD 10 Disease Block C00-C14, C15-C26, C30-39, C40-41, C43-C44, C45-C49, C50, C51-C58, C60-C63, C64-C68, C69-C72, C73-C75, C76-C80, C7A, C7B, C81-C96, D00-D09,</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td>
<table>
<tr><td>Hydrocodone, extended release (Zohydro ER/ Hysingla)</td><td>GSNs = 071602, 073621, 071603, 073622, 071604, 073623, 071605, 073624, 071606, 073625, 071607, 073626, 073176, 073177, 073179, 073180, 073181, 073182, 073183</td></tr>
<tr><td>Hydromorphone (Exalgo)</td><td>GSNs = 066200, 069860, 069889, 069890</td></tr>
<tr><td>Methadone (Dolophine)</td><td>GSNs = 004235, 004237, 004238, 004239, 004240, 004242</td></tr>
<tr><td>morphine sulfate ER (MS Contin/ Kadian ER, Arymo ER, Morphabond ER)</td><td>GSNs = 011887, 004096, 004097, 011886, 016522, 050222, 064739, 050221, 064740, 050220, 050219, 060355, 060356, 061748, 069899, 060357, 061749, 061722, 060358, 062358, 077053, 077054, 077055, 074968,074969, 074970, 074971</td></tr>
<tr><td>morphine sulfate/ naltrexone ER (Embeda)</td><td>GSNs = 073302, 073303, 073304, 073305, 073306, 073307</td></tr>
</table>

<table>
<tr><th colspan="2"><Long Acting Opioid List>
(continued)</th></tr>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Oxycodone/Acetaminophen ER (Xartemis ER)</td><td>GSN = 072134</td></tr>
<tr><td>oxycodone ER (OxyContin)</td><td>GSNs = 072862, 072863, 072864, 072865, 072866, 072867, and 072868</td></tr>
<tr><td>Oxycodone Myristate (Xtampza ER)</td><td>GSNs = 076031, 076032, 076033, 076034, 076035</td></tr>
<tr><td>oxymorphone (Opana)</td><td>GSNs = 061091, 070397, 063782, 070320, 061092, 070398, 063783, 070321, 061093, 070399, 063784, 070400, 061094, 070401</td></tr>
<tr><td>Tapentadol (Nucynta ER)</td><td>GSNs = 067266, 067267, 067268, 067270, 067271</td></tr>
<tr><td>Tramadol (Ultram ER/ Ryzolt/ Conzip)</td><td>GSNs = 043536, 043537, 060274, 063422, 063423, 063424, 067760, 067761, 067762, 068721</td></tr>
<tr><td>transdermal buprenorphine (Butrans)</td><td>GSNs = 059589, 059590, 059591, 072673, 071432</td></tr>
</table>
</td><td>D10-D36, D37-D48, D3A, D49, ICD-10-K31.7, K63.5, Q85.00, Q85.01,Q85.02 (cancer) or ICD10 Disease Group D56, D57, D58 (sickle cell disease) or an LTC indicator or Patient Residence 03 on the claim. . If found, CLAIM PAYS, Otherwise rejects NCPDP 76 with additional message “PA Req’d. Max of 1 LA Opioid per month: Fax PA 877-614-1078”

Note: This edit does NOT override the 4 Controlled Substance limit (or 6 for recipients with a diagnosis of cancer or sickle cell disease) per rolling 27 days

Note: This edit does NOT override the Oxycontin AP logic.

Note: This edit does NOT override existing age limits, quantity limits, or Non PDL coding.</td></tr>
<tr><td>Gonadotropin-Releasing Hormone (GnRH) analog Auto PA</td><td>
<table>
<tr><th colspan="3">GnRH analog List A</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>leuprolide acetate</td><td>Lupron Depot 3.75 mg (1 month)</td><td>GSN =045017</td></tr>
<tr><td>leuprolide</td><td>Lupron Depot 11.25 mg</td><td>GSN =044980</td></tr>
</table>
</td><td>Incoming drug in GnRH Analog List A:
Step 1: If the incoming claim is for a GnRH analog <List A> look back in medical claims history 730 days for any of the following ICD codes: ICD-10 Disease Group N80 (Endometriosis), OR ICD 10 Disease Group D25 (leiomyoma of uterus), . If found, NO PA REQUIRED. Otherwise, deny for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I</td></tr>
</table>

AHCA Automated Prior Authorizations and Bypass Lists 01-2023

Edit	Drugs	Steps

Edit: Automated PA approval satisfies L=Auto PA drug logic

*Automated PA approval will NOT override R = Non-PDL edit and will not satisfy the automation logic

acetate	(3 month)	
leuprolide acetate/ norethindrone	Lupaneta Pack 3.75–5 mg (1 month)	GSN = 070481
leuprolide acetate/ norethindrone	Lupaneta Pack 11.25 mg–5 mg (3 month)	GSN = 070480
Norethindrone AC (Lupaneta)		NDC = 00074104902 00074104904 00074104930

GnRH analog List B

Generic Name	Brand Name	Drug Code
leuprolide acetate	Fensolvi 45mg (6 month)	GSN = 081002
leuprolide acetate	Lupron Depot Ped 7.5 mg	GSN = 047666
leuprolide acetate	Lupron Depot Ped 11.25 mg	GSN = 047665
leuprolide acetate	Lupron Depot Ped 11.25 mg (3 months)	GSN = 067738
leuprolide acetate	Lupron Depot Ped 15 mg	GSN = 047851
leuprolide acetate	Lupron Depot Ped 30 mg	GSN = 067737
triptorelin pamoate	Triptodur 22.5mg vial	GSN = 077557

GnRH analog List C

Generic Name	Brand Name	Drug Code
leuprolide acetate	Lupron 1mg/0.2ml kit	GSN = 044967
leuprolide acetate	Lupron 1mg/0.2ml vial	GSN = 044969
goserelin acetate	Zoladex 10.8mg implant	GSN = 044961
leuprolide acetate	Lupron Depot 7.5mg (1 month)	GSN = 067356
leuprolide acetate	Lupron Depot 22.5mg (3 month)	GSN = 044964
leuprolide acetate	Lupron Depot 30mg (4 month)	GSN = 044968
leuprolide acetate	Lupron Depot 45mg (6 month)	GSN = 067506
leuprolide mesylate	Camcevi 42mg (6 month)	GSN = 082352

Steps:

Diagnosis Code"

Incoming drug in GnRH Analog List B:

Step 1: If the incoming claim is for a GnRH analog **<List B>**look back in medical claims history 730 days for any of the following ICD codes: ICD-10 E30.1 (precocious puberty), E22.8 (other hyperfunction of pituitary gland), OR E22.9 (hyperfunction of pituitary) If found, NO PA REQUIRED. Otherwise, deny for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message "M/I Diagnosis Code"

Incoming drug in GnRH Analog List C:

Step 1: If the incoming claim is for a GnRH analog **<List C>** look back in medical claims history 730 days for any of the following ICD codes: ICD-10 Code C61 (prostate cancer)

If found, NO PA REQUIRED. Otherwise, deny for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message "M/I Diagnosis Code"

Incoming drug in GnRH Analog List D:

Step 1: If the incoming claim is for a GnRH analog (**List D**) look back in medical claims history 730 days for any of the following ICD codes: ICD 10 Disease Group: N80 (Endometriosis), ICD-10: E30.1 (precocious puberty), E22.8 (other hyperfunction of pituitary gland), OR E22.9 (hyperfunction of pituitary) If found, NO PA REQUIRED. Otherwise, deny for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message "M/I Diagnosis Code"

Incoming drug in GnRH Analog List E:

Step 1: If the incoming claim is for a GnRH analog (**List E**) look back in medical claims history 730 days for any of the following ICD codes: ICD-10 Disease Group N80 (Endometriosis), ICD 10: N93.8 (other specified abnormal uterine and vaginal bleeding), N93.9 (abnormal uterine and vaginal bleeding, unspecified), ICD 10 codes:

C50.011-C50.019

C50.111-C50.119,

C50.211-C50.219,

C50.311-C50.319,

C50.411-C50.419,

C50.511-C50.519,

C50.611-C50.619,

C50.811-C50.819,

C50.911-C50.919 (malignant neoplasm of breast), OR

ICD-10 : C61 (prostate cancer)

If found, NO PA REQUIRED. Otherwise, deny for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message "M/I Diagnosis Code"

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td>
<table>
<tr><th colspan="3">GnRH analog List D</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>nafarelin acetate</td><td>Synarel 2mg/ml nasal spray</td><td>GSN =044984</td></tr>
</table>
<table>
<tr><th colspan="3">GnRH analog List E</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>goserelin acetate</td><td>Zoladex 3.6mg implant</td><td>GSN =044962</td></tr>
</table>
<table>
<tr><th colspan="2">Approvable Diagnosis Codes</th></tr>
<tr><th>ICD 10 Codes</th><th>Description</th></tr>
<tr><td>C50.011-C50.019
C50.111-C50.119,
C50.211-C50.219,
C50.311-C50.319,
C50.411-C50.419,
C50.511-C50.519,
C50.611-C50.619,
C50.811-C50.819,
C50.911-C50.919</td><td>Malignant neoplasm of female breast</td></tr>
<tr><td>C61</td><td>Prostate cancer</td></tr>
<tr><td>Disease Group D25</td><td>Leiomyoma of uterus</td></tr>
<tr><td>E22.8
E22.9</td><td>Hyperfunction of pituitary gland</td></tr>
<tr><td>E30.1</td><td>Precocious puberty
Other</td></tr>
<tr><td>Disease Group N80</td><td>Endometriosis</td></tr>
<tr><td>N93.8</td><td>Other specified abnormal uterine and vaginal bleeding</td></tr>
<tr><td>N93.9</td><td>Abnormal uterine and vaginal bleeding, unspecified</td></tr>
</table>
*blue font indicates manufacturer obsolete
</td><td></td></tr>
<tr><td>GI Motility Auto PA

Automated PA approval satisfies L=Auto PA drug logic

*Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic</td><td>
<table>
<tr><th colspan="3">GI Motility Agents</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>Linaclotide</td><td>Linzess</td><td>HSN= 039583</td></tr>
<tr><td>Lubiprostone</td><td>Amitiza</td><td>HSN= 033451</td></tr>
<tr><td>Naloxegol</td><td>Movantik</td><td>HSN= 041686</td></tr>
<tr><td>Plecanatide</td><td>Trulance</td><td>HSN = 044054</td></tr>
<tr><th colspan="3">Lactulose List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
</table>
</td><td>Step 1: If the incoming claim is from <GI Motility Agents List> and there is no previous history of itself in the past 180 days: PROCEED TO STEP 2. If there is a previous history of itself in the past 180 days, NO PA REQUIRED.

Step 2: Look back in drug history 90 days for a fill of <Lactulose>: If found, claim pays, NO PA REQUIRED. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75), with supplemental messaging “Missing Prerequisite Drug Therapy

Note: This edit does NOT override existing age or quantity limits.</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td>
<table>
<tr><td>Lactulose</td><td>Constulose, Enulose, Generlac, Kristalose</td><td>HSN = 001396</td></tr>
</table>
</td><td>
<table>
<tr><th>Drug Name</th><th>Age Limit (Min Age)</th><th>Quantity Limitations</th></tr>
<tr><td>Amitiza</td><td>18</td><td>Maximum of 60 tablets per fill</td></tr>
<tr><td>Linzess</td><td>18</td><td>Max 1 tablet per day</td></tr>
<tr><td>Movantik</td><td>18</td><td>Max 1 tablet per day</td></tr>
<tr><td>Trulance</td><td>18</td><td>Max 1 tablet per day</td></tr>
</table>
Note:

PA approval SATISFIES L = Auto PA drug edit
Automated PA approval will NOT override R= Non-PDL edit

</td></tr>
<tr><td>Compound Claims Max Limit</td><td>Compound Claims</td><td>The maximum payable amount on compound claims with a dosage form of cream, lotion, ointment, powder, emulsion, or shampoo is $300.00</td></tr>
<tr><td>Cuvposa Automation

Automated PA approval
Satisfies L=Auto PA
drug edit

Automated PA approval
will NOT override R = Non-PDL edit</td><td>
<table>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Cuvposa (glycopyrrolate)</td><td>GSN = 066914</td></tr>
</table>
</td><td>
Step 1: If incoming claim for a drug in GSN 066914 (Cuvposa) look back in medical claims 730 days for chronic severe drooling (sialorrhea) or neurological diagnosis (see approvable ICD -9s and ICD-10s below). If found, NO PA REQUIRED; Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code”
<table>
<tr><th colspan="2">Chronic Severe Drooling (Sialorrhea) Approvable Diagnosis ICD-10 Codes</th></tr>
<tr><th>ICD-10-CM Code</th><th>Description</th></tr>
<tr><td>K 11. 1</td><td>(Hypertrophy of salivary gland)</td></tr>
<tr><td>K 11.5</td><td>(Sialothiasis)</td></tr>
<tr><td>K11.7</td><td>(Disturbances of Salivary Secretion)</td></tr>
</table>
<table>
<tr><th colspan="2">Neurologic Approvable Diagnosis ICD-10 Codes</th></tr>
<tr><th>ICD-10-CM Code</th><th>Description</th></tr>
<tr><td>G90.1</td><td>Familial dysautonomia [Riley-Day]</td></tr>
<tr><td>T74.12XA
T74.12XD
T74.12XS
T74.4XXA
T74.4XXD
T74.4XXS
T76.12XA
T76.12XD
T76.12XS</td><td>Child physical abuse, confirmed/suspected, initial encounter
Shaken infant syndrome, initial encounter</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>S09.8XXA
S09.8XXD
S09.8XXS
S09.90XD
S09.90XS</td><td>Other/unspecified injuries of the head, initial encounter</td></tr>
<tr><td>ICD 10 Disease Group: G80</td><td>Cerebral Palsy</td></tr>
<tr><td>ICD 10 Disease Group: S06</td><td>Intracranial Injury</td></tr>
<tr><td>ICD 10 Disease Group: G45, G46</td><td>Transient cerebral ischemic attacks and related syndromes
Vascular syndromes of brain in Cerebrovascular diseases</td></tr>
<tr><td>ICD 10 Disease Block: I60-I69</td><td>Cerebrovascular Disease</td></tr>
<tr><td>ICD 10 Disease Block: Q00-Q07</td><td>Congenital Malformations of the brain, spinal cord, nervous system</td></tr>
<tr><td>ICD 10 Disease Block:
F70-F79</td><td>Intellectual Disabilities</td></tr>
</table>
</td></tr>
<tr><td>Abuse Deterrent Narcotic (ADN.) & Short Acting (SA) before Long Acting (LA) Narcotic Edit</td><td>
<table>
<tr><th colspan="3"><Abuse Deterrent Narcotic (ADN) List></th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>hydrocodone bitartrate ER</td><td>Hysingla ER</td><td>GSNs = 073176, 073177, 073179, 073180, 073181, 073182, 073183</td></tr>
<tr><td>oxycodone ER</td><td>OxyContin</td><td>GSNs = 072862, 072863, 072864, 072865, 072866, 072867, 072868</td></tr>
<tr><td>oxycodone myristate</td><td>Xtampza ER</td><td>GSNs = 076031, 076032, 076033, 076034, 076035</td></tr>
</table>
</td><td>Step 1: If incoming claim is for <ADN List>
or <LA Narcotic List> look back 365 days in patient's medical history for ICD 10 Disease Block C00-C14, C15-C26, C30-39, C40-41, C43-C44, C45-C49, C50, C51-C58, C60-C63, C64-C68, C69-C72, C73-C75, C76-C80, C7A, C7B, C81-C96, D00-D09, D10-D36, D37-D48, D3A, D49, ICD-10-K31.7, K63.5, Q85.00, Q85.01, Q85.02 (cancer) or ICD10 Disease Group D56, D57, D58 (sickle cell disease) or an LTC indicator or Patient Residence 03 on the claim. If found, CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply). Otherwise, PROCEED TO STEP 2.

Step 2: If incoming claim is for <OxyContin> is Patient >/=11 and </= 17. If Yes, CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply). Otherwise, PROCEED TO STEP 3. If incoming claim is for any other product in < LA Narcotic List> or <ADN List> PROCEED TO STEP 3.

Step 3: If incoming claim is from <ADN List>, is patient >/= 18 years? If Yes, PROCEED TO STEP 7.
If incoming claim is from <LA Narcotic List> is patient >/= 18 years? If Yes, PROCEED TO STEP 4. Otherwise, DENY for Product Not Cov'd for Patient Age (60/31021), Min age 18 except OxyContin min age 11 (supplemental message)</td></tr>
</table>

Edit	Drugs			Steps
	morphine sulfate ER	Arymo ER	GSNs = 077053, 077054, 077055	**Step 4**: If incoming claim is from <LA Narcotic List> look back 60 days in patient drug history for another fill from <LA Narcotic List> or itself. If found, CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply). Otherwise, PROCEED TO STEP 5. **Step 5**: If incoming claim from <LA Narcotic List> look back 60 days in patient drug history for ≥ 14 days' supply utilized from the <SA Narcotic List>. If found, PROCEED TO STEP 6. Otherwise, DENY for PRIOR AUTHORIZATION (75/31031), Patient Must Have a Trial of at least 14 Days of an IR before an ER (supplemental message) **Step 6**: If incoming claim is from < LA Narcotic List >(Excluding generic MS Contin: GSNs: 004096, 004097, 011886, 011887, 016522 and generic drug code = 1) DENY for PRIOR AUTHORIZATION (75/31032), Patient Must Try generic MS Contin First (supplemental message). Otherwise, CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply). **Step 7**: If incoming claim from <ADN List> look back 60 days in patient drug history for another fill from <ADN List>, <LA Narcotic>, or itself. If found, CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply). Otherwise, PROCEED TO STEP 8. **Step 8**: If incoming claim is from <ADN list> look back 60 days in patient drug history for ≥ 14 days' supply utilized from the <SA Narcotic List>. If found, CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply). Otherwise, DENY for PRIOR AUTHORIZATION (75/31031), Patient Must Have a Trial of at least 14 Days of an IR before an ER (supplemental message) **Note:** This edit does **NOT** override the following existing edits: • 4 Controlled Substance limit (or 6 for recipients with a diagnosis of cancer or sickle cell disease) per rolling 27 days • Long Acting Opioid Polypharmacy logic • OxyContin AP logic. Any existing age limits, quantity limits, or Non PDL coding.
	morphine sulfate ER	Morphabond ER	GSNs = 074968, 074969, 074970, 074971	
	morphine sulfate/ naltrexone ER	Embeda	GSNs = 073302, 073303, 073304, 073305, 073306, 073307	
	*purple font indicates a non-preferred medication			
	<Long Acting (LA) Narcotic List>			
	Generic Name	**Brand Name**	**Drug Code**	
	buprenorphine	Belbuca	GSNs = 075050, 075051, 075052, 075053, 075054, 075055, 075056	
	fentanyl	Duragesic	GSNs = 015880, 015881, 015882, 015883, 059102, 073524, 073525, 073532	
	hydrocodone bitartrate ER	Zohydro	GSNs = 073621, 073622,073623, 073624, 073625, 073626	
	hydromorphone ER	Exalgo	GSNs = 066200, 069860, 069889, 069890	

Edit	Drugs			Steps
	methadone	Dolophine	GSNs = 004235, 004237, 004238, 004239, 004240, 004242, 082101	
	morphine sulfate ER tabs, caps	MS Contin/ Kadian	GSNs = 011887, 004096, 004097, 011886, 016522, 050222, 064739, 050221, 064740, 050220, 050219, 060355, 060356, 061748, 069899, 060357, 061749, 061722, 060358, 062358	
	oxycodone/ acetaminophen ER	Xartemis XR	GSN = 072134	
	oxymorphone ER	Opana ER	GSNs = 061091, 061092, 061093, 061094, 063782, 063783, 063784, 070397, 070320, 070398, 070321, 070399, 070400, 070401	
	tapentadol ER	Nucynta ER	GSNs = 067266, 067267, 067268, 067270, 067271,	

Edit	Drugs			Steps
	tramadol ER	Ultram ER/ Ryzolt/ Conzip	GSNs = 043536, 043537, 060274 , 063422, 063423, 063424, 067760, 067761, 067762, 068721	
	transdermal buprenorphine	Butrans	GSNs = 059589, 059590, 059591, 072673, 071432	

*purple font indicates a non-preferred medication

<Short Acting (SA) Narcotic List>

Generic Name	Brand Name	Drug Code
acetaminophen/ codeine	Capital/ Codeine Tylenol/ Codeine	GSNs = 004161, 004163, 004165, 004169, 045155, 070212, 070222, 070224
acetaminophen/ caffeine/ dihydrocodeine	Trezix	GSN = 073169
aspirin/caffeine/ dihydrocodeine	Synalgos-DC	GSN = 062407
benzhydrocodone/ acetaminophen	Apadaz	GSNs = 079489, 078222, 079488
carisoprodol/ aspirin/codeine	Soma Compound/ codeine	GSNs = 048518
codeine sulfate	N/A	GSNs =004185, 004186, 004187

Edit	Drugs			Steps
	codeine/ butalbital/ APAP/ caffeine	N/A	GSNs = 004149, 071253	
	codeine/ butalbital/ ASA/ caffeine	Ascomp/ Codeine Fiorinal/ Codeine	GSNs = 004120	
	fentanyl spray	Subsys	GSNs = 068412, 068413, 068414, 068415, 068416, 068756, 068757	
	fentanyl citrate	Abstral, Actiq, Fentora, Lazanda	GSNs = 022358, 022360, 041339, 041340, 041341, 041342, 061492, 061493, 061495, 061496, 061497, 064712, 064713, 064714, 064715, 064716, 064717, 065633, 066764, 076221	

Edit	Drugs			Steps
	hydrocodone/ acetaminophen	Hycet, Lorcet/HD/Plus, Lortab, Norco, Verdrocet, Vicodin/ES/HP, Xodol, Zamicet	GSNs =004201, 030623, 047430, 047431, 053582, 057726, 060338, 060533, 063727, 064261, 066836, 068600, 071384, 071385, 064753, 064754	
	hydrocodone/ ibuprofen	Ibudone, Reprexain, Vicoprofen, Xylon	GSNs = 034068, 054674, 063650, 064781	
	hydromorphone	Dilaudid	GSNs = 004110, 004112, 015190, 016156	
	levorphanol	N/A	GSNs =004228, 079449	
	meperidine	Demerol	GSNs = 004051, 004052, 004053	
	morphine sulfate	N/A	GSNs = 004087, 004089, 004090, 004091, 004092, 069602, 071396	
	oxycodone	Oxaydo, Roxicodone, Roxybond	GSNs = 004224, 004225, 013467, 015065, 024507, 045298, 046474, 046475,	

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td>068467,
069101
076361,
078532,
078533</td></tr>
<tr><td>oxycodone/
acetaminophen</td><td>Endocet,
Percocet,
Primlev, Prolate</td><td>GSNs =
004221,
004222,
013998,
048976,
048977,
060727,
060728,
060729,
082012</td></tr>
<tr><td>oxycodone/ aspirin</td><td>N/A</td><td>GSNs =
060638</td></tr>
<tr><td>oxycodone/
ibuprofen</td><td>N/A</td><td>GSNs =
058402</td></tr>
<tr><td>oxymorphone</td><td>Opana IR</td><td>GSNs =
061086,
061087</td></tr>
<tr><td>pentazocine/
naloxone</td><td>N/A</td><td>GSNs =
004292</td></tr>
<tr><td>tapentadol</td><td>Nucynta</td><td>GSNs =
065319,
065320,
065321</td></tr>
<tr><td>tramadol</td><td>Ultram, Qdolo</td><td>GSNs =
023139,
044975,
081474</td></tr>
<tr><td>tramadol/
acetaminophen</td><td>Ultracet</td><td>GSNs =
048456</td></tr>
<tr><td>tramadol/ celecoxib</td><td>Seglentis</td><td>GSN = 082830</td></tr>
</table>
*blue font indicates manufacturer obsolete
</td><td></td></tr>
<tr><td>Modafinil Automation

Automated PA approval</td><td></td><td>Step 1: If incoming claim is for <Modafinil> PROCEED TO STEP 2. If incoming claim is for <Armodafinil> <Nuvigil>, or <Provigil>, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “Patient Must try Modafinil Prior to Nuvigil/Provigil”
Step 2: If incoming claim is for Modafinil, look back 730 days in</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr>
<td>Satisfies L=Auto PA
drug edit

Automated PA approval
will NOT override R = Non-PDL edit</td>
<td>
<table>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>Armodafinil</td><td>Nuvigil</td><td>HSN = 034868</td></tr>
<tr><td>Modafinil</td><td>Provigil</td><td>HSN = 010865</td></tr>
</table>
</td>
<td>
medical claims for Narcolepsy Obstructive Sleep Apnea, Circadian Rhythm Sleep Disorder, or S hift Work Type diagnosis (see approvable ICD-10s below), If Found CLAIM PAYS. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message: “M/I Diagnosis Code”
<table>
<tr><th colspan="2">Approvable ICD 10 Codes</th></tr>
<tr><th>ICD 10 CM Code</th><th>Description</th></tr>
<tr><td>G47.411</td><td>Narcolepsy with cataplexy</td></tr>
<tr><td>G47.419</td><td>Narcolepsy without cataplexy</td></tr>
<tr><td>G47.421</td><td>Narcolepsy in conditions classified elsewhere with cataplexy</td></tr>
<tr><td>G47.429</td><td>Narcolepsy in conditions classified elsewhere without cataplexy</td></tr>
<tr><td>G47.33</td><td>Obstructive sleep apnea for adult, pediatric</td></tr>
<tr><td>G47.26</td><td>Circadian Rhythm Sleep Disorder, Shift Work Type</td></tr>
</table>
Note: This edit does NOT override existing age limits, quantity limits, or Non PDL coding.
<table>
<tr><th colspan="2">Quantity Limitations</th></tr>
<tr><td>Nuvigil (Armodafinil) 50mg</td><td>2 tablets per day</td></tr>
<tr><td>Nuvigil (Armodafinil) 150mg, 200mg, 250mg tablets</td><td>1 tablet per day</td></tr>
<tr><td>Provigil (Modafinil) 100mg</td><td>3 tablets per day</td></tr>
<tr><td>Provigil (Modafinil) 200mg</td><td>2 tablets per day</td></tr>
</table>
</td>
</tr>
<tr>
<td>Enbrel/Humira/ Xeljanz IR/ Xeljanz Solution Auto PA

Automated PA approval satisfies L=Auto PA drug logic

*Automated PA approval will NOT override R = Non-PDL edit and will not satisfy the automation logic</td>
<td>
<table>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Enbrel 25mg vial, 25mg/0.5ml Syringe
Enbrel 50m/ml Syringe & Pen Injection</td><td>HSN = 018830</td></tr>
<tr><td>Humira 10mg/0.2ml Syringe Kit
Humira 20mg/0.4ml Syringe Kit
Humira Ped Crohn 40mg/0.8ml Starter kit</td><td>HSN = 024800</td></tr>
</table>
</td>
<td>
Step 1: If incoming claim is for <GSN 070233 or 078538 (Xeljanz IR)>, PROCEED TO STEP 2. If incoming claim is for <HSN 018830 (Enbrel)>, PROCEED TO STEP 3. If incoming claim is for <GSN 081537 (Xeljanz solution)>, PROCEED TO STEP 4. If incoming claim is for <HSN 024800 (Humira)>, look back in medical claims history 730 days for a diagnosis of Ankylosing Spondylitis, Crohn’s Disease, Ulcerative Colitis, Juvenile Rheumatoid Arthritis, Hidradenitis, Psoriasis including Psoriatic Arthritis, Other Endophthalmitis, or Iridocyclitis (see approvable ICD-10s below) If found, NO PA REQUIRED; Otherwise, PROCEED TO STEP 2.
</td>
</tr>
</table>

Edit	Drugs	Steps

Humira Crohn-UC-HS 40mg/0.8ml Starter kit Humira 40mg/0.8ml Psoriasis-Uveitis Starter Kit	
Xeljanz 5mg Tablet	GSN = 070233
Xeljanz 10mg Tablet	GSN = 078538
Xeljanz 1 mg/mL Solution	GSN = 081537

ICD 10-CM Code	Description
H44.111-H44.119 H44.121-H44.129 H44.131-H44.139 H44.19	Other Endophthalmitis
ICD-10 Disease Group: H20	Iridocyclitis
ICD10 Disease Group: K50, K52	Crohn's Disease
ICD10 Disease Group: K51	Ulcerative Colitis
ICD10 Disease Group: L40	Psoriasis, including psoriatic arthritis
L73.2	Hidradenitis Suppurativa
ICD-10 Disease Group: M08	Juvenile Rheumatoid Arthritis
ICD-10 Disease Group: M45	Ankylosing Spondylitis

Step 2: If incoming claim is for <HSN 024800 (Humira)> or <GSN 070233 or 078538 (Xeljanz IR)>, look back in medical claims history 730 days for A diagnosis of Psoriatic Arthritis, Rheumatoid Arthritis, Ulcerative Colitis, Unspecified Inflammatory Polyarthropathies or Ankylosing Spondylitis (see approvable ICD-10s below). If found, NO PA REQUIRED; Otherwise, deny for PRIOR AUTHORIZATION REQUIRED (75/31008) with supplemental message ***M/I Diagnosis Code***

ICD 10-CM Code	Description
ICD10 Disease Group: K51	Ulcerative Colitis
ICD10 Disease Group: L40	Psoriasis, including psoriatic arthritis
ICD-10 Disease Group: M05 M06	Rheumatoid arthritis with or without Rheumatoid Factor

Edit	Drugs	Steps

M06.4	Inflammatory Polyarthopathy
ICD-10 Disease Group: M45	Ankylosing Spondylitis

Step 3: If incoming claim is for <HSN 018830 (Enbrel)>, look back in medical claims history 730 days for a diagnosis of Juvenile Rheumatoid Arthritis, Rheumatoid Arthritis, or Unspecified Inflammatory Polyarthropathies (see approvable ICD-10s below). If found, NO PA REQUIRED; Otherwise, deny for PRIOR AUTHORIZATION REQUIRED (75/31008) with supplemental message "M/I" Diagnosis Code.

ICD 10-CM Code	Description
ICD-10 Disease Group: M05 M06	Rheumatoid arthritis with or without Rheumatoid Factor
ICD-10 Disease Group: M08	Juvenile Rheumatoid Arthritis
M06.4	Inflammatory Polyarthopathy
ICD10 Disease Group: L40	Psoriasis, including psoriatic arthritis
ICD-10 Disease Group: M45	Ankylosing Spondylitis

Step 4: If incoming claim is for <GSN 081537 (Xeljanz solution)>, look back in medical claims history 730 days for a diagnosis of Juvenile Rheumatoid Arthritis (see approvable ICD-10s below). If found, NO PA REQUIRED; Otherwise, deny for PRIOR AUTHORIZATION REQUIRED (75/31008) with supplemental message "M/I" Diagnosis Code.

ICD 10-CM Code	Description
ICD-10 Disease Group: M08	Juvenile Rheumatoid Arthritis

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>
Note: This edit does NOT override existing age limits, quantity limits, or Non PDL coding.
<table>
<tr><th colspan="2">Quantity Limitations</th></tr>
<tr><td>Enbrel 50mg/ml Sure Click, Syringe
Enbrel 25mg Kit
Enbrel 25mg/0.5ml Syringe/Vial</td><td>7.84mls every 28 days
2 kits every 28 days
4.08mls every 28 days</td></tr>
<tr><td>Humira 10mg/0.2ml, 20mg/0.4ml Syringe Kit
Humira Ped Crohn 40mg/0.8ml Starter kit Humira Crohn-UC-HS 40mg/0.8ml Starter kit
Humira 40mg/0.8ml Psoriasis- Uveitis Starter Kit</td><td>1 Kit every 28 days</td></tr>
<tr><td>Humira 40mg/0.8ml Syringe/Pen kit</td><td>2 kits every 28 days</td></tr>
<tr><td>Xeljanz 5mg Tablet
Xeljanz 10mg Tablet</td><td>2 Tablets per day</td></tr>
<tr><td>Xeljanz solution</td><td>10mL’s per day</td></tr>
</table>
</td></tr>
<tr><td>Transderm Scop Automation

Automated PA approval
Satisfies L=Auto PA
drug edit

Automated PA approval
will NOT override
R = Non-PDL edit</td><td>
<table>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>Scopolamine</td><td>Transderm Scop</td><td>HSN = 012306</td></tr>
</table>
</td><td>
Step 1: If incoming claim is for <Transderm Scop> look back 60 days in claims history for itself. If Found, CLAIM PAYS, Otherwise, PROCEED TO STEP 2.

Step 2: Look back 365 days in medical history for diagnosis of sickle cell or cancer (see approvable ICD-10s below). If Found, CLAIM PAYS, Otherwise, PROCEED TO STEP 3
<table>
<tr><th colspan="2">Approvable ICD 10 Codes</th></tr>
<tr><th>ICD 10 CM Code</th><th>Description</th></tr>
<tr><td>D56
D57
D58</td><td>Thalassemia, Sickle Cell,
Other Hereditary hemolytic anemias</td></tr>
<tr><td>C00-C14
C15-C26
C30-C39
C40-C41
C43-C44
C45-C49
C50
C51-C58
C60-C63
C64-C68</td><td>Neoplasms</td></tr>
</table>
</td></tr>
</table>

Edit

Drugs

Antiemetic List

Generic drug name = 1 or 2
Rx Indicator = Yes

Generic Name	Brand Name	Drug Code
Aprepitant	Emend	HSN = 025058
Dimenhydrinate	N/A	HSN = 004716
Dolasetron	Anzemet	HSN = 016576
Doxylamine/ Vitamin B6	Diclegis	HSN = 001970
Dronabinol	Marinol	HSN = 001955
Fosaprepitant	Emend Vial	HSN = 035346
Granisetron	Sancuso Sustol	HSN = 035877
Granisetron HCL	N/A	HSN = 007611
Granisetron HCL/PF	N/A	HSN = 034765
Meclizine	N/A	HSN = 001975
Metoclopramide	Reglan	HSN = 002148
Nabilone	Cesamet	HSN = 001956
Netupitant/ Palonosetron HCL	Akynzeo	HSN = 041467
Ondansetron	Zofran ODT Zuplenz	HSN = 019058
Ondansetron HCL	Zofran	HSN = 006055
Ondansetron HCL in 0.9% NACL	N/A	HSN = 017785
Ondansetron HCL in D5W	N/A	HSN = 009765

Steps

C69-C72 C73-C75 C7A C7B C76-C80 C81-C96 D00-D09 D10-D36 D3A D37-D48 D49 K31.7 K63.5 Q85.00 Q85.01 Q85.02	

Step 3: Look back 90 days in medical history for diagnosis of Motion Sickness or Postoperative Nausea and Vomiting (see approvable ICD-10s below). If Found, PROCEED TO STEP 4. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message: "M/I Diagnosis Code"

Approvable ICD 10 Codes

ICD 10 CM Code	Description
K91.89	Other Postprocedural complications and disorder of digestive system
R11.2	Nausea with vomiting, unspecified
T75.3XXA	Motion Sickness: Initial Encounter
T75.3XXD	Motion Sickness: Subsequent Encounter
T75.3XXS	Motion Sickness: Sequela

Step 4: Look back 90 days in claim history for 2 medications (different chemical entities HSN's) in <Antiemetic List>. If Found, PROCEED TO STEP 5. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message: "Missing Prerequisite Drug Therapy"

Step 5: Look back 90 days in claim history for <Meclizine> If Found, CLAIM PAYS, Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message "Patient Must try Meclizine Prior to Transderm Scop"

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td>
<table>
<tr><th colspan="3">Antiemetic List Continued
Generic drug name = 1 or 2
Rx Indicator = Yes</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>Ondansetron HCL/ PF</td><td>N/A</td><td>HSN = 033598</td></tr>
<tr><td>Palonosetron HCL</td><td>Aloxi</td><td>HSN = 025512</td></tr>
<tr><td>Prochlorperazine</td><td>Compro
Compazine
Suppository</td><td>HSN = 004588</td></tr>
<tr><td>Prochloperazine Edisylate</td><td>N/A</td><td>HSN = 001628</td></tr>
<tr><td>Prochlorperazine Maleate</td><td>Compazine</td><td>HSN = 001629</td></tr>
<tr><td>Promethazine HCL</td><td>Phenadoz
Phenergan
Promethegan</td><td>HSN = 012014</td></tr>
<tr><td>Rolapitant HCL</td><td>Varubi</td><td>HSN = 042468</td></tr>
<tr><td>Trimethobenzamide HCL</td><td>Tigan</td><td>HSN = 001952</td></tr>
</table>
</td><td>Note: This edit does NOT override existing age limits, quantity limits, or Non PDL coding.
<table>
<tr><th colspan="2">Quantity Limitations</th></tr>
<tr><td>Transderm Scop 1.5mg/3day Patch</td><td>10 patches every 30 days</td></tr>
</table>
</td></tr>
<tr><td>Solaraze 3% Gel Automation
Automated PA approval Satisfies L=Auto PA drug edit
Automated PA approval will NOT override
R = Non-PDL edit</td><td>
<table>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Solaraze 3% Gel (diclofenac sodium)</td><td>GSN = 039826</td></tr>
</table>
</td><td>Step 1: If incoming claim for <Solaraze> look back in medical claims 365 days for actinic keratosis diagnosis (see approvable ICD-10s below). If found, NO PA REQUIRED; Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code”
<table>
<tr><th colspan="2">Actinic Keratosis Approvable ICD 10Codes</th></tr>
<tr><th>ICD-10-CM Code</th><th>Description</th></tr>
<tr><td>L57.0</td><td>Actinic Keratosis</td></tr>
</table>
<table>
<tr><th colspan="2">Quantity Limitations</th></tr>
<tr><td>Solaraze 3% Gel (diclofenac sodium)</td><td>200gm every 30 days</td></tr>
</table>
Note: This edit does NOT override existing age limits, quantity limits, or Non PDL coding.</td></tr>
<tr><td>Clomipramine Automation
Automated PA approval
Satisfies L=Auto PA drug edit
Automated PA approval
will NOT override</td><td>
<table>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Clomipramine</td><td>GSN = 046120
046121, 046122
(Generic only)</td></tr>
</table>
<table>
<tr><th colspan="3">SSRI List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
</table>
</td><td>Step 1: If incoming claim is for <Clomipramine Generic only> look back 180 days in patient’s drug history for <Anafranil/Clomipramine-GSNs 046120, 046121, 046122 brand or generic> If found, CLAIM PAYS, NO PA REQUIRED; Otherwise, Proceed to STEP 2.
Step 2: Look back in patient’s medical claim history 365 days for a diagnosis Obsessive Compulsive Disorder <ICD 10 listed below> If Found, PROCEED to Step 3. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code”
Step 3: Look back 30 days in patient’s drug history for claim in <SSRI List> and a day supply >/= 24. If Found, CLAIM</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td>R = Non-PDL edit</td><td>
<table>
<tr><td>Citalopram hydrobromide</td><td>Celexa</td><td>HSN = 010321</td></tr>
<tr><td>Escitalopram oxalate</td><td>Lexapro</td><td>HSN = 024022</td></tr>
<tr><td>Fluoxetine HCL</td><td>Prozac, Prozac Weekly</td><td>HSN = 001655 (excluding GSN 046216-Rapiflux) 046219, 065296 - Sarafem)</td></tr>
<tr><td>Fluvoxamine maleate CR</td><td>Luvox CR</td><td>HSN = 006338</td></tr>
<tr><td>Paroxetine/ER HCL</td><td>Paxil, Paxil CR</td><td>HSN = 007344</td></tr>
<tr><td>Paroxetine Mesylate</td><td>Pexeva</td><td>HSN = 025796 excluding GSN 071167 – Brisdelle)</td></tr>
<tr><td>Sertraline HCL</td><td>Zoloft</td><td>HSN = 006324</td></tr>
</table>
</td><td>
PAYS. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “Missing Prerequisite Drug Therapy”
<table>
<tr><th colspan="2">Approvable ICD 10 CM Codes</th></tr>
<tr><th>ICD-10-CM Code</th><th>Description</th></tr>
<tr><td>F42</td><td>Obsessive-compulsive disorder</td></tr>
<tr><td>F42.2</td><td>Mixed obsessional thoughts and acts</td></tr>
<tr><td>F42.3</td><td>Hoarding disorder</td></tr>
<tr><td>F42.4</td><td>Excoriation (skin-picking) disorder</td></tr>
<tr><td>F42.8</td><td>Other obsessive-compulsive disorder</td></tr>
<tr><td>F42.9</td><td>Obsessive-compulsive disorder, unspecified</td></tr>
</table>
Note: The meds below do not have an FDA indication for OCD or Depression thus were omitted from the automation:
<table>
<tr><th colspan="4">SSRIs</th></tr>
<tr><td>Fluoxetine</td><td>Sarafem
Rapiflux</td><td>GSN = 046216, 065296 046219</td><td>Premenstrual dysphoric disorder (PMDD)</td></tr>
<tr><td>Paroxetine mesylate</td><td>Brisdelle</td><td>GSN = 071167</td><td>Hot Flashes</td></tr>
</table>
Note: Blue font indicates product Is no longer available
</td></tr>
<tr><td>Vivitrol 380mg Sus ER Rec Automation

Automated PA approval Satisfies L=Auto PA drug edit

Automated PA approval will NOT override
R = Non-PDL edit</td><td>
<table>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Vivitrol 380mg Sus ER Rec (Naltrexone Microspheres)</td><td>HSN = 033782</td></tr>
</table>
</td><td>
Step 1: If incoming claim for <Vivitrol> look back in medical history 365 days for diagnosis of Opioid Use Disorder or Alcoholism (see approvable ICD-10s below). If found, NO PA REQUIRED; Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code”
<table>
<tr><th colspan="2">Approvable ICD 10Codes</th></tr>
<tr><th>ICD-10-Disease Group</th><th>Description</th></tr>
<tr><td>F10</td><td>Alcohol related disorders</td></tr>
<tr><td>F11</td><td>Opioid Related Disorders</td></tr>
</table>
POS Bypass Logic: The Pharmacy may enter a 3 in the PA Type Code Field (NCPDP Field # 461-EU) to bypass 75/31008 (Vivitrol AutoPA logic) if a diagnosis of Pregnancy and Opioid Related Disorder (see approvable ICD 10 codes below) is verified via phone or on the prescription.
<table>
<tr><th>ICD 10 Disease Group</th><th>Description</th></tr>
<tr><td>F11</td><td>Opioid Related Disorder</td></tr>
<tr><td>Z33
Z3A</td><td>Pregnant State Weeks of Gestation</td></tr>
</table>
Limitation: The pharmacy may enter a 3 in the PA Type Code
</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>Field (NCPDP Field # 461-EU) a maximum of 12 times per year

Note: This edit does NOT override existing age limits, quantity limits, or Non PDL coding.

<table>
<tr><th colspan="2">Quantity Limitations</th></tr>
<tr><td>Vivitrol 380 ER Injectable Suspension
(Naltrexone Microspheres)</td><td>1 (380mg) Injection every 28 days</td></tr>
</table>
</td></tr>
<tr><td>Long Acting Injectable (LAI) AutoPA

Automated PA approval satisfies L = AutoPA drug logic

*Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic

Products coded S-PDL will bypass Automated logic</td><td>
<table>
<tr><th colspan="3"><Long Acting Injectable (LAI) Antipsychotic List></th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>aripiprazole</td><td>Abilify Maintena</td><td>GSNs= 070669, 070670, 073298, 073299</td></tr>
<tr><td>aripiprazole lauroxil</td><td>Aristada ER</td><td>HSN = 042595</td></tr>
<tr><td>aripiprazole lauroxil submicr</td><td>Aristada Initio</td><td>HSN = 045050</td></tr>
<tr><td>haloperidol decanoate</td><td>Haldol Decanoate</td><td>HSN = 001660</td></tr>
<tr><td>paliperidone palmitate</td><td>Invega Sustenna, Invega Trinza,

Invega Hafyera</td><td>HSN = 036479</td></tr>
<tr><td>fluphenazine decanoate</td><td>N/A</td><td>HSN = 001624</td></tr>
<tr><td>risperidone</td><td>Perseris</td><td>GSNs = 078740, 078741</td></tr>
<tr><td>risperidone microspheres</td><td>Risperdal Consta</td><td>HSN = 025509</td></tr>
<tr><td>olanzapine pamoate</td><td>Zyprexa Relprevv*</td><td>HSN = 036716</td></tr>
</table>
</td><td>Step 1: If incoming claim is from <LAI Antipsychotic List> and Prior Auth = L-AutoPA, look back 365 days in paid claims history for <itself- products with the same HSN/GSN>. If found, claim MOVES OUT OF EDIT (Quantity Limit (QL) and Age (AG) limitations still apply). Otherwise, Proceed to Step 2.
Step 2: If incoming claim from <LAI Antipsychotic List> look back 730 days in medical claim history for a diagnosis of Schizophrenia or Schizoaffective disorder (see approvable ICD 10 codes below). If found, claim MOVES OUT OF EDIT (QL and AG limitations still apply). Otherwise, proceed to Step 3.
<table>
<tr><th colspan="2">Approvable Diagnosis Codes</th></tr>
<tr><th>ICD 10 Disease Group</th><th>Description</th></tr>
<tr><td>F20</td><td>Schizophrenia</td></tr>
<tr><td>F25</td><td>Schizoaffective Disorder</td></tr>
</table>
Step 3: If incoming claim is for <Abilify Maintena or Risperdal Consta> look back 730 days in medical claim history for diagnosis of Bipolar Disorder (see approvable ICD 10 codes below). If found, claim MOVES OUT OF EDIT (QL and AG limitations still apply). Otherwise, DENY for NCPDP 75 with supplemental messaging “M/I Diagnosis Code”.
<table>
<tr><th colspan="2">Approvable Diagnosis Codes</th></tr>
<tr><th>ICD 10 Disease Group</th><th>Description</th></tr>
<tr><td>F31</td><td>Bipolar Disorder</td></tr>
</table>
<table>
<tr><th>Drug Name</th><th>Age Limit (Min Age)</th><th>Quantity Limitation</th></tr>
<tr><td>Abilify Maintena</td><td>18</td><td>1 every 28 days</td></tr>
<tr><td>Aristada</td><td>18</td><td>441mg: 1.6mLs every 28 days</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td></td><td>662mg: 2.4mLs every 28 days
882mg: 3.2mLs every 28 days
1064mg: 3.9mLs every 60 days</td></tr>
<tr><td>Aristada Initio</td><td>18</td><td>2.4mLs every 180 days</td></tr>
<tr><td>Invega Hafyera</td><td>18</td><td>1092mg: 3.5mLs every 180 days
1560mg: 5mLs every 180 days</td></tr>
<tr><td>Invega Sustenna</td><td>18</td><td>390mg every 28 days
2 fills every 28 days</td></tr>
<tr><td>Invega Trinza</td><td>18</td><td>273mg: 0.880mLs every 84 days
410mg: 1.32mLs every 84 days
546mg: 1.75mLs every 84 days
819mg: 2.63mLs every 84 days</td></tr>
<tr><td>Perseris</td><td>18</td><td>1 every 25 days</td></tr>
<tr><td>Risperdal Consta</td><td>18</td><td>2 every 28 days</td></tr>
<tr><td>Zyprexa Relprevv</td><td>18</td><td>210mg & 300mg: 2 every 28 days
405mg: 1 every 28 days</td></tr>
</table>
</td></tr>
<tr><td>Sublocade Automation</td><td>
<table>
<tr><th colspan="3">Sublocade List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td rowspan="2">buprenorphine</td><td>Sublocade 100mg/0.5ml Soler Syringe</td><td>GSN = 078000</td></tr>
<tr><td>Sublocade 300mg/1.5ml Soler Syringe</td><td>GSN = 077999</td></tr>
</table>
</td><td>Step1: Incoming Claim for a drug in <Sublocade List> look back 30 days in recipient's paid claim history for Brand or Generic Bunavail Buccal Film, Suboxone Film/SL Tablets, Zubsolv Tab SL (HSN 024846), or Subutex SL Tablets (GSN 029312, 029313) with a Day Supply Utilized >/= 7. If found, CLAIM PAYS. Otherwise, DENY NCPDP EC 75 with supplemental messaging "M/I Prereq Drug Therapy-Minimal 7 day transmucosal buprenorphine req, Fax PA form to 877-614-1078"

Note: This edit will not override existing age limits, quantity limits, or the 4 Controlled Substance limit (6 for recipients with a diagnosis of cancer or sickle cell disease) per 30 days</td></tr>
</table>

AHCA Automated Prior Authorizations and Bypass Lists 01-2023

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td>Ambien/Edluar Automation</td><td>
<table>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug code</th></tr>
<tr><td rowspan="6">Zolpidem</td><td>Ambien 5mg Tablets</td><td>GSN = 019187</td></tr>
<tr><td>Ambien 10mg Tablets</td><td>GSN = 019188</td></tr>
<tr><td>Ambien 6.25mg CR Tablets</td><td>GSN = 059696</td></tr>
<tr><td>Ambien 12.5mg CR Tablets</td><td>GSN = 059697</td></tr>
<tr><td>Edluar 5mg SL Tablets</td><td>GSN = 065335</td></tr>
<tr><td>Edluar 10mg SL Tablets</td><td>GSN = 065334</td></tr>
</table>
</td><td>Step 1: If incoming claim <Ambien 10mg>, <Ambien CR 12.5mg>, or <Edluar 10mg> look back 30 days in recipient's paid claim history for itself. If found, CLAIM PAYS. Otherwise, PROCEED TO STEP 2.
Step 2: Look back 90 days in recipient's paid claim history for <Ambien 5mg>, <Ambien CR 6.25mg>, or <Edluar 5mg> with a Day Supply Utilized >/= 24. If found, CLAIM PAYS. Otherwise, DENY NCPDP EC 75 with supplemental messaging "Pt must have trial of lower strengths (5mg or 6.25mg) prior to higher strengths (10mg or 12.5mg), Fax PA form to 877-614-1078"

Note: This edit does NOT override any existing age limits, quantity limits, or Non PDL coding.</td></tr>
<tr><td>Overlapping Stimulant- BZP DUR edit</td><td>
<table>
<tr><th colspan="3">Stimulants-Benzodiazepine (BZP) List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td colspan="3">Stimulants</td></tr>
<tr><td>amphetamine</td><td>Adzenys XR ODT, Dyanavel XR</td><td>HSN = 043652</td></tr>
<tr><td>amphetamine sulfate</td><td>Evekeo</td><td>HSN = 002064</td></tr>
<tr><td>dexmethlyphenidate</td><td>Focalin,
Focalin XR</td><td>HSN = 022987</td></tr>
<tr><td>dextroamphetamine</td><td>Dexedrine, Procentra,
Zenzedi</td><td>HSN = 002065</td></tr>
<tr><td>dextroamphetamine/amphetamine</td><td>Adderall,
Adderall XR, Mydayis ER</td><td>HSN = 013449</td></tr>
<tr><td>lisdexamfetamine dimesylate</td><td>Vyvanse</td><td>HSN = 034486</td></tr>
<tr><td>methamphetamine</td><td>Desoxyn</td><td>HSN = 002067</td></tr>
<tr><td>methylphenidate</td><td>Daytrana, Cotempla XR ODT</td><td>HSN = 033556</td></tr>
</table>
</td><td>Step 1: If incoming claim from <Stimulant List> lookback 30 days for a fill from the <BZP List> If found, PROCEED TO STEP 2. Otherwise CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply)

Step 2: If incoming claim from <Stimulant List> look back 60 days for fill from <BZP List> and <Stimulant List>. If found, claim rejects NCPDP 76 with additional message "DD - Caution Overlapping BZP-Stimulant therapy. Review & submit appropriate DUR cd Max:2 BZP-Stimulant DD ovr/180 dys." Otherwise, DENY for PRIOR AUTHORIZATION (75), with additional message "PA Req'd. Overlapping BZP-Stimulant therapy: Fax PA 877-614-1078"

Limitation:
Allow 2 pharmacy level overrides in 180 days for claims that deny out of the Stimulant-BZP AutoPA. Pharmacy must submit DUR Reason for Service Code: DD-Drug to Drug Interaction for pharmacy level override. Deny the third, and subsequent attempts of a pharmacy level overrides (within a rolling 180 days) NCPDP 75 PA required with additional message "PA Req'd.Max:2 BZP-Stimulant DD ovr/180 dys. Fax PA 877-614-1078"</td></tr>
</table>

Edit	Drugs			Steps
	methylphenidate HCL	Adhansia XR, Aptensio XR, Concerta, Jornay PM, Metadate CD, Metadate ER, Methylin, Methylphenidate LA, Quillichew, Quillivant, Relexxii ER, Ritalin, Ritalin LA, Ritalin SR	HSN = 001682	
	Serdexmethylphenidate / dexmethylphenidate	Azstarys	HSN = 047187	
	Benzodiazepines			
	alprazolam	Xanax, Xanax XR	HSN = 001617	
	chlordiazepoxide	Librium, Poxi	HSN = 001610	
	chlordiazepoxide/ amitriptyline	Limbitrol	HSN = 001656	
	chlordiazepoxide/ clidinium	Librax	HSN = 002037	
	clonazepam	Klonopin, Cerberclon	HSN = 001894	
	clobazam	Onfi, Sympazan	HSN = 006536	
	clorazepate	Tranxene, Gen-Xene	HSN = 001612	
	diazepam	Valium	GSNs = 003761, 003762, 003763, 003764, 003765, 003766, 003767, 003768, 034017, 034018, 034019, 068715, 078712, 079289	
	estazolam	Prosom	HSN = 006036	
	flurazepam	Dalmane	HSN = 001593	
	lorazepam	Ativan, Loreev XR	HSN = 004846	

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td>
<table>
<tr><td>midazolam</td><td>n/a</td><td>HSN = 001619</td></tr>
<tr><td>oxazepam</td><td>Serax</td><td>HSN = 001616</td></tr>
<tr><td>Quazepam</td><td>Doral</td><td>HSN = 001595</td></tr>
<tr><td>temazepam</td><td>Restoril</td><td>HSN = 001592</td></tr>
<tr><td>triazolam</td><td>Halcion</td><td>HSN = 001594</td></tr>
</table>
</td><td></td></tr>
<tr><td>Benzodiazepine (BZP) – LA Opioid DUR Edit</td><td>
<table>
<tr><th colspan="3"><Benzodiazepine (BZP) ></th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>alprazolam</td><td>Xanax, Xanax XR</td><td>HSN = 001617</td></tr>
<tr><td>chlordiazepoxide</td><td>Librium, Poxi</td><td>HSN = 001610</td></tr>
<tr><td>chlordiazepoxide / amitriptyline</td><td>Limbitrol</td><td>HSN = 001656</td></tr>
<tr><td>chlordiazepoxide / clidinium</td><td>Librax</td><td>HSN = 002037</td></tr>
<tr><td>clonazepam</td><td>Klonopin, Cerberclon</td><td>HSN = 001894</td></tr>
<tr><td>clobazam</td><td>Onfi, Sympazan</td><td>HSN = 006536</td></tr>
<tr><td>clorazepate</td><td>Tranxene, Gen-Xene</td><td>HSN = 001612</td></tr>
<tr><td>diazepam</td><td>Valium</td><td>GSNs = 003761, 003762, 003763, 003764, 003765, 003766, 003767, 003768, 034017, 034018, 034019, 068715, 078712, 079289</td></tr>
<tr><td>estazolam</td><td>Prosom</td><td>HSN = 006036</td></tr>
<tr><td>flurazepam</td><td>Dalmane</td><td>HSN = 001593</td></tr>
<tr><td>lorazepam</td><td>Ativan, Loreev XR</td><td>HSN = 004846</td></tr>
<tr><td>midazolam</td><td>n/a</td><td>HSN = 001619</td></tr>
<tr><td>oxazepam</td><td>Serax</td><td>HSN = 001616</td></tr>
<tr><td>quazepam</td><td>Doral</td><td>HSN = 001595</td></tr>
<tr><td>temazepam</td><td>Restoril</td><td>HSN = 001592</td></tr>
<tr><td>triazolam</td><td>Halcion</td><td>HSN = 001594</td></tr>
<tr><th colspan="3"><Long Acting Opioid Lists></th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>buprenorphine</td><td>Belbuca, Butrans</td><td rowspan="2">GSNs = 075050, 075051, 075052, 075053, 075054, 075055, 075056, 059589, 059590,</td></tr>
<tr><td></td><td></td></tr>
</table>
</td><td>Step 1: If incoming claim from <BZP List> lookback 30 days for a fill from the <LA Opioid List>. If found, PROCEED TO STEP 2. Otherwise CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply)

Step 2: If incoming claim from <BZP List> look back 60 days for fill from the <BZP List>. If found, claim rejects NCPDP 76 with additional message "DD – Toxicity Warning-Overlapping BZP-LA Opioid therapy. Review & submit DUR cd; Max:2 BZP DD ovr/180 dys." Otherwise, DENY for PRIOR AUTHORIZATION (75), with additional message "PA Req'd. Overlapping BZP-LA Opioid therapy: Fax PA 877-614-1078".

Limitation:
Allow 2 pharmacy level overrides in 180 days for claims that deny out of the BZP-LA Opioid Edit for NCPDP 76. Pharmacy must submit DUR Reason for Service Code: DD-Drug to Drug Interaction for pharmacy level override. Deny the third, and subsequent attempts of pharmacy level overrides (within a rolling 180 days) NCPDP 75 PA required with additional message "PA Req'd.Max:2 BZP-LA Opioid DD ovr/180 dys. Fax PA 877-614-1078"

**** Excluding recipients with LTC indicator or Patient Residence 03 on the claim and those with the following approvable cancer, sickle cell, or seizure diagnosis in claims history within 730 days:

The provider will be able to override the 1st -two denials, for non-treatment naïve recipients.

<table>
<tr><th colspan="2">Approvable Seizure Diagnosis ICD-10 Codes</th></tr>
<tr><th>ICD-10-CM Code</th><th>Description</th></tr>
<tr><td>ICD 10 Disease Block C00-C14, C15-C26, C30-39, C40-41, C43-C44, C45-C49, C50, C51-C58, C60-C63, C64-C68, C69-C72, C73-C75, C76-C80, C7A, C7B, C81-C96, D00-D09, D10-</td><td>Cancer</td></tr>
</table>
</td></tr>
</table>

Edit	Drugs			Steps	
			059591, 072673, 071432	D36, D37-D48, D3A, D49, ICD-10-K31.7, K63.5, Q85.00, Q85.01, Q85.02	
	fentanyl	Duragesic	GSNs = 015880, 015881, 015882, 015883, 059102, 073524, 073525, 073532	ICD 10 Disease Group: D56, D57, D58	Sickle Cell
				ICD 10: G25.3	Myoclonus
	hydrocodone bitartrate ER	Hysingla ER, Zohydro	GSNs = 073176, 073177, 073179, 073180, 073181, 073182, 073183, 073621,073622,073623, 073624, 073625, 073626, 071602, 071603, 071604, 071605, 071606, 071607	ICD 10 Disease Group: G80	Cerebral Palsy
				ICD 10 Disease Group: G40	Epilepsy
				ICD 10 Disease Group: G45, G46	Transient cerebral ischemic attacks and related syndromes Vascular syndromes of brain in cerebrovascular diseases
	hydromorphone ER	Exalgo	GSNs = 066200, 069860, 069889, 069890	ICD 10 Disease Block: I60-I69	Cerebrovascular Disease
	methadone	Dolophine, Methadose	GSNs = 004235, 004237, 004238, 004239, 004240, 004242, 082101	ICD 10: G90.1	Familial dysautonomia [Riley –Day]
	morphine sulfate ER	Arymo ER, Morphabond ER, MS Contin, Kadian ER	GSNs= 077053, 077054, 077055, 074968,074969, 074970, 074971, 011887, 004096, 004097, 011886, 016522, 050222, 064739, 050221, 064740, 050220, 050219, 060355, 060356, 061748, 069899, 060357, 061749, 061722, 060358, 062358	ICD 10 Disease Block: Q00-Q07	Congenital Malformations of the brain, spinal cord, nervous system
				ICD 10 Disease Group: R56	Convulsions not elsewhere classified
				ICD 10 Disease Group: S06	Intracranial Injury
	morphine sulfate/ naltrexone ER	Embeda	GSNs = 073302, 073303, 073304, 073305, 073306, 073307	ICD 10: T74.12XA T74.12XD T74.12XS T74.4XXA T74.4XXD T74.4XXS T76.12XA T76.12XD T76.12XS	Child physical abuse, confirmed/suspected, initial encounter Shaken infant syndrome, initial encounter
	oxycodone ER	OxyContin	GSNs = 072862, 072863, 072864, 072865, 072866, 072867, 072868		
	oxycodone/acetaminophen ER	Xartemis ER	GSN = 072134		
	oxycodone myristate	Xtampza ER	GSNs = 076031, 076032, 076033, 076034, 076035		
	oxymorphone ER	Opana ER	GSNs = 061091, 061092, 061093, 061094, 063782, 063783, 063784, 070320, 070321, 070397, 070398, 070399, 070400, 070401		

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td>
<table>
<tr><td>tapentadol ER</td><td>Nucynta ER</td><td>GSNs = 067266, 067267, 067268, 067270, 067271</td></tr>
<tr><td>tramadol ER</td><td>Conzip, Ryzolt, Ultram ER</td><td>GSNs = 043536, 043537, 060274, 063422, 063423, 063424, 067760, 067761, 067762, 068721</td></tr>
</table>
</td><td></td></tr>
<tr><td>Austedo-Tetrabenazine Automation

Automated PA approval satisfies L=Auto PA drug edit

Automated PA approval will NOT override R=Non-PDL edit</td><td>
<table>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Austedo (Deutetrabenazine)</td><td>HSN = 044192</td></tr>
<tr><td>Ingrezza</td><td>HSN = 044202 (excluding Ingrezza Initiation Pack)</td></tr>
<tr><td>Tetrabenazine</td><td>HSN = 007350 (excluding Xenazine)</td></tr>
</table>
</td><td>Step 1: If incoming claim is for <Austedo> look back 730 days in medical claim history for ICD-10 in Disease Group G10 (Huntington's Disease), G24 (Dystonia), G25 (other extrapyramidal and movement disorders) or G26 (extrapyramidal and movement disorders in diseases classified elsewhere). If found, claim MOVES OUT OF EDIT (QL and AG limitations still apply). Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message "M/I Diagnosis Code"

If incoming claim is for <Ingrezza> look back 730 days in medical claim history for ICD-10 in Disease Group G24 (Dystonia), G25 (other extrapyramidal and movement disorders) or G26 (extrapyramidal and movement disorders in diseases classified elsewhere). If found, claim MOVES OUT OF EDIT (QL and AG limitations still apply). Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message "M/I Diagnosis Code"

If incoming claim is for <Tetrabenazine> look back 730 days in medical claim history for ICD-10 in Disease Group G10 (Huntington's Disease). If found, claim MOVES OUT OF EDIT (QL and AG limitations still apply). Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message "M/I Diagnosis Code"

Note: This edit does NOT override existing age limits, quantity limits, or Non PDL coding.
<table>
<tr><th>Drug Name</th><th>Age Limit (Min Age)</th><th>Quantity Limitations</th></tr>
<tr><td>Austedo (Deutetrabenazine)</td><td>18</td><td>Maximum of 48mg per day
For 6 mg tablets:
Maximum of 2 tablets per day
For 9 mg & 12 mg tablets:
Maximum of 4 tablets per day</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Tetrabenazine</td><td>18</td><td>Maximum of 100mg per day
For 12.5 mg tablets:
Maximum of 3 tablets per day
For 25mg tablets:
Maximum of 4 tablets per day</td></tr>
</table>
</td></tr>
<tr><td>Asthma- Inhaled Corticosteroid</td><td>
<table>
<tr><th colspan="3">Inhaled Corticosteroid List (ICS)</th></tr>
<tr><th colspan="3">Single Agent-Inhaled Corticosteroid</th></tr>
<tr><th>Generic</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>beclomethasone dipropionate</td><td>Qvar/RediHaler</td><td>GSNs = 046698, 046699, 077643, 077644</td></tr>
<tr><td>budesonide</td><td>Pulmicort Flexhaler/Respules</td><td>GSNs = 062240, 062241, 018165, 022232, 046525, 046526</td></tr>
<tr><td>ciclesonide</td><td>Alvesco</td><td>GSNs = 058671, 058672</td></tr>
<tr><td>flunisolide</td><td>Aerospan</td><td>GSNs = 071756</td></tr>
<tr><td>fluticasone furoate</td><td>Arnuity Ellipta</td><td>GSNs = 072722, 072723, 078449</td></tr>
<tr><td>fluticasone propionate</td><td>ArmonAir RespiClick, Flovent HFA/Diskus</td><td>GSNs = 077089, 077090, 077091, 019319, 019318, 019317, 021251, 021253, 021483</td></tr>
<tr><td>mometasone furoate</td><td>Asmanex HFA/Twisthaler</td><td>GSNs = 051649, 059326, 059327,</td></tr>
</table>
</td><td>Step 1: If incoming claim is for a drug in <Inhaled Corticosteroid List> look back 730 days in recipient's medical claims history for diagnosis of Asthma (ICD 10 Disease group J45). If found PROCEED TO STEP 2. Otherwise, CLAIM MOVES OUT OF EDIT (other clinical edits for products apply).

Step 2: Is patient < 12 years of age? If so, proceed to step 3. Otherwise, CLAIM MOVES OUT OF EDIT (other clinical edits for products apply).

Step 3: Look back 180 days in recipient's paid claim history for a fill from <SABA- Rescue Therapy List>. If found, CLAIM PAYS. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message "M/I PreReq Therapy: SABA Req'd prior to/concomitantly with ICS Therapy, Review & submit appropriate DUR cd"

Note: The provider may override the denial utilizing only the approved intervention/professional service codes, outcome/result of service codes

Note: This edit will not override existing age limits, quantity limits, or Non PDL edit</td></tr>
</table>

Edit	Drugs			Steps
			059328, 064010, 064012, 073197, 073198, 080669	
	Combination Agents- Inhaled Corticosteroid			
	Generic	Brand Name	Drug Code	
	budesonide/ formoterol	Symbicort	HSN = 021993	
	fluticasone furoate/ vilanterol	Breo Ellipta	HSN = 040319	
	fluticasone propionate/ salmeterol	Advair HFA/Diskus, Wixela Inhub, AirDuo RespiClick/Digihaler	HSN = 019963	
	mometasone/ formoterol	Dulera	HSN = 037050	
	budesonide/glycopyrolate/formoterol	Breztri Aerosphere	HSN = 046753	
	Rescue Therapy List			
	Short Acting Beta Agonist (SABA)			
	Generic	Brand Name	Drug Code	
	albuterol	AccuNeb, ProAir HFA/RespiClick/Digihaler, Proventil HFA, Ventolin HFA	HSN = 002073	
	levalbuterol HCl	Xopenex	HSN = 019858	
	levalbuterol tartrate	Xopenex HFA	HSN = 032814	
	metaproterenol	Alupent	HSN = 002058	

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td>
<table>
<tr><td>terbutaline</td><td>Brethine</td><td>HSN = 002071</td></tr>
</table>

Blue font = manufacturer obsolete products
</td><td></td></tr>
<tr><td>Overlapping TNF Inhibitors-Related Agents DUR Edit</td><td>
<table>
<tr><th colspan="4">Tumor Necrosis Factor Inhibitors (TNFi) List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th colspan="2">HSN Drug Codes</th></tr>
<tr><td>adalimunab</td><td>Humira/ Pediatric Crohn's/ Crohn’s-UC-HS Starter/ Psoriasis-Uveitis</td><td>HSN = 024800</td><td rowspan="8">HIC3 = S2J</td></tr>
<tr><td>certolizumab pegol</td><td>Cimzia</td><td>HSN = 035554</td></tr>
<tr><td>etanercept</td><td>Enbrel/Mini/ Sureclick</td><td>HSN = 018830</td></tr>
<tr><td>golimunab</td><td>Simponi/ Aria</td><td>HSN = 036278</td></tr>
<tr><td>infliximab</td><td>Remicade</td><td>HSN = 018747</td></tr>
<tr><td>infliximab-abda</td><td>Renflexis</td><td>HSN = 044432</td></tr>
<tr><td>Infliximab-dyyb</td><td>Inflectra</td><td>HSN = 043249</td></tr>
</table>
</td><td>Step 1: If incoming claim from <TNFi List> PROCEED to STEP 3.

If incoming claim from <Non-Biologics List> PROCEED to STEP 2.

If incoming claim from < Non-TNFi Biologics List> look back 60 days for fill from <TNFi List> or <Non-Biologics List>. If found, claim rejects NCPDP 75 with additional message “DD- Caution Overlapping TNFi, Non-TNFi Biologics, or Non-Biologics (Otezla, Olumiant, Xeljanz/XR, Rinvoq ER) Therapy. PA Req’d”: Fax PA to 877-614-1078”. Otherwise, CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply).

Step 2: If incoming claim from <Non-Biologics List> look back 60 days for fill from <TNFi List> or <Non TNFi Biologics List>. If found, claim rejects NCPDP 75 with additional message “DD- Caution Overlapping TNFi, Non-TNFi Biologics, or Non-Biologics (Otezla, Olumiant, Xeljanz/XR, Rinvoq ER) Therapy. PA Req’d”: Fax PA to 877-614-1078”. Otherwise, CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply).

Step 3: If incoming claim from <TNFi List (HIC3)> look back 60 days for fill from < Non-TNFi Biologics List> or <Non-Biologics List>. If found, claim rejects NCPDP 75 with additional message “DD- Caution Overlapping TNFi, Non-TNFi Biologics,</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td>
<table>
<tr><th colspan="3">Non TNFi Biologic List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Codes</th></tr>
<tr><td>abatacept</td><td>Orencia</td><td>HIC3 = S2Q</td></tr>
<tr><td>anakinra</td><td>Kineret</td><td rowspan="2">HIC3 = S2M</td></tr>
<tr><td>rilonacept</td><td>Arcalyst</td></tr>
<tr><td>brodalumab</td><td>Siliq</td><td>HSN = 044102</td></tr>
<tr><td>canakinumab</td><td>Ilaris</td><td>HIC3 = S2V</td></tr>
<tr><td>guselkumab</td><td>Tremfya</td><td>HSN = 044418</td></tr>
<tr><td>ixekizumab</td><td>Taltz</td><td>HSN = 043193</td></tr>
<tr><td>risankizumab-rzaa</td><td>Skyrizi</td><td>HSN = 045699</td></tr>
<tr><td>rituximab</td><td>Rituxan</td><td>HSN = 016848</td></tr>
<tr><td>sarilumab</td><td>Kevzara</td><td rowspan="2">HIC3 = Z2V</td></tr>
<tr><td>tocilizumab</td><td>Actemra</td></tr>
<tr><td>secukinumab</td><td>Cosentyx</td><td>HSN = 041715</td></tr>
<tr><td>tildrakizumab-asmn</td><td>Ilumya</td><td>HSN =044823</td></tr>
<tr><td>ustekinumab</td><td>Stelara</td><td>HIC3 = Z2U</td></tr>
<tr><td>vedolizumab</td><td>Entyvio</td><td>HIC3 = D6K</td></tr>
</table>
<table>
<tr><th colspan="3">Non-Biologics List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Codes</th></tr>
<tr><td>apremilast</td><td>Otezla</td><td>HIC3 = S2Z</td></tr>
<tr><td>baricitinib</td><td>Olumiant</td><td rowspan="3">HIC3 = Z2Z</td></tr>
<tr><td>tofacitinib</td><td>Xeljanz/XR</td></tr>
<tr><td>upadacitinib</td><td>Rinvoq ER</td></tr>
</table>
</td><td>or Non-Biologics (Otezla, Olumiant, Xeljanz/XR, Rinvoq ER) Therapy. PA Req'd": Fax PA to 877-614-1078". Otherwise, PROCEED to STEP 4.

Step 4: If incoming claim is from <TNFi List (HSN)> look back 60 days in patient drug history for another fill from < TNFi List (HSN)> excluding itself. If found claim rejects NCPDP 75 with additional message "TD- Caution Overlapping TNFi Therapy. PA Req'd": Fax PA to 877-614-1078". Otherwise, CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply).

Note: This edit does NOT override existing age limits, quantity limits, or Non PDL edit</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr>
<td>Overlapping Dipeptidyl-Peptidase IV Inhibitor (DPP-4) and Glucagon-Like Peptide 1 Agonist (GLP-1) DUR edit</td>
<td>
<table>
<tr><th colspan="3">Dipeptidyl-Peptidase IV Inhibitor List (DPP-4)</th></tr>
<tr><th colspan="3">Single Agent: DPP-4 Inhibitors</th></tr>
<tr><th>HIC3</th><th>Drug Name</th><th>HSN</th></tr>
<tr><td>C4J</td><td>Januvia
Nesina
Onglyza
Tradjenta</td><td>034126
039968
036471
037576</td></tr>
<tr><th colspan="3">Combination Agents: DPP-4 Inhibitors</th></tr>
<tr><th>HIC3</th><th>Drug Name</th><th>HSN</th></tr>
<tr><td>C4A</td><td>Juvisync</td><td>038054</td></tr>
<tr><td>C4C</td><td>Oseni</td><td>039967</td></tr>
<tr><td>C4F</td><td>Janumet/XR
Jentadueto/XR
Kazano
Kombiglyze XR</td><td>034665
038464
039970
037246</td></tr>
<tr><td>C4W</td><td>Glyxambi
Qtern
Steglujan</td><td>041724
043957
044706</td></tr>
</table>
<table>
<tr><th colspan="3">Glucagon-Like Peptide 1 Agonist (GLP-1)</th></tr>
<tr><th colspan="3">Single Agent: GLP-1 Agonist</th></tr>
<tr><th>HIC3</th><th>Drug Name</th><th>HSN</th></tr>
<tr><td>C4I</td><td>Adlyxin
Bydureon
Byetta
Ozempic
Tanzeum
Trulicity
Victoza</td><td>040782
038451
032893
044675
041163
041421
036436
(Excluding: GSNs 073258-Saxenda)</td></tr>
<tr><th colspan="3">Combination Agents: GLP-1 Agonist</th></tr>
<tr><td>C4X</td><td>Soliqua
Xultophy</td><td>043944
041880</td></tr>
</table>
</td>
<td>
Step 1: If incoming claim from <DPP-4 Inhibitor List (HIC3)> PROCEED to STEP 2.

If incoming claim from <GLP-1 Receptor Agonist List (HIC3)> look back 90 days for fill from <DPP-4 Inhibitor List (HIC3)>. If found, claim rejects NCPDP 76 with additional message “DD- Caution Overlapping DPP-4 Inhibitor & GLP-1 Receptor Agonist Therapy. Review & submit appropriate DUR cd.” If not found, PROCEED to STEP #3.

Step 2: If incoming claim from <DPP-4 Inhibitor List (HIC3)> look back 90 days for fill from <GLP-1 Receptor Agonist List (HIC3)>. If found, claim rejects NCPDP 76 with additional message “DD- Caution Overlapping DPP-4 Inhibitor & GLP-1 Receptor Agonist Therapy. Review & submit appropriate DUR cd”. If not found, PROCEED to STEP 4.

Step 3: If incoming claim from <GLP-1 Receptor Agonist List (HSN)> look back 90 days for fill from <GLP-1 Receptor Agonist List (HSN)>, excluding itself. If found, claim rejects NCPDP 76 with additional message “TD of GLP-1 Receptor Agonist Therapy. Review & submit appropriate DUR cd.” Otherwise, CLAIM PAYS.

Step 4: If incoming claim from <DPP-4 Inhibitor List (HSN)> look back 90 days for fill from <DPP-4 Inhibitor List (HSN)>, excluding itself. If found, claim rejects NCPDP 76 with additional message “TD of DPP-4 Inhibitor Therapy. Review & submit appropriate DUR cd.” Otherwise, CLAIM PAYS

Limitation:
Allow 1 pharmacy level override in 90 days for claims that deny out of the DPP-4/GLP-1 automation logic. Pharmacy must submit DUR Reason for Service Code for pharmacy level override. Deny the second, and subsequent attempts of a pharmacy level override, within a rolling 90-day period, for NCPDP 75 PA required with additional message “PA Req’d. Max: 1 DPP-4/GLP-1 TD override/90 days. Fax PA to 877-614-1078”

Note: This edit does NOT override existing age limits, quantity limits, or Non PDL edit
</td>
</tr>
<tr>
<td>Short Acting Narcotic Max Day Supply Edit</td>
<td>
<table>
<tr><th colspan="3"><Short Acting (SA) Narcotic List></th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>acetaminophen/ codeine</td><td>Capital/ Codeine Tylenol/</td><td>GSNs = 004161, 004163, 004165, 004169, 045155,</td></tr>
</table>
</td>
<td>
Limitation:
Allow a maximum day supply = 3 for products in the SA Narcotic List with a DEA code = 2

Limitation:
Allow a maximum of two -3 day supplies per 30 days. Please reject the 3rd request for a 3-day supply within 30-day period for NCPDP 76 with supplemental messaging “Schedule II SA Narcotic – Acute Therapy - Max of 6 days of therapy per month”
</td>
</tr>
</table>

Edit	Drugs			Steps
		Codeine	070212, 070222, 070224	**Limitation**: Allow a maximum day supply = 7 for products in the SA Narcotic list with a DEA code = 2 with a PA Type Code Field NCPDP Field code # 461-EU) = 5 entered on the incoming claim **Limitation**: Allow a maximum of two -7 day supplies per 30 days. Please reject the 3rd request for a 7-day supply within 30 days period for NCPDP 76 with supplemental messaging "Schedule II SA Narcotic - ACUTE PAIN EXEMPTION- Max of 14 days of therapy per month" **Limitation (CIII-CV):** Allow a maximum of 14 days supply every 30 days. Please reject claims that exceed 14 days supply every 30 days for NCPDP EC 76 – Plan limitation exceeded with additional message "Schedule III-V SA Narcotic- Acute therapy- Max of 14 days supply of therapy per month" **Limitation**: Allow a maximum of two -3 day supplies per 30 days. Please reject the 3rd request for a 3-day supply within 30-day period for NCPDP 76 with supplemental messaging "*Schedule II SA Narcotic– Acute Therapy-Max of 6 days of therapy per month*" **Limitation**: Allow a maximum of two -7 day supplies per 30 days. Please reject the 3rd request for a 7-day supply within 30 days period for NCPDP 76 with supplemental messaging "*Schedule II SA Narcotic - ACUTE PAIN EXEMPTION- Max of 14 days of therapy per month*" Please exclude recipients with LTC indicator or Patient Residence 03 on the claim OR a diagnosis of ICD 10 Disease Block C00-C14, C15-C26, C30-39, C40-41, C43-C44, C45-C49, C50, C51-C58, C60-C63, C64-C68, C69-C72, C73-C75, C76-C80, C7A, C7B, C81-C96, D00-D09, D10-D36, D37-D48, D3A, D49, ICD-10-K31.7, K63.5, Q85.00, Q85.01, Q85.02 (cancer) or ICD10 Disease Group D56, D57, D58 (sickle cell disease) or ICD 10 D55.0, D55.1, D55.2, D55.3, D55.8, D55.9, G11.0, G11.2, G11.3, G11.8, G12.0, G12.9, G12.1,G12.8, G12.21, G95.0, G95.19, G95.11, G32.0, G99.2, G95.89, G95.81, G95.9, G95.29, G95.20, G90.50, G90.519, G90.511, G90.512, G90.513 , G90.521, G90.522, G90.523, G90.529, G90.59 ,G35, G36.0, G37.0, G37.5, G73.3, G37.3, G37.1, G37.2, G37.8, G36.1, G36.8, G37.9,G36.9, G82.50, G82.20, G04.1, G82.21, G82.22, G83.0, G83.10, G83.20, G83.30,G83.31, G83.32, G83.33, G83.34, G83.4, (G83.5), G83.81, G83.82, G83.83, G83.84, G83.89, G83.9, G54.6, G54.7, G60.0, G60.2 G61.0, G63, M47.12, M47.011, M47.012, M47.013, M47.014, M47.015, M47.016, M47.019, M47.021, M47.022, M47.029, M47.11, M47.13 , M47.14, M47.15 ,M47.16, M48.20, M48.21, M48.22, M48.23, M48.24, M48.25, M48.26, M48.27, M48.10, M48.11, M48.12, M48.13, M48.14, M48.15, M48.16, M48.17, M48.18, M48.19, M48.9, M25.78, M47.10, M50.20, M50.21, M50.22, M50.23, M51.26, M51.27, M51.24, M51.25, M51.9, M51.34, M51.35, M51.36, M51.37, M50.00, M50.01, M50.02, M50.03, M51.04, M51.05 ,M51.06, M96.1, M46.40, M46.48, M46.49, M50.80, M50.90, M46.41, M46.42, M46.43, M50.81, M50.82, M50.83, M50.91,
	acetaminophen/ caffeine/ dihydrocodeine	Trezix	GSN = 073169	
	aspirin/caffeine/ dihydrocodeine	Synalgos-DC	GSN = 062407	
	benzhydrocodone/ acetaminophen	Apadaz	GSNs = 079489, 078222, 079488	
	carisoprodol/ aspirin/codeine	Soma Compound/ codeine	GSNs = 048518	
	codeine sulfate	N/A	GSNs =004185, 004186, 004187	
	codeine/ butalbital/ ASA/ caffeine	Ascomp/ Codeine Fiorinal/ Codeine	GSNs = 004120	
	fentanyl spray	Subsys	GSNs = 068412, 068413, 068414, 068415, 068416, 068756, 068757	
	fentanyl citrate	Abstral, Actiq, Fentora, Lazanda	GSNs = 022358, 022360, 041339, 041340, 041341, 041342, 061492, 061493, 061495, 061496, 061497, 064712, 064713, 064714, 064715, 064716, 064717, 065633, 066764, 076221	
	hydrocodone/ acetaminophen	Hycet, Lorcet/HD/Plus, Lortab, Norco, Verdrocet, Vicodin/ES/HP, Xodol, Zamicet	GSNs =004201, 030623, 047430, 047431, 053582, 057726, 060338, 060533, 063727, 064261, 066836, 068600, 071384, 071385, 064753, 064754	
	hydrocodone/ ibuprofen	Ibudone, Reprexain, Vicoprofen,	GSNs = 034068, 054674, 063650, 064781	

Edit	Drugs			Steps
		Xylon		M50.92, M50.93, M46.45, M51.84, M51.85, M46.44, M46.47, M51.86, M51.87, M46.46, M48.02, M48.01, M48.03, M99.20, M99.21, M99.30, M99.31, M99.40, M99.41, M99.50, M99.51, M99.60, M99.61, M99.70, M99.71, M54.12, M54.13, M50.10, M50.11, M50.12, M50.13, M54.11, M54.02, M54.00, M54.01, M67.88, M48.00, M48.04, M48.05, M99.22, M99.32, M99.42, M99.52, M99.62, M99.72, M48.06, M99.43, M99.53, M99.63, M99.73, M48.07, M99.23, M99.33, M48.08, M99.34, M99.35, M99.36, M99.37, M99.38, M99.39, M99.44, M99.45, M99.46, M99.47, M99.48, M99.49, M99.55, M99.56, M99.57, M99.58, M99.59, M99.64, M99.65, M99.66, M99.67, M99.68, M99.69, M99.74, M99.75, M99.76, M99.77, M99.78, M99.79, M99.24, M99.25, M99.26, M99.27, M99.28, M99.29, M54.14, M54.15, M54.16, M54.17, M51.14, M51.15, M51.16, M51.17, M89.00, M89.011, M89.012, M89.019, M89.021, M89.022, M89.029, M89.031, M89.032, M89.039, M89.041, M89.042, M89.049, M89.051, M89.052, M89.059, M89.061, M89.062, M89.069, M89.071, M89.072, M89.079, M89.08, M89.09 (CNMP) in medical claims history within 365 days from the DOS of incoming claim.
	hydromorphone	Dilaudid	GSNs = 004110, 004112, 015190, 016156	
	levorphanol	N/A	GSNs =004228, 079449	
	meperidine	Demerol, Meperitab	GSNs = 004051, 004052, 004053	
	morphine sulfate	N/A	GSNs = 004087, 004089, 004090, 004091, 004092, 069602, 071396, 004086, 004085, 004084, 004083	
	oxycodone	Oxaydo, Roxicodone	GSNs = 004224, 004225, 013467, 015065, 024507, 045298, 046474, 046475, 068467, 069101, 076361, 078532, 078533	
	oxycodone/ acetaminophen	Endocet, Percocet, Primlev, Prolate	GSNs = 004221, 004222, 013998, 048976, 048977, 060727, 060728, 060729	
	oxycodone/ aspirin	N/A	GSNs = 060638	
	oxycodone/ ibuprofen	N/A	GSNs = 058402	
	oxymorphone	Opana IR	GSNs = 061086, 061087	
	pentazocine/ naloxone	N/A	GSNs = 004292	
	tapentadol	Nucynta	GSNs = 065319, 065320, 065321	
	tramadol	Ultram, Qdolo	GSNs = 023139, 044975, 081474	
	tramadol/ acetaminophen	Ultracet	GSNs = 048456	
	tramadol/ celecoxib	Seglentis	GSN = 082830	

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr>
<td>Doxepin 5% cream AutoPA

Automated PA approval satisfies L = AutoPA drug logic

*Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic</td>
<td>
<table>
<tr><th>Drug Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>Doxepin 5% Cream</td><td>Zonalon</td><td>GSN = 021715

Excluding Prudoxin (NDCs:

00064360045

00378813045

40076051145)</td></tr>
</table>

Blue font = manufacturer obsolete
</td>
<td>
Step 1: If incoming claim is for <Doxepin 5% cream> look back 365 days in medical claim history for a diagnosis of Atopic dermatitis ICD 10 Disease group: L20) or Lichen simplex chronicus (ICD 10 Disease group: L28). If found, no PA REQUIRED; Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code”

Note: This edit does NOT override existing age limits, quantity limits, or Non PDL coding

<table>
<tr><th>Drug Name</th><th>Age Limit (Min Age)</th><th>Quantity Limitations</th></tr>
<tr><td>Doxepin 5% Cream

Prudoxin 5% Cream

Zonalon 5% Cream</td><td>18</td><td>90 grams every 30 days</td></tr>
</table>

Note:

PA approval SATISFIES L = Auto PA drug edit
Automated PA approval will NOT override R= Non-PDL edit

</td>
</tr>
<tr>
<td>Calcipotriene 0.005% AutoPA

Automated PA approval satisfies L=Auto PA drug logic

*Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic</td>
<td>
<table>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Calcipotriene 0.005% cream</td><td>GSN = 021134</td></tr>
<tr><td>Calcipotriene 0.005% ointment</td><td>GSN = 019160</td></tr>
<tr><td>Calcipotriene 0.005% solution</td><td>GSN = 022483</td></tr>
</table>
</td>
<td>
If incoming claim is for <Calcipotriene 0.005% cream, ointment or solution> and Prior Auth = L- AutoPA, look back 365 days in medical history for a diagnosis of Chronic Plaque Psoriasis (ICD 10 Disease group Psoriasis: L40). If found, No PA REQUIRED. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code”

Note: This edit does NOT override existing age limits, quantity limits, or Non PDL coding.

<table>
<tr><th>Drug Name</th><th>Age Limit (Min Age)</th><th>Quantity Limitations</th></tr>
<tr><td>Calcipotriene 0.005% cream, ointment</td><td>18</td><td>120 grams every 30 days
2 fills every 90 days</td></tr>
<tr><td>Calcipotriene 0.005% solution</td><td>18</td><td>60mls every 30 days</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td>Dual Statin Blockade DUR edit</td><td>
<table>
<tr><th colspan="3">HMG-CoA Reductase Inhibitors (Statins) List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>GSN</th></tr>
<tr><td>Atorvastatin</td><td>Lipitor</td><td>012404</td></tr>
<tr><td>Atorvastatin/ Amlodipine</td><td>Caduet</td><td>025951</td></tr>
<tr><td>Atorvastatin/ Ezetimibe</td><td>Liptruzet</td><td>040279</td></tr>
<tr><td>Ezetimibe / Simvastatin</td><td>Vytorin</td><td>026505</td></tr>
<tr><td>Fluvastatin/ER</td><td>Lescol, Lescol XL</td><td>008946</td></tr>
<tr><td>Lovastatin</td><td>Altoprev, Mevacor</td><td>002793</td></tr>
<tr><td>Pitavastatin Calcium</td><td>Livalo</td><td>036983</td></tr>
<tr><td>Pitavastatin Magnesium</td><td>Zypitamag</td><td>044422</td></tr>
<tr><td>Pravastatin</td><td>Pravachol</td><td>006227</td></tr>
<tr><td>Rosuvastatin</td><td>Crestor, Ezallor</td><td>025009</td></tr>
<tr><td>Rosuvastatin/ Ezetimibe</td><td>Roszet</td><td>041633</td></tr>
<tr><td>Simvastatin</td><td>Flolipid, Zocor</td><td>006312</td></tr>
</table>
Blue font = manufacturer obsolete
</td><td>Step 1: If incoming claim from <Statins List> look back 30 days for fill from <Statins List> excluding itself. If found, claim rejects NCPDP 76 with additional message “TD of Statin Therapy. Review & submit appropriate DUR cd.” Otherwise, CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply).

Limitation:
Allow 1 pharmacy level override in 180 days for claims that deny out of the Dual Statin AutoPA logic. Pharmacy must submit DUR Reason For Service Code: TD-Therapeutic Duplication for pharmacy level override. Deny the second, and subsequent attempts of a pharmacy level overrides (within a rolling 180 days) NCPDP 75 PA required with additional message “PA Req’d. Max 1 Statin TD override/180 days. Fax PA to 877-614-1078.

Note: This edit will not override existing quantity limits or Non PDL edit.</td></tr>
<tr><td>Dual Long Acting Insulins DUR edit</td><td>
<table>
<tr><th colspan="3">Long Acting Insulin List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>GSN</th></tr>
<tr><td rowspan="3">Insulin Degludec</td><td>Tresiba Flextouch 100 units/ml</td><td>071842</td></tr>
<tr><td>Tresiba Flextouch 200 units/ml</td><td>071843</td></tr>
<tr><td>Tresiba 100 unit/ml Vial</td><td>079385</td></tr>
<tr><td>Insulin</td><td>Levemir 100 unit/ml Vial</td><td>059586</td></tr>
</table>
</td><td>Step 1: If incoming claim from <Long Acting Insulin List> look back 30 days for fill from <Long Acting Insulin List> excluding itself. If found, claim rejects NCPDP 76 with additional message “TD of long acting insulin therapy. Review & submit appropriate DUR cd.” Otherwise, CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply).

The provider will be able to override the denial utilizing only the approved intervention/professional service codes, outcome/result of service codes

Limitation:
Allow 1 pharmacy level override in 180 days for claims that deny out of the Dual Long Acting Insulins DUR logic. Pharmacy must submit DUR Reason For Service Code: TD-Therapeutic</td></tr>
</table>

Edit	Drugs			Steps
	Detemir	Levemir Flexpen 100 unit/ml, Levemir Flextouch 100 unit/ml	057439	Duplication for pharmacy level override. Deny the second, and subsequent attempts of a pharmacy level overrides (within a rolling 180 days) NCPDP 75 PA required with additional message "PA Req'd. Max 1 long acting insulin TD override/180 days. Fax PA to 877-614-1078. **Note**: This edit will not override existing quantity limits or Non PDL edit.
	Insulin Glargine	Lantus, Semglee 100 unit/ml Vial	047780	
		Lantus 100 units/ml Cartridge	050836	
		Lantus, Semglee 100 unit/ml Solostar, Basaglar 100 unit/ml Kwikpen	062867	
		Toujeo Solostar 300 unit/ml	073567	
		Toujeo Max Solostar 300 unit/ml	078265	
	Insulin Glargine-YFGN	Semglee (YFGN) 100 unit/ml Vial	082541	
		Semglee (YFGN) 100 unit/ml Pen	082542	
	Insulin Degludec/ Liraglutide	Xultophy 100 unit-3.6 mg/ml Pen	073919	
	Insulin Glargine/ Lixisenatide	Soliqua 100 unit-33 mcg/ml Pen	076864	

Edit	Drugs			Steps
Oral Antipsychotic Polypharmacy Edit	Oral Antipsychotic Agents			**Automation Logic:** **Step 1: If** incoming claim from <Oral Antipsychotic List with a *Formulary Ind = OAP*>, look back 90 days for a fill from the LAI AP List. If found, proceed to step 2. If not found, procced to step 3. **Step 2: If** incoming claim from <Oral Antipsychotic List with a *Formulary Ind = OAP*>, and recipient has paid claim history of >/= 1 fill of a product from the LAI AP List within the past 90 days AND >/= 91 days supply of any product(s) from the LAI AP List within the past 120 days; claim will reject NCPDP 75 with additional message *"PA Req'd; Max* Overlapping Oral and Long Acting Antipsychotics 90 days: *Fax PA 877-614-1078."* Otherwise, proceed to step 3. **Step 3: If** incoming claim from <Oral Antipsychotic List with a *Formulary Ind = OAP*>, look back 60 days for two fills from <Oral Antipsychotic List with a *Formulary Ind = OAP*> of a different chemical entity (HSN), excluding itself. If found, claim rejects NCPDP 75 with additional message *"PA Req'd; Max* of 2 Oral Antipsychotics per 60 days: *Fax PA 877-614-1078."* Otherwise, claim MOVES OUT OF EDIT (other clinical edits still apply). Note: Products within the same HSN should continue to pay regardless of number of fills within a month.
	Generic Name	**Brand Name**	**Drug Code**	
	Aripiprazole	Abilify	HSN = 024551	
	Asenapine	Saphris	HSN = 036576	
	Brexpiprazole	Rexulti	HSN = 042283	
	Cariprazine	Vraylar	HSN = 042552	
	Chlorpromazine	N/A	HSN = 001621	
	Clozapine	Clozaril; Fazaclo; Versacloz	HSN = 004834	
	Fluphenazine	N/A	HSN = 001626	
	Haloperidol	Haldol	HSN = 001662	
	Haloperidol Lactate	Haldol	HSN = 001661	
	Iloperidone	Fanapt	HSN = 036778	
	Loxapine; Loxapine Succinate	Loxitane	HSN = 001664	
	Lumateperone Tosylate	Caplyta	HSN = 046280	
	Lurasidone	Latuda	HSN = 037321	
	Molindone	N/A	HSN = 001666	
	Olanzapine	Zyprexa	HSN = 011814	
	Olanzapine/ Fluoxetine	Symbyax	HSN = 025800	
	Olanzapine/ Samidorphan Malate	Lybalvi	HSN = 047406	
	Paliperidone	Invega	HSN = 034343	
	Perphenazine	Trilafon	HSN = 001627	

Edit	Drugs			Steps
	Perphenazine/Amitriptyline	Etrafon; Etrafon-A; Triavil	HSN = 013819	
	Pimavanserin	Nuplazid	HSN = 043373	
	Pimozide	Orap	HSN = 001637	
	Prochlorperazine Maleate	Compazine	HSN = 001629	
	Quetiapine Fumarate	Seroquel; Seroquel XR	HSN = 014015	
	Risperidone	Risperdal; Risperdal M-Tab	HSN = 008721	
	Thioridazine HCL	Mellaril	HSN = 001631	
	Thiothixene	Navane	HSN = 001668	
	Trifluoperazine	Stelazine	HSN = 001630	
	Ziprasidone HCL	Geodon	HSN = 021974	
	PLUS			
	<Long Acting Injectable (LAI) Antipsychotic List>			
	Generic Name	**Brand Name**	**Drug Code**	
	aripiprazole	Abilify Maintena	GSNs= 070669, 070670, 073298, 073299	
	aripiprazole lauroxil	Aristada ER	HSN = 042595	
	aripiprazole lauroxil submicr	Aristada Initio	HSN = 045050	
	haloperidol decanoate	Haldol Decanoate	HSN = 001660	
	paliperidone palmitate	Invega Sustenna, Invega Trinza, Invega Hafyera	HSN = 036479	
	fluphenazine decanoate	N/A	HSN = 001624	

Edit	Drugs			Steps
	risperidone	Perseris	GSNs = 078740, 078741	
	risperidone microspheres	Risperdal Consta	HSN = 025509	
	olanzapine pamoate	Zyprexa Relprevv	HSN = 036716	

Edit	Drugs			Steps
Antipsychotics and Opioids ProDUR edit	**Antipsychotics List**			. **Automation Logic**: 1. **Exclude** patients with ICD 10 from Disease Block C00-C14, C15-C26, C30-39, C40-41, C43-C44, C45-C49, C50, C51-C58, C60-C63, C64-C68, C69-C72, C73-C75, C76-C80, C7A, C7B, C81-C96, D00-D09, D10-D36, D37-D48, D3A, D49, or ICD-10-K31.7, K63.5, Q85.00, Q85.01, Q85.02 (cancer) or ICD10 from Disease Group D56, D57, D58 (sickle cell disease) in medical history within the past 365 days. 2. Exclude LTC Residents and claims that include Patient Residence Code = 3-Nursing Facility. 3. If incoming claim is from the <Antipsychotic List>: look back 30 days for fill from <Opioid List>. If found, claim rejects NCPDP 6W with additional message *"DD - Caution Overlapping Opioid-Antipsychotic therapy. Review & submit appropriate DUR cd."* 4. If incoming claim is from <Opioid List> look back 30 days for fill from <Antipsychotic List> excluding Aristada ER (HSN: 042595), Invega Hafyera (GSNs: 082645, 082646), and Invega Trinza (GSNs: 074140, 074141, 074142, 074143). If found, claim rejects NCPDP 6W with additional message *"DD - Caution Overlapping Opioid-Antipsychotic therapy. Review & submit appropriate DUR cd."* 5. If incoming claim is from <Opioid List> look back 60 days for fill of Aristada <HSN 042595>. If found, claim rejects NCPDP 6W with additional message *"DD - Caution Overlapping Opioid-Antipsychotic therapy. Review & submit appropriate DUR cd."* 6. If incoming claim is from <Opioid List> look back 180 days for fill of Invega Hafyera (GSNs: 082645, 082646). If found, claim rejects NCPDP 6W with additional message *"DD - Caution Overlapping Opioid-Antipsychotic therapy. Review & submit appropriate DUR cd."* 7. If incoming claim is from <Opioid List> look back 90 days for fill of Invega Trinza (GSNs: 074140, 074141, 074142, 074143). If found, claim rejects NCPDP 6W with additional message *"DD - Caution Overlapping Opioid-Antipsychotic therapy. Review & submit appropriate DUR cd."* *The provider will be able to override the denial utilizing only the approved intervention/professional service codes, outcome/result of service codes* **Note:** This edit does **NOT** override existing age limits, quantity limits, or Non PDL coding.
	Generic Name	Brand Name	Drug Code	
	Aripiprazole	Abilify; Abilify Maintena; Abilify Mycite	HSN = 024551	
		Aristada ER	HSN = 042595	
		Aristada Initio	HSN = 045050	
	Asenapine	Saphris	HSN = 036576	
		Secuado	HSN = 046175	
	Brexpiprazole	Rexulti	HSN = 042283	
	Cariprazine	Vraylar	HSN = 042552	
	Chlorpromazine	N/A	HSN = 001621	
	Clozapine	Clozaril; Fazaclo; Versacloz	HSN = 004834	
	Fluphenazine Decanoate	N/A	HSN = 001624	
	Fluphenazine	N/A	HSN = 001626	
	Haloperidol Decanoate	Haldol Decanoate	HSN = 001660	
	Haloperidol	Haldol	HSN = 001662	
	Iloperidone	Fanapt	HSN = 036778	
	Loxapine; Loxapine Succinate	Loxitane	HSN = 001664	
	Lumateperone Tosylate	Caplyta	HSN = 046280	
	Lurasidone	Latuda	HSN = 037321	
	Molindone	N/A	HSN = 001666	
	Olanzapine	Zyprexa	HSN = 011814	
		Zyprexa Relprevv	HSN = 036716	

Edit	Drugs			Steps
	Olanzapine/ Fluoxetine	Symbyax	HSN = 025800	
	Olanzapine/ Samidorphan Malate	Lybalvi	HSN = 047406	
	Paliperidone ER	Invega	HSN = 034343	
	Paliperidone ER	Invega Hafyera	GSNs = 082645, 082646	
		Invega Sustenna	GSNs = 065448, 065449, 065450, 065451, 065452	
		Invega Trinza	GSNs = 074140, 074141, 074142, 074143	
	Perphenazine	Trilafon	HSN = 001627	
	Perphenazine/ Amitriptyline	Etrafon; Etrafon-A; Triavil	HSN = 013819	
	Pimavanserin	Nuplazid	HSN = 043373	
	Pimozide	Orap	HSN = 001637	
	Prochlorperazine Maleate	Compazine	HSN = 001629	
	Quetipaine Fumarate	Seroquel; Seroquel XR	HSN = 014015	
	Risperidone	Risperdal; Risperdal M-Tab; Perseris	HSN = 008721	
		Risperdal Consta	HSN = 025509	
	Thioridazine HCL	Mellaril	HSN = 001631	
	Thiothixene	Navane	HSN = 001668	
	Trifluoperazine	Stelazine	HSN = 001630	

Edit	Drugs	Steps

Ziprasidone HCL	Geodon	HSN = 021974

PLUS

Opioids List		
Generic Name	Brand Name	Drug Code
acetaminophen/ codeine	Capital/ Codeine, Tylenol/ Codeine	HSN = 001717
acetaminophen/ caffeine/ dihydrocodeine	Dvorah, Panlor, Trezix	HSN = 001739
aspirin/caffeine/ dihydrocodeine	Synalgos-DC	HSN = 034574
benzhydrocodone/APAP	Apadaz	HSN = 044795
buprenorphine	Buprenex, Belbuca, Probuphine	HSN = 001762
buprenorphine transdermal	Butrans, Sublocade	HSN = 023438
butorphanol spray/vial	N/A	HSN = 001777
carisoprodol/ aspirin/codeine	N/A	HSN = 001720
codeine sulfate	N/A	HSN = 001722
codeine/ butalbital/ APAP/ caffeine	Fioricet	HSN = 001713
codeine/ butalbital/ASA/ caffeine	Ascomp/ Codeine Fiorinal/ Codeine	HSN = 001699
fentanyl	Duragesic, Subsys	HSN = 006438
fentanyl citrate	Abstral, Actiq, Fentora, Lazanda	HSN = 001747

Edit	Drugs			Steps
	hydrocodone bitartrate	Hysingla, Zohydro	HSN = 001731	
	hydrocodone/ acetaminophen	Lorcet/HD/Plus, Lortab, Norco, Verdrocet, Vicodin/ES/HP, Xodol, Zamicet	HSN = 001730	
	hydrocodone/ ibuprofen	Ibudone, Reprexain, Xylon	HSN = 014296	
	hydromorphone/ER	Dilaudid, Exalgo	HSN = 001695	
	levorphanol	N/A	HSN = 001743	
	meperidine	Demerol	HSN = 001687	
	methadone	Dolophine, Methadose	HSN = 001745	
	morphine sulfate/ER	MS Contin, Kadian, MorphaBond, Arymo ER	HSN = 001694	
	morphine sulfate/ naltrexone ER	Embeda	HSN = 036577	
	nalbuphine	N/A	HSN = 001744	
	opium/belladonna alkaloids	N/A	HSN = 001758	
	oxycodone/ER	Oxaydo, Oxycontin, Roxicodone, Roxybond	HSN = 001742	
	oxycodone/ acetaminophen/ER	Endocet, Nalocet, Percocet, Primlev, Prolate	HSN = 001741	
	oxycodone/ aspirin	N/A	HSN = 004576	
	oxycodone/ ibuprofen	N/A	HSN = 026757	
	oxycodone myristate	Xtampza ER	HSN = 043376	

Edit	Drugs			Steps
	oxymorphone/ER	Opana IR/ ER	HSN = 001696	
	pentazocine/ naloxone	N/A	HSN = 001781	
	sufentanil citrate	Dsuvia	HSN = 001749	
	tapentadol	Nucynta/ ER	HSN = 036411	
	tramadol	Conzip, Qdolo, Ultram	HSN = 008317	
	tramadol/ acetaminophen	Ultracet	HSN = 022880	
	tramadol/ celecoxib	Seglentis	HSN = 047670	

AHCA Automated Prior Authorizations and Bypass Lists 01-2023

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr>
<td>Non-BZP Sedative – LA Opioid ProDUR

Automated PA approval does not satisfy Non-PDL edit</td>
<td>
<table>
<tr><th colspan="3">Non-BZP Sedative List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td rowspan="3">Eszopiclone</td><td>Lunesta 1mg Tablet</td><td rowspan="3">HSN = 026791</td></tr>
<tr><td>Lunesta 2mg Tablet</td></tr>
<tr><td>Lunesta 3mg Tablet</td></tr>
<tr><td rowspan="2">Zaleplon</td><td>Sonata 5mg Capsule</td><td rowspan="2">HSN = 020347</td></tr>
<tr><td>Sonata 10mg Capsule</td></tr>
<tr><td rowspan="10">Zolpidem</td><td>Ambien 5mg Tablets</td><td rowspan="10">HSN = 007842</td></tr>
<tr><td>Ambien 10mg Tablets</td></tr>
<tr><td>Ambien CR 6.25mg Tablets</td></tr>
<tr><td>Ambien CR 12.5 mg Tablets</td></tr>
<tr><td>Edluar 5mg SL Tablet</td></tr>
<tr><td>Edluar 10mg SL Tablet</td></tr>
<tr><td>Intermezzo 1.75mg SL Tablet</td></tr>
<tr><td>Intermezzo 3.5mg SL Tablet</td></tr>
<tr><td>Zolpimist 5mg Oral Spray</td></tr>
</table>

PLUS

**Please note: Blue font denotes manufacturer obsolete products

<table>
<tr><th colspan="3"><Long Acting Opioids Lists></th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>buprenorphine</td><td>Belbuca</td><td>GSNs = 075050, 075051, 075052,</td></tr>
</table>
</td>
<td>Step 1: If incoming claim is from <Non-BZP Sedative List> lookback 30 days for a fill from the <LA Opioid List>. If found, PROCEED TO STEP 2. Otherwise CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply)

Step 2: If incoming claim from <Non-BZP Sedative List> Look back 60 days for a fill from the <Non-BZP Sedative List>. If found, deny NCPDP EC 76 with additional message “DD – Toxicity Warning-Overlapping Non-BZP Sedative-LA Opioid therapy. Review & submit DUR cd; Max:2 Non-BZP Sedative DD ovr/180 dys.” Otherwise, deny for PRIOR AUTHORIZATION NCPDP EC 75 with additional message “PA Req’d. Overlapping Non-BZP Sedative-LA Opioid therapy: Fax PA 877-614-1078”.

Limitation:
Allow 2 pharmacy level overrides in 180 days for claims that deny out of the Non-BZP Sedative-LA Opioid Edit for NCPDP 76. Pharmacy must submit DUR Reason for Service Code: DD-Drug to Drug Interaction for pharmacy level override. Deny the third, and subsequent attempts of pharmacy level overrides (within a rolling 180 days) NCPDP 75 PA required with additional message “PA Req’d.Max:2 Non-BZP Sedative-LA Opioid DD ovr/180 dys. Fax PA 877-614-1078”

The provider will be able to override the 1st -two denials, for non-treatment naïve recipients, utilizing only the approved intervention/professional service codes, outcome/result of service codes that are listed in the QuikChek

**** Please exclude recipients with LTC indicator or Patient Residence 03 on the claim OR a diagnosis in ICD 10 Disease Block C00-C14, C15-C26, C30-39, C40-41, C43-C44, C45-C49, C50, C51-C58, C60-C63, C64-C68, C69-C72, C73-C75, C76-C80, C7A, C7B, C81-C96, D00-D09, D10-D36, D37-D48, D3A, D49, ICD-10-K31.7, K63.5, Q85.00, Q85.01, Q85.02 (cancer) or ICD10 Disease Group D56, D57, D58 (sickle cell disease)

Note: This edit does NOT override existing age limits, quantity limits, or Non PDL coding.</td>
</tr>
</table>

Edit	Drugs			Steps
			075053, 075054, 075055, 075056	
	fentanyl	Duragesic	GSNs = 015880, 015881, 015882, 015883, 059102, 073524, 073525, 073532	
	Hydrocodone bitartrate ER	Hysingla ER, Zohydro	GSNs = 073176, 073177, 073179, 073180, 073181, 073182, 073183, 073621,073622,073623, 073624, 073625, 073626, 071602, 071603, 071604, 071605, 071606, 071607	
	hydromorphone ER	Exalgo	GSNs = 066200, 069860, 069889, 069890	
	morphine sulfate ER	Arymo ER, Morphabond ER MS Contin, Kadian ER	GSNs= 077053, 077054, 077055, 074968,074969, 074970, 074971, 011887, 004096, 004097, 011886, 016522, 050222, 064739, 050221, 064740, 050220, 050219, 060355, 060356, 061748, 069899, 060357, 061749, 061722, 060358, 062358	
	morphine sulfate/ naltrexone ER	Embeda	GSNs = 073302, 073303, 073304, 073305, 073306, 073307	
	methadone	Dolophine, Methadose	GSNs = 004235, 004237, 004238, 004239, 004240, 004242	

Edit	Drugs			Steps
	oxycodone ER	OxyContin	GSNs = 072862, 072863, 072864, 072865, 072866, 072867, 072868	
	oxycodone/ acetaminophen	Xartemis ER	GSN =072134	
	oxycodone myristate	Xtampza ER	GSNs = 076031, 076032, 076033, 076034, 076035	
	oxymorphone ER	Opana ER	GSNs = 061091, 061092, 061093, 061094, 063782, 063783, 063784, 070320, 070321, 070397, 070398, 070399, 070400, 070401	
	tapentadol ER	Nucynta ER	GSNs = 067266, 067267, 067268, 067270, 067271	
	tramadol ER	Conzip	GSNs = 043536, 043537, 060274, 063422, 063423, 063424, 067760, 067761, 067762, 068721	
	transdermal buprenorphine	Butrans	GSNs = 059589, 059590, 059591, 072673, 071432	

Edit	Drugs			Steps
Anticonvulsant Polypharmacy edit Automated PA approval will NOT override R = Non-PDL edit	Anticonvulsant Lists			**Step 1:** If incoming claims is from <Anticonvulsants List with a Formulary Ind = ACD> look back 60 days for two fills from <Anticonvulsants List with a Formulary Ind = ACD> with a different chemical entity (HSN), excluding itself. If found, claim rejects NCPDP 76 with additional message *"TD – Caution Overlapping Anticonvulsants. Review & submit appropriate DUR cd."* Otherwise, claim MOVES OUT OF EDIT (other clinical edits still apply). *The provider will be able to override the denial utilizing intervention/professional service codes, outcome/result of service codes* **Note:** This edit does **NOT** override existing age limits, quantity limits, or Non PDL coding.
	HSN	Gen Name	Brand Name	
	043088	Brivaracetam	Briviact	
	045006	Cannabidiol (CBD) Extract	Epidiolex	
	001893	Carbamazepine	Tegretol/XR, Carbatrol, Epitol, Equetro	
	046241	Cenobamate	Xcopri	
	006536	Clobazam	Sympazan, Onfi	
	001894	Clonazepam	Klonopin	
	001615 (excluding Diazepam kit GSNs: 034015, 059781, 059782)	Diazepam		
	001884	Divalproex Sodium	Depakote	
	036675	Eslicarbazepine Acetate	Aptiom	
	001891	Ethosuximide	Zarontin	
	001880	Ethotoin	Peganone	
	037667	Ezogabine	Potiga	
	008186	Felbamate	Felbatol	
	008831	Gabapentin	Neurontin	
	035872	Lacosamide	Vimpat	
	007378	Lamotrigine	Lamictal/ODT/XR, Subvenite	
	020952	Levetiracetam	Keppra, Roweepra XR, Spritam	
	001890	Methsuximide	Celontin	
	011735	Oxcarbazepine	Trileptal, Oxtellar XR	
	039628	Perampanel	Fycompa	

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td>
<table>
<tr><td>001879</td><td>Phenytoin Infatab</td><td>Dilantin</td></tr>
<tr><td>001877</td><td>Phenytoin Sodium Extended</td><td>Dilantin, Phenytek</td></tr>
<tr><td>001561</td><td>Phenobarbital</td><td></td></tr>
<tr><td>026470</td><td>Pregabalin</td><td>Lyrica/CR</td></tr>
<tr><td>001886</td><td>Primidone</td><td>Mysoline</td></tr>
<tr><td>034982</td><td>Rufinamide</td><td>Banzel</td></tr>
<tr><td>035461</td><td>Stiripentol</td><td>Diacomit</td></tr>
<tr><td>015773</td><td>Tiagabine HCL</td><td>Gabitril</td></tr>
<tr><td>011060</td><td>Topiramate</td><td>Topamax, Qudexy XR, Trokendi XR,</td></tr>
<tr><td>001883</td><td>Valproic Acid</td><td>Depakene</td></tr>
<tr><td>001882</td><td>Valproic Acid (As Sodium Salt)</td><td>Depakene, Depacon</td></tr>
<tr><td>007377</td><td>Vigabatrin</td><td>Vigadrone, Sabril</td></tr>
<tr><td>021140</td><td>Zonisamide</td><td>Zonegran</td></tr>
</table>
***Please Note: Blue font indicates product is no longer available
</td><td></td></tr>
<tr><td>Pancreatic Enzyme AP Logic</td><td>
<table>
<tr><th colspan="3">Pancreatic Enzyme List</th></tr>
<tr><th>Drug Code</th><th>Generic Name</th><th>Brand Name</th></tr>
<tr><td rowspan="5">HSN = 008060</td><td rowspan="5">Lipase/ Protease/ Amylase</td><td>Creon/ DR Capsule</td></tr>
<tr><td>Pancreaze DR Capsule</td></tr>
<tr><td>Pertzye DR Capsule</td></tr>
<tr><td>Viokace Tablet</td></tr>
<tr><td>Zenpep Capsule</td></tr>
</table>
</td><td>If incoming claim is from <Pancreatic Enzyme List> look back in medical claims history 730 days for a diagnosis of Malignant neoplasm of the pancreas, Cystic Fibrosis, Other disease of the pancreas, Other congenital malformations of digestive system, or Acquired absence of pancreas (see approvable ICD-10s below). If found, claim MOVES OUT OF EDIT. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code”
<table>
<tr><th>ICD-10 Code</th><th>Description</th></tr>
<tr><td>Disease group: C25</td><td>Malignant neoplasm of the pancreas</td></tr>
<tr><td>Disease group: E84</td><td>Cystic Fibrosis</td></tr>
<tr><td>Disease group: K86</td><td>Other disease of the pancreas</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Disease group: Q45</td><td>Other congenital malformations of digestive system</td></tr>
<tr><td>Z90.41</td><td>Acquired absence of pancreas</td></tr>
<tr><td>Z90.410</td><td>Acquired total absence of pancreas</td></tr>
<tr><td>Z90.411</td><td>Acquired partial absence of pancreas</td></tr>
</table>
</td></tr>
<tr><td>Eucrisa AP Logic</td><td>
<table>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Eucrisa 2% Ointment</td><td>HSN= 043999</td></tr>
</table>
<table>
<tr><th colspan="3">Topical Calcineurin Inhibitors</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>Tacrolimus</td><td>Protopic</td><td>GSN = 047346, 047347</td></tr>
<tr><td>Pimecrolimus</td><td>Elidel</td><td>GSN = 049724</td></tr>
</table>
<table>
<tr><th colspan="3">Topical Corticosteroids</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>Alclometasone Dipropionate</td><td></td><td>GSN = 007636, 007637</td></tr>
<tr><td>Amcinonide</td><td></td><td>GSN = 007631, 007632, 007633</td></tr>
<tr><td>Betamethasone Dipropionate</td><td>Diprolene (AF), Sernivo</td><td>GSN = 007561, 007562, 007568, 007569, 007570, 014219, 016429, 075550</td></tr>
<tr><td>Betamethasone Valerate</td><td>Luxiq</td><td>GSN = 007572, 007573, 007574, 026471</td></tr>
</table>
</td><td>
Step 1: If incoming claim is for <Eucrisa> look back 180 days within claims history for <Eucrisa>. If found, NO PA REQUIRED; Otherwise PROCEED TO STEP 2.

Step 2: Look back 180 days within claim history for a previous fill of a <Topical Calcineurin Inhibitor> or <Topical Corticosteroid>. If found, CLAIM PAYS. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “Missing Prerequisite Drug Therapy.”

Note: This edit does NOT override existing quantity limits
<table>
<tr><th colspan="2">Quantity Limitations</th></tr>
<tr><td>Eucrisa 2% Ointment</td><td>60 grams every 30 days</td></tr>
</table>
</td></tr>
</table>

Edit	Drugs			Steps
	Clobetasol Propionate	Clobex, Clodan, Cormax, Impoyz, Olux (E), Temovate, Tovet	GSN = 007634, 007635, 015349, 018288, 021904, 021986, 046803, 053749, 059967, 061865, 072507, 077979, 080288	
	Clocortolone Pivalate	Cloderm	GSN = 007585	
	Desonide	Desonate, Desowen, Tridesilon, Verdeso	GSN = 007620, 007622, 016650, 061463, 062148	
	Desoximetasone	Topicort (LP)	GSN = 007581, 007582, 007583, 007584, 041987, 070883	
	Diflorasone Diacetate	Apexicon E, Psorcon E	GSN = 007629, 007630, 041729	
	Fluocinolone Acetonide	Capex, Derma-Smoothe, Synalar	GSN = 007507, 007608, 007609, 007611, 007612, 015562, 058950, 069952, 070318, 070319	
	Fluocinonide	Fluovix, Vanos	GSN = 007614, 007615, 007616, 007617, 007618, 058794, 079822	
	Flurandrenolide	Cordran, Nolix	GSN = 007601, 007602, 007603, 007605, 007606	
	Fluticasone Propionate	Beser, Cutivate	GSN = 016015, 016255, 059177, 079738	
	Halcinonide	Halog	GSN = 007625, 007627, 007628	
	Halobetasol Propionate	Bryhali, Lexette, Ultravate(X),	GSN = 015605, 015606, 069538, 069539, 075826, 079214, 079262	

Edit	Drugs			Steps
	Hydrocortisone	Ala-Cort, Aqua Glycolic HC, Dermasorb HC, Procto-Pak, Proctocort, Scalacort, Texacort	GSN = 006859, 007544, 007545, 007547, 007548, 007553, 007554, 007555, 019151, 064718, 068786, 071713	
	Hydrocortisone Butyrate	Locoid	GSN = 007530, 007531, 016897, 018275, 053275	
	Hydrocortisone Probutate	Pandel	GSN = 030797	
	Hydrocortisone Valerate		GSN = 007532, 007533	
	Mometasone Furoate	Elocon, Quinixil, Quinosone	GSN = 007638, 007639, 035527, 065215, 080080	
	Prednicarbate	Dermatop	GSN = 021191, 040785	
	Triamcinolone Acetonide	Ellzia, Kenalog, Sila III, Silalite, Silazone, Trianex, Triderm	GSN = 007593, 007594, 007595, 007596, 007597, 007598, 007599, 007600, 015542, 062564, 071710, 074811, 077163, 078715, 080519	

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Edit

Nurtec ODT/Qulipta/Ubrelvy Auto PA

Automated PA approval satisfies L=Auto PA drug logic

*Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic

Drugs

Generic Name	Brand Name	Drug Code
Rimegepant	Nurtec ODT	HSN = 046383
Atogepant	Qulipta	HSN = 047599
Ubrogepant	Ubrelvy	HSN = 046273

Triptans		
Generic Name	**Brand Name**	**Drug Code**
Almotriptan	Axert	HSN = 021894
Eletriptan	Relpax	HSN = 023093
Frovatriptan	Frova	HSN = 022988
Naratriptan	Amerge	HSN = 013266
Rizatriptan	Maxalt/MLT	HSN = 018535
Sumatriptam Succinate	Alsuma, Imitrex, Onzetra Xsail, Sumavel, Tosymra, Zecuity, Zembrace	HSNs = 006587, 012779
Sumatriptan Succinate/ Naproxen Sodium	Treximet	HSN = 035534
Zolmitriptan	Zomig/ZMT	HSN = 012958

Blue font = manufacturer obsolete

Steps

Step 1: If incoming claim is for HSN 046383-Nurtec ODT, HSN 047599-Qulipta or HSN 046273-Ubrelvy and Prior Auth = L-Auto PA, PROCEED TO STEP 2. Otherwise, Stop.

Step 2: Look back 180 days in paid claim history for itself (a product within the same HICL as incoming claim). If found, APPROVE. Otherwise, PROCEED TO STEP 3.

Step 3: If incoming claim is for HSN 046383-Nurtec ODT or HSN 047599-Qulipta, PROCEED TO STEP 4. If incoming claim is for HSN 046273-Ubrelvy, PROCEED TO STEP 6.

Step 4: If incoming claim is for HSN 046383-Nurtec ODT or HSN 047599-Qulipta, look back in medical claims history 730 days for a diagnosis from *<Approvable Nurtec/Qulipta (ICD-10) Diagnosis List>*. If found, APPROVE. Otherwise, PROCEED TO STEP 5.

Step 5: If incoming claim is for HSN 046383-Nurtec ODT, PROCEED TO STEP 6. Otherwise (if claim is for HSN 047599-Qulipta), DENY for PRIOR AUTHORIZATION REQUIRED (75/31008) with supplemental message *M/I Diagnosis Code*

Step 6: If incoming claim is for HSN 046383-Nurtec ODT or HSN 046273-Ubrelvy, look back 180 days within paid claim history for >/= two fills from <Triptans List> of a different chemical entity (HSN). If found, CLAIM PAYS. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75/31006) with supplemental message *Missing Prerequisite drug therapy*

Approvable Nurtec/Qulipta (ICD-10) Diagnosis List	
ICD-10-CM Code	**Description**
G43.5	Persistent migraine aura without cerebral infarction
G43.50	Persistent migraine aura without cerebral infarction, not intractable
G43.501	Persistent migraine aura without cerebral infarction, not intractable with status migrainosus
G43.509	Persistent migraine aura without cerebral infarction, not intractable without status migrainosus

Edit	Drugs	Steps	
		G43.51	Persistent migraine aura without cerebral infarction, intractable
		G43.511	Persistent migraine aura without cerebral infarction, intractable with status migrainosus
		G43.519	Persistent migraine aura without cerebral infarction, intractable without status migrainosus
		G43.6	Persistent migraine aura with cerebral infarction
		G43.60	Persistent migraine aura with cerebral infarction, not intractable
		G43.601	Persistent migraine aura with cerebral infarction, not intractable with status migrainosus
		G43.609	Persistent migraine aura with cerebral infarction, not intractable without status migrainosus
		G43.61	Persistent migraine aura with cerebral infarction, intractable
		G43.611	Persistent migraine aura with cerebral infarction, intractable with status migrainosus
		G43.619	Persistent migraine aura with cerebral infarction, intractable without status migrainosus
		G43.7	Chronic migraine without aura
		G43.70	Chronic migraine without aura, not intractable
		G43.701	Chronic migraine without aura, not intractable with status migrainosus
		G43.709	Chronic migraine without aura, not intractable without status migrainosus
		G43.71	Chronic migraine without aura, intractable

Edit	Drugs	Steps

G43.711	Chronic migraine without aura, intractable with status migrainosus
G43.719	Chronic migraine without aura, intractable without status migrainosus

Note: This logic does **NOT** override existing age or quantity limits

Drug Name	Age Limit (Min Age)	Quantity Limitations
Nurtec ODT	18	Max of 1 tablet per day Max of 16 tablets per 30 days
Qulipta	18	Max of 1 tablet per day
Ubrelvy	18	Max of 2 tablets per day Max of 16 tablets per 30 days

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Edit	Drugs	Steps
Jornay PM Automation Automated PA approval satisfies L=Auto PA drug edit		**Step 1:** If incoming claim is for <Jornay PM> look back 180 days within claims history for <Jornay PM>. If found, CLAIM PAYS; Otherwise PROCEED TO STEP 2. **Step 2:** If incoming claim is for <Jornay PM> look back 180 days within claims history for two fills from the <ADHD list>. If found, CLAIM PAYS. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message "Missing Prerequisite Drug Therapy" (Internal Error Code 31006). **Note:** Automated PA approval will NOT override age, quantity, or mg per day limits.

Jornay PM List

Generic Name	Brand Name	Drug Code
methylphenidate ER cap	Jornay PM	GSNs = 078724, 078725, 078726, 078727, 078728

ADHD list

Generic Name	Brand Name	Drug Code
amphetamine	Adzenys ER/XR ODT, Dyanavel XR	HSN = 043652
amphetamine	Evekeo/ Evekeo ODT	HSN = 002064
atomoxetine	Strattera	HSN = 024703
clonidine ER	N/A	GSN = 066895
dexmethylphenidate	Focalin/Focalin XR	HSN = 022987
dextroamphetamine	Dexedrine, Procentra, Zenzedi	HSN = 002065
dextroamphetamine/ amphetamine	Adderall/Adderall XR, Mydayis	HSN = 013449
guanfacine ER	Intuniv ER	GSN = 065570, 065572, 065573, 065574
lisdexamfetamine	Vyvanse	HSN = 034486
methamphetamine	Desoxyn	HSN = 002067
methylphenidate	Cotempla XR ODT, Daytrana	HSN = 033556
	Adhansia XR, Aptensio XR, Concerta, Metadate ER, Methylin, Methylin ER, Quillichew, Quillivant, Ritalin/	HSN = 001682

Drug Name	Age Limit (Min Age)	Quantity Limitations*
Jornay PM	6	Max of 100mg per day Max of 1 capsule per day

*bypass quantity limitations for ages 6 to < 18 years

Edit	Drugs	Steps
	Ritalin LA	

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Edit	Drugs			Steps
Opioid - MAT ProDUR Edit	**Opioids List**			**Step 1:** If incoming claim is from <Opioids List> look back 365 days in patient's medical history for cancer (ICD 10 Disease Block C00-C14, C15-C26, C30-39, C40-41, C43-C44, C45-C49, C50, C51-C58, C60-C63, C64-C68, C69-C72, C73-C75, C76-C80, C7A, C7B, C81-C96, D00-D09, D10-D36, D37-D48, D3A, D49, ICD-10-K31.7, K63.5, Q85.00, Q85.01, Q85.02) or sickle cell disease (ICD 10 Disease Group D56, D57, D58) or an LTC indicator or Patient Residence 03 on the claim. If found, CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply). Otherwise, PROCEED TO STEP 2. **Step 2:** Look back in medical history 30 days for a diagnosis of Opioid Use Disorder (ICD-10 Disease Group: F11). If found, claim rejects NCPDP 76 with additional message *"DD – Caution overlapping Opioid - MAT therapy. Review & submit appropriate DUR cd."* Otherwise, PROCEED TO STEP 3. **Step 3:** Look back 30 days for a fill from the <Opioid MAT Therapy List>. If found, claim rejects NCPDP 76 with additional message *"DD – Caution overlapping Opioid - MAT therapy. Review & submit appropriate DUR cd."* Otherwise, CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply). *The provider will be able to override the denial utilizing only the approved intervention/professional service codes, outcome/result of service codes* **Note:** This edit does **NOT** override existing age limits, quantity limits, or Non PDL coding.
	Generic Name	Brand Name	Drug Code	
	acetaminophen/ codeine	Capital/ Codeine, Tylenol/ Codeine	HSN = 001717	
	acetaminophen/ caffeine/ dihydrocodeine	Dvorah, Panlor, Trezix	HSN = 001739	
	aspirin/caffeine/ dihydrocodeine	Synalgos-DC	HSN = 034574	
	benzhydrocodone /APAP	Apadaz	HSN = 044795	
	buprenorphine	Belbuca, Buprenex	HSN = 001762 (excluding Probuphine: GSN 001762 and Subutex: GSNs 029312, 029313)	
	buprenorphine transdermal	Butrans	HSN = 023438 (excluding Sublocade: GSNs 077999, 078000)	
	butorphanol spray/vial	N/A	HSN = 001777	
	carisoprodol/ aspirin/codeine	N/A	HSN = 001720	
	codeine sulfate	N/A	HSN = 001722	
	codeine/ butalbital/ APAP/ caffeine	Fioricet-Cod	HSN = 001713	
	codeine/ butalbital/ASA/ caffeine	Ascomp/ Codeine Fiorinal/ Codeine	HSN = 001699	
	fentanyl	Duragesic, Subsys	HSN = 006438	
	fentanyl citrate	Abstral, Actiq, Fentora, Lazanda	HSN = 001747	
	Hydrocodone bitartrate	Hysingla, Zohydro	HSN = 001731	
	hydrocodone/ acetaminophen	Lorcet/HD/Plus, Lortab, Norco, Verdrocet, Vicodin/ES/HP, Xodol, Zamicet	HSN = 001730	
	hydrocodone/ ibuprofen	Ibudone, Reprexain, Xylon	HSN = 014296	
	hydromorphone/ ER	Dilaudid, Exalgo	HSN = 001695	
	levorphanol	N/A	HSN = 001743	

Edit	Drugs			Steps
	meperidine	Demerol	HSN = 001687	
	methadone	Dolophine, Methadose	HSN = 001745	
	morphine sulfate/ER	Arymo ER, Kadian ER, MorphaBond, MS Contin	HSN = 001694	
	morphine sulfate/ naltrexone ER	Embeda	HSN = 036577	
	nalbuphine	N/A	HSN = 001744	
	opium/belladonn a alkaloids	N/A	HSN = 001758	
	oxycodone/ER	Oxaydo, Oxycontin, Roxicodone, Roxybond	HSN = 001742	
	oxycodone/ acetaminophen/ ER	Endocet, Nalocet, Percocet, Primlev, Prolate	HSN = 001741	
	oxycodone/ aspirin	N/A	HSN = 004576	
	oxycodone/ ibuprofen	N/A	HSN = 026757	
	oxycodone myristate	Xtampza ER	HSN = 043376	
	oxymorphone/ER	Opana	HSN = 001696	
	pentazocine/ naloxone	N/A	HSN = 001781	
	sufentanil citrate	Dsuvia	HSN = 001749	
	tapentadol	Nucynta/ ER	HSN = 036411	
	tramadol	Conzip, Ultram	HSN = 008317	
	tramadol/ acetaminophen	Ultracet	HSN = 022880	

Opioid MAT Therapy List		
Generic Name	**Brand Name**	**Drug Codes**
buprenorphine HCL	Probuphine, Subutex	GSNs = 029312, 029313, 076145
buprenorphine ER	Sublocade	GSNs = 077999, 078000
buprenorphine/ naloxone	Bunavail, Suboxone, Zubsolv	HSN = 024846
Naloxone	Narcan	HSN = 001874
Naltrexone		GSN = 004518

Edit	Drugs			Steps
	Naltrexone microspheres	Vivitrol	HSN = 033782	

AHCA Automated Prior Authorizations and Bypass Lists 01-2023

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr>
<td>Lyrica AP Logic

Automated PA approval satisfies L=Auto PA drug edit

Automated PA approval will NOT override R = Non-PDL edit’</td>
<td>
<table>
<tr><th colspan="3">Drug/Antitoxin List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Other Criteria</th></tr>
<tr><td>Pregabalin</td><td>*Lyrica</td><td>HSN = 026470
(excluding GSN 069339 Pregabalin 20mg/mL Solution)</td></tr>
</table>
*Denotes: R-Non PDL agents and non-preferred agents will NOT satisfy the automation logic
</td>
<td>
Step 1: If incoming claim is from <Pregabalin list> look back 60 days within claims history for HSN 026470. If found, claim PAYS.

Step 2: If incoming claim is from <Pregabalin List> look back in medical claims history 730 days for a diagnosis from <Approvable Lyrica (ICD-10) Diagnoses List> below. If found, claim PAYS. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75/31008) with supplemental message “M/I Diagnosis Code”.

<table>
<tr><th colspan="2">Approvable Lyrica (ICD-10) Diagnoses List</th></tr>
<tr><th>ICD-10-CM Code</th><th>Description</th></tr>
<tr><td>E10.4</td><td>Type 1 diabetes mellitus with neurological complications</td></tr>
<tr><td>E10.40</td><td>Type 1 diabetes mellitus with diabetic neuropathy, unspecified</td></tr>
<tr><td>E10.41</td><td>Type 1 diabetes mellitus with diabetic mononeuropathy</td></tr>
<tr><td>E10.42</td><td>Type 1 diabetes mellitus with diabetic polyneuropathy</td></tr>
<tr><td>E10.43</td><td>Type 1 diabetes mellitus with diabetic autonomic (poly)neuropathy</td></tr>
<tr><td>E10.44</td><td>Type 1 diabetes mellitus with diabetic amyotrophy</td></tr>
<tr><td>E10.49</td><td>Type 1 diabetes mellitus with other diabetic neurological complication</td></tr>
<tr><td>E11.4</td><td>Type 2 diabetes mellitus with neurological complications</td></tr>
<tr><td>E11.40</td><td>Type 2 diabetes mellitus with diabetic neuropathy, unspecified</td></tr>
<tr><td>E11.41</td><td>Type 2 diabetes mellitus with diabetic mononeuropathy</td></tr>
<tr><td>E11.42</td><td>Type 2 diabetes mellitus with diabetic polyneuropathy</td></tr>
<tr><td>E11.43</td><td>Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy</td></tr>
<tr><td>E11.44</td><td>Type 2 diabetes mellitus with diabetic amyotrophy</td></tr>
<tr><td>E11.49</td><td>Type 2 diabetes mellitus with other diabetic neurological complication</td></tr>
<tr><td>E13.4</td><td>Other diabetes mellitus with neurological complications</td></tr>
<tr><td>E13.40</td><td>Other diabetes mellitus with diabetic neuropathy, unspecified</td></tr>
<tr><td>E13.41</td><td>Other diabetes mellitus with diabetic mononeuropathy</td></tr>
<tr><td>E13.42</td><td>Other diabetes mellitus with diabetic</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td>polyneuropathy</td></tr>
<tr><td>E13.43</td><td>Other diabetes mellitus with diabetic autonomic (poly)neuropathy</td></tr>
<tr><td>E13.44</td><td>Other diabetes mellitus with diabetic amyotrophy</td></tr>
<tr><td>E13.49</td><td>Other diabetes mellitus with other diabetic neurological complication</td></tr>
<tr><td>B02.22</td><td>Postherpetic trigeminal neuralgia</td></tr>
<tr><td>B02.23</td><td>Postherpetic polyneuropathy</td></tr>
<tr><td>B02.29</td><td>Other postherpetic nervous system involvement</td></tr>
<tr><td>Disease Group: G40</td><td>Epilepsy and recurrent seizures</td></tr>
<tr><td>M79.7</td><td>Fibromyalgia</td></tr>
<tr><td>Disease Group: S34</td><td>Injury of lumbar and sacral spinal cord and nerves at abdomen, lower back and pelvis level</td></tr>
</table>
Note: This edit does NOT override existing quantity limits.
<table>
<tr><th>Drug Name</th><th>Quantity Limitations</th></tr>
<tr><td>Pregabalin</td><td>Max of 600mg per day</td></tr>
</table>
</td></tr>
</table>

AHCA Automated Prior Authorizations and Bypass Lists 01-2023

Edit	Drugs	Steps
Vraylar Auto PA Automated PA approval satisfies L=Auto PA drug edit *Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic	See tables below	See tables below

Vraylar List

Generic Name	Brand Name	Drug Code
Cariprazine	Vraylar	HSN = 042552

Oral Atypical Antipsychotics List

Generic Name	Brand Name	Drug Code
Aripiprazole (solution/tablets)	Abilify	GSN = 058594, 060225, 052898, 051333, 051334, 051335, 051336
Clozapine tablets	Clozaril	GSN = 013648, 027037, 013649, 046416
Iloperidone tablets	Fanapt	GSN = 065901, 065902, 065903, 065904, 065905, 065906, 065907
Lurasidone tablets	Latuda	GSN = 068448, 066932, 071415, 066933, 069894
Olanzapine (tablets/ODT)	Zyprexa	GSN = 029077, 027961, 027959, 027960, 041026, 041027, 045190, 045191, 047285, 047286
Quetiapine/ER tablets	Seroquel	GSN = 034187, 060292, 034188, 034189, 047198, 060293, 063240, 064725, 062748, 062749, 062750
Risperidone (solution, tablets/ODT)	Risperdal	GSN = 026177, 065235, 052049, 051799, 051800, 059402, 059403, 042922, 042923, 021154, 021155, 021156, 021157
Ziprasidone capsules	Geodon	GSN = 047563, 047564, 047567, 047568

Step 1: If incoming claim is for <Vraylar> look back 365 days within claims history for <Vraylar>. If found, CLAIM PAYS; Otherwise PROCEED TO STEP 2. (AG and quantity limitations still apply).

Step 2: Look back in drug history 365 days for a fill from <Oral Atypical Antipsychotics List> of a preferred drug. If found, CLAIM PAYS. Otherwise, deny for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message "*Missing Prerequisite Drug Therapy*".

Note: Automated PA approval will NOT override age or quantity limits.

Drug Name	Age Limit (Min Age)	Quantity Limitations
Vraylar	18	Max of 6mg per day
		Max of 1 capsule per day per GSN

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr>
<td>Gabapentinoids Overlapping Therapy ProDUR Edit</td>
<td>
<table>
<tr><th colspan="3">Gabapentinoids List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>Gabapentin</td><td>Gralise, Neurontin</td><td>HSN = 008831</td></tr>
<tr><td>Gabapentin Enacarbil</td><td>Horizant</td><td>HSN = 037574</td></tr>
<tr><td>Pregabalin</td><td>Lyrica</td><td>HSN = 026470</td></tr>
</table>
PLUS
<table>
<tr><th colspan="3">Overlapping Therapy List</th></tr>
<tr><th colspan="3">Gabapentinoids List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>Gabapentin</td><td>Gralise, Neurontin</td><td>HSN = 008831</td></tr>
<tr><td>Gabapentin Enacarbil</td><td>Horizant</td><td>HSN = 037574</td></tr>
<tr><td>Pregabalin</td><td>Lyrica</td><td>HSN = 026470</td></tr>
<tr><th colspan="3">Benzodiazepine (BZP) List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>alprazolam</td><td>Xanax, Nivaram</td><td>HSN= 001617</td></tr>
<tr><td>chlordiazepoxide</td><td>Librium, Poxi</td><td>HSN= 001610</td></tr>
<tr><td>chlordiazepoxide/ amitriptyline</td><td>Limbitrol</td><td>HSN= 001656</td></tr>
<tr><td>chlordiazepoxide/ clidinium</td><td>Librax, Lidox</td><td>HSN= 002037</td></tr>
<tr><td>clonazepam</td><td>Klonopin, Cerberclon</td><td>HSN= 001894</td></tr>
<tr><td>clorazepate</td><td>Tranxene, Gen-Xene</td><td>HSN= 001612</td></tr>
<tr><td>diazepam</td><td>Valium, Valtoco</td><td>HSN= 001615</td></tr>
<tr><td>estazolam</td><td>Prosom</td><td>HSN= 006036</td></tr>
<tr><td>flurazepam</td><td>Dalmane</td><td>HSN= 001593</td></tr>
<tr><td>lorazepam</td><td>Ativan</td><td>HSN= 004846</td></tr>
<tr><td>midazolam</td><td>n/a</td><td>HSN= 034908,</td></tr>
</table>
</td>
<td>If incoming claim is from the <Gabapentinoids List> look back 30 days for any fill from the <Overlapping Therapy List>, excluding itself (HSN). If found, claim rejects NCPDP 76 with additional message “DD – Caution Risk of breathing difficulties with combination of these medications. Review & submit appropriate DUR cd.” Otherwise, CLAIM MOVES OUT OF EDIT (other clinical edits for products still apply).

The provider will be able to override the denial utilizing only the approved intervention/professional service codes, outcome/result of service codes.

Note: This edit does NOT override existing age limits or quantity limits.</td>
</tr>
</table>

Edit	Drugs			Steps
			001619	
	oxazepam	Serax	HSN= 001616	
	quazepam	Doral	HSN= 001595	
	temazepam	Restoril	HSN= 001592	
	triazolam	Halcion	HSN= 001594	
	Opioid List			
	Generic Name	**Brand Name**	**Drug Code**	
	acetaminophen/ codeine	Capital/ Codeine, Tylenol/ Codeine	HSN= 001717	
	acetaminophen/ caffeine/ dihydrocodeine	Dvorah, Panlor, Trezix	HSN= 001739	
	aspirin/caffeine/ dihydrocodeine	Synalgos-DC	HSN= 034574	
	benzhydrocodone/ APAP	Apadaz	HSN= 044795	
	buprenorphine	Belbuca, Buprenex	HSN= 001762	
	buprenorphine transdermal	Butrans	HSN= 023438	
	butorphanol spray/vial	N/A	HSN= 001777	
	carisoprodol/ aspirin/codeine	N/A	HSN= 001720	
	codeine sulfate	N/A	HSN= 001722	
	codeine/ butalbital/ APAP/ caffeine	Fioricet-Cod	HSN= 001713	
	codeine/ butalbital/ASA/ caffeine	Ascomp/ Codeine	HSN= 001699	
		Fiorinal/ Codeine		
	fentanyl	Duragesic, Subsys	HSN= 006438	
	fentanyl citrate	Abstral, Actiq, Fentora, Lazanda	HSN= 001747	
	hydrocodone bitartrate	Hysingla, Zohydro	HSN= 001731	

Edit	Drugs			Steps
	hydrocodone/ acetaminophen	Lorcet/HD/Plus, Lortab, Norco, Verdrocet, Vicodin/ES/HP, Xodol, Zamicet	HSN= 001730	
	hydrocodone/ ibuprofen	Ibudone, Reprexain, Xylon	HSN= 014296	
	hydromorphone/ER	Dilaudid, Exalgo	HSN= 001695	
	levorphanol	N/A	HSN= 001743	
	meperidine	Demerol	HSN= 001687	
	methadone	Dolophine, Methadose	HSN= 001745	
	morphine sulfate/ER	Arymo ER, Kadian ER, MorphaBond, MS Contin	HSN= 001694	
	morphine sulfate/ naltrexone ER	Embeda	HSN= 036577	
	nalbuphine	N/A	HSN= 001744	
	opium/belladonna alkaloids	N/A	HSN= 001758	
	oxycodone/ER	Oxaydo, Oxycontin, Roxicodone, Roxybond	HSN= 001742	
	oxycodone/ acetaminophen/ER	Endocet, Nalocet, Percocet, Primlev, Prolate	HSN= 001741	
	oxycodone/ aspirin	N/A	HSN= 004576	
	oxycodone/ ibuprofen	N/A	HSN= 026757	
	oxycodone myristate	Xtampza ER	HSN= 043376	
	oxymorphone/ER	Opana	HSN= 001696	
	pentazocine/ naloxone	N/A	HSN= 001781	
	sufentanil citrate	Dsuvia	HSN= 001749	
	tapentadol	Nucynta/ ER	HSN= 036411	
	tramadol	Conzip, Ultram	HSN= 008317	

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td>
<table>
<tr><td>tramadol/ acetaminophen</td><td>Ultracet</td><td>HSN= 022880</td></tr>
<tr><th colspan="3">Skeletal Muscle Relaxant (SMR) List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>baclofen</td><td>N/A</td><td>HSN= 001949</td></tr>
<tr><td>carisoprodol</td><td>Soma</td><td>HSN= 001944</td></tr>
<tr><td>chlorzoxazone</td><td>Lorzone</td><td>HSN= 001941</td></tr>
<tr><td>cyclobenzaprine</td><td>Flexeril/Amrix/Fexmid</td><td>HSN= 001950</td></tr>
<tr><td>metaxalone</td><td>Skelaxin</td><td>HSN= 001945</td></tr>
<tr><td>methocarbamol</td><td>Robaxin</td><td>HSN= 001938</td></tr>
<tr><td>orphenadrine</td><td>N/A</td><td>HSN= 001906</td></tr>
<tr><td>tizanidine</td><td>Zanaflex</td><td>HSN= 011582</td></tr>
</table>
Blue font = Manufacturer obsolete product
</td><td></td></tr>
<tr><td>Buprenorphine AutoPA

Automated PA approval satisfies L=Auto PA drug edit

*Automated PA approval will NOT override R = NonPDL edit and will not satisfy the automation logic</td><td>
<table>
<tr><th colspan="3"><Preferred Buprenorphine List></th></tr>
<tr><th>GSN</th><th>Drug</th><th></th></tr>
<tr><td>051640</td><td>Buprenorphine-Naloxone 2-0.5mg SL</td><td>Generic</td></tr>
<tr><td>051641</td><td>Buprenorphine-Naloxone 8-2mg SL</td><td>Generic</td></tr>
<tr><td>066635</td><td>Suboxone 2mg-0.5mg film</td><td>Brand</td></tr>
<tr><td>066636</td><td>Suboxone 8mg-2mg film</td><td>Brand</td></tr>
<tr><td>070259</td><td>Suboxone 4mg-1mg film</td><td>Brand</td></tr>
<tr><td>070262</td><td>Suboxone 12mg-3mg film</td><td>Brand</td></tr>
<tr><td>029312</td><td>Buprenorphine 2mg SL</td><td>Generic</td></tr>
<tr><td>029313</td><td>Buprenorphine 8mg SL</td><td>Generic</td></tr>
<tr><td>071189</td><td>Zubsolv 1.4-0.36mg SL</td><td>Brand</td></tr>
<tr><td>071190</td><td>Zubsolv 5.7-1.4mg SL</td><td>Brand</td></tr>
<tr><td>073424</td><td>Zubsolv 8.6-2.1mg SL</td><td>Brand</td></tr>
<tr><td>073425</td><td>Zubsolv 11.4-2.9mg SL</td><td>Brand</td></tr>
<tr><td>074685</td><td>Zubsolv 2.9-0.71mg SL</td><td>Brand</td></tr>
<tr><td>076981</td><td>Zubsolv 0.7-0.18mg SL</td><td>Brand</td></tr>
</table>
</td><td>If the incoming claim is from the <Preferred Buprenorphine List> with FMT Prior Auth = L-Auto PA Drug, look back in medical claims history 365 days for an ICD 10 in disease group = F11 (Opioid Related Disorder). If found, NO PA REQUIRED. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code”

POS Bypass Logic: If the incoming claim is from the <Preferred Buprenorphine List> with FMT Prior Auth = L-Auto PA Drug, the Pharmacy may enter a 3 in the PA Type Code Field (NCPDP Field # 461-EU) to bypass 75/2462 (prior authorization required), if the above diagnosis code is verified via phone or on the prescription.

Note: This edit does NOT override existing age limits or quantity limits</td></tr>
</table>

Edit	Drugs	Steps
Hydroxy/ Chloroquine Auto PA Automated PA approval satisfies L=Auto PA drug logic *Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic	**Hydroxy/Chloroquine List** **Generic Name** / **Brand Name** / **Drug Code** Hydroxy-chloroquine / Plaquenil* / HSN = 004151 Chloroquine / Aralen / HSN = 004147	**Step 1:** If incoming claim is from < Hydroxy/Chloroquine list> look back in medical claims history, 730 days, for a diagnosis from <Approvable Hydroxy/Chloroquine (ICD-10) Diagnoses List> below. If found, claim PAYS. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75/31008) with supplemental message "M/I Diagnosis Code".

Approvable Hydroxy/Chloroquine (ICD-10) Diagnoses List

ICD-10-CM Code	Description
A06.4	Amebic liver abscess
A06.5	Amebic lung abscess
A06.6	Amebic brain abscess
A06.7	Cutaneous amebiasis
A06.81	Amebic cystitis
A06.82	Other amebic genitourinary infections
A06.89	Other amebic infections
A06.9	Amebiasis, unspecified
B52.0	Plasmodium malariae malaria with nephropathy
B52.8	Plasmodium malariae malaria with other complications
B52.9	Plasmodium malariae malaria without complication
B53.0	Plasmodium ovale malaria
B53.1	Malaria due to simian plasmodia
B53.8	Other malaria, not elsewhere classified
B54	Unspecified malaria
L93.0	Discoid lupus erythematosus

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>M05.9</td><td>Rheumatoid arthritis with rheumatoid factor, unspecified</td></tr>
<tr><td>M32.0</td><td>Drug-induced systemic lupus erythematosus</td></tr>
<tr><td>M32.10</td><td>Systemic lupus erythematosus, organ or system involvement unspecified</td></tr>
<tr><td>M32.8</td><td>Other forms of systemic lupus erythematosus</td></tr>
<tr><td>M32.9</td><td>Systemic lupus erythematosus, unspecified</td></tr>
</table>

Note: This edit does NOT override existing quantity limits.
<table>
<tr><th>Drug Name</th><th>Quantity Limitations</th></tr>
<tr><td>Hydroxychloroquine</td><td>Max of 600mg per day</td></tr>
<tr><td>100mg</td><td>1 per day</td></tr>
<tr><td>200mg</td><td>3 per day</td></tr>
<tr><td>300mg</td><td>2 per day</td></tr>
<tr><td>400mg</td><td>1 per day</td></tr>
<tr><td>Chloroquine</td><td>Max of 1,000mg per day</td></tr>
<tr><td>250mg</td><td>1 per day</td></tr>
<tr><td>500mg</td><td>2 per day</td></tr>
</table>
</td></tr>
<tr><td>Endari/Siklos Auto PA

Automated PA approval satisfies L=Auto PA drug logic

*Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic</td><td>
<table>
<tr><th colspan="3">Sickle Cell List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>L-glutamine</td><td>Endari</td><td>GSN = 078050</td></tr>
<tr><td>hydroxyurea</td><td>Siklos</td><td>GSNs = 067584, 078316</td></tr>
</table>
</td><td>Step 1: Is incoming claim for GSN 078050 <Endari> or GSN 067584 or GSN 078316 <Siklos> and Prior Auth = L-Auto PA? If yes, PROCEED TO STEP 2. Otherwise, STOP.

Step 2: Is incoming claim for GSN 078050 <Endari>? If yes, PROCEED TO STEP 3. Otherwise (claim is for Siklos), PROCEED TO STEP 4.

Step 3: Look back 180 days within claims history for GSN 078050 <Endari>. If found, CLAIM PAYS; Otherwise PROCEED TO STEP 5.

Step 4: If incoming claim is for GSN 067584 or GSN 078316 <Siklos> look back 180 within claim history for GSN 067584 or 078316 <Siklos>. If found, CLAIM PAYS; Otherwise PROCEED TO STEP 5.</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>Step 5: Look back 730 days in the patient's medical history for ICD-10 in Disease Group D56, D57, D58 (sickle cell disease). If found, CLAIM PAYS. If not found, deny for NCPDP 75/2462 with additional message "Recip doesn't have Req Diagnosis on file for this Medication"

Note: Automated PA approval will NOT override age or quantity limits

<table>
<tr><th>Drug Name</th><th>Age Limit (Min Age)</th><th>Quantity Limitations</th></tr>
<tr><td>Endari</td><td>5</td><td>Max of 180 packets every 30 days</td></tr>
<tr><td>Siklos</td><td>2</td><td>Max of 3,500 mg per day</td></tr>
</table>
</td></tr>
<tr><td>Zirabev Auto PA

Automated PA approval satisfies L=Auto PA drug logic

*Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic</td><td>
<table>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Zirabev 25 mg/ml vial</td><td>HSN = 045849</td></tr>
</table>
</td><td>Step 1: If incoming claim is for <Zirabev vial > and Prior Auth = L – Auto PA, look back 365 days in medical history for a diagnosis from Approvable Diagnosis Codes below. If found, CLAIM PAYS. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message "M/I Diagnosis Code"

<table>
<tr><th colspan="2">Approvable Diagnosis Codes</th></tr>
<tr><th>ICD 10 Codes</th><th>Description</th></tr>
<tr><td>C18.0</td><td>Malignant neoplasm of cecum</td></tr>
<tr><td>C18.2</td><td>Malignant neoplasm of ascending colon</td></tr>
<tr><td>C18.3</td><td>Malignant neoplasm of hepatic flexure</td></tr>
<tr><td>C18.4</td><td>Malignant neoplasm of transverse colon</td></tr>
<tr><td>C18.5</td><td>Malignant neoplasm of splenic flexure</td></tr>
<tr><td>C18.6</td><td>Malignant neoplasm of descending colon</td></tr>
<tr><td>C18.7</td><td>Malignant neoplasm of sigmoid colon</td></tr>
<tr><td>C18.8</td><td>Malignant neoplasm of overlapping sites of colon</td></tr>
<tr><td>C18.9</td><td>Malignant neoplasm of</td></tr>
</table>
</td></tr>
</table>

Edit	Drugs	Steps	
			colon, unspecified
		C19	Malignant neoplasm of rectosigmoid junction
		C20	Malignant neoplasm of rectum
		C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
		C78.5	Secondary malignant neoplasm of large intestine and rectum
		C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
		D37.4	Neoplasm of uncertain behavior of colon
		D37.5	Neoplasm of uncertain behavior of rectum
		C34.0	Malignant neoplasm of main bronchus
		C34.00	Malignant neoplasm of unspecified main bronchus
		C34.01	Malignant neoplasm of right main bronchus
		C34.02	Malignant neoplasm of left main bronchus
		C34.1	Malignant neoplasm of upper lobe, bronchus or lung
		C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
		C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
		C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
		C34.2	Malignant neoplasm of middle lobe, bronchus or lung

Edit	Drugs	Steps	
		C34.3	Malignant neoplasm of lower lobe, bronchus or lung
		C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
		C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
		C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
		C34.8	Malignant neoplasm of overlapping sites of bronchus and lung
		C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
		C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
		C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
		C34.9	Malignant neoplasm of unspecified part of bronchus or lung
		C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
		C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
		C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
		C71	Malignant neoplasm of brain
		C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
		C71.1	Malignant neoplasm of

Edit	Drugs	Steps	
			frontal lobe
		C71.2	Malignant neoplasm of temporal lobe
		C71.3	Malignant neoplasm of parietal lobe
		C71.4	Malignant neoplasm of occipital lobe
		C71.5	Malignant neoplasm of cerebral ventricle
		C71.6	Malignant neoplasm of cerebellum
		C71.7	Malignant neoplasm of brain stem
		C71.8	Malignant neoplasm of overlapping sites of brain
		C71.9	Malignant neoplasm of brain, unspecified
		C72.0	Malignant neoplasm of spinal cord
		C64.1	Malignant neoplasm of right kidney, except renal pelvis
		C64.2	Malignant neoplasm of left kidney, except renal pelvis
		C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
		C53.0	Malignant neoplasm of endocervix
		C53.1	Malignant neoplasm of exocervix
		C53.8	Malignant neoplasm of overlapping sites of cervix uteri
		C53.9	Malignant neoplasm of cervix uteri, unspecified
		C56.1	Malignant neoplasm of right ovary
		C56.2	Malignant neoplasm of left ovary

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>C56.3</td><td>Malignant neoplasm of bilateral ovaries</td></tr>
<tr><td>C56.9</td><td>Malignant neoplasm of unspecified ovary</td></tr>
<tr><td>C57.0</td><td>Malignant neoplasm of fallopian tube</td></tr>
<tr><td>C57.00</td><td>Malignant neoplasm of unspecified fallopian tube</td></tr>
<tr><td>C57.01</td><td>Malignant neoplasm of right fallopian tube</td></tr>
<tr><td>C57.02</td><td>Malignant neoplasm of left fallopian tube</td></tr>
<tr><td>C48.0</td><td>Malignant neoplasm of retroperitoneum</td></tr>
<tr><td>C48.1</td><td>Malignant neoplasm of specified parts of peritoneum</td></tr>
<tr><td>C48.2</td><td>Malignant neoplasm of peritoneum, unspecified</td></tr>
<tr><td>C48.8</td><td>Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum</td></tr>
</table>
Note:
Automated PA approval will NOT override age limits or quantity limits
<table>
<tr><th>Drug Name</th><th>Age Limit (Min Age)</th><th>Quantity Limitations</th></tr>
<tr><td>Zirabev 25 mg/ml vial</td><td>18</td><td>110 mL’s every 30 days</td></tr>
</table>
</td></tr>
<tr><td>Ellence Auto PA

Automated PA approval satisfies L=Auto PA drug logic

*Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic</td><td>
<table>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Ellence 2 mg/ml vial</td><td>HSN = 006578</td></tr>
</table>
</td><td>
Step 1: If incoming claim is for < Ellence > and Prior Auth = L-AutoPA, look back 365 days in medical history for a diagnosis from Approvable Diagnosis Codes below. If found, CLAIM PAYS. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code”
<table>
<tr><th colspan="2">Approvable Diagnosis Codes</th></tr>
<tr><th>ICD 10 Codes</th><th>Description</th></tr>
<tr><td>C50.011-C50.019

C50.111-C50.119,</td><td>Malignant neoplasm of female breast</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>C50.211-C50.219,
C50.311-C50.319,
C50.411-C50.419,
C50.511-C50.519,
C50.611-C50.619,
C50.811-C50.819,
C50.911-C50.919</td><td></td></tr>
</table>
Note:
Automated PA approval will NOT override age limits or quantity limits
<table>
<tr><th>Drug Name</th><th>Age Limit (Min Age)</th><th>Quantity Limitations</th></tr>
<tr><td>Ellence 2 mg/ml vial</td><td>18</td><td>1125mL's per lifetime</td></tr>
</table>
</td></tr>
<tr><td>Ruxience Auto PA

Automated PA approval satisfies L=Auto PA drug logic

*Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic</td><td>
<table>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Ruxience 10mg/mL Vial</td><td>HSN = 045899</td></tr>
</table>
</td><td>Step 1: If incoming claim is for <Ruxience vial > and Prior Auth = L – Auto PA, look back 365 days in medical history for a diagnosis from Approvable Diagnosis Codes below. If found, CLAIM PAYS. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message "M/I Diagnosis Code"
<table>
<tr><th colspan="2">Approvable Diagnosis Codes</th></tr>
<tr><th>ICD 10 Codes</th><th>Description</th></tr>
<tr><td>Disease Group: C85</td><td>Other specified and unspecified types of non-Hodgkin lymphoma</td></tr>
<tr><td>C91.1</td><td>Chronic lymphocytic leukemia of B-cell type</td></tr>
<tr><td>C91.10</td><td>Chronic lymphocytic leukemia of B-cell type not having achieved remission</td></tr>
<tr><td>C91.11</td><td>Chronic lymphocytic leukemia of B-cell type in remission</td></tr>
<tr><td>C91.12</td><td>Chronic lymphocytic leukemia of B-cell type in relapse</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Disease Group:

M05

M06</td><td>Rheumatoid arthritis with or without Rheumatoid Factor</td></tr>
<tr><td>M31.3</td><td>Wegener's granulomatosis</td></tr>
<tr><td>M31.7</td><td>Microscopic polyangiitis</td></tr>
</table>

Note:
• Automated PA approval will NOT override age limits or quantity limits

<table>
<tr><th>Drug Name</th><th>Age Limit (Min Age)</th><th>Quantity Limitations</th></tr>
<tr><td>Ruxience 10mg/mL Vial</td><td>18</td><td>736 mL's every 30 days</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr>
<td>Doxil Auto PA

Automated PA approval satisfies L=Auto PA drug logic

Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic</td>
<td>
<table>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Doxil 2 mg/mL Vial</td><td>NDC11 = 00338006301, 00338006701</td></tr>
</table>
</td>
<td>
If incoming claim is from <Doxil> and Prior Auth = L- AutoPA, look back in medical claims history 365 days for a diagnosis of Multiple Myeloma, Ovarian cancer, or AIDS-related Kaposi Sarcoma (see approvable ICD-10s below). If found, claim MOVES OUT OF EDIT. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code”
<table>
<tr><th>ICD-10 Code</th><th>Description</th></tr>
<tr><td>Disease group: C90</td><td>Multiple myeloma</td></tr>
<tr><td>Disease group: C56</td><td>Malignant neoplasm of ovary</td></tr>
<tr><td>Disease group: C46</td><td>Kaposi's sarcoma</td></tr>
</table>
Note:
Automated PA approval will NOT override age limits or quantity limits.
<table>
<tr><th>Drug Name</th><th>Age Limit (Min Age)</th><th>Quantity Limitations</th></tr>
<tr><td>Doxil 2 mg/mL Vial</td><td>18</td><td>60mL every 18 days</td></tr>
</table>
</td>
</tr>
<tr>
<td>Vidaza Auto PA

Automated PA approval satisfies L=Auto PA drug logic

Automated PA approval will NOT override R = Non-PDL coding and will not satisfy the automation logic</td>
<td>
<table>
<tr><th>Drug Name</th><th>Drug Code</th></tr>
<tr><td>Vidaza 100 mg Vial</td><td>GSN = 054660</td></tr>
</table>
</td>
<td>
If incoming claim is from <Vidaza> and Prior Auth = L- AutoPA, look back in medical claims history 365 days for a diagnosis of Chronic Monocytic Leukemia, Juvenile Myelomonocytic Leukemia or Myelodysplastic Syndromes (see approvable ICD-10s below). If found, claim MOVES OUT OF EDIT. Otherwise, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code”
<table>
<tr><th>ICD-10 Code</th><th>Description</th></tr>
<tr><td>C93.10 - C93.12</td><td>Chronic Monocytic Leukemia</td></tr>
<tr><td>C93.30 - C93.32</td><td>Juvenile Myelomonocytic Leukemia</td></tr>
<tr><td>Disease group: D46</td><td>Myelodysplastic Syndromes</td></tr>
</table>
Note:
Automated PA approval will NOT override age limits or quantity limits.
</td>
</tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th>Drug Name</th><th>Quantity Limitations</th></tr>
<tr><td>Vidaza 100 mg Vial</td><td>17 vials every 28 days</td></tr>
</table>
</td></tr>
<tr><td>Reset
AutoPA

Automated PA approval satisfies L=Auto PA drug edit

*Automated PA approval will NOT override R = NonPDL edit and will not satisfy the automation logic</td><td>
<table>
<tr><th colspan="2">Reset List</th></tr>
<tr><th>HSN</th><th>Device</th></tr>
<tr><td>048063</td><td>RESET (SUD)
RESET (SUD) (NON-MONETARY CM)</td></tr>
<tr><td>048064</td><td>RESET-O (OUD)
RESET-O (OUD)(NON-MONETARY CM)</td></tr>
</table>
</td><td>
Step 1: : If the incoming claim is for HSN 048063 – Reset SUD with FMT Prior Auth = L-Auto PA Drug, PROCEED TO STEP 2. If the incoming claim is for HSN 048064 – RESET-O with FMT Prior Auth = L-Auto PA Drug, PROCEED TO STEP 3.

Step 2: If the incoming claim is for HSN 048063 – Reset look back in claims history 365 days for an ICD 10 in disease group = F19 (Other psychoactive substance related disorders). If found, APPROVE. If not, PROCEED TO STEP 4.

Step 3: If the incoming claim is for HSN 048064 – RESET-O look back in claims history 365 days for an ICD 10 in disease group = F11 (Opioid Use Disorder). If found, APPROVE. If not, PROCEED TO STEP 4.

Step 4: If the incoming claim includes Prior Auth Type Code = 3 – EPSDT, APPROVE. If not, DENY for PRIOR AUTHORIZATION REQUIRED (75) with supplemental message “M/I Diagnosis Code” (INTERNAL ERROR CODE 2462).

Note: This logic does NOT override existing age or quantity limits

<table>
<tr><th colspan="3">Approvable ICD-10 Disease Groups</th></tr>
<tr><th>Device Name</th><th>Disease Group</th><th>Diagnosis</th></tr>
<tr><td>RESET (SUD)
RESET (SUD) (NON-MONETARY CM)</td><td>F19</td><td>Other Psychoactive Substance Related Disorders</td></tr>
<tr><td>RESET-O (OUD)
RESET-O (OUD)(NON-MONETARY CM)</td><td>F11</td><td>Opioid Use Disorder</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th>Drug Name</th><th>Age Limit (Min Age)</th><th>Quantity Limitations</th></tr>
<tr><td>RESET (SUD)
RESET (SUD) NON-MONETARY CM</td><td rowspan="2">18</td><td>Max 1 fill every 90 days;
Max of 2 fills per 328 days</td></tr>
<tr><td>RESET-O (OUD)
RESET-O (OUD) NON-MONETARY CM</td><td>Max 1 fill every 84 days;
Max of 2 fills per 328 days</td></tr>
</table>
</td></tr>
</table>

Notes:

- Quantity limits as found on drug file will still apply to all drugs in edits above, regardless of passing edits as noted.
- All edits are to be effective back to start of plan.
- All edits are date of service driven.

Bypass List:

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr>
<td>50 Morphine Milligram Equivalent (MME) HD (high dose) Bypass Logic</td>
<td>
<table>
<tr><th colspan="2">Opioid HIC4 List</th></tr>
<tr><th>Drug Code = HIC4</th><th>Generic Name</th></tr>
<tr><td>H3AA</td><td>Meperidine</td></tr>
<tr><td>H3AD</td><td>Morphine</td></tr>
<tr><td>H3AE</td><td>Hydromorphone</td></tr>
<tr><td>H3AF</td><td>Oxymorphone</td></tr>
<tr><td>H3AH</td><td>Codeine</td></tr>
<tr><td>H3AJ</td><td>Hydrocodone</td></tr>
<tr><td>H3AK</td><td>Dihydrocodeine</td></tr>
<tr><td>H3AL</td><td>Oxycodone</td></tr>
<tr><td>H3AN</td><td>Levorphanol</td></tr>
<tr><td>H3AR</td><td>Methadone</td></tr>
<tr><td>H3AT</td><td>Fentanyl</td></tr>
<tr><td>H3AY</td><td>Opium</td></tr>
<tr><td>H3AZ</td><td>Buprenorphine</td></tr>
<tr><td>H3BH</td><td>Tramadol</td></tr>
<tr><td>H3BL</td><td>Butorphanol</td></tr>
<tr><td>H3BS</td><td>Tapentadol</td></tr>
<tr><td>H3BM</td><td>Pentazocine</td></tr>
<tr><td>H3BV</td><td>Benzhydrocodone/Acetaminophen</td></tr>
</table>
</td>
<td>
Limitation:
Maximum of 50 MME per day across the HIC4

Logic:
Please deny all High Dose (HD) claims for opioid tolerant recipients that exceed the limitation.

Opioid tolerant is defined as having a paid opioid claim, within 60 days, of the incoming claim

The provider will be able to override the denial utilizing the DUR Reason for Service Code: HD- High Dose and only the approved intervention/professional service codes, outcome/result of service codes.

Exclusions:
Recipients with an LTC indicator, a patient residence = 03-Nursing facility, or an active diagnosis of cancer or sickle cell in medical claims history (within 365 days from the DOS of the incoming claim) of ICD 10 Disease Block C00-C14, C15-C26, C30-39, C40-41, C43-C44, C45-C49, C50, C51-C58, C60-C63, C64-C68, C69-C72, C73-C75, C76-C80, C7A, C7B, C81-C96, D00-D09, D10-D36, D37-D48, D3A, D49, ICD-10-K31.7, K63.5, Q85.00, Q85.01, Q85.02 (cancer), ICD10 Disease Group D56, D57, D58 (sickle cell disease) will bypass the 50MME limitation.

Note: Naïve recipients (recipients that do not have a paid opioid claim, within 60 days of the incoming claim) will continue to follow the 90 MME per day limit.
</td>
</tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr>
<td>90 Morphine Milligram Equivalent (MME) Bypass Logic</td>
<td>
<table>
<tr><th colspan="2"><Opioid HIC4 List></th></tr>
<tr><th>Drug Code = HIC4</th><th>Generic Name</th></tr>
<tr><td>H3AA</td><td>Meperidine</td></tr>
<tr><td>H3AD</td><td>Morphine</td></tr>
<tr><td>H3AE</td><td>Hydromorphone</td></tr>
<tr><td>H3AF</td><td>Oxymorphone</td></tr>
<tr><td>H3AH</td><td>Codeine</td></tr>
<tr><td>H3AJ</td><td>Hydrocodone</td></tr>
<tr><td>H3AK</td><td>Dihydrocodeine</td></tr>
<tr><td>H3AL</td><td>Oxycodone</td></tr>
<tr><td>H3AN</td><td>Levorphanol</td></tr>
<tr><td>H3AR</td><td>Methadone</td></tr>
<tr><td>H3AT</td><td>Fentanyl</td></tr>
<tr><td>H3AY</td><td>Opium</td></tr>
<tr><td>H3AZ</td><td>Buprenorphine</td></tr>
<tr><td>H3BH</td><td>Tramadol</td></tr>
<tr><td>H3BL</td><td>Butorphanol</td></tr>
<tr><td>H3BS</td><td>Tapentadol</td></tr>
<tr><td>H3BM</td><td>Pentazocine</td></tr>
<tr><td>H3BV</td><td>Benzhydrocodone/Acetaminophen</td></tr>
</table>
</td>
<td>Bypass Logic:
If incoming Claim for a drug in <Opioid HIC4 List> look back 60 days in recipient's paid claim history for any product in <Opioid HIC4 List, including itself>. If found, Bypass 90MME per accumulation limitation

Exclusions:
Look back 365 in patient's medical claim history for ICD 10 Disease Block C00-C14, C15-C26, C30-39, C40-41, C43-C44, C45-C49, C50, C51-C58, C60-C63, C64-C68, C69-C72, C73-C75, C76-C80, C7A, C7B, C81-C96, D00-D09, D10-D36, D37-D48, D3A, D49, ICD-10-K31.7, K63.5, Q85.00, Q85.01, Q85.02 (cancer) or ICD10 Disease Group D56, D57, D58 (sickle cell disease) OR an LTC indicator or Patient Residence 03 on the claim. If found, Bypass 90MME per accumulation limitation.
.
Limitation:
Maximum of 90 MME per day across the HIC4</td>
</tr>
<tr>
<td>Mercaptopurine Non-PDL and QL bypass

75/2462 OVERRIDE IS NO LONGER ACTIVE
Generic Mercaptopurine (HICL 003908) changed to S-PDL effective 10/01/2016 so 75/2462 bypass is</td>
<td>
<table>
<tr><th>HICL</th><th>Drug Name</th></tr>
<tr><td>003908</td><td>Mercaptopurine (Generic only)</td></tr>
</table>
</td>
<td>If the incoming claim is GENERIC Mercaptopurine (HSN 003908- excluding Brand Purinethol), look back in medical claims history 730 days for ICD 10 Disease Group: K40, K41, K42, K43, K44, K45, K46, K50, K52 (Crohn's disease), or 556.0-556.9, ICD 10 Disease Group: K51 (Ulcerative colitis): IF FOUND BYPASS THE NON-PDL REQUIREMENT (NO PA REQUIRED) AND BYPASS THE QUANTITY LIMITATION OF 90 per 27 days.

<table>
<tr><th colspan="2">Approvable ICD-10 Disease Groups</th></tr>
<tr><td>K40, K41, K42, K43, K44, K45, K46, K50, K52</td><td>Crohn's disease</td></tr>
<tr><td>K51</td><td>Ulcerative colitis</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr><td>no longer required. Continue to bypass 76 for quantity limit if criteria met.</td><td></td><td></td></tr>
<tr><td>Hydroxyurea Non-PDL and QL bypass</td><td>
<table>
<tr><th colspan="3"><Hydroxyurea Drug List></th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>Hydroxyurea 500mg capsules</td><td>Hydrea</td><td>GSN 008775 and Generic Named Drug Cd = 1-Generic (Excludes Brand name Hydrea)</td></tr>
<tr><td>Hydroxyurea</td><td>Droxia 200mg capsules</td><td>GSN 040162</td></tr>
<tr><td>Hydroxyurea</td><td>Droxia 300mg capsules</td><td>GSN 040163</td></tr>
<tr><td>Hydroxyurea</td><td>Droxia 400mg capsules</td><td>GSN 040164</td></tr>
</table>
</td><td>If the incoming claim is in <Hydroxyurea Drug List>, look back in medical claims history 730 days for ICD 10: D45(polycythemia vera), D75.0 (familial polycythemia), D47.3 (essential thrombocythemia), Disease Group D56, D57, D58 (sickle cell): IF FOUND BYPASS THE NON-PDL REQUIREMENT (NO PA REQUIRED) AND BYPASS THE QUANTITY LIMITATION OF 90 per 27 days.
<table>
<tr><th colspan="2">Approvable ICD-10 Disease Groups</th></tr>
<tr><td>D56, D57, D58</td><td>Sickle Cell</td></tr>
</table>
<table>
<tr><th colspan="2">Approvable ICD-10 CM Codes</th></tr>
<tr><td>D45</td><td>Polycythemia vera</td></tr>
<tr><td>D75.0</td><td>Familial Polycythemia</td></tr>
<tr><td>D47.3</td><td>Essential Thrombocythemia</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Edit</th><th>Drugs</th><th>Steps</th></tr>
<tr>
<td>Zanaflex (Tizanidine) and Baclofen FDB limit Bypass</td>
<td>
<table>
<tr><th colspan="3">SMR List</th></tr>
<tr><th>Generic Name</th><th>Brand Name</th><th>Drug Code</th></tr>
<tr><td>Baclofen
Tizanidine</td><td>N/A
Zanaflex</td><td>HICL = 001949
HICL = 011582</td></tr>
</table>
</td>
<td>
If incoming claim is for Baclofen <HSN 001949> or Zanaflex (Tizanidine) <HSN 011582), look back in medical claims history 730 days for ICD 10s: listed below, in history, if found, BYPASS HIGH DOSE(HD) PRODUR MAXIMUM DAILY DOSE EDIT – CLAIM PAYS.
<table>
<tr><th>ICD -10 CM Code</th><th>Description</th></tr>
<tr><td>ICD 10 Disease Group: G11, ICD 10: G32.81</td><td>Hereditary Ataxia:</td></tr>
<tr><td>ICD 10: G12.20, G12.21, G12.22, G12.29, G12.8</td><td>Motor Neuron disease: Other spinal muscle atrophis and related syndromes</td></tr>
<tr><td>ICD 10: I69.053, I69.051, I69.052 I69.053, I69.054, I69.059, I69.151, I69.152, I69.153, I69.154, I69.159, I69.251, I69.252, I69.253, I69.254, I69.259, I69.351, I69.352, I69.353, I69.354, I69.359, I69.851, I69.852, I69.853, I69.854, I69.859, I69.951, I69.952, I69.953, I69.954, I69.959</td><td>Hemiplegia and hemiparesis following unspecified cerebrovascular disease</td></tr>
<tr><td>ICD 10: I69.031, I69.032, I69.033, I69.034, I69.039, I69.131, I69.132, I69.133, I69.134, I69.139, I69.231, I69.232, I69.233, I69.234, I69.239, I69.331, I69.332, I69.333, I69.334, I69.339, I69.831, I69.832, I69.833, I69.834, I69.839, I69.931, I69.932, I69.933, I69.934, I69.939</td><td>Monoplegia of upper limb following unspecified cerebrovascular disease</td></tr>
<tr><td>ICD 10: I69.041 I69.042, I69.043, I69.044, I69.049, I69.141, I69.142, I69.143, I69.144, I69.149, I69.241, I69.242, I69.243, I69.244, I69.249, I69.341, I69.342, I69.343, I69.344, I69.349, I69.841, I69.842, I69.843, I69.844, I69.849, I69.949, I69.941, I69.942, I69.943, I69.944, I69.949</td><td>Monoplegia of lower limb following unspecified cerebrovascular disease</td></tr>
<tr><td>ICD 10: I69.061, I69.062, I69.063, I69.064, I69.065 I69.069, I69.161, I69.162, I69.163, I69.164, I69.165 I69.169, I69.261, I69.262, I69.263, I69.264, I69.265, I69.269, I69.361, I69.362, I69.363, I69.364, I69.365, I69.369, I69.861, I69.862, I69.863, I69.864, I64.865, I69.869, I69.961, I69.962, I69.963, I69.964, I69.965, I69.969</td><td>Other paralytic syndrome following unspecified cerebrovascular disease</td></tr>
</table>
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Edit	Drugs	Steps	
		ICD 10: I69.00, I69.10, I69.20, I69.30, I69.80, I69.90	Unspecified sequelae of unspecified cerebrovascular disease
		ICD 10: G35	Multiple sclerosis
		ICD 10 Disease Groups: G36, G37	Other demyelinating diseases of central nervous system
		ICD 10 Disease Group: G81	Hemiplegia/Hemiparesis
		ICD 10 Disease Group: G80	Cerebral Palsy
		ICD 10: Disease Group: G82, G83	Paraplegia (parapaesis) and quadriplegia (quadriparesis) Other paralytic syndromes
		ICD 10: R53.2	Functional Quadriplegia
		ICD 10: R29.0	Tetany
		ICD 10: S14.101A, S14.102A, S14.103A, S14.104A, S14.105A, S14.106A, S14.107A, S14.108A, S14.109A, S14.111A, S14.112A, S14.113A, S14.114A, S14.115A, S14.116A, S14.117A, S14.118A, S14.119A, S14.121A, S14.122A, S14.123A, S14.124A, S14.125A, S14.126A, S14.127A, S14.128A, S14.129A, S14.131A, S14.132A , S14.133A, S14.134A, S14.135A, S14.136A, S14.137A, S14.138A, S14.139A, S14.141A, S14.142A, S14.143A, S14.144A, S14.145A, S14.146A, S14.147A, S14.148A, S14.149A, S14.0XXA, S14.151A, S14.152A, S14.153A, S14.154A, S14.155A, S14.156A, S14.157A, S14.158A, S14.159A, S24.101A, S24.102A, S24.103A, S24.104A, S24.109A, S24.111A, S24.112A, S24.113A, S24.114A, S24.119A, S24.131A, S24.132A, S24.133A, S24.134A, S24.139A, S24.141A, S24.142A, S24.143A, S24.144A, S24.149A, S24.151A, S24.152A, S24.153A, S24.154A, S24.159A, S24.0XXA, S24.01XA, S34.101A, S34.102A, S34.103A, S34.104A, S34.105A,	Spinal Cord Injury without evidence of spinal bone injury

Edit	Drugs	Steps
		S34.109A, S34.111A, S34.112A, S34.113A, S34.114A, S34.115A, S34.119A, S34.121A, S34.122A, S34.123A, S34.124A, S34.125A, S34.129A, S34.131A, S34.132A, S34.139A, S34.02XA, S34.3XXA

TESTOSTERONE

DRUGDEX Evaluations

Pl. Trial Ex. 025

DOSING/ADMINISTRATION

Adult Dosing

Normal Dosage

Important Note

Testosterone

Topical testosterone products are not interchangeable as they have different strengths, doses, and application instructions that may result in different systemic exposure [1][2][3][4][5].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Cypionate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Enanthate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Undecanoate

Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone

Buccal mucosa route

Hypogonadism, Male

1) FDA Dosage, Striant(R)

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [17].

b) Usual dose: One 30-mg buccal system applied to the gum approximately every 12 hours, applying to opposite sides of the mouth with each dose; monitor testosterone levels at 4 to 12 weeks after initiation, and discontinue if levels are consistently outside normal range [23]

c) Dosing notes: If the system fails to adhere or falls off within 8 hours of application, a new system may be applied and continued for a total of 12 hours from the placement of the first system; however, if it is within 8 hours of the next scheduled dose, apply the new system for 12 hours and then continue with the next dose. Remove system prior to oral care and apply a new system after [23].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Striant(R) testosterone buccal system is not indicated for use in women [23].

Nasal route

Hypogonadism, Male

1) FDA Dosage, Natesto(TM)

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [16].

b) Usual dose: 1 actuation per nostril (2 pump actuations, 11 mg) intranasally 3 times a day (morning, afternoon, and evening, 6 to 8 hours apart) at the same time each day for a total daily dose of 33 mg; after 1 month check testosterone levels periodically [22]

c) If total testosterone level usually below 300 nanograms/dL, consider alternative therapy [22].

d) If total testosterone level generally greater than 1050 nanograms/dL, discontinue treatment with testosterone nasal gel [22].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Natesto(TM) testosterone nasal gel is not indicated for use in women [22].
There is insufficient evidence of long-term safety (ie, cardiovascular and prostate cancer risks) for Natesto(TM) testosterone gel treatment in geriatric patients [22].
The safety and efficacy of Natesto(TM) testosterone gel treatment have not been established in patients with a BMI greater than 35 kg/m(2) [22].

Topical application

Hypogonadism, Male

1) FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [5][15][1][3][2][18].

2) FDA Dosage, Axiron(R)

a) Initial dose: 60 mg (1 pump or twist actuation of 30 mg to each axilla) applied once daily at the same time each morning to clean, dry, intact skin of the axilla; do not apply to any other parts of the body; obtain serum testosterone concentration at least 14 days after initiation; draw 2 to 8 hours after application [20]

b) Dose titration: decrease or increase dose by 30-mg increments based on serum testosterone concentration from a single blood draw 2 to 8 hours after application and at least 14 days after starting treatment or following dose adjustment, according to the following recommendation [20][20]:

Serum testosterone concentration below 300 nanogram/deciliter (ng/dL): Increase daily dose from 60 to 90 mg or from 90 mg to 120 mg

Serum testosterone concentration exceeds 1050 ng/dL: Decrease daily dose from 60 mg to 30 mg, or discontinue therapy if at the lowest daily dose of 30 mg

3) FDA Dosage, AndroGel(R) 1%

a) Initial dosage: 50 mg topically once daily (4 pump actuations, or 5 g of gel) preferably in the morning to clean, dry, intact skin on shoulders and upper arms and/or abdomen [5]

b) Dose titration: May increase once-daily dose to 75 mg (6 pump actuations, or 7.5 g of gel) and further to 100 mg (8 pump actuations, or 10 g of gel) if testosterone concentration below normal physiologic level [5]

c) Discontinue use if serum testosterone concentrations consistently exceed the normal range at a daily dose of 50 mg [5]

4) FDA Dosage, AndroGel(R) 1.62%

a) Initial dosage: 40.5 mg (2 pump actuations or 2.5 g of gel) applied topically once daily in the morning to clean, dry, intact skin of the shoulders and upper arms; measure predose morning serum testosterone concentration at approximately 14 and 28 days [15]

b) Dosage titration: Decrease or increase dose to minimum of 20.25 mg/day (1 pump actuation or 1.25 g of gel) up to 81 mg/day (4 pump actuations, or 5 g of gel), based on predose morning serum testosterone concentration drawn approximately 14 and 28 days after starting treatment or following dose adjustment, according to the following recommendation [15]:

Pre-Dose Morning Total Serum Testosterone Concentration	Dose Titration
Greater than 750 ng/dL	Decrease daily dose by 20.25 mg (1 pump actuation or 1.25 g of gel)
Equal to or greater than 350 and equal to or less than 750 ng/dL	No change: continue current dose
Less than 350 ng/dL	Increase daily dose by 20.25 mg (1 pump actuation or 1.25 g of gel)
Key: ng = nanograms	

c) The application site and dose of AndroGel(R) 1.62% are not interchangeable with other topical testosterone products [15]

5) FDA Dosage, Fortesta(TM)

a) Initial dose: 40 mg (4 pump actuations) applied once daily to clean, dry, intact skin of the front and inner thighs in the morning; measure serum testosterone level at approximately 14 and 35 days, draw 2 hours post-application [21]

b) Dose titration: decrease or increase dose to a minimum of 10 mg/day or maximum of 70 mg/day, based on serum testosterone concentrations, drawn 2 hours after application at approximately 14 days and 35 days after treatment initiation or following dose adjustments, according to the following recommendation [21]:

Total Serum Testosterone Concentrations 2 hours Post Fortesta(TM) Application	Dose Titration
Equal to or greater than 2500 ng/dL	Decrease daily dose by 20 mg (2 pump actuations)
Equal to or greater than 1250 and less than 2500 ng/dL	Decrease daily dose by 10 mg (1 pump actuation)
Equal to or greater than 500 and less than 1250 ng/dL	No change: continue current dose
Less than 500 ng/dL	Increase daily dose by 10 mg (1 pump actuation)
Key: ng = nanograms	

c) The application site and dose of Fortesta(TM) are not interchangeable with other topical testosterone products [21].

6) FDA Dosage, Testim(R) 1% Gel

a) Initial dose: one 5 g tube applied once daily (preferably in morning) to clean, dry, intact skin on the shoulder and/or upper arms; measure morning testosterone level 2 weeks after initiation [24].

b) Dose titration: increase dose to 10 g/day (2 tubes) if serum testosterone concentration is below the normal physiologic range or if desired clinical

response is not observed [24]

7) FDA Dosage, Vogelxo(TM)

a) Initial dose: 50 mg (1 tube or packet or 4 pump actuations) applied topically to clean, dry, intact skin of shoulders or upper arms once daily; measure morning predose testosterone level after approximately 14 days [25]

b) Dose titration: may increase to 100 mg (2 tubes or packets or 8 pump actuations) once daily if morning predose testosterone level remains below normal (ie, 300 to 1000 nanograms/dL) [25]

c) Maximum dose: 100 mg/day [25]

8) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Topical application route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage (1.6% gel): 50 to 100 mg applied topically once daily. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used). Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

AndroGel(R), 1%, Androgel(R) 1.62%, Natesto(TM), Striant(R), Testim(R), and Vogelxo(TM) topical testosterone gel products are not indicated for use in women [25][22][49][27][24][23]

Transdermal route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage (patch): 2.5 to 7.5 mg/day. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions (guideline dosage) [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage, Androderm(R) 2 mg/day and 4 mg/day System

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [14].

b) Initial dose: One 4 mg/day transdermal system (not two 2 mg/day systems) applied every 24 hours at night; measure early morning serum testosterone level 2 weeks later [19]

c) Dose titration: Increase dose to 6 mg daily at night (one 4 mg/day plus one 2 mg/day system) or decrease dose to 2 mg daily at night (one 2 mg/day system) if early morning serum testosterone level drawn 2 weeks after starting therapy is outside the target range (400 to 930 nanograms/dL) [19].

2) FDA Dosage, Switching from Androderm(R) 2.5 mg/day, 5 mg/day, and 7.5 mg/day System to Androderm(R) 2 mg/day, 4 mg/day, and 6 mg/day System

At next scheduled dose, make switch according to following recommendation [19]:

patients currently on the 2.5 mg/day system may switch to the 2 mg/day system [19]

patients currently on the 5 mg/day system may switch to the 4 mg/day system [19]

patients currently on the 7.5 mg/day system may switch to the 6 mg/day system [19]

Two weeks after switching therapy, measure an early morning serum testosterone level [19]

3) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone Cypionate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg IM every 2 weeks. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Primary hypogonadism, Male

1) FDA Dosage

a) Usual dosage: 50 to 400 mg IM every 2 to 4 weeks. Base dosage (initial, maintenance, and adjustments) on patient response and presence of adverse reactions [82].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone cypionate is not interchangeable with testosterone propionate because of differences in the duration of action [82].

Testosterone Enanthate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg IM every 2 weeks [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Usual dosage: 50 to 400 mg IM every 2 to 4 weeks as replacement therapy; dose based on diagnosis, response to treatment, and presence of adverse effects. Doses above 400 mg per month are generally not required and injections are usually not administered more than every 2 weeks [73].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Metastatic breast cancer, Female

1) Usual dosage (women): 200 to 400 mg IM every 2 to 4 weeks [73].

Subcutaneous route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg subQ every 2 weeks or 50% of the dose subQ once weekly [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Prior to initiation: Confirm the diagnosis of hypogonadism with serum testosterone concentration below the normal range when measured in the morning on at least 2 separate days [74].

b) Initial dosage: 75 mg subQ in the abdominal region once a week [74]

c) Dosage titration: Measure total testosterone trough concentration (Ctrough) 7 days after the most recent dose after 6 weeks of dosing, following 6 weeks after dose adjustment, and periodically while on treatment. If Ctrough is 650 nanograms (ng)/dL or higher, decrease the dose by 25 mg. If Ctrough is less than 350 ng/dL, increase the dose by 25 mg. If Ctrough is 350 to less than 650 ng/dL, maintain the same dose [74].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone Undecanoate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Initial dosage: 1000 mg IM at 0 and 6 weeks and then every 12 weeks to maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [58].

b) Usual dosage: 750 mg IM, and then 750 mg IM 4 weeks later, and then 750 mg IM every 10 weeks thereafter [59]

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

3) Off-label Dosage

a) Off-Label Dosage: 1000 mg IM, and then 1000 mg IM at week 6, and then 1000 mg IM every 12 weeks [60]

Oral route

Hypogonadism, Male

1) Tlando(R) - FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [53].

b) Dosage: 225 mg (2 capsules) orally twice daily in the morning and evening with food; do not adjust dosage [53].

c) Measure serum testosterone following 3 to 4 weeks of treatment and periodically thereafter; draw level 8 to 9 hours after the morning dose [53].

d) Continue treatment if serum testosterone is 300 to 1080 ng/dL, otherwise discontinue treatment [53].

2) Jatenzo(R) - FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [57].

b) Initial dosage: 237 mg twice daily in the morning and evening with food [57]

c) Adjust dose based on serum testosterone concentrations measured 6 hours after the morning dose in plain tubes, clotted at room temperature for 30 minutes prior to centrifugation. Wait seven days after starting treatment or adjusting the dose before checking the serum testosterone concentration. Thereafter, periodically monitor serum testosterone concentrations 6 hours after the morning dose. Administer the same dose in the morning and evening according to the following table [57]:

Testosterone Concentration in Serum From Plain Tube Drawn 6 hours After Morning Dose	Current dose (mg, twice daily)	New dose (mg, twice daily)
Less than 425 nanograms/dL	158	198
	198	237
	237	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	396 (two 198 mg capsules)
425 to 970 nanograms/dL	No dose change	
More than 970 nanograms/dL	396 (two 198 mg capsules)	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	237
	237	198
	198	158
	158	Discontinue therapy

d) Maximum dosage: 396 mg (two 198 mg capsules) twice daily [57]

3) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Dosage in Renal Failure

A) Testosterone Enanthate

1) No specific recommendations are available [76]

Dosage in Hepatic Insufficiency

A) Testosterone Enanthate

1) No specific recommendations are available [76]

Dosage in Other Disease States

A) Testosterone Enanthate

1) In patients who develop edema with or without congestive heart failure, discontinue testosterone enanthate and restart at a lower dose [73].

Pediatric Dosing

Normal Dosage

Important Note

Testosterone

Topical testosterone products are not interchangeable as they have different strengths, doses, and application instructions that may result in different systemic exposure [1][2][3][4][5].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Cypionate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Enanthate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Undecanoate

Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone

Buccal mucosa route

a) The safety and effectiveness of Striant(R) testosterone buccal system have not been established in males younger than 18 years [23].

Nasal route

a) The safety and efficacy of Natesto(TM) testosterone gel have not been established in patients younger than 18 years [22].

Topical application route

Female-to-male transsexual - Gender dysphoria

1) Off-label Dosage, Adolescent

a) Dosage (gel): 50 mg applied topically once daily [8]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

The safety and efficacy of AndroGel(R) 1%, AndroGel(R) 1.62%, Axiron(R), Fortesta(TM), Testim(R) 1%, and Vogelxo(TM) have not been established in males younger than 18 years [20][25][27][24][49][21]. Acceleration of bone age and premature closure of epiphyses may occur with improper use [21].

Transdermal route

a) Safety and efficacy of testosterone transdermal system have not been established in males younger than 18 years. Acceleration of bone age and premature closure of epiphyses may occur with improper use [19].

Testosterone Cypionate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [Z]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [Z]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [Z]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Primary hypogonadism, Male

1) Usual dosage (12 years or older): 50 to 400 mg IM every 2 to 4 weeks as replacement therapy. Base dosage (initial, maintenance, and adjustments) on patient response, presence of adverse reactions, age, and skeletal age. Some regimens include low initial doses and gradual increases with progressing puberty and may or may not include decreased maintenance doses. Other regimens include higher initial doses for the induction of puberty followed by lower maintenance doses [82].

Testosterone cypionate is not interchangeable with testosterone propionate because of differences in the duration of action [82].

Testosterone Enanthate

Intramuscular route

Delayed puberty, Male

1) Usual dosage (adolescent males): 50 to 200 mg IM every 2 to 4 weeks for a limited duration, such as 4 to 6 months. Some dosage regimens include low initial doses and gradual increases with progressing puberty and may or may not include decreased maintenance doses. Other regimens include higher initial doses for the induction of puberty followed by lower maintenance doses. Although various dosing regimens may be used, the patient's chronological and skeletal age should be considered when determining initial and maintenance doses in addition to patient response and adverse effects [73].

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [Z]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [Z]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [Z]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) Usual dosage (adolescent males): 50 to 400 mg IM every 2 to 4 weeks as replacement therapy. Although various dosing regimens may be used to induce pubertal changes in hypogonadal males, the patient's chronological and skeletal age should be considered when determining initial and maintenance doses. Doses above 400 mg per month are generally not required and injections are usually not administered more than every 2 weeks [73].

Subcutaneous route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) subQ every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [Z]

b) Postpubertal transgender male: 75 mg subQ every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [Z]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [Z]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Testosterone Undecanoate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [Z]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [Z]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [Z]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

General Dosage Information

1) The safety and effectiveness of testosterone undecanoate have not been established in pediatric patients younger than 18 years [59].

Oral route

a) General Dosage Information

1) The safety and effectiveness of testosterone undecanoate have not been established in pediatric patients younger than 18 years. Improper use may result in acceleration of bone age and premature closure of epiphyses [53][57].

FDA Uses

Testosterone

Hypogonadism, Male

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Replacement therapy in congenital or acquired conditions associated with a deficiency or absence of endogenous testosterone, as follows:

Primary hypogonadism (congenital or acquired): Testicular failure from conditions such as cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals [20][22][23][25][19][27][28][24][21]
Hypogonadotropic hypogonadism (congenital or acquired): Idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation [20][22][23][25][19][27][28][24][21]

Limitations of Use

The safety and efficacy of testosterone therapy have not been established in men with late-onset (age-related) hypogonadism [14][5][15][1][3][16][17][2][18].

Evidence (Topical Gel)

In several randomized clinical trials in men with hypogonadism, 75% or more achieved normal serum testosterone levels with administration of testosterone gel for 2 to 3 months [29][21], with effects sustained for 6 months [30] and up to 3 years [31] in several extension studies.

Lean body mass (LBM) significantly increased with testosterone 1% gel compared with placebo at 6 months in symptomatic men 50 to 80 years old with low to low-normal testosterone levels (LBM change, 1.28 vs 0.02 kg; N=362). Fat mass decreased 1.16 kg with testosterone versus 0.14 kg with placebo, an effect that was more pronounced in patients with a BMI of 30 kg/m(2) or greater. Fat mass progressively decreased during 12 additional months of testosterone therapy, but LBM was not further affected [32].

Evidence (Buccal)

During a randomized, 12-week trial in men with hypogonadism, 86.6% of 82 evaluable patients treated with buccal testosterone twice daily had mean serum testosterone concentrations within the physiologic range [23].

Evidence (Intranasal)

In an open-label trial in hypogonadal men, 90% of 73 subjects treated with testosterone nasal gel 3 times daily had an average testosterone level within normal range after 90 days of treatment; no patients had levels above the normal range (N=306) [22].

Testosterone Cypionate

Primary hypogonadism, Male

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (12 years or older)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIa; Pediatric, Class IIa

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Testosterone cypionate is indicated for replacement therapy for congenital or acquired deficiency or absence of endogenous testosterone.

Primary hypogonadism: Testicular failure caused by cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchiectomy [82]
Hypogonadotropic hypogonadism: Deficiency of gonadotropin or luteinizing hormone-

releasing hormone (LHRH); pituitary-hypothalamic injury from tumors, trauma, or radiation [82]

Limitations of Use

Safety and efficacy not established in men with late-onset (age-related) hypogonadism [82].

Use androgens cautiously in the pediatric population because of adverse effects on bone maturation. The risk of compromising final mature height increases as age decreases. Assess bone age in the wrist and hand every 6 months [83].

Testosterone Enanthate

Delayed puberty, Male

FDA Labeled Indication

a) Overview

FDA Approval: Adult, no; Pediatric, yes (adolescent males, IM only)

Efficacy: Pediatric, Evidence favors efficacy

Recommendation: Pediatric, Class IIb

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Testosterone enanthate IM injection is indicated to stimulate puberty in select male patients with delayed puberty [73].

Cautious use of androgens in the pediatric population is necessitated by the likelihood of adverse effects on bone maturation. The risk of a compromised final mature height is greater the younger the child. Assessment of bone age in the wrist and hand every 6 months is recommended [73].

c) Pediatric:

1) Only carefully selected males should receive testosterone for the treatment of delayed puberty. Delayed puberty should not be secondary to a pathological disorder. Most patients have a familial pattern of delayed puberty and are expected to attain puberty spontaneously at a relatively late date. For patients unresponsive to psychological support, a brief treatment with conservative doses may occasionally be justified [73].

Hypogonadism, Male

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (adolescent males, IM only)

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Testosterone enanthate is indicated for testosterone replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone, such as:

Primary hypogonadism (congenital or acquired), including testicular failure from conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy [74][75], Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicular-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range [74].
Hypogonadotropic hypogonadism (congenital or acquired), including gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation [74][75]. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range [74].

Limitations of Use

Safety and efficacy of subQ testosterone enanthate in male patients less than 18 years old have not been established [76]

Evidence (Adult)

In a single-arm study of men with hypogonadism who received subQ testosterone enanthate, 90% achieved normal serum testosterone levels at week 12 [74].

c) Adult:

1) IM Preparation

a) Replacement therapy needed prior to puberty will be needed during adolescence for secondary sexual characteristic development. Replacement therapy needed following puberty will require prolonged duration of therapy to maintain sexual characteristics [73].

b) Several dosage regimens of IM testosterone enanthate were compared in the treatment of primary hypogonadism in 23 men. Patients received testosterone enanthate 100 mg weekly, 200 mg every 2 weeks, 300 mg every 3 weeks, or 400 mg every 4 weeks for 12 to 16 weeks. The 200 and 300 mg regimens appeared to be the most effective in terms of suppression of the serum luteinizing hormone (LH) concentration and infrequency of administration [77].

2) SubQ Preparation

a) In a 52-week, single-arm study of men with hypogonadism (N=150), 90% of testosterone enanthate-treated patients achieved a time-averaged serum total testosterone concentration over 7 days within the normal range (300 to 1100 nanograms (ng)/dL) at week 12. No patient had a maximum total testosterone concentration greater than 1500 ng/dL at week 12. The initial self-administered dose of 75 mg subQ once weekly was increased by 25 mg at week 7 if the week 6 total testosterone concentration at the end of the dosing interval (trough concentration [Ctrough]) was less than 350 ng/dL ,and was decreased by 25 mg if Ctrough was 650 ng/dL or greater [74].

d) Pediatric:

1) Cautious use of androgens in the pediatric population is necessitated by the likelihood of adverse effects on bone maturation. The risk of a compromised final mature height is greater the younger the child. Assessment of bone age in the wrist and hand every 6 months is recommended [73].

Metastatic breast cancer, Female

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (IM only); Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Indication
IM testosterone enanthate is indicated for palliation of inoperable metastatic (skeletal) mammary cancer in women who are 1 to 5 years postmenopausal [73].

c) Adult:
1) May be used in the palliative treatment of advancing, inoperable metastatic (skeletal) mammary cancer in women who are 1 to 5 years postmenopausal with the primary goal of ovary ablation. Therapy may also be used in premenopausal women who have benefited from oophorectomy with hormone-responsive tumors. Androgen therapy may accelerate metastatic breast carcinoma; therefore, these patients should be monitored closely [73].

Testosterone Undecanoate

Hypogonadism, Male

FDA Labeled Indication
a) Overview
FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Indication
Testosterone undecanoate is indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone, such as
Primary hypogonadism (congenital or acquired): Testicular failure from conditions such as cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals; in these conditions, men have low serum testosterone concentrations and gonadotropins above the normal range [53][57][59].
Hypogonadotropic hypogonadism (congenital or acquired): Idiopathic gonadotropin deficiency, luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation; in these conditions, men have low serum testosterone concentrations and gonadotropins in the normal or low range [53][57][59].
Testosterone undecanoate IM should be used only in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis [59].

Limitations of Use
Safety and efficacy of testosterone capsules in males less than 18 years old have not been established [53][57]

The safety and efficacy of testosterone undecanoate IM therapy has not been established in men with late-onset (age-related) hypogonadism [58].

Evidence
Testosterone undecanoate therapy increases testosterone levels in hypogonadal male patients [61][57][62][60][59].

c) Adult:
1) Oral Capsules - Tlando(R)

a) In an open-label, single-arm study enrolling hypogonadal men, a mean 24-hour serum testosterone level within normal range (eugonadal, 300 to 1080 nanograms[ng]/dL) was achieved in 80% (95% CI, 72% to 88%) of patients receiving testosterone undecanoate capsules 225 mg twice daily with food for 24 days (N=95); no dosage adjustments were permitted. Around 19% (n=18) of subjects, majority of whom were obese, did not achieve a eugonadal range. Cmax of testosterone throughout the studied interval did not exceed 1.5 x ULN (1620 ng/dL) in 82% of patients, while 5% experienced levels between 1.8 x ULN (1944 ng/mL) and 2.5 x ULN (2700 ng/dL); no patients experienced testosterone Cmax over 2.5 x ULN. Mild to moderate adverse events were reported in 20% of the treatment population. The most frequently reported treatment-emergent adverse events were blood prolactin increase (6.3%), headache (2.1%), weight increase (2.1%), and musculoskeletal pain (2.1%). Mean age was 56 years, 16.8% were over 65 years, 69.5% had a BMI of 30 kg/m(2) or greater, and baseline total testosterone on average was 202 +/- 74 ng/dL [61].

2) Oral Capsules - Jatenzo(R)

a) Mean plasma total testosterone over 24 hours was within the normal eugonadal range in 87% of patients in a 4-month study of adult hypogonadal males who received testosterone undecanoate capsules (N=166). The percentage of patients who had Cmax 1500 nanograms (ng)/dL or less, between 1800 and 2500 ng/dL, and greater than 2500 ng/dL at the final visit were 83%, 3%, and 3%, respectively Testosterone undecanoate was taken orally at a starting dose of 237 mg twice per day with meals. The dose was adjusted on Days 21 and 56 between a minimum of 158 mg twice per day and a maximum of 396 mg twice per day on the basis of the average testosterone concentration obtained over 24 hours post-morning dose [57].

3) Intramuscular

a) In 3 studies, testosterone undecanoate therapy significantly increased testosterone levels in hypogonadal male patients [62][60][59] with injection site reactions [62][60] occurring in less than 1% in 1 study [62] and 25.9% in another study [60]

Non-FDA Uses

Testosterone

Antineoplastic adverse reaction - Leydig cell failure in adult

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone therapy did not result in significant changes in bone mineral density, body composition, lipids, or quality of life in one study conducted in men [33].

c) Adult:

1) Testosterone was not effective in men with mild Leydig cell insufficiency following cytotoxic chemotherapy. Men (n=35) aged 40 to 49 years with the diagnosis of mild Leydig cell dysfunction due to chemotherapy were randomized to 2.5 to 5 mg transdermal testosterone daily or placebo for 1 year. Upon completion of the study, total and calculated free testosterone increased significantly with the testosterone group compared with the placebo group (p=0.05 and p=0.02, respectively). Mean total and calculated free testosterone levels increased from 13.3 nanomoles/liter (nmol/L) and 342.9 nmol/L at baseline to 17.3 nmol/L and 454.8 nmol/L during the study. No significant changes in testosterone levels were observed in the placebo group. There were no significant changes in bone mineral density or in body mass in either group.

There was a significant reduction in fatigue and a moderate improvement in activity score compared with the placebo group (p=0.008 and p=0.05, respectively). Mood or sexual function did not change with either group and only a small reduction in low density lipoprotein was reported in the testosterone treated group [33].

Congenital hypoplasia of penis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Successful penile enlargement to normal size for age was reported following the administration of topically applied testosterone [34][35].

c) Pediatric:

1) Eight cases of micropenis from childhood through adulthood (age range, 22 to 31 years) were followed. Diagnosis included 4 patients with hypogonadism, 2 patients with genetic or familial adiposogenital dystrophy, and 2 with miscellaneous types of endocrine abnormalities. In 5 cases, the micropenis was treated with testosterone propionate 2% in a stearin-lanolin base for a variable period of time in infancy or childhood. Topical treatment caused an increase in penis size that was disproportionate to the rest of the body. However, in adolescence and adulthood, patients with a prior history of treatment with topical testosterone during childhood had no size advantage over untreated patients. The authors felt topical testosterone only postponed the age at which an individual had to cope with a micropenis [34].

2) Parenteral (testosterone enanthate 25 mg given IM monthly for a total of 3 doses) and topical testosterone cream (2% to 10%) have been used short term to induce temporary enlargement of a micropenis prior to surgical repair [36][37][38].

3) Successful penile enlargement to normal size for age following the administration of topically applied testosterone 5% cream for 21 days was reported in 5 boys with normal XY karyotype who had microphallus and hypopituitarism. The cream was applied to the penis in 4 of the patients and to the right axilla in one. The investigators concluded that topical testosterone acted systemically to produce phallic growth; serum testosterone levels were equivalent to normal adult levels on the last day of therapy [35].

Coronary arteriosclerosis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Supplementation of low-dose testosterone effectively reduced exercise-induced myocardial ischemia in men with stable angina [10].

c) Adult:

1) Low-dose (5 mg/day) testosterone supplementation was effective in reducing exercise-induced myocardial ischemia in men diagnosed with stable angina. Forty-six men were randomized to transdermal testosterone or placebo for 12 weeks. Treatment with testosterone was associated with an increase in time to 1 mm ST-segment depression from 309 seconds at baseline to 343 seconds at 4 weeks and 361 seconds at 12 weeks, as measured by treadmill exercise testing. The changes were statistically

significant when compared with placebo (p=0.02). Additionally, the treatment group reported significant improvements in pain perception (p=0.026) and role limitation resulting from physical problems (p=0.024) compared with placebo [10].

Deficiency of testosterone biosynthesis, Female

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone transdermal patch demonstrated favorable results in bone density, body composition, and neurobehavioral function in women with androgen deficiency due to hypopituitarism [12].

Testosterone improved well-being, mood, and sexual function in premenopausal women with low libido and low testosterone [13].

c) Adult:

1) Transdermal testosterone application resulted in increased bone mineral density at the hip and radius, increased mean fat-free mass, increased thigh muscle area, and improved mood and sexual function in women with androgen deficiency due to hypopituitarism. The study participants (n=51, aged 19 to 50 years) had a serum free testosterone level of less than 3.1 picograms/milliliter (pg/mL) at the time of screening and were estrogen replete for at least 1 year prior to the study. Of the women participating, 59% were depressed at baseline and 46% and 68% had sexual function scores that were more than 2 or more than 1 standard deviation(s), respectively, below the normal mean (as measured by the Derogatis Interview for Sexual Function-Female Version). Participants were randomized to transdermal testosterone patches which delivered 300 mcg (in the form of 150 mcg patches) daily or placebo patches for 12 months. Study visits occurred at 1, 3, 6, 9, and 12 months after the baseline visit. At baseline, mean free testosterone was below normal for women of reproductive age, and 55% of women had undetectable levels, which increased into the normal range during testosterone administration. The dose of testosterone was decreased to 150 mcg daily in 37.8% of participants randomized to testosterone due to free testosterone levels being above the ULN for females of reproductive age. There were no changes in estradiol, insulin-like growth factor I, and sex hormone binding globulin levels with either testosterone or placebo administration. Bone density at the hip and radius increased significantly (p=0.023 and p=0.007, respectively) with mean percent changes at the hip being 0.9 +/- 0.5 and -1.2 +/- 0.6% for testosterone and placebo, respectively, and 0.8 +/- 0.2 and -0.5 +/- 0.4%, respectively, at the radius. Testosterone was associated with a 3.4 +/- 0.9% mean increase in fat-free mass compared with a 0.6 +/- 0.9% increase for placebo (p=0.04). There was a significant increase in muscle area of the thigh associated with testosterone administration compared with placebo (p=0.038). The mean increase in the testosterone and placebo groups was 6.6 +/- 1.4% and 1.5 +/-1.3%, respectively. Compared with placebo, mood significantly improved in patients receiving testosterone (p=0.029) as did sexual function (p=0.044). In women receiving testosterone, quality of life improved in the following areas: self-control (p=0.005), energy/fatigue (p=0.017), general health (p=0.026), and sleep (p=0.038). When compared with placebo, there was no improvement in spatial function or any other changes in cognitive function. Testosterone was well tolerated with increased acne being reported in one-third of patients. A mean increase in total cholesterol of 6% was reported in the testosterone group. Mild local irritation at patch site was reported in 65% of participants; the reactions were distributed equally between the testosterone and placebo groups [12].

2) Testosterone cream was effective in improving well-being, mood, and sexual function in premenopausal women in a randomized, placebo-controlled, crossover, double-blind trial. Thirty-four women completed the trial, with 31 women (mean age 39.7 years and mean serum testosterone 1.07 nanomoles/L) providing complete data. The trial

consisted of two 12-week treatment periods, separated by a 4-week washout period, in which the women were randomized to 10 mg testosterone 1% cream daily or placebo. The women using testosterone demonstrated significant improvements in scores of general well being (+12.9; 95% CI, +4.6 to +21.2; p=0.003) and of sexual self-rating (+15.7; 95% CI, +6.5 to +25; p=0.001) compared with placebo. Mean total testosterone levels during treatment were at the high end of normal and estradiol levels were unchanged. Testosterone was well tolerated with no adverse effects reported [13].

Depression

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone gel supplementation may produce antidepressant effects in depressed men with low testosterone levels [11].

c) Adult:

1) Testosterone 1% topical gel produced antidepressant effects in a small study involving 22 depressed men with low or borderline testosterone levels (morning serum levels of 350 nanograms/dL or less. The men were randomized to 1% testosterone gel (10 g/day) or placebo gel for 8 weeks. Each subject continued his existing antidepressant regimen. Testosterone-treated patients had a significantly greater rate of decrease in scores on the Hamilton Depression Rating Scale compared with placebo (p=0.0004). This improvement was noted on both the vegetative and affective subscales of the Hamilton Depression Rating Scale (p=0.01 and p=0.05, respectively). In addition, testosterone gel was associated with a significantly greater rate of decrease in the Clinical Global Impression severity scores (p=0.04). There were no significant differences between the 2 groups regarding changes in body fat percentages or changes in muscle mass. One subject receiving testosterone reported increased nocturia and difficulty initiating urination. No other subject reported adverse effects attributable to testosterone [11].

Female-to-male transsexual - Gender dysphoria

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adult)

Testosterone in 3 different formulations, including transdermal gel, significantly increased testosterone levels from the physiological range for women to the normal male range by week 30 of treatment in an observational study in female-to-male transsexual individuals [9]. Hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy in 1 cross-sectional study [8].

Evidence (Adolescent)

In a cross-sectional study in transsexual individuals attending a gender identity unit, hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving

hormonal therapy [8].

Guidelines (Adult)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender. Either parenteral or transdermal testosterone may be used to achieve and maintain testosterone levels in the normal male range. Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7].

Guidelines (Adolescent)

Initiation of gender-affirming hormone therapy, at gradually increasing doses, is recommended in adolescents with confirmed persistence of gender dysphoria/gender incongruence who request such therapy and who have sufficient mental capacity to give informed consent, usually by age 16 years. Compelling reasons may exist to initiate therapy at younger than 16 years; although, studies in this population are minimal. Initial therapy to undergo suppression of pubertal development at Tanner stages G2/B2 is suggested. Neither puberty suppression nor gender-affirming hormone therapy are recommended in pre-pubertal children [7].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Adult:

1) Testosterone in 3 different formulations significantly increased total testosterone levels from the physiological range for women to the normal male range by week 30 of treatment with no significant differences among formulations in an observational study in female-to-male transsexual individuals (N=45). At week 54, testosterone remained elevated and sex hormone-binding globulin, prolactin, and estradiol levels were significantly decreased from baseline while body weight and body mass index (BMI) were significantly increased in all groups. Results for selected hormonal and anthropometric outcomes are shown in the table below. Amenorrhea occurred at a mean 29.8 to 41 weeks. Significant changes from baseline were observed in HDL-C (decreased) and LDL-C (increased), but not total cholesterol. Fasting glucose increased significantly, but insulin and homeostasis model assessment for fasting insulin resistance (HOMA-IR) were similar to baseline. Hematocrit and hemoglobin increased from baseline. No significant changes were detected in liver enzymes, renal function, or bone mineral density. Patients were randomly assigned to testosterone enanthate 100 mg IM every 10 days, testosterone gel 50 mg once every evening, or testosterone undecanoate 1000 mg IM at week 0, week 6, and every 12 weeks thereafter. No subject had undergone sexual reassignment surgery [9].

Selected Hormonal and Anthropometric Parameters at Baseline and Week 54 Posttreatment		
Parameter	Baseline Range *	Week 54 Posttreatment Range*
Testosterone (ng/mL)	0.44 to 0.54	5.89 to 7.39 **
Estradiol (pg/mL)	102.9 to 167.3	70.6 to 81.9 **
Luteinizing hormone (international units/L)	5.8 to 12.8	5.1 to 9.2
Follicle stimulating hormone (international units/L)	4.6 to 6.2	5.1 to 5.6
Prolactin (ng/mL)	15.7 to 18.2	9.8 to 15.6 **
Sex hormone-binding globulin (nmol/L)	60.3 to 65.4	31.6 to 34.3 **
Body weight (kg)	57.8 to 67.3	60.5 to 68.7 **
BMI (kg/m(2))	22.1 to 23.9	22.4 to 24.3 **

Fat (%)	26.7 to 30.1	22.4 to 27.6 **
KEY: BMI=body mass index; ng=nanograms; pg=picograms		
* Range is among the 3 different testosterone formulations with no significant difference among the formulations at baseline or week 54.		
** Significant difference between baseline and week 54 values.		

2) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy		
Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
HAD-A ^	9	6.4 **
HAD-D ^	5.2	3.3 **
KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale		
* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.		
** Significant difference versus no-hormone-therapy group		
^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.		

d) Pediatric:

1) Adolescents

a) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible

symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy		
Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
HAD-A ^	9	6.4 **
HAD-D ^	5.2	3.3 **
KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale		
* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.		
** Significant difference versus no-hormone-therapy group		
^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.		

Osteoporosis, Male

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone therapy in men with osteoporosis significantly increased bone mineral density [40].

See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy
See Drug Consult reference: Canadian: Management of Osteoporosis in Men and Women

c) Adult:

1) Transdermal testosterone gel was associated with a small but significant increase in bone mineral density (BMD) in a prospective, multicenter study involving 227 men with hypogonadism. The men were randomized to testosterone gel delivering 5 to 10 mg/day or 2 testosterone patches delivering 5 mg/day. After 90 days, the gel dose was adjusted to 75 mg/day for another 3 months. At completion of the study, the 10 mg/day gel was associated with a 1.4 and 1.9-fold higher serum testosterone concentration than the 5 mg/day gel and the patch groups. The 10 mg/day gel group was also associated with a decreased bone resorption and with small but significant increases in BMD of the hip and spine (1.1% and 2.2%, respectively; p=0.0001) [40].

Postmenopausal osteoporosis; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

The addition of testosterone to estradiol is not associated with increased benefits on bone mineral density [39].

c) Adult:

1) Testosterone 100 mg implants added to estradiol 50 mg implants had no significant effects on bone markers and may not be necessary for prevention of osteoporosis if adequate estradiol levels are maintained. Women (n=25) were given estradiol after a total hysterectomy with bilateral salpingo-oophorectomy. At 16 weeks, testosterone 100 mg was added to the treatment regimen. The bone formation marker, PICP was associated with a significant increase after estradiol alone (p=0.0032) but the addition of testosterone had no significant effects on bone markers when measured at 32 weeks. These biochemical changes confirm previous studies [39].

Sexual disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Improvements in sexual function have been reported in both female and male patients [41][42][43].

c) Adult:

1) Transdermal testosterone improved sexual function and psychological well-being in women with sexual dysfunction following oophorectomy and hysterectomy. A 36-week trial enrolled 75 women, ages 31 to 56 years old, who had reported impaired sexual functioning after surgically-induced menopause, despite estrogen replacement. The 75 women received at least 0.625 mg of conjugated equine estrogens orally per day. Randomly selected, the women also received placebo, 150 micrograms (mcg) of testosterone, or 300 mcg of testosterone per day transdermally for 12 weeks each. The mean serum free testosterone concentration increased during each treatment regimen. The higher testosterone dose resulted in the greatest physical and psychological improvement [41].

2) In one 16-month, open-label, multicenter study with 4 consecutive periods, 37 men with hypogonadism received intramuscular and transdermal testosterone (nonscrotal). Period 1 consisted of 3 weeks and patients were monitored following an IM testosterone injection. During period 2, patients received no replacement testosterone for 8 weeks. During period 3, single-dose pharmacokinetic studies were performed for 3 to 4 weeks. During period 4 (12 months) efficacy and safety of the transdermal system were compared with the results obtained during periods 1 and 2. Along with other symptoms, decreased libido, impotence, fatigue, depression, and hot flushes were evaluated. After one month of transdermal treatment, the prevalence of decreased libido and fatigue had decreased to levels seen during IM treatment and remained so for the duration of transdermal treatment [42]. Similar results were found in another study [43].

Weight gain

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone did not increase weight, body cell mass, or quality of life in patients with HIV infection [44].

Testosterone has produced an increase in fat free mass, muscle size, and strength [45] [46].

A significant increase in weight was observed in female patients with AIDS who received 1 active testosterone patch and 1 placebo patch versus 2 placebo skin patches but did not increase significantly in patients who received 2 active testosterone patches [47].

c) Adult:

1) Transscrotal testosterone did not increase weight, body cell mass, or quality of life in patients with HIV infection. In a multicenter, randomized, double-blinded, placebo-controlled study, men infected with HIV used transdermal scrotal testosterone patches (6 mg/day) (n=67) or placebo (n=66) for 12 weeks. Patches were applied and worn for 22 to 24 hours each day. Testosterone patches were effective in increasing serum testosterone levels [44].

2) There was 1.35 kg gain in lean body mass, increased red cell count, and improvements in the subcategory of role limitation due to emotional problems in HIV-infected men treated with transdermal testosterone [45]. In a double-blind, placebo-controlled randomized study, 41 HIV-infected men received 2 placebo patches or 2 testosterone transdermal system patches applied to the abdomen, back, arms, or thighs every 24 hours (total testosterone dose 5 mg/24 hr) for 12 weeks.

3) Androgen deficiency has been shown to be prevalent among women with AIDS wasting syndrome. It may result from undernutrition generalized illness, or more direct effects of HIV on the hypothalamic-pituitary-gonadal axis. Forty-five out of 53 women with AIDS wasting syndrome finished the study. Patients were randomized into 1 of 3 groups: 2 placebo skin patches (PP group); 1 active/1 placebo patch (AP group); or 2 active patches (AA group) which were applied twice weekly for 12 weeks. The delivery rates of testosterone were 150 and 300 mcg/day for the AP and AA groups, respectively. Therapy was well tolerated with no adverse effects with regard to hirsutism, lipid profiles, or liver function tests. A significant increase in weight was observed in the AP group (1.9 +/- 0.7 kg) versus the PP group (0.6 kg +/- 0.8 kg; p=0.043), but did not increase significantly in the AA group (0.9 +/- 0.4 kg) versus the PP group [47].

4) Testosterone increased lean body mass and improved quality of life in androgen-deficient men with AIDS wasting syndrome. In a randomized, double-blind, placebo-controlled trial, patients received testosterone enanthate 300 mg intramuscularly weekly for 6 months (n=26) or placebo (n=25). In the testosterone-treated group, 22 patients completed the trial and 19 patients in the placebo group completed the trial. Compared to placebo, testosterone-treated patients demonstrated a gain in fat free mass, lean body mass, and muscle mass (change, -0.6 kg and 2 kg; change, 0 kg and 1.9 kg; and change, -0.8 kg and 2.4 kg, respectively) [46].

5) Sublingual testosterone 5 mg three times daily for 6 months was administered to 67 men with hypogonadism which resulted in an increase in total body (p=0.0104) and lean body mass (p=0.007), mainly in the legs. There was no significant change in bone mineral density throughout the study. Longer studies are needed in this population [48].

Testosterone Cypionate

Female-to-male transsexual - Gender dysphoria

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adult)

Hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy in 1 cross-sectional study [8]. In a prospective study, significant changes in several domains of psychological functioning were observed for transgender men following 3 months of testosterone therapy compared with female controls and there were no significant differences for transgender men after therapy versus male controls [66]. Male physical characteristics were effectively achieved in an open-label time-series trial [81].

Evidence (Adolescent)

In a cross-sectional study in transsexual individuals attending a gender identity unit, hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy [8].

Guidelines (Adult)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender. Either parenteral or transdermal testosterone may be used to achieve and maintain testosterone levels in the normal male range. Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7].

Guidelines (Adolescent)

Initiation of gender-affirming hormone therapy, at gradually increasing doses, is recommended in adolescents with confirmed persistence of gender dysphoria/gender incongruence who request such therapy and who have sufficient mental capacity to give informed consent, usually by age 16 years. Compelling reasons may exist to initiate therapy at younger than 16 years; although, studies in this population are minimal. Initial therapy to undergo suppression of pubertal development at Tanner stages G2/B2 is suggested. Neither puberty suppression nor gender-affirming hormone therapy are recommended in pre-pubertal children [7].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Adult:

1) Significant changes in several domains of psychological functioning, as assessed using the Minnesota Multiphasic Personality Inventory second edition (MMPI-2), were observed for transgender men following 3 months of testosterone therapy compared with female controls and there were no significant differences for transgender men after therapy versus male controls (N=163; 48 transgender men, 53 male controls, 62 female controls). The MMPI-2 contains 10 clinical scales. Transgender men were compared with female controls using the female template of MMPI-2 and compared with male controls using the male template. Higher scores on each scale equate with lower levels of psychological functioning. Relative to female controls, transgender men had a significant change from baseline on the Hypochondria (-3.14), Depression (-3.28), Hysteria (-3.66), Paranoia (-4.62), and Masculinity-femininity (+5.05) scales after 3 months of therapy. No significant differences were observed after therapy versus female controls on the Psychopathic Deviate, Psychasthenia, Schizophrenia, Hypomania, or Social Inversion

scales or on any of the 10 scales relative to male controls. Testosterone was administered as 50 to 400 mg IM every 10 to 14 days (or 50% weekly) for most participants (n=32) [66].

2) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy		
Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
HAD-A ^	9	6.4 **
HAD-D ^	5.2	3.3 **
KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale		
* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.		
** Significant difference versus without-hormone-therapy group		
^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.		

3) Testosterone cypionate was effective in suppressing menses and increasing clitoral size and body hair in an open-label time-series trial that examined the effects of cross-sex hormones on both female-to-male and male-to-female transsexuals. Eleven of the 28 (31%) enrolled female-to-male transsexuals had previously been on testosterone in various formulations for a median duration of 24 months (range, 6 to 240 months). All previous treatment was discontinued and patients were started on testosterone cypionate (Depo-testosterone(R)) IM at doses of 50 to 200 mg every 2 weeks, with doses increased until cessation of menstruation or suppression of luteinizing hormone (LH) or follicle-stimulating hormone (FSH) in castrated patients. Some patients self-administered doses up to 400 mg per week against medical advice. Mean duration of follow-up was 16.6 +/- 15 months. Of patients who had never had any previous hormonal treatment or hysterectomy (n=12), all had reported previous normal menstrual histories. These patients all had cessation of menses by 4 months of treatment with testosterone cypionate 200 mg every 2 weeks. The mean total cholesterol level (n=28) at baseline was 209 +/- 46 mg/dL. At doses of 100 to 300 mg per month after a duration of 27 patient-months, the mean cholesterol level increased to 288 +/- 53 mg/dL, while at doses of 400 mg per month after a duration of 217 patient-months, the mean cholesterol level was 212 +/- 53 mg/dL. Significance (p less than 0.05) was reported for the change in cholesterol (all doses) from baseline. Triglycerides

were also significantly (p less than 0.05) increased to just over the ULN (normal range, 10 to 160 mg/dL). SGPT significantly (p less than 0.05) increased, but remained within the normal range. No significant changes were found in blood pressure, SGOT, bilirubin, or glucose. The amount and coarseness of hair on the chest, abdomen, and face were reported to be "strikingly" increased. No significant changes were reported for breast size, body weight, estradiol levels, or androstenedione levels. LH and FSH levels were suppressed to prepubertal levels only when the patient's testosterone level was over 1000 nanograms/deciliter or until the dose was greater than 800 mg per month. Clitoris growth increased rapidly over 1 year, with the longest clitoris measuring 6 cm [81].

d) Pediatric:

1) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy		
Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
HAD-A ^	9	6.4 **
HAD-D ^	5.2	3.3 **
KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale		
* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.		
** Significant difference versus without-hormone-therapy group		
^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.		

Testosterone Enanthate

Anemia

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in combination with other androgens for increasing the hematocrit in anemic patients who are receiving hemodialysis [67]

c) Adult:

1) A randomized clinical trial was conducted to compare the erythropoietic effects of several androgens in 143 patients (103 males, 40 females) with anemia who were receiving maintenance hemodialysis . Patients received either testosterone enanthate 4 mg/kg IM weekly (the female patients did not receive testosterone), fluoxymesterone 0.4 mg/kg orally daily, oxymetholone 1 mg/kg orally daily, or nandrolone decanoate 3 mg/kg intramuscularly weekly. Control periods of at least 2 months were followed by treatment periods consisting of one of the androgens for 6 months followed by another control period; 3 courses utilizing a different drug each time were administered. Seventy-seven, 56, and 35 patients completed the first, second, and third treatment periods, respectively. The 2 agents administered by injection, which included testosterone, were judged superior to the orally administered agents in terms of patient response and mean rise in hematocrit. Approximately 50% of the patients had an increase of at least 5 percentage points in hematocrit following the administration of either injectable androgen [67].

Burn, Severe; Adjunct

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Administration of testosterone enanthate can ameliorate muscle catabolism in severe burns [78].

c) Adult:

1) Testosterone enanthate 200 mg IM per week for 2 weeks restored serum testosterone levels and ameliorated the muscle catabolism in 6 severely burned (greater than 70% total body surface area) male patients. After the second injection, protein synthetic efficiency increased 2-fold (p less than 0.01) and protein breakdown decreased almost 2-fold (p less than 0.05) [78].

Congenital hypoplasia of penis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

IM testosterone enanthate and topical testosterone cream have been used short term to induce temporary enlargement of a micropenis prior to surgical repair [36][37][38].

c) Pediatric:

1) Testosterone enanthate 25 mg IM given monthly for a total of 3 doses and topical testosterone cream (2% to 10%) have been used short term to induce temporary

enlargement of a micropenis prior to surgical repair [36][37][38].

Contraception, Male

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

IM testosterone enanthate plus oral desogestrel was an effective and safe regimen for suppression of spermatogenesis [68].

Testosterone enanthate and cyproterone induced azoospermia more effectively than testosterone alone [69].

Testosterone enanthate plus levonorgestrel was more effective in producing azoospermia than testosterone enanthate alone [70].

Weekly injections effectively induced azoospermia in healthy fertile men [71].

Approximately 50% of healthy males become azoospermic and the other 50% become severely oligospermic following administration during clinical trials [72].

c) Adult:

1) Testosterone Enanthate and Desogestrel

a) IM testosterone enanthate plus oral desogestrel was an effective and safe regimen for suppression of spermatogenesis in a study of 24 healthy men aged 20 to 49 years. The men were randomized to 50 mg testosterone enanthate plus 150 mcg desogestrel (n=9), 100 mg testosterone enanthate plus 150 mcg desogestrel (n=7), or 100 mg testosterone enanthate plus 300 mcg desogestrel (n=8). Additionally, these 3 groups were compared with 2 control groups receiving 100 mg testosterone enanthate alone (n=18) or 100 mg testosterone enanthate plus 125 mcg oral levonorgestrel (n=18). At the end of 6 months, azoospermia was achieved in 100% of men receiving testosterone enanthate 100 mg plus desogestrel 150 mcg, 88% of men receiving testosterone enanthate 100 mg plus desogestrel 300 mcg, and 57% of men receiving testosterone enanthate 50 mg and desogestrel 150 mcg. This was compared with 61% for testosterone enanthate 100 mg plus levonorgestrel 125 mcg and 33% for testosterone enanthate 100 mg alone. All groups tended to gain weight compared with baseline and serum HDL was moderately suppressed in all groups [68].

2) Testosterone Enanthate and Cyproterone

a) In a smaller study, all men who received testosterone and cyproterone became azoospermic compared with 3 of 5 men receiving testosterone only. Fifteen men were randomized to receive cyproterone 50 mg orally twice daily plus testosterone enanthate 100 mg IM weekly; cyproterone 25 mg orally twice daily plus testosterone 100 mg IM weekly; or testosterone 100 mg IM weekly alone for 16 weeks. Patients in the cyproterone 100 mg, cyproterone 50 mg, and testosterone only groups achieved azoospermia at mean times of 6.8, 8.4, and 14 weeks, respectively. After treatment, baseline sperm counts were achieved in all men. Lipoprotein profiles nor liver function tests were detected in any patient. No significant differences in sexual behavior were reported among the 3 groups [69].

3) Testosterone Enanthate and Levonorgestrel

a) Testosterone enanthate 100 mg IM weekly plus levonorgestrel 500 mcg orally daily was more effective in producing azoospermia than testosterone enanthate alone at 6 months (67% vs 33%; p=0.06). A pregnancy rate was not mentioned [70].

4) Clinical trials have indicated that approximately 50% of healthy males become azoospermic and the other 50% become severely oligospermic following administration

of testosterone enanthate. Additionally, severe oligospermia appears to be associated with effective contraception [72].

Female-to-male transsexual - Gender dysphoria

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adult)

Voice deepening, facial hair increase, cessation of menses, and significant increases in testosterone levels were achieved within 6 months of initiating IM testosterone replacement therapy in individuals with female-to-male gender dysphoria in a retrospective study [65]. Hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy in 1 cross-sectional study [8]. In a prospective study, significant changes in several domains of psychological functioning were observed for transgender men following 3 months of testosterone therapy compared with female controls and there were no significant differences for transgender men after therapy versus male controls [66]

Evidence (Adolescent)

In a cross-sectional study in transsexual individuals attending a gender identity unit, hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy [8].

Guidelines (Adult)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender. Either parenteral or transdermal testosterone may be used to achieve and maintain testosterone levels in the normal male range. Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7].

Guidelines (Adolescent)

Initiation of gender-affirming hormone therapy, at gradually increasing doses, is recommended in adolescents with confirmed persistence of gender dysphoria/gender incongruence who request such therapy and who have sufficient mental capacity to give informed consent, usually by age 16 years. Compelling reasons may exist to initiate therapy at younger than 16 years; although, studies in this population are minimal. Initial therapy to undergo suppression of pubertal development at Tanner stages G2/B2 is suggested. Neither puberty suppression nor gender-affirming hormone therapy are recommended in pre-pubertal children [7].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Adult:

1) Significant changes in several domains of psychological functioning, as assessed using the Minnesota Multiphasic Personality Inventory second edition (MMPI-2), were observed for transgender men following 3 months of testosterone therapy compared with female controls and there were no significant differences for transgender men after therapy versus male controls (N=163; 48 transgender men, 53 male controls, 62 female

controls). The MMPI-2 contains 10 clinical scales. Transgender men were compared with female controls using the female template of MMPI-2 and compared with male controls using the male template. Higher scores on each scale equate with lower levels of psychological functioning. Relative to female controls, transgender men had a significant change from baseline on the Hypochondria (-3.14), Depression (-3.28), Hysteria (-3.66), Paranoia (-4.62), and Masculinity-femininity (+5.05) scales after 3 months of therapy. No significant differences were observed after therapy versus female controls on the Psychopathic Deviate, Psychasthenia, Schizophrenia, Hypomania, or Social Inversion scales or on any of the 10 scales relative to male controls. Testosterone was administered as 50 to 400 mg IM every 10 to 14 days (or 50% weekly) for most participants (n=32) [66].

2) Therapeutic effects of voice deepening, facial hair increase, and cessation of menses were achieved with 3 different dosages of testosterone enanthate by 6 months after initiation of therapy in individuals with female to male gender dysphoria undergoing testosterone replacement therapy in a retrospective study (N=138). At 1 month, onset of treatment effects occurred in more patients with higher doses. However, no dose dependent effects were evident at 6 months, and 96.3% to 100% of patients achieved deepening of voice, 72.7% to 97.4% achieved increase in facial hair, and 85.7% to 96.6% achieved cessation of menses. Serum testosterone levels were significantly increased to around 700 nanograms/dL and serum estradiol levels were significantly decreased from baseline to month 6, with no significant differences among the different dosages of testosterone. No significant adverse events were reported in any group and there were no clinically relevant changes in liver enzymes, coagulation parameters, or urinalysis results. Testosterone enanthate was administered as 250 mg IM every 2 weeks (n=30), 250 mg IM every 3 weeks (n=50), or 125 mg every 2 weeks (n=58) based on patient preference relating to frequency of administration and cost [65].

3) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy		
Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
HAD-A ^	9	6.4 **
HAD-D ^	5.2	3.3 **
KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale		
* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.		
** Significant difference versus without-hormone-therapy group		

^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.

d) Pediatric:

1) Adolescent

a) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

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* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.		
** Significant difference versus without-hormone-therapy group		
^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.		

Sexual disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone enanthate prevented the loss of potency in patients receiving concomitant luteinizing hormone-releasing hormone (LHRH) agonist therapy [79].

c) Adult:

1) Reversible oligospermia without impotence in male patients treated with an luteinizing hormone-releasing hormone (LHRH) agonist plus testosterone was reported. When an LHRH agonist is used to produce reversible oligospermia, a reduction in plasma testosterone, libido, and potency occurs. Testosterone enanthate 100 mg IM every 2 weeks prevented the loss of potency in 6 patients receiving concomitant LHRH agonist therapy [79].

Weight gain

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone has produced an increase in fat-free mass, muscle size, and strength [45] [46][80].

c) Adult:

1) Testosterone increased lean body mass and improved quality of life in androgen-deficient men with AIDS wasting syndrome. In a randomized, double-blind, placebo-controlled trial, patients received testosterone enanthate 300 mg IM weekly for 6 months (n=26) or placebo (n=25). In the testosterone-treated group, 22 patients completed the trial and 19 patients in the placebo group completed the trial. Compared with placebo, testosterone-treated patients demonstrated a gain in fat-free mass, lean body mass, and muscle mass (change, -0.6 kg and 2 kg; change, 0 kg and 1.9 kg; and change, -0.8 kg and 2.4 kg, respectively) [46].

2) Testosterone enanthate 600 mg weekly for 10 weeks produced an increase in fat-free mass, muscle size, and strength in males. A standardized exercise program was additive to the effects of testosterone. Because anabolic steroids have potentially serious adverse effects, their use in athletics is not justified; however, it is postulated that short-term administration of androgens may be advantageous for immobilized, cachectic, AIDS patients, or those with chronic wasting disease [80].

Testosterone Undecanoate

Female-to-male transsexual - Gender dysphoria

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adult)

Testosterone undecanoate significantly increased testosterone levels in transsexual men (ie, female-to-male) from the physiological range for women to the normal male range in observational [9] and prospective studies [54]. Significant physical changes including body weight, lean body mass, body fat redistribution [55], and facial and body hair growth occurred during the first year of therapy [56]. Additionally, hormonal sex

reassignment therapy significantly reduced symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy in 1 cross-sectional study [8]. Major adverse events have not been observed, but changes in lipid profiles, hematocrit, liver enzymes [54], and fasting plasma glucose have been reported during 1-year studies [9]. Regular monitoring for adverse effects of hormone therapy is recommended [7].

Evidence (Adolescent)

In a cross-sectional study in transsexual individuals attending a gender identity unit, hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy [8].

Guidelines (Adult)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender. Either parenteral or transdermal testosterone may be used to achieve and maintain testosterone levels in the normal male range. Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7].

Guidelines (Adolescent)

Initiation of gender-affirming hormone therapy, at gradually increasing doses, is recommended in adolescents with confirmed persistence of gender dysphoria/gender incongruence who request such therapy and who have sufficient mental capacity to give informed consent, usually by age 16 years. Compelling reasons may exist to initiate therapy at younger than 16 years; although, studies in this population are minimal. Initial therapy to undergo suppression of pubertal development at Tanner stages G2/B2 is suggested. Neither puberty suppression nor gender-affirming hormone therapy are recommended in pre-pubertal children [7].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Adult:

1) During the first year of treatment, body weight and lean body mass (LBM) were significantly increased by 3% and 10%, respectively, in transsexual men undergoing cross-sex hormonal therapy with testosterone during an observational study (n=162 transsexual men). Total body fat was decreased by a significant 9%, with redistribution of body fat significant in the leg (-16%) and gynoid (-14%), but not android regions. LBM was increased in all body parts by between 9% and 19%. Hip circumference was significantly changed by -1.9 cm, but there was no significant difference for waist circumference or the waist-to-hip ratio. Testosterone was administered as testosterone gel 50 mg/day, testosterone undecanoate 1000 mg IM once every 12 weeks, or testosterone esters 250 mg IM once every 2 weeks (not an FDA-approved product). Mean follow-up was 380 days [55].

2) Testosterone undecanoate injections significantly increased testosterone levels to the normal male range in 100% of hormone-naïve transgender men (female-to-male) in a 1-year prospective study (n=53 trans men). At baseline, serum testosterone levels were 30.2 nanograms/dL (ng/dL) and increased to a mean 595.8 ng/dL. Body weight was significantly increased from 68.4 to 70.6 kg, with an increase in lean body mass and decrease in total body fat. Waist-to-hip ratio was significantly increased (0.82 to 0.84) due to decreased hip circumference. Small, but significant, changes in total cholesterol (171.9 to 178.2 mg/dL), LDL-C (98.4 to 116.1 mg/dL), triglycerides (69 to 81.1 mg/dL), and HDL-C (56.3 to 47.8 mg/dL) occurred. Erythrocytosis was present in 2 men based on the male reference range (Hct level above 52%) and 20.1% had Hct levels above the female reference range of 48%. Liver enzyme elevations greater than 2 x ULN were reported with respect to the female reference range (1.9%), but none were 2 x the ULN of the male reference range. No cardiovascular events, venous thromboses, pulmonary

embolisms, deaths, or osteoporotic fractures were reported. Testosterone undecanoate was administered as 1000 mg IM at initiation, at 6 weeks, and then every 12 weeks thereafter. In cases of intolerance, participants could switch to testosterone esters 250 mg (not an FDA-approved product) every 2 weeks [54].

3) Testosterone in 3 different formulations significantly increased total testosterone levels from the physiological range for women to the normal male range by week 30 of treatment with no significant differences among formulations in an observational study in female-to-male transsexual individuals (N=45). At week 54, testosterone remained elevated and sex hormone-binding globulin, prolactin, and estradiol levels were significantly decreased from baseline while body weight and body mass index (BMI) were significantly increased in all groups. Results for selected hormonal and anthropometric outcomes are shown in the table below. Amenorrhea occurred at a mean 29.8 to 41 weeks. Significant changes from baseline were observed in HDL-C (decreased) and LDL-C (increased), but not total cholesterol. Fasting glucose increased significantly, but insulin and homeostasis model assessment for fasting insulin resistance (HOMA-IR) were similar to baseline. Hematocrit and hemoglobin increased from baseline. No significant changes were detected in liver enzymes, renal function, or bone mineral density. Patients were randomly assigned to testosterone enanthate 100 mg IM every 10 days, testosterone gel 50 mg once every evening, or testosterone undecanoate 1000 mg IM at week 0, week 6, and every 12 weeks thereafter. No subject had undergone sexual reassignment surgery [9].

Selected Hormonal and Anthropometric Parameters at Baseline and Week 54 Posttreatment

Parameter	Baseline Range *	Week 54 Posttreatment Range*
Testosterone (ng/mL)	0.44 to 0.54	5.89 to 7.39 **
Estradiol (pg/mL)	102.9 to 167.3	70.6 to 81.9 **
Luteinizing hormone (international units/L)	5.8 to 12.8	5.1 to 9.2
Follicle stimulating hormone (international units/L)	4.6 to 6.2	5.1 to 5.6
Prolactin (ng/mL)	15.7 to 18.2	9.8 to 15.6 **
Sex hormone-binding globulin (nmol/L)	60.3 to 65.4	31.6 to 34.3 **
Body weight (kg)	57.8 to 67.3	60.5 to 68.7 **
BMI (kg/m(2))	22.1 to 23.9	22.4 to 24.3 **
Fat (%)	26.7 to 30.1	22.4 to 27.6 **

KEY: BMI=body mass index; ng=nanograms; pg=picograms

* Range is among the 3 different testosterone formulations with no significant difference among the formulations at baseline or week 54.

** Significant difference between baseline and week 54 values.

4) Facial and body hair growth was significantly increased over time with testosterone undecanoate administration in hormone-naïve transsexual men in a prospective study (N=20). The Ferriman and Gallway score (FG; 0 to 36 scale with a score of greater than 8 in an androgen-dependent area indicating hirsutism) was a median 0.5 at baseline and increased to 12 after 12 months of therapy, but there was wide interindividual variability (range, 2 to 25). In an associated cross-sectional study in transgender men who had undergone sexual reassignment surgery and had been using testosterone for an average of 9.9 years (N=50), the median PG score was 24 with a range of 6 to 34. Moderate to severe alopecia was reported in 31%. Neither the FG score nor alopecia was positively correlated with duration or type of testosterone therapy in the cross-sectional group. Alopecia was correlated with age. In the prospective study group, all participants received testosterone undecanoate 1000 mg IM every 3 months. In the cross-sectional study group, testosterone was administered as testosterone esters 250 mg (not an FDA-approved product) IM every 2 or 3 weeks (n=35), testosterone undecanoate 1000 mg

IM every 12 weeks (n=7), or transdermal testosterone 50 mg/day (n=8); one participant used an oral and transdermal formulation together [56].

5) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy		
Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
HAD-A ^	9	6.4 **
HAD-D ^	5.2	3.3 **
KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale		
* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.		
** Significant difference versus no-hormone-therapy group		
^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.		

d) Pediatric:

1) Adolescent

a) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and

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^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.		

Dose Adjustments

Adult Dosage

Normal Dosage

Important Note

Testosterone

Topical testosterone products are not interchangeable as they have different strengths, doses, and application instructions that may result in different systemic exposure [1][2][3][4][5].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Cypionate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Enanthate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Undecanoate

Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone

Buccal mucosa route

Hypogonadism, Male

1) FDA Dosage, Striant(R)

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [17].

b) Usual dose: One 30-mg buccal system applied to the gum approximately every 12 hours, applying to opposite sides of the mouth with each dose; monitor testosterone levels at 4 to 12 weeks after initiation, and discontinue if levels are consistently outside normal range [23]

c) Dosing notes: If the system fails to adhere or falls off within 8 hours of application, a new system may be applied and continued for a total of 12 hours from the placement of the first system; however, if it is within 8 hours of the next scheduled dose, apply the new system for 12 hours and then continue with the next dose. Remove system prior to oral care and apply a new system after [23].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Striant(R) testosterone buccal system is not indicated for use in women [23].

Nasal route

Hypogonadism, Male

1) FDA Dosage, Natesto(TM)

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [16].

b) Usual dose: 1 actuation per nostril (2 pump actuations, 11 mg) intranasally 3 times a day (morning, afternoon, and evening, 6 to 8 hours apart) at the same time each day for a total daily dose of 33 mg; after 1 month check testosterone levels periodically [22]

c) If total testosterone level usually below 300 nanograms/dL, consider alternative therapy [22].

d) If total testosterone level generally greater than 1050 nanograms/dL, discontinue treatment with testosterone nasal gel [22].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Natesto(TM) testosterone nasal gel is not indicated for use in women [22].
There is insufficient evidence of long-term safety (ie, cardiovascular and prostate cancer risks) for Natesto(TM) testosterone gel treatment in geriatric patients [22].
The safety and efficacy of Natesto(TM) testosterone gel treatment have not been established in patients with a BMI greater than 35 kg/m(2) [22].

Topical application

Hypogonadism, Male

1) FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [5][15][1][3][2][18].

2) FDA Dosage, Axiron(R)

a) Initial dose: 60 mg (1 pump or twist actuation of 30 mg to each axilla) applied once daily at the same time each morning to clean, dry, intact skin of the axilla; do not apply to any other parts of the body; obtain serum testosterone concentration at least 14 days after initiation; draw 2 to 8 hours after application [20]

b) Dose titration: decrease or increase dose by 30-mg increments based on serum testosterone concentration from a single blood draw 2 to 8 hours after application and at least 14 days after starting treatment or following dose adjustment, according to the following recommendation [20][20]:

Serum testosterone concentration below 300 nanogram/deciliter (ng/dL): Increase daily dose from 60 to 90 mg or from 90 mg to 120 mg

Serum testosterone concentration exceeds 1050 ng/dL: Decrease daily dose from 60 mg to 30 mg, or discontinue therapy if at the lowest daily dose of 30 mg

3) FDA Dosage, AndroGel(R) 1%

a) Initial dosage: 50 mg topically once daily (4 pump actuations, or 5 g of gel) preferably in the morning to clean, dry, intact skin on shoulders and upper arms and/or abdomen [5]

b) Dose titration: May increase once-daily dose to 75 mg (6 pump actuations, or 7.5 g of gel) and further to 100 mg (8 pump actuations, or 10 g of gel) if testosterone concentration below normal physiologic level [5]

c) Discontinue use if serum testosterone concentrations consistently exceed the normal range at a daily dose of 50 mg [5]

4) FDA Dosage, AndroGel(R) 1.62%

a) Initial dosage: 40.5 mg (2 pump actuations or 2.5 g of gel) applied topically once daily in the morning to clean, dry, intact skin of the shoulders and upper arms; measure predose morning serum testosterone concentration at approximately 14 and 28 days [15]

b) Dosage titration: Decrease or increase dose to minimum of 20.25 mg/day (1 pump actuation or 1.25 g of gel) up to 81 mg/day (4 pump actuations, or 5 g of gel), based on predose morning serum testosterone concentration drawn approximately 14 and 28 days after starting treatment or following dose adjustment, according to the following recommendation [15]:

Pre-Dose Morning Total Serum Testosterone Concentration	Dose Titration
Greater than 750 ng/dL	Decrease daily dose by 20.25 mg (1 pump actuation or 1.25 g of gel)
Equal to or greater than 350 and equal to or less than 750 ng/dL	No change: continue current dose
Less than 350 ng/dL	Increase daily dose by 20.25 mg (1 pump actuation or 1.25 g of gel)
Key: ng = nanograms	

c) The application site and dose of AndroGel(R) 1.62% are not interchangeable with other topical testosterone products [15]

5) FDA Dosage, Fortesta(TM)

a) Initial dose: 40 mg (4 pump actuations) applied once daily to clean, dry, intact skin of the front and inner thighs in the morning; measure serum testosterone level at approximately 14 and 35 days, draw 2 hours post-application [21]

b) Dose titration: decrease or increase dose to a minimum of 10 mg/day or maximum of 70 mg/day, based on serum testosterone concentrations, drawn 2 hours after application at approximately 14 days and 35 days after treatment initiation or following dose adjustments, according to the following recommendation [21]:

Total Serum Testosterone Concentrations 2 hours Post Fortesta(TM) Application	Dose Titration

Equal to or greater than 2500 ng/dL	Decrease daily dose by 20 mg (2 pump actuations)
Equal to or greater than 1250 and less than 2500 ng/dL	Decrease daily dose by 10 mg (1 pump actuation)
Equal to or greater than 500 and less than 1250 ng/dL	No change: continue current dose
Less than 500 ng/dL	Increase daily dose by 10 mg (1 pump actuation)
Key: ng = nanograms	

c) The application site and dose of Fortesta(TM) are not interchangeable with other topical testosterone products [21].

6) FDA Dosage, Testim(R) 1% Gel

a) Initial dose: one 5 g tube applied once daily (preferably in morning) to clean, dry, intact skin on the shoulder and/or upper arms; measure morning testosterone level 2 weeks after initiation [24].

b) Dose titration: increase dose to 10 g/day (2 tubes) if serum testosterone concentration is below the normal physiologic range or if desired clinical response is not observed [24]

7) FDA Dosage, Vogelxo(TM)

a) Initial dose: 50 mg (1 tube or packet or 4 pump actuations) applied topically to clean, dry, intact skin of shoulders or upper arms once daily; measure morning predose testosterone level after approximately 14 days [25]

b) Dose titration: may increase to 100 mg (2 tubes or packets or 8 pump actuations) once daily if morning predose testosterone level remains below normal (ie, 300 to 1000 nanograms/dL) [25]

c) Maximum dose: 100 mg/day [25]

8) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Topical application route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage (1.6% gel): 50 to 100 mg applied topically once daily. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used). Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

AndroGel(R), 1%, Androgel(R) 1.62%, Natesto(TM), Striant(R), Testim(R), and Vogelxo(TM) topical testosterone gel products are not indicated for use in women [25][22][49][27][24][23]

Transdermal route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage (patch): 2.5 to 7.5 mg/day. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions (guideline dosage) [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage, Androderm(R) 2 mg/day and 4 mg/day System

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [14].

b) Initial dose: One 4 mg/day transdermal system (not two 2 mg/day systems) applied every 24 hours at night; measure early morning serum testosterone level 2 weeks later [19]

c) Dose titration: Increase dose to 6 mg daily at night (one 4 mg/day plus one 2 mg/day system) or decrease dose to 2 mg daily at night (one 2 mg/day system) if early morning serum testosterone level drawn 2 weeks after starting therapy is outside the target range (400 to 930 nanograms/dL) [19].

2) FDA Dosage, Switching from Androderm(R) 2.5 mg/day, 5 mg/day, and 7.5 mg/day System to Androderm(R) 2 mg/day, 4 mg/day, and 6 mg/day System

At next scheduled dose, make switch according to following recommendation [19]:

patients currently on the 2.5 mg/day system may switch to the 2 mg/day system [19]
patients currently on the 5 mg/day system may switch to the 4 mg/day system [19]
patients currently on the 7.5 mg/day system may switch to the 6 mg/day system [19]

Two weeks after switching therapy, measure an early morning serum testosterone level [19]

3) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone Cypionate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg IM every 2 weeks. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Primary hypogonadism, Male

1) FDA Dosage

a) Usual dosage: 50 to 400 mg IM every 2 to 4 weeks. Base dosage (initial, maintenance, and adjustments) on patient response and presence of adverse reactions [82].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone cypionate is not interchangeable with testosterone propionate because of differences in the duration of action [82].

Testosterone Enanthate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg IM every 2 weeks [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Usual dosage: 50 to 400 mg IM every 2 to 4 weeks as replacement therapy; dose based on diagnosis, response to treatment, and presence of adverse effects. Doses above 400 mg per month are generally not required and injections are usually not administered more than every 2 weeks [73].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Metastatic breast cancer, Female

1) Usual dosage (women): 200 to 400 mg IM every 2 to 4 weeks [73].

Subcutaneous route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg subQ every 2 weeks or 50% of the dose subQ once weekly [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Prior to initiation: Confirm the diagnosis of hypogonadism with serum testosterone concentration below the normal range when measured in the morning on at least 2 separate days [74].

b) Initial dosage: 75 mg subQ in the abdominal region once a week [74]

c) Dosage titration: Measure total testosterone trough concentration (Ctrough) 7 days after the most recent dose after 6 weeks of dosing, following 6 weeks after dose adjustment, and periodically while on treatment. If Ctrough is 650 nanograms (ng)/dL or higher, decrease the dose by 25 mg. If Ctrough is less than 350 ng/dL, increase the dose by 25 mg. If Ctrough is 350 to less than 650 ng/dL, maintain the same dose [74].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone Undecanoate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Initial dosage: 1000 mg IM at 0 and 6 weeks and then every 12 weeks to maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [58].

b) Usual dosage: 750 mg IM, and then 750 mg IM 4 weeks later, and then 750 mg IM every 10 weeks thereafter [59]

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

3) Off-label Dosage

a) Off-Label Dosage: 1000 mg IM, and then 1000 mg IM at week 6, and then 1000 mg IM every 12 weeks [60]

Oral route

Hypogonadism, Male

1) Tlando(R) - FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [53].

b) Dosage: 225 mg (2 capsules) orally twice daily in the morning and evening with food; do not adjust dosage [53].

c) Measure serum testosterone following 3 to 4 weeks of treatment and periodically thereafter; draw level 8 to 9 hours after the morning dose [53].

d) Continue treatment if serum testosterone is 300 to 1080 ng/dL, otherwise discontinue treatment [53].

2) Jatenzo(R) - FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [57].

b) Initial dosage: 237 mg twice daily in the morning and evening with food [57]

c) Adjust dose based on serum testosterone concentrations measured 6 hours after the morning dose in plain tubes, clotted at room temperature for 30 minutes prior to centrifugation. Wait seven days after starting treatment or adjusting the dose before checking the serum testosterone concentration. Thereafter, periodically monitor serum testosterone concentrations 6 hours after the morning dose. Administer the same dose in the morning and evening according to the following table [57]:

Testosterone Concentration in Serum From Plain Tube Drawn 6 hours After Morning Dose	Current dose (mg, twice daily)	New dose (mg, twice daily)
Less than 425 nanograms/dL	158	198
	198	237
	237	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	396 (two 198 mg capsules)
425 to 970 nanograms/dL	No dose change	
More than 970 nanograms/dL	396 (two 198 mg capsules)	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	237
	237	198
	198	158
	158	Discontinue therapy

d) Maximum dosage: 396 mg (two 198 mg capsules) twice daily [57]

3) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Dosage in Renal Failure

A) Testosterone Enanthate

1) No specific recommendations are available [76]

Dosage in Hepatic Insufficiency

A) Testosterone Enanthate

1) No specific recommendations are available [76]

Dosage in Other Disease States

A) Testosterone Enanthate

1) In patients who develop edema with or without congestive heart failure, discontinue testosterone enanthate and restart at a lower dose [73].

Pediatric Dosage

Normal Dosage

Important Note

Testosterone

Topical testosterone products are not interchangeable as they have different strengths, doses, and application instructions that may result in different systemic exposure [1][2][3][4][5].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Cypionate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Enanthate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Undecanoate

Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone

Buccal mucosa route

a) The safety and effectiveness of Striant(R) testosterone buccal system have not been established in males younger than 18 years [23].

Nasal route

a) The safety and efficacy of Natesto(TM) testosterone gel have not been established in patients younger than 18 years [22].

Topical application route

Female-to-male transsexual - Gender dysphoria

1) Off-label Dosage, Adolescent

a) Dosage (gel): 50 mg applied topically once daily [8]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

The safety and efficacy of AndroGel(R) 1%, AndroGel(R) 1.62%, Axiron(R), Fortesta(TM), Testim(R) 1%, and Vogelxo(TM) have not been established in males younger than 18 years [20][25][27][24][49][21]. Acceleration of bone age and premature closure of epiphyses may occur with improper use [21].

Transdermal route

a) Safety and efficacy of testosterone transdermal system have not been established in males younger than 18 years. Acceleration of bone age and premature closure of epiphyses may occur with improper use [19].

Testosterone Cypionate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Primary hypogonadism, Male

1) Usual dosage (12 years or older): 50 to 400 mg IM every 2 to 4 weeks as replacement therapy. Base dosage (initial, maintenance, and adjustments) on patient response, presence of adverse reactions, age, and skeletal age. Some regimens include low initial doses and gradual increases with progressing puberty and may or may not include decreased maintenance doses. Other regimens include higher initial doses for the induction of puberty followed by lower maintenance doses [82].

Testosterone cypionate is not interchangeable with testosterone propionate because of differences in the duration of action [82].

Testosterone Enanthate

Intramuscular route

Delayed puberty, Male

1) Usual dosage (adolescent males): 50 to 200 mg IM every 2 to 4 weeks for a limited duration, such as 4 to 6 months. Some dosage regimens include low initial doses and gradual increases with progressing puberty and may or may not include decreased maintenance doses. Other regimens include higher initial doses for the induction of puberty followed by lower maintenance doses. Although various dosing regimens may be used, the patient's chronological and skeletal age should be considered when determining initial and maintenance doses in addition to patient response and adverse effects [73].

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) Usual dosage (adolescent males): 50 to 400 mg IM every 2 to 4 weeks as replacement therapy. Although various dosing regimens may be used to induce pubertal changes in hypogonadal males, the patient's chronological and skeletal age should be considered when determining initial and maintenance doses. Doses above 400 mg per month are generally not required and injections are usually not administered more than every 2 weeks [73].

Subcutaneous route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) subQ every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg subQ every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Testosterone Undecanoate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

General Dosage Information

1) The safety and effectiveness of testosterone undecanoate have not been established in pediatric patients younger than 18 years [59].

Oral route

a) General Dosage Information

1) The safety and effectiveness of testosterone undecanoate have not been established in pediatric patients younger than 18 years. Improper use may result in acceleration of bone age and premature closure of epiphyses [53][57].

Administration

A) Testosterone

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the compounding and administration of a hazardous topical drug, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator, and use eye/face and respiratory protection if not prepared in a control device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection, and if there is inhalation potential use respiratory protection [50].

b) Buccal mucosa route

1) Administration

a) The rounded side of the buccal system surface should be placed against the gum and held firmly in place with a finger over the lip for 30 seconds to ensure adhesion [23].

b) If the buccal system falls off during the first 8 hours after application, replace with a new system that should be retained until a total of 12 hours have elapsed from placement of the first system; then continue usual dosing schedule. If the buccal system falls off 8 or more hours after application, apply a new buccal system that may be retained for 12 hours; then continue usual dosing schedule [23].

c) The buccal system should not be chewed or swallowed. Remove system prior to oral care and apply a new system after [23].

c) Nasal route

1) Preparation

a) Prime the pump prior to the first use by depressing the pump 10 times, discarding initial drug delivered. Wash off the gel with warm water then wipe tip with clean, dry tissue. If the product comes into contact with hands, wash hands with soap and water [22].

2) Administration

a) Completely depress the pump 1 time in each nostril; do not apply to any other part of the body. To administer, blow nose, uncap pump, and place the finger on the actuator. Then insert pump until the finger reaches the bottom of the nose. Apply gel to lateral nasal wall and remove pump once fully depressed, wiping the tip along the inside of the lateral nostril. Press on the nostrils just below the bridge of the nose and lightly massage the applied product. Do not blow nose or sniff for 1 hour [22].

d) Topical application route

1) Axiron(R)

a) If using antiperspirant or deodorant stick, roll-on, or spray, apply these 2 minutes prior to the application of testosterone topical solution as part of a normal, consistent, daily routine [20].

b) When using for the first time, prime the pump by depressing the pump-actuated or by twisting the dose dial 3 times; discard product dispensed directly into a basin, sink, or toilet and then wash the liquid away thoroughly [20].

c) Pump actuated: After priming, depress the pump completely only 1 time each time (1 pump actuation equals 30 mg) [20].

d) Pump actuated: Apply using the applicator provided. Position the nozzle over the applicator cup and depress the pump fully once. Do not fill the cup with more than 30 mg (1 pump actuation) [20].

e) Twist actuated: After priming, completely twist (180 degree turn) the dose dial 1 time (1 twist actuation equals 30 mg). The applicator should be filled with no more than 30 mg (1 twist

actuation). Dosing that requires greater than 1 twist actuation must be applied in increments of 30 mg [20]

f) Keep the applicator upright. Place it up into the axilla and wipe steadily down and up into the axilla. If the solution drips or runs, wipe it back up with the applicator cup. Do not rub the solution into the skin with fingers or hand [20].

g) Apply each morning to clean, dry, intact skin of the axilla. Do not apply to any other parts of the body. Allow each application site to dry completely prior to the next application (for higher doses) or dressing [20].

h) 30 mg, 1 pump or twist actuation: Apply once to 1 axilla only (left or right) [20].

i) 60 mg, 2 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla [20].

j) 90 mg, 3 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla. Wait for the product to dry and then apply once again 1 actuation to the left or right axilla [20].

k) 120 mg, 4 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla. Wait for the product to dry and then apply once again 1 actuation to the left axilla and 1 actuation to the right axilla [20].

l) After use, rinse the applicator under room temperature, running water, and then pat dry with a tissue. Place the applicator and cap on the bottle for storage [20].

m) Wash hands thoroughly with soap and water after applying testosterone topical solution [20].

n) Cover the application site with clothing or dressing after the solution has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [20].

o) Wait at minimum 2 hours prior to washing the application site or swimming [20].

p) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [20].

2) AndroGel(R)

a) Prime the AndroGel(R) pump by depressing the actuator 3 times while canister is in upright position. Safely discard the gel dispensed from the first 3 actuations. Priming is only necessary before the first dose [27][49].

b) Apply to clean, dry, intact skin of shoulder or upper arm that will be covered by clothing. For the 40.5 mg (2.5-g packets), squeeze a portion of the gel from the packet into the palm of hand and apply to application sites (as this size packet needs to be split between the left and right shoulder) and repeat until entire contents have been applied. The gel may be delivered from the actuator into the palm of one hand, then applied to the intended site, or may be applied directly from the pump to the intended application site [24][27][49].

c) Apply AndroGel(R) 1.62%, to the shoulder or upper arm (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt); do not apply to any other part of the body, including abdomen or genitals. Wait a minimum of 2 hours prior to washing the application site or swimming [49].

d) AndroGel(R) 1%, apply to the shoulder and upper arm and/or abdomen (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt); do not apply to genitals. Avoid swimming or showering for at least 5 hours after application [51].

e) Patients should wash hands thoroughly with soap and water immediately after applying testosterone topical gel [27][49].

f) Cover the application site with clothing or dressing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [27][49].

g) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [27][49].

h) Children and women should avoid contact with unwashed or unclothed application site [27] [49].

i) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [27][49].

j) Application recommendations for AndroGel(R) 1.62% for pump or packets are in the table below [15]:

AndroGel(R) 1.62%						
Total Dose of Testosterone	Total Pump Actuations	Pump Actuations per Upper Arm and Shoulder		Total Packets *	Gel Applications per Upper Arm and Shoulder *	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	1	1	0	One 1.25-g packet	One 1.25-g packet	0
40.5 mg	2	1	1	One 2.5-g packet	Half the contents of one 2.5-g packet	Half the contents of one 2.5-g packet
60.75 mg	3	2	1	One 1.25-g AND one 2.5-g packet	One 2.5-g packet	One 1.25-g packet
81 mg	4	2	2	Two 2.5-g packets	One 2.5-g packet	One 2.5-g packet
* Weight given as gel content of packet.						

k) Application recommendations for AndroGel(R) 1% 75-g pump are in the table below [5]:

Dosing Guidelines for the AndroGel(R) 1% 75-g Multi-Dose Pump	
Prescribed Testosterone Dose	Number of Pump Actuations
50 mg daily	4 pumps once daily
75 mg daily	6 pumps once daily
100 mg daily	8 pumps once daily

3) Fortesta(TM)

a) Prime the pump by depressing the actuator 8 times while canister is in upright position; safely discard the gel dispensed from the first 8 actuations; only necessary to prime pump before the first dose [21].

b) Apply to clean, dry, intact skin of the front and inner thighs; do not apply to genitals or other parts of the body; use one finger to apply gel [21].

c) After the application site is dry, site should be covered with clothing (with sufficient length to cover application site); wash hands thoroughly with soap and water after applying gel [21].

d) Children and women should avoid contact with unwashed or unclothed application site [21].

e) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [21].

f) If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [21].

g) Application recommendations for Fortesta(TM) are in the table below [21]:

Total Dose of Testosterone	Total Pump Actuations	Pump Actuations per Thigh	
		Thigh #1	Thigh #2
10 mg	1	1	0
20 mg	2	1	1

30 mg	3	2	1
40 mg	4	2	2
50 mg	5	3	2
60 mg	6	3	3
70 mg	7	4	3

4) Testim(R)

a) Apply to clean, dry, intact skin of shoulder or upper arm; do not apply to genitals or abdomen. Wash hands thoroughly with soap and water immediately after applying [24].

b) Do not wash application site for at least 2 hours after application. Cover the application site with clothing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [24].

c) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [24].

d) Children and women should avoid contact with unwashed or unclothed application site [24].

e) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [24].

5) Vogelxo(TM)

a) With multidose bottle, prime the pump 3 times before first use (discard any product released). Depress pump 4 times or empty entire contents of 1 unit-dose tube or packet into palm of the hand and immediately apply to clean, dry, intact skin of shoulder and upper arm. When the daily dosage is 100 mg, repeat on the opposite shoulder [25].

b) Do not apply to abdomen or genitals. Wash hands thoroughly with soap and water immediately after applying [25].

c) Do not wash site for at least 2 hours after application. Cover the application site with clothing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [25].

d) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [25].

e) Children and women should avoid contact with unwashed or unclothed application site [25].

f) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [25].

e) Transdermal route

1) Administration

a) Immediately after opening the pouch, apply the adhesive side of the Androderm(R) system to the back, abdomen, upper arm, or thigh in a clean, dry area of the skin. Press system firmly in place, ensuring good contact with the skin, especially around the edges. Avoid application to oily, damaged, or irritated skin. Do not apply to the scrotum, and avoid bony prominences or areas of prolonged pressure during sitting or sleeping [19].

b) Avoid swimming, showering, or washing the administration site for at least 3 hours after application [19].

c) Rotate application sites, with at least 7 days between applications to the same site [19].

B) Testosterone Cypionate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due

to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Administration

a) Administer IM injection slowly and deeply into the gluteal muscle; it is not for IV injection [83].

b) If crystals formed because product was stored at lower than recommended temperatures, they can be dissolved by warming or shaking the vial [83].

C) Testosterone Enanthate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Administration

a) Administer IM injection slowly and deeply into the gluteal muscle, avoiding intravascular injection. Crystals formed during storage at lower than recommended temperatures can be dissolved by warming or shaking the vial. A wet syringe or wet needle may turn the solution cloudy but does not affect product potency [73].

c) Subcutaneous route

1) Administration

a) Xyosted(TM) is for subQ injection in the abdominal region only. Avoid IM or intravascular injection. Do not use if the liquid in the syringe is cloudy or if visible particles are present; an air bubble is normal. Do not use if the seal is broken [74].

D) Testosterone Undecanoate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Preparation

a) Carefully remove gray plastic cap from vial; leave the aluminum metal ring and crimp seal

around the gray rubber stopper [63].

b) Using an 18-gauge needle at a 45-degree angle with the bevel oriented upward, inject 3 mL of air through the gray rubber stopper to create positive pressure in the vial, and then withdraw 3 mL (750 mg) of solution [64].

c) Expel any air bubbles from the syringe and change the syringe needle to a new IM needle [63].

d) .

2) Administration

a) For IM use only [63]

b) Slowly (over 60 to 90 seconds) inject IM deep into the gluteal muscle; care must be taken to avoid intravascular administration as this may lead to pulmonary oil microembolism; also avoid the superior gluteal arteries and sciatic nerve [63].

c) Discard any unused portion [63].

d) Alternate injection sites between left and right buttock between consecutive injections [63].

c) Oral route

1) Administration

a) Give with food [53][57].

E) Testosterone

1) Buccal mucosa route

a) Patch, Extended Release

1) Store at 20 to 25 degrees C (68 to 77 degrees F). Protect from heat and moisture [108].

2) Intramuscular route

a) Solution

1) Store at room temperature. Warming and rotating the vial between hands will redissolve any crystals that may have formed when stored at lower temperatures [88].

3) Nasal route

a) Gel/Jelly

1) Store at a controlled room temperature between 20 and 25 degree C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) [22].

4) Oral route

a) Capsule

1) Refrigerate between 2 and 8 degrees C before dispensing. Do not refrigerate after dispensing. The shelf life is 3 years before opening when stored between 2 and 8 degrees C and 90 days at room temperature after the container has been opened [208].

5) Topical application route

a) Gel/Jelly/Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [28][25]. Do not freeze [21].

2) Store upright at a controlled room temperature of 25 degrees C (77 degrees F); excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) [209][183].

6) Transdermal route

a) Patch, Extended Release

1) Store at 25 degrees C (77 degrees F); excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [182].

F) Testosterone Cypionate

1) Injection route

a) Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F); protect from light [83].

G) Testosterone Enanthate

1) Intramuscular route

a) Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F). If crystals form, warm and rotate vial between palms of hands to dissolve [73].

2) Subcutaneous route

a) Solution

1) Store in original carton at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F). Protect from light; do not refrigerate or freeze [74].

H) Testosterone Undecanoate

1) Intramuscular route

a) Solution

1) Store in original carton at a controlled room temperature of 25 degrees C (77 degrees F) , with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Discard any unused portion [59].

2) Oral route

a) Capsule

1) Store at a temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Store in a dry place and protect from moisture [57].

b) Capsule, Liquid Filled

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [53].

Comparative Efficacy

Acetylcarnitine

Aging, Male

a) Carnitines and testosterone both improved sexual dysfunction, depressed mood, and fatigue associated with male aging. However, testosterone treatment caused prostate enlargement, which carnitine treatment did not. In a randomized, placebo- controlled trial, men over age 60 with symptoms of decreased libido and erectile quality, depressed mood and intellectual concentration ability, irritability, fatigue, and serum testosterone lower than 6 picograms/milliliter were randomized to receive testosterone undecanoate 160 milligrams/day (mg/d) (n=40), propionyl-L-carnitine 2 grams/day (g/d) plus acetyl-L-carnitine 2 g/d (n=45), or placebo (n=45) for 6 months. At 6 months, peak systolic velocity, resistive index of the right cavernosal artery, and nocturnal penile tumescence were increased in both the testosterone group and the carnitines group and unchanged in the placebo group. Erectile function, sexual desire, and sexual satisfaction increased at 3 or 6 months or both in both active treatment groups. Carnitine scores were significantly better than testosterone scores with respect to erectile function at 3 months (p less than 0.05) and 6 month (p less than 0.01), orgasm at 6 months (p less than 0.01), and sexual well-being at 6 months (p less than 0.01). Other physiological scores were not different for the 2 groups. Both active treatments lowered the Hamilton Depression and Melancholia Scale scores, but carnitines more so (p less than 0.01, carnitines vs testosterone). Carnitines and testosterone equally decreased fatigue scale scores. Prostate volume increased with testosterone treatment from 15 cubic centimeters at baseline to 25 cubic centimeters at 6 months. Prostate volume was unchanged by carnitine or placebo treatment. In the testosterone group, prostate volume had decreased (to 18 cubic centimeters) by 6 months after termination of therapy but

remained elevated above baseline. All other parameters reverted to baseline levels by 6 months after termination of therapy [214].

Chlorotrianisene

Engorgement of breasts

a) SUMMARY: Chlorotrianisene is less effective than the combination of testosterone enanthate plus estradiol valerate in the treatment of postpartum breast engorgement.
b) In a double-blind study of lactation suppression in clinic patients, testosterone enanthate with estradiol valerate (Deladumone OB) 2 milliliters IM immediately prior to delivery was compared to chlorotrianisene 72 mg orally every 12 hours for 4 doses. At day 4, Deladumone OB(R) patients experienced significantly less breast tenderness and lactation than did patients receiving chlorotrianisene. Both drugs were significantly more effective than placebo [212].
c) In a study of 484 puerperal patients who did not wish to breast feed, testosterone enanthate with estradiol valerate was more effective than chlorotrianisene for inhibition of lactation and relief of breast engorgement and discomfort [213].

Chorionic Gonadotropin

Male hypogonadotropic hypogonadism

a) Weekly 5000 unit chorionic gonadotropin injections (n=16) were compared with monthly 250 milligram long-acting testosterone injections (n=22) in male hypogonadotropic hypogonadism patients [216]. Both treatments produced comparable virilizing effects measured as progression through Tanner stages. Chorionic gonadotropin, however, produced increases in testicular volume to near-normal, which did not occur with testosterone. This additional benefit of chorionic gonadotropin may enhance later induction of fertility when such treatment is undertaken.

Cyproterone

Contraception, Male

a) In a small study all men who received testosterone and cyproterone became azoospermic compared to 3 of 5 men receiving testosterone only. Fifteen men were randomized to receive cyproterone 50 mg orally twice daily plus testosterone enanthate 100 mg intramuscularly (IM) weekly; cyproterone 25 mg orally twice daily plus testosterone 100 mg IM weekly; or testosterone 100 mg IM weekly alone for 16 weeks. Patients in the cyproterone 100 mg, cyproterone 50 mg, and testosterone only groups achieved azoospermia at mean times of 6.8, 8.4, and 14 weeks, respectively. After treatment baseline sperm counts were achieved in all men. Lipoprotein profiles nor liver function tests were detected in any patient. No significant differences in sexual behavior were reported among the three groups [215].

Estrogen

Disorder of bone development

a) In a case report concerning a 31-year old hypogonadal male with aromatase deficiency, 50 micrograms of estradiol, given transdermally twice weekly for 9 months, was able to affect epiphyseal closure and improvement in bone pain. Prior treatment with testosterone enanthate, 250 milligrams intramuscularly every ten days for six months had not achieved these results. The baseline bone age of 14.8 years did not change with testosterone enanthate, but increased to more than 16 years after 9 months of estradiol therapy. Further research is required to confirm these results [211].

Fluoxymesterone

Anemia

a) A randomized clinical trial was conducted to compare the erythropoietic effects of several androgens in 143 patients (103 males, 40 females) with anemia who were receiving maintenance hemodialysis [210]. The patients received either testosterone enanthate 4 milligrams/kilogram intramuscularly weekly (the female patients did not receive testosterone), fluoxymesterone 0.4 mg/kg orally daily, oxymetholone 1 mg/kg orally daily, or nandrolone decanoate 3 mg/kg intramuscularly weekly. Control periods of at least 2 months were followed by treatment periods consisting of one of the androgens for 6 months followed by another control period; three courses utilizing a different drug each time were administered. Seventy-seven, 56, and 35 patients completed the first, second, and third treatment periods, respectively. The 2 agents administered by injection, which included testosterone, were judged superior to the orally administered agents in terms of patient response and mean rise in hematocrit. Approximately 50% of the patients had an increase of at least 5 percentage points in hematocrit following the administration of either injectable androgen.

Nandrolone

Anemia

a) A randomized clinical trial compared the erythropoietic effects of several androgens in 143 patients (103 males, 40 females) with anemia who were receiving maintenance hemodialysis. The patients received either testosterone enanthate 4 milligrams/kilogram of body weight intramuscularly weekly (the female patients did not receive testosterone), fluoxymesterone 0.4 mg/kg of body weight orally daily, oxymetholone 1 mg/kg of body weight orally daily, or nandrolone decanoate 3 mg/kg of body weight intramuscularly weekly. Control periods of at least 2 months were followed by treatment periods consisting of one of the androgens for 6 months followed by another control period; three courses utilizing a different drug each time were administered. Seventy-seven, 56, and 35 patients completed the first, second, and third treatment periods, respectively. The 2 agents administered by injection, which included testosterone, were judged superior to the orally administered agents in terms of patient response and mean rise in hematocrit. Approximately 50% of the patients had a 5% increase in hematocrit following the administration of either injectable androgen [217].

Oxymetholone

Anemia secondary to renal failure

a) A randomized clinical trial compared the erythropoietic effects of several androgens in 143 patients (103 males, 40 females) with anemia who were receiving maintenance hemodialysis. The patients received either testosterone enanthate 4 milligrams/kilogram intramuscularly weekly (the female patients did not receive testosterone), fluoxymesterone 0.4 milligram/kilogram orally daily, oxymetholone 1 milligram/kilogram orally daily, or nandrolone decanoate 3 milligrams/kilogram intramuscularly weekly. Control periods of at least 2 months were followed by treatment periods consisting of one of the androgens for 6 months followed by another control period; three courses utilizing a different drug each time were administered. Seventy-seven, 56, and 35 patients completed the first, second, and third treatment periods, respectively. The 2 agents administered by injection, which included testosterone, were judged superior to the orally administered agents in terms of patient response and mean rise in hematocrit. Approximately 50% of the patients had an increase of at least 5 percentage points in hematocrit following the administration of either injectable androgen [218].

Propionyl-L-Carnitine

Aging, Male

a) Carnitines and testosterone both improved sexual dysfunction, depressed mood, and fatigue associated with male aging. However, testosterone treatment caused prostate enlargement, which carnitine treatment did not. In a randomized, placebo- controlled trial, men over age 60 with symptoms of decreased libido and erectile quality, depressed mood and intellectual concentration ability, irritability, fatigue, and serum testosterone lower than 6 picograms/milliliter were randomized to receive testosterone undecanoate

160 milligrams/day (mg/d) (n=40), propionyl-L-carnitine 2 grams/day (g/d) plus acetyl-L-carnitine 2 g/d (n=45), or placebo (n=45) for 6 months. At 6 months, peak systolic velocity, resistive index of the right cavernosal artery, and nocturnal penile tumescence were increased in both the testosterone group and the carnitines group and unchanged in the placebo group. Erectile function, sexual desire, and sexual satisfaction increased at 3 or 6 months or both in both active treatment groups. Carnitine scores were significantly better than testosterone scores with respect to erectile function at 3 months (p less than 0.05) and 6 month (p less than 0.01), orgasm at 6 months (p less than 0.01), and sexual well-being at 6 months (p less than 0.01). Other physiological scores were not different for the 2 groups. Both active treatments lowered the Hamilton Depression and Melancholia Scale scores, but carnitines more so (p less than 0.01, carnitines vs testosterone). Carnitines and testosterone equally decreased fatigue scale scores. Prostate volume increased with testosterone treatment from 15 cubic centimeters at baseline to 25 cubic centimeters at 6 months. Prostate volume was unchanged by carnitine or placebo treatment. In the testosterone group, prostate volume had decreased (to 18 cubic centimeters) by 6 months after termination of therapy but remained elevated above baseline. All other parameters reverted to baseline levels by 6 months after termination of therapy [214].

Stanozolol

1) Efficacy

a) Oral stanozolol 6 mg/day produced more undesirable lipoprotein effects than intramuscular testosterone 200 mg once weekly in male weight lifters in a 6-week, crossover study [219]. Stanozolol reduced HDL-cholesterol and the HDL-2 subfraction by 33% and 71%, respectively; however, the HDL-cholesterol concentration was decreased by only 9% with testosterone, with the decrease being in the HDL-3 subfraction. Apolipoprotein A-1 levels were reduced by 8% and 40% with testosterone and stanozolol, respectively. LDL-cholesterol concentrations decreased 16% with testosterone, but increased by 29% with stanozolol. An increase in the postheparin hepatic triglyceride lipase activity of 123% was observed with stanozolol, however, increases with testosterone (25%) were not significant. Intramuscular testosterone is preferable to oral stanazolol for clinical indications requiring prolonged androgen or anabolic steroids.

Place In Therapy

A) Testosterone

1) Transdermal, Topical, Buccal, Intranasal

a) Testosterone preparations are indicated for primary hypogonadism (congenital or acquired) due to testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. Typically, low serum testosterone concentrations and high gonadotropin (FSH, LH) concentrations are present. Additionally, it is indicated for hypogonadotropic hypogonadism (congenital or acquired) due to idiopathic gonadotropin or luteinizing hormone releasing hormone (LHRH) deficiency or pituitary-hypothalmic injury from tumors, trauma or radiation. Typically, low serum testosterone concentrations and low to normal gonadotropin (FSH, LH) concentrations are present [22][23][85][84].

b) Testosterone preparations are also indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone including congenital or acquired primary hypogonadism and congenital or acquired hypogonadotropic hypogonadism [22][23][28][84].

B) Testosterone Cypionate

Testosterone cypionate is indicated for replacement therapy in adults and pediatric patients age 12 and older for conditions associated with a deficiency or absence of endogenous testosterone, such as:

Primary hypogonadism (congenital or acquired): testicular failure from conditions such as cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, orchiectomy [83]
Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing

hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation [83]

1) Cautious use of androgens in the pediatric population is necessitated by the likelihood of adverse effects on bone maturation. The risk of a compromised final mature height is greater the younger the child. Assessment of bone age in the wrist and hand is recommended every 6 months [83].

C) Testosterone Enanthate

1) Delayed Puberty

a) Testosterone enanthate injection is indicated to stimulate puberty in select male patients with delayed puberty, for a limited duration of treatment such as 4 to 6 months. Cautious use of androgens in the pediatric population is necessitated by the likelihood of adverse effects on bone maturation. The risk of a compromised final mature height is greater in the younger child. Assessment of bone age in the wrist and hand every 6 months is recommended [73].

2) Male Hypogonadotropic hypogonadism

a) Testosterone enanthate injection is indicated in adult men for replacement therapy in congenital or acquired hypogonadotropic hypogonadism, such as gonadotropin or luteinizing hormone–releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation [74][75]. Testosterone enanthate IM injection is also indicated in adolescent males. Concurrent treatment with appropriate adrenal cortical and thyroid hormone replacement therapy are of primary importance, however. Replacement therapy needed prior to puberty will be needed during adolescence for secondary sexual characteristic development. Replacement therapy needed following puberty will require prolonged duration of therapy to maintain sexual characteristics [73].

3) Male Primary Hypogonadism

a) Testosterone enanthate injection is indicated in adult men for replacement therapy in primary congenital or acquired hypogonadism, such as testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy [74][75], Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals[74]. Testosterone enanthate IM injection is also indicated in adolescent males. Replacement therapy needed prior to puberty will be needed during adolescence for secondary sexual characteristic development. Replacement therapy needed following puberty will require prolonged duration of therapy to maintain sexual characteristics [73].

4) Metastatic Mammary Cancer in Women

a) IM testosterone enanthate is indicated for palliation of inoperable metastatic (skeletal) mammary cancer in women who are 1 to 5 years postmenopausal, when a goal of therapy includes ablation of the ovaries. Testosterone enanthate injection has also been used in premenopausal women with breast cancer who have benefited from oophorectomy and have a hormone-responsive tumor [73].

D) Testosterone Undecanoate

1) Testosterone undecanoate IM and oral capsules are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone. These include primary hypogonadism (congenital or acquired): testicular failure from conditions such as cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals (men with these conditions have low serum testosterone concentrations and gonadotropins above the normal range) and hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation (men with these conditions have low serum testosterone concentrations and gonadotropins in the normal or low range) [53][57][59]. Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53]. Testosterone undecanoate IM should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis [59]. Safety and efficacy of testosterone undecanoate have not been established in males younger than 18 years old [57][59].

2) A mean 24-hour serum testosterone level within normal range (300 to 1080 nanograms/dL) was achieved in 80% of patients receiving testosterone undecanoate capsules (Tlando(R)) 225 mg twice daily with food for 24 days (N=95); no dosage adjustments were permitted. Majority of those not achieving a eugonadal range had a BMI of 30 kg/m(2) or greater [61].

3) Mean plasma total testosterone over 24 hours was within the normal eugonadal range in 87% of patients in a 4-month study of adult hypogonadal males who received testosterone undecanoate capsules [57].

4) In an 84-week study of hypogonadal adult male patients with low serum testosterone, 94% of patients maintained an average testosterone concentration within the normal range following the third injection of testosterone undecanoate IM [59].

MEDICATION SAFETY

Contraindications

A) Testosterone

1) Breast cancer, male [25][22][23][84][28][21][85][86][87][88]

2) Females who are pregnant, may become pregnant, or who are breastfeeding; known teratogen; exposure of female fetus or nursing infant to testosterone residue may result in varying degrees of virilization [25][22][23][84][28][21][85][86][87][88]

3) Hypersensitivity to testosterone or any component of the product [86][87][88]

4) Prostate cancer, known or suspected [25][22][23][84][28][21][85][86][87][88]

5) Use in women [84][86]

B) Testosterone Cypionate

1) Breast cancer, male [82]

2) Cardiac, hepatic, or renal disease, serious [82]

3) Women who are pregnant or may become pregnant [82]

4) Hypersensitivity to testosterone cypionate [82]

5) Prostate cancer, known or suspected [82]

C) Testosterone Enanthate

1) Breast cancer in males [74][75][73]

2) Females who are pregnant or may become pregnant; known teratogen [74][75][73]

3) Hypersensitivity to testosterone enanthate or any component of the product, including sesame oil [74][75][73]

4) Known or suspected prostate cancer [74][75][73]

5) Men with hypogonadal conditions, such as age-related hypogonadism, that are not associated with structural or genetic etiologies [74].

D) Testosterone Undecanoate

1) Breast carcinoma [57][59]

2) Hypersensitivity to testosterone undecanoate or any component of the product (eg, refined castor oil, benzyl benzoate) [57][59]

3) Pregnancy, nursing, or women of childbearing potential; may cause fetal harm and serious adverse reactions in nursing infants, such as virilization [57][92]

4) Known or suspected prostate carcinoma [57][59]

5) Hypogonadal conditions, such as age-related hypogonadism, that are not associated with structural or genetic etiologies [57]

Precautions

A) Testosterone

1) Beers Criteria: Avoid use unless indicated for symptomatic hypogonadism due to potential for cardiac toxicities. Contraindicated in men with prostate cancer [6].

2) Abuse: Abuse, usually at higher than prescribed doses and usually in conjunction with other anabolic androgenic steroids, has been reported and may result in serious safety risks (eg, heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, infertility); if suspected, measure serum testosterone [89].

3) Cardiovascular: A possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [17][2][1][14][16][5][15][3][18].

4) Cardiovascular: Edema, with or without congestive heart failure, may occur in patients with preexisting cardiac, renal or hepatic disease [25][22][23][84][28][21][85][86][88][87]; discontinuation and diuretic therapy may be required [25][22][23].

5) Dermatologic: Use of magnetic resonance imaging has caused skin burns at application site due to the presence of aluminum in the patch [84].

6) Endocrine and metabolic: Increased risk of hypercalcemia and associated hypercalciuria in cancer patients; monitoring recommended [25][22][23][84][28][21][85][87][88]

7) Endocrine and metabolic: Dyslipidemia may occur; monitoring recommended [25][22][23]; dosage adjustment or discontinuation may be warranted [84][28][21][87][85].

8) Endocrine and metabolic: Decreased levels of thyroxine-binding globulins, resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4, may occur [90].

9) Flammability: Alcohol-based formulations are flammable until dry [25][28][21][85][86][87].

10) Gastrointestinal: Gum-related adverse reactions, including severe gum irritation, have been reported and may warrant dental consultation; monitoring recommended [23].

11) Hematologic: Venous thromboembolic events, including DVT and pulmonary embolism, have been reported; monitoring recommended; discontinue use if suspected [17][2][1][14][16][5][15][3][18].

12) Hematologic: Polycythemia may occur; monitoring recommended [25][22] and dose adjustment may be warranted [25][23][84][28][21][85][86][88][87].

13) Hepatic: Serious hepatic adverse effects, including cholestatic jaundice, liver cancer, and peliosis hepatitis have been reported with prolonged use of high doses of orally active androgens [25][22][23][84][28][21][85][86][88][87]; discontinue use until cause is determined [25][22][23].

14) Musculoskeletal: Osteolysis may be stimulated by periods of immobilization and can result in hypercalcemia [88].

15) Neurologic: A possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [17][2][1][14][16][5][15][3][18].

16) Reproductive: Secondary exposure in children and women may result in virilization, inappropriate changes in genital size, and other serious adverse effects [25][28][21][85][86][87][91]; discontinue use until cause of virilization is determined [25].

17) Reproductive: Increased risk of worsening benign prostatic hyperplasia [25][22][23][84][28][21][85][86]; monitoring recommended [25][22][23][84][28][21][85]

18) Reproductive: Increased risk of prostate cancer with androgen use; monitoring recommended [25][22][23][84][28][21][85][86][87]

19) Reproductive: Gynecomastia, possibly persistent, may occur [25][22][23][84][28][21][85][86][88][87].

20) Reproductive: Suppression of spermatogenesis may occur with large doses [25][22][23].

21) Reproductive: Avoid use in men who are trying to conceive [26]

22) Respiratory: Nasal adverse reactions (ie, nasopharyngitis, rhinorrhea, epistaxis) have been reported and may require further evaluation or discontinuation [22].

23) Respiratory: Use is not recommended in patients with mucosal inflammatory disorders, sinus disease, or a history of nasal disorders, nasal or sinus surgery, nasal fracture (within last 6 months), or nasal fracture resulting in deviation of the anterior nasal septum [22].

24) Respiratory: Increased risk of sleep apnea in patients with obesity or chronic lung diseases [25][22][23][84][28][21][85][86][87]

B) Testosterone Cypionate

1) Beers Criteria: Avoid use unless indicated for symptomatic hypogonadism due to potential for cardiac toxicities. Contraindicated in men with prostate cancer [6].

2) Abuse: Abuse, usually at higher than prescribed doses and usually in conjunction with other anabolic androgenic steroids, has been reported and may result in serious safety risks (eg, heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, infertility); if suspected, measure serum testosterone [89].

3) Cardiovascular: Possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [93]

4) Cardiovascular: Possible increased risk of major adverse cardiovascular events (eg, cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) have been reported with testosterone therapy in men [82]

5) Cardiovascular: Preexisting cardiac disease; edema may occur, with or without congestive heart failure [82]

6) Endocrine and metabolic: Gynecomastia may occur [82]

7) Endocrine and metabolic: Hypercalcemia may occur in immobilized patients; discontinue if occurs [82]

8) Hematologic: Thromboembolic events (eg, DVT and pulmonary embolism) have been reported with testosterone therapy; discontinue use if suspected [82]

9) Hepatic: Increased risk of hepatic adenomas, hepatocellular carcinoma, or peliosis hepatitis with prolonged use at high doses [82]

10) Hepatic: Preexisting hepatic disease; edema may occur, with or without congestive heart failure [82]

11) Neurologic: Possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [93]

12) Renal: Preexisting renal disease; edema may occur, with or without congestive heart failure [82]

13) Reproductive: Delayed puberty in healthy male children; use may accelerate bone maturation and result in compromised adult stature; monitoring recommended [82]

14) Reproductive: Priapism or excessive sexual stimulation may occur; interrupt use and reduce the dosage if restarting therapy [82]

15) Reproductive: Oligospermia may occur with prolonged or excessive use; interrupt use and reduce the dosage if restarting therapy [82]

16) Reproductive: Avoid use in men who are trying to conceive [26]

17) Reproductive: Benign prostatic hypertrophy; increased risk of acute urethral obstruction; interrupt use and reduce the dosage if restarting therapy [82]

18) Special populations: Athletic performance enhancement; use not recommended [82]

19) Special populations: Contains benzyl alcohol, which may cause "gasping syndrome" and death in pediatric patients, with an increased risk in premature and low-birth weight infants [82]

20) Special populations: Elderly patients may be at increased risk of developing prostatic hypertrophy or prostatic carcinoma [82]

C) Testosterone Enanthate

1) Beers Criteria: Avoid unless indicated for symptomatic hypogonadism due to potential for cardiac toxicities. Contraindicated in men with prostate cancer [6].

2) Abuse: Abuse, usually at higher than prescribed doses and usually in conjunction with other anabolic androgenic steroids, has been reported and may result in serious cardiovascular and psychiatric adverse reactions; if suspected, measure serum testosterone [74].

3) Cardiovascular: Possible increased risk of heart attack, stroke, or death has been reported [75] [93]; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [93]

4) Cardiovascular: Edema, with or without congestive heart failure, may occur, especially in patients with preexisting cardiac, hepatic, or renal disease; discontinuation may be necessary [74] and/or

lower restarting dose used [75][73]

5) Endocrine and metabolic: Hypercalcemia may occur in patients with breast cancer or who are immobilized; discontinue use if occurs [75][73]

6) Endocrine and metabolic: Hypercalcemia, and associated hypercalciuria, may occur in cancer patients at risk; monitoring recommended [74]

7) Endocrine and metabolic: Altered serum cholesterol concentrations may occur, and caution should be used, especially in patients with history of myocardial infarction or coronary artery disease; monitoring recommended [75][73]

8) Endocrine and metabolic: Changes in serum lipid profile may occur; monitoring recommended and discontinuation of therapy may required [74]

9) Endocrine and metabolic: Thyroxine-binding globulin concentrations may be decreased [74]

10) Hematologic: Venous thromboembolic events, including DVT, have been reported with testosterone therapy; discontinue use if suspected [74][75]

11) Hematologic: Increases in hematocrit reflective of increases in red blood cell mass may occur; monitoring recommended and discontinuation may be required [74]

12) Hepatic: Prolonged use of high doses has been associated with serious hepatic adverse effects (peliosis hepatitis, hepatic neoplasms, cholestatic hepatitis, and jaundice); discontinue therapy if hepatic dysfunction occurs [74]

13) Hepatic: Life threatening or fatal peliosis hepatitis or hepatic neoplasms (eg, hepatocellular carcinoma) may occur with prolonged use at high doses[74][75][73]

14) Hepatic: Cholestatic hepatitis accompanied by jaundice may occur; discontinue use [75][73]

15) Hepatic: Liver function test abnormalities may occur; discontinue use [75][73]

16) Musculoskeletal: Use cautiously in healthy males with delayed puberty, as effects on bone maturation may occur; monitoring recommended and dosage adjustment may be necessary [75] [73]

17) Musculoskeletal: Use caution in pediatric patients, as bone maturation may be accelerated, resulting in compromised adult stature; monitoring recommended [75][73]

18) Neurologic: Possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [93]

19) Psychiatric: Depression and suicidal ideation and behavior, including completed suicide, have been reported; monitoring recommended [74]

20) Reproductive: Elderly patients; increased risk for prostatic hypertrophy or prostatic carcinoma [75][73]

21) Reproductive: Gynecomastia may occur and can possibly persist in those being treated for hypogonadism [74][75][73]

22) Reproductive: Use cautiously in female patients, as virilization may occur; monitoring recommended and discontinue use if suspected [75][73]

23) Reproductive: Worsening of benign prostatic hyperplasia may occur in patients with condition; monitoring recommended [74]

24) Reproductive: Increased risk of prostate cancer; evaluate for prostate cancer prior to and during therapy [74]

25) Reproductive: Spermatogenesis may be suppressed and result in adverse effects on semen parameters including sperm count [74]

26) Reproductive: Avoid use in men who are trying to conceive [26]

27) Respiratory: Venous thromboembolic events, including pulmonary embolism, have been reported; discontinue use if suspected [74][75]

28) Respiratory: Sleep apnea may occur, especially in patients with risk factors such as obesity or chronic lung disease [74]

D) Testosterone Undecanoate

1) Beers Criteria: Avoid use unless indicated for symptomatic hypogonadism due to potential for cardiac toxicities. Contraindicated in men with prostate cancer [6].

2) Abuse: Abuse, usually at higher than prescribed doses and usually in conjunction with other anabolic androgenic steroids, has been reported and may result in serious safety risks (eg, heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, infertility); if suspected, measure serum testosterone [57][89].

3) Cardiovascular: A possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [57][63].

4) Cardiovascular: Edema with or without congestive heart failure may occur in patients with cardiac, hepatic, or renal disease; discontinuation may be necessary [57][92].

5) Endocrine and metabolic: Lipid abnormalities may occur; discontinuation may be necessary [57][92]; monitoring recommended [57].

6) Endocrine and metabolic: Cancer patients at risk for hypercalcemia or hypercalciuria; monitoring recommended [57][92]

7) Hematologic: Hematocrit and red blood cell mass increases may occur and increase risk for thromboembolism; monitoring recommended and interrupt or discontinue if necessary [57][92].

8) Hematologic: Venous thromboembolic events, including DVT and pulmonary embolism, have been reported; monitoring recommended; discontinue use if suspected [57][63].

9) Hepatic: Serious hepatic adverse effects (eg, peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, jaundice) have been reported with prolonged use of high doses of other androgens (eg, oral methyltestosterone); discontinue use if suspected [57][92].

10) Neurologic: A possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [57][63].

11) Psychiatric: Depression and suicidal ideation have been reported [57]

12) Reproductive: Prostate cancer may occur; monitoring recommended [57][92].

13) Reproductive: Worsening of signs and symptoms of benign prostatic hyperplasia (BPH) may occur in patients with BPH; monitoring recommended [57][92].

14) Reproductive: Virilizing effects may occur in women (unapproved use) [57][92].

15) Reproductive: Spermatogenesis suppression, resulting in adverse effects on sperm count, may occur with large doses of androgens [57][92].

16) Reproductive: Avoid use in men who are trying to conceive [26]

17) Reproductive: Gynecomastia may occur in patients treated for hypogonadism [57][92].

18) Respiratory: Sleep apnea may occur; increased risk with obesity or chronic lung disease [57][92].

Adverse Effects

Cardiovascular Effects

Testosterone

Death, Cardiovascular

a) General Information

1) May increase risk of major adverse cardiovascular events, such as cardiovascular death [17][2][1][14][16][5][15][3][18].

Disease of cardiovascular system, acute

a) General Information

1) Risk of acute cardiovascular events may be increased following initiation of IM injection versus the transdermal gel [105].

b) Adult Clinical Trials

1) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with a 26% increased risk of composite acute cardiovascular (CV) events (myocardial infarction, unstable angina, stroke) compared with transdermal

gels when assessed over a 1-year followup period. There was no significant difference in the risk of acute CV events between the transdermal gel or patch [105].

Edema

a) General Information

1) Androgens may promote sodium and water retention [23][25][22]

2) Edema, with or without congestive heart failure, may be serious complication in patients with cardiac, renal, or hepatic disease [23][25][22][99][86][100][88][87][94]

b) Prevention and Management

1) Discontinuation and diuretic therapy may be required if edema occurs [23][25][22][86][100][88][87][94]

c) Adult Postmarketing

1) Edema has been reported [87]

Hypertension

a) Incidence: Up to 3% [28][87][99][100]

b) Prevention and Management

1) Clinicians should monitor development of hypertension in elderly patients are at increased risk for cardiovascular disease [106].

c) Adult Clinical Trials

1) Replacement therapy (transdermal route): Less than 1% [100]

2) Replacement therapy (topical route): 2.1% vs 0% with placebo [28]

3) Replacement therapy (topical route): 0% to 3% [87][28]

4) Replacement therapy (topical route): At least 2 of 155 patients [99]

Increased blood oxygen pressure

a) Incidence: 3% or less [25][22][99][86]

b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Less than 3% [22]

2) Replacement therapy (topical route): Less than 1% [99]

3) Replacement therapy (topical route): 1% vs 0% with placebo [25][86]

Myocardial infarction

a) General Information

1) Myocardial infarction has been reported with use of anabolic steroids [101][102].

2) May increase risk of major adverse cardiovascular events, such as myocardial infarction [17][2][1][14][16][5][15][3][18].

3) An increased risk of serious cardiovascular effects has been reported in men treated with testosterone therapy [103][104].

4) Risk may be increased following initiation of IM injection versus the transdermal gel [105].

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [97].

b) Adult Clinical Trials

1) Low serum testosterone levels: increased risk of myocardial infarction, stroke, and all-cause mortality, 29% [103]

2) Low serum testosterone levels: 2-fold increased risk of acute nonfatal myocardial infarction within 90 days among men 65 years or older [104].

3) Low serum testosterone levels: 2- to 3-fold increased risk of heart attack within the 90 days in men younger than 65 years with preexisting heart disease [104]

4) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with a 30% increased risk of myocardial infarction (MI) compared with transdermal gels when assessed over a 1-year followup period. Risk of MI was slightly increased with use of patch versus gel, but there was no significant difference in overall risk of acute cardiovascular events (ie, MI, unstable angina, stroke) between the 2 transdermal forms [105].

c) Postmarketing

1) Has been reported [17][2][1][14][16][5][15][3][18]

Unstable angina

a) General Information

1) Risk may be increased following initiation of IM injection versus the transdermal gel [105].

b) Adult Clinical Trials

1) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with a 21% increased risk of unstable angina compared with transdermal gels when assessed over a 1-year followup period. There was no significant difference in the risk of unstable angina between the transdermal gel or patch [105].

Vasodilatation

a) Incidence: Less than 1% [87]

b) Adult Clinical Trials

1) Replacement therapy (topical route): Less than 1% [87]

Testosterone Cypionate

Myocardial infarction

a) General Information

1) Has occurred with some androgens [82]

2) Increased risk of major adverse cardiovascular events reported in some, but not all, studies of testosterone replacement therapy in men [82]

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [97].

Testosterone Enanthate

Death, Cardiovascular

a) General Information

1) May increase risk of major adverse cardiovascular events, such as cardiovascular death [75].

Hypertension

a) Incidence: 2.3% to 12.7% [74]

b) General Information

1) In clinical trials, systolic blood pressure increased by an average of 4 mmHg during the first 12 weeks of treatment, and by an average of 4 mmHg from baseline following 1 year of treatment [74].

2) Ten percent of patients required initiation or adjustment of antihypertensive medications [74].

3) Increases in blood pressure may increase risk for major adverse cardiovascular events, especially in patients with established cardiovascular disease. In some patients the blood pressure elevation may be too small to detect but may still lead to increased cardiovascular risk [74].

c) Prevention and Management

1) Prior to initiation, consider baseline cardiovascular risk and ensure blood pressure is adequately controlled [74].

2) Initiation or adjustment of antihypertensive medication may be necessary [74].

d) Adult Clinical Trials

1) Hypogonadism (subQ route): 12.7% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 2.3% with testosterone enanthate (n=133) [74]

Myocardial infarction

a) General Information

1) May increase risk of major adverse cardiovascular events, such as myocardial infarction [75].

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in transwomen or transmen compared with reference men [97].

b) Postmarketing

1) Has been reported [75]

Peripheral edema

a) Incidence: 2.7% [74]

b) General Information

1) Edema, with or without congestive heart failure, may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease [74].

2) Androgens may promote sodium and water retention [74].

c) Prevention and Management

1) Diuretic therapy may be necessary [74].

2) Drug discontinuation may be required [74].

d) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Testosterone Undecanoate

Angina pectoris

a) Postmarketing

1) Has been reported [58]

Death, Cardiovascular

a) General Information

1) May increase risk of major adverse cardiovascular events, such as cardiovascular death [53][58].

b) Postmarketing

1) Has been reported [58]

Edema

a) Incidence: Greater than 2% [57]

b) General Information

1) May promote sodium and water retention [53][57][58]

2) May be a serious complication in patients with preexisting renal, cardiac, or hepatic disease [53][57][58]

c) Prevention and Management

1) Discontinuation and diuretic therapy may be required [53][57][58]

d) Adult Clinical Trials

1) Testosterone replacement (oral route): Peripheral edema, greater than 2% with testosterone undecanoate (Study N=569) [57]

Hypertension

a) Incidence: Greater than 2% to 5.1% [53][57][58]

b) General Information

1) In clinical trials after 4 months of treatment, systolic blood pressure increased by an average of 4.9 mmHg and 2.8 mmHg [57], and 4.3 mmHg and 4.8 mmHg [53], as measured by ambulatory blood pressure monitoring and blood pressure cuff, respectively; and average blood pressure had not plateaued by trial termination [57].

2) Led to initiation of antihypertensive medication or intensification of preexisting antihypertensives medications in 7% of patients in clinical trials over 4 months [57].

3) Increases risk for major adverse cardiovascular events (MACE), with greatest risk in patients with established cardiovascular disease or risk factors for cardiovascular disease [53][57].

4) In some patients, increase in blood pressure may be too small to detect, but may still increase the risk for MACE [53][57].

5) Increases in blood pressure were larger in patients with a history of hypertension [57].

c) Management

1) Treat new-onset or exacerbations of preexisting hypertension [53][57].

d) Adult Clinical Trials

1) Testosterone replacement (Tlando(R), oral route): 5.1% with testosterone undecanoate (Study N=138); lead to treatment discontinuation in 1.4% [53]

2) Testosterone replacement (Jatenzo(R), oral route): 3.6% with testosterone undecanoate (Study N=166) [57]

3) Testosterone replacement (Jatenzo(R), oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

4) Hypogonadism (IM route): At least 3% [58]

Myocardial infarction

a) General Information

1) May increase risk of major adverse cardiovascular events, such as myocardial infarction [53][58].

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [97].

b) Postmarketing

1) Has been reported [53][57][58]

Dermatologic Effects

Testosterone

Acne

a) Incidence: Up to 8% [25][28][87][100]
b) Adult Clinical Trials

1) Replacement therapy (transdermal route) Less than 1% [100]

2) Replacement therapy (topical route): Less than 1% [25]

3) Replacement therapy (topical route): 1% to 8% (incidence increases with increasing dose) [87]

4) Replacement therapy (topical route): 2% or less [28]

5) Replacement therapy (topical route): 3.1% [87]

6) Replacement therapy (topical route): At least 2 out of 155 patients [99]

c) Adult Case Reports

1) Acne fulminans on face and shoulders developed in a 21-year-old man following self-administration of testosterone or other anabolic steroids for 4 weeks [112].

Alopecia

a) Incidence: Up to 1% [87]
b) General Information

1) Hair loss has been reported with anabolic steroid use [102].

c) Adult Clinical Trials

1) Replacement therapy (topical route): Up to 1% [87].

Application site erythema

a) Incidence: 5% to 7% [99][100]
b) Prevention and Management

1) Applying a small amount of 0.1% triamcinolone acetonide cream to the skin under the central drug reservoir of the Androderm(R) system has been shown to reduce the incidence and severity of skin irritation, and does not significantly alter transdermal absorption of testosterone from the system (Wilson et al, 1998).

2) Ointment formulations should not be used for pretreatment, however, as they may significantly reduce testosterone absorption (Wilson et al, 1998).

c) Adult Clinical Trials

1) Replacement therapy (topical route): 5% to 7% [99]

2) Replacement therapy (transdermal route): 7% [100]

Application site irritation

a) Incidence: Up to 8% [28][99]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 0.9% [28]

2) Replacement therapy (topical route): 7% to 8% [99]

Application site reaction

a) Incidence: 2% to 16.1% [110][25]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 16.1% with testosterone gel (N=149) [110]

2) Replacement therapy (topical route): 2% to 4% vs 3% with placebo [25]

Burning pain

a) Incidence: 3% [100]
b) Adult Clinical Trials

1) Replacement therapy (transdermal route): 3% [100]

Contact dermatitis

a) Incidence: 2.1% to 4% [28][100]
b) General Information

1) Nonscrotal systems produced contact allergy and more topical irritation than scrotal systems in one study [111].

c) Adult Clinical Trials

1) Replacement therapy (topical route): 2.1% vs 0% with placebo [28].

2) Replacement therapy (transdermal route): 4% [100].

Erythema, Generalized

a) Adult Clinical Trials

1) Replacement therapy (topical route): At least 2 out of 155 patients [99]

Flushing

a) Adult Clinical Trials

1) Replacement therapy (topical route): Hot flushes, 1% with testosterone 50 mg (n=103) and 0% with testosterone 100 mg (n=149) vs 0% with placebo (n=99) [90]

Injection site pain, Intramuscular injection

a) General Information

1) Inflammation and pain at the site of IM injection has been reported [88][94].

Pruritus

a) Incidence: 37% [100]

b) Prevention and Management

1) Applying a small amount of 0.1% triamcinolone acetonide cream to the skin under the central drug reservoir of the Androderm(R) system has been shown to reduce the incidence and severity of skin irritation, and does not significantly alter transdermal absorption of testosterone from the system (Wilson et al, 1998).

2) Ointment formulations should not be used for pretreatment, however, as they may significantly reduce testosterone absorption (Wilson et al, 1998).

c) Adult Clinical Trials

1) Replacement therapy (transdermal route): 37% [100]

2) Replacement therapy (topical route): Pruritus, 1.9% [87]

Psoriasis

a) Adult Case Reports

1) Exacerbation of psoriasis was precipitated by an estradiol 50 mg/testosterone 100 mg implant in a 47-year-old woman [113].

Rash

a) Incidence: 2% [100]

b) Prevention and Management

1) Applying a small amount of 0.1% triamcinolone acetonide cream to the skin under the central drug reservoir of the Androderm(R) system has been shown to reduce the incidence and severity of skin irritation, and does not significantly alter transdermal absorption of testosterone from the system (Wilson et al, 1998).

2) Ointment formulations should not be used for pretreatment, however, as they may significantly reduce testosterone absorption (Wilson et al, 1998).

c) Adult Clinical Trials

1) Replacement therapy (transdermal route): 2% [100]

Scab of skin, Nasal

a) Incidence: 3.8% to 5.8% [22]

b) General Information

1) One of the most common adverse reactions with intranasal form [22]

2) Symptoms usually mild to moderate [22]

c) Prevention and Management

1) Consider further evaluation or possible withdrawal if condition occurs [22]

d) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 5.8% [22]

Skin eschar

a) Adult Case Reports

1) A 78-year-old man who received testosterone 5 mg transdermal patches for hypogonadism experienced occasional irritation and subsequent eschar formation at the application site [114].

Testosterone Cypionate

Acne

a) Acne may occur in patients receiving testosterone cypionate [83].

Alopecia

a) Male pattern baldness may occur in patients receiving testosterone cypionate [83].

Hirsutism

a) Hirsutism may occur in patients receiving testosterone cypionate [83].

Injection site inflammation

a) Inflammation at the injection site may occur in patients receiving testosterone cypionate [83].

Injection site pain

a) Pain at the injection site may occur in patients receiving testosterone cypionate [83].

Seborrheic dermatitis

a) Seborrhea may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Acne

a) Incidence: 2.7% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Alopecia

a) General Information

1) Male pattern baldness has been reported following administration of testosterone enanthate [73].

Erythema at injection site

a) Incidence: 2.7% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Hirsutism

a) General Information

1) Hirsutism has been reported following administration of testosterone enanthate [73].

Injection site bruising

a) Incidence: 3.8% to 6.7% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 6.7% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 3.8% with testosterone enanthate (n=133) [74]

Injection site hemorrhage

a) Incidence: 3.3% to 6% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 3.3% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 6% with testosterone enanthate (n=133) [74]

Injection site inflammation

a) General Information

1) Inflammation at the injection site has been reported following administration of testosterone enanthate [73].

Injection site pain

a) General Information

1) Pain at the injection site has been reported following administration of testosterone enanthate [73].

Testosterone Undecanoate

Acne

a) Incidence: 5.2% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 5.2% with testosterone undecanoate (Study N=153) [59]

Erythema at injection site

a) Incidence: 1.3% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Hyperhidrosis

a) Incidence: 1.3% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Injection site pain

a) Incidence: 4.6% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 4.6% with testosterone undecanoate (Study N=153) [59]

Endocrine/Metabolic Effects

Testosterone

Decreased body growth

a) General Information

1) May accelerate bone maturation and cause premature closure of epiphyses in pediatric patients [25][22][88]

2) Use in pediatric patients may reduce adult stature, with greatest impact among youngest children [88]

b) Pediatric Clinical Trials

1) Replacement therapy: Height stunting in adolescents has been reported with anabolic steroid use [102]

Gynecomastia

a) Incidence: 1% to 3% [25][86][87]
b) General Information

1) May occur with testosterone therapy for hypogonadism [23][25][22][100][94][88]

2) Symptoms may include breast pain, breast tenderness or nipple tenderness [26]

c) Management

1) If symptoms occur, a period of monitoring based on clinical judgment should be considered as breast symptoms sometimes abate [26].

d) Adult Clinical Trials

1) Replacement therapy (topical route): 1% vs 0% with placebo [25][86]

2) Replacement therapy (topical route): 1% to 3% [87]

Hypercalcemia

a) General Information

1) Increased risk among those with cancer [23][25][22] and immobilized patients [88][94].

b) Prevention and Management

1) Regularly monitor at-risk patients [23][25][22]

2) Discontinue if condition occurs [88][94]

Hyperthyroidism

a) Adult Clinical Trials

1) Replacement therapy (intranasal route): 1 patient [22]

Hypokalemia

a) Adult Clinical Trials

1) Replacement therapy (topical route): Abnormal laboratory tests including hypokalemia, less than 1% [87]

Increased glucose level

a) General Information

1) Insulin sensitivity or glycemic control may change in patients treated with androgens [25][87].

2) In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements [25][87].

b) Adult Clinical Trials

1) Replacement therapy (topical route): Increased blood glucose in at least 2 of 155 patients [85]

2) Replacement therapy (topical route): Abnormal laboratory tests, including elevated glucose levels in less than 1% [87]

Lipids abnormal

a) Incidence: Up to 2% [28]

b) General Information

1) The serum lipid profile may change[23], including lipid abnormalities, such as LDL-C elevations and severe HDL-C reductions [102].

c) Prevention and Management

1) Monitor lipid profiles periodically, especially after treatment initiation [23][25] [22] and with dosage increases [25].

2) Discontinuation may be required with changes in serum lipid profile [22].

d) Adult Clinical Trials

1) Replacement therapy (topical route): Hyperlipidemia, up to 2% [28]

2) Replacement therapy (topical route): Changes in serum lipid levels (ie, hyperlipidemia, elevated triglycerides, and decreased HDL), less than 1% [87]

Thyroxine transport defect

a) General Information

1) Androgens may decrease thyroxine-binding globulin concentrations [25][22] [23]; however, there has been no clinical evidence of thyroid dysfunction with androgen use [23].

Testosterone Cypionate

Gynecomastia

a) General Information

1) Gynecomastia may occur in patients receiving testosterone cypionate [83].

2) Symptoms may include breast pain, breast tenderness or nipple tenderness [26]

b) Management

1) If symptoms occur, a period of monitoring based on clinical judgment should be considered as breast symptoms sometimes abate [26].

Testosterone Enanthate

Hypercalcemia

a) General Information

1) Hypercalcemia has been reported following administration of testosterone enanthate. If hypercalcemia occurs, therapy should be discontinued [73].

b) Prevention

1) Use caution in cancer patients at risk for hypercalcemia [74]

Hypernatremia

a) General Information

1) Sodium and water retention has been reported following administration of testosterone enanthate. In patients with preexisting cardiac, renal, or hepatic disease, there is an increased risk of edema with or without congestive heart failure [73].

Increased cholesterol esters

a) General Information

1) Increased serum cholesterol has been reported following administration of testosterone enanthate [73].

b) Management

1) Adjustment of lipid lowering therapy or discontinuation of testosterone therapy may be necessary [74]

Increased testosterone level

a) Incidence: 2.7% [74]

b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Testosterone Undecanoate

Decreased HDL level

a) Incidence: 3% [57]

b) Management

1) Adjustment of lipid lowering drugs may be necessary [57].

2) Discontinuation may be necessary [57].

c) Adult Clinical Trials

1) Testosterone replacement (oral route): 3% with testosterone undecanoate (Study N=166) [57]

Diabetes mellitus

a) Postmarketing

1) Diabetes mellitus was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Disorder of lipid metabolism

a) General Information

1) Changes in serum lipid profile may occur [53][57].

b) Management

1) Adjustment of lipid lowering drugs may be necessary [53][57].

2) Discontinuation may be necessary [53][57].

Gynecomastia

a) General Information

1) May develop and persist in patients being treated for hypogonadism [53][57] [59]

2) Symptoms may include breast pain, breast tenderness or nipple tenderness [26]

b) Management

1) If symptoms occur, a period of monitoring based on clinical judgment should be considered as breast symptoms sometimes abate [26].

c) Postmarketing

1) Gynecomastia was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Hyperprolactinemia

a) Incidence: 6.3% [53]
b) General Information

1) The mean increase from baseline in serum prolactin was 7 nanograms/mL in a 24-day study (Study N=93) [53]

c) Management

1) If serum prolactin remains elevated, discontinue [53]

d) Adult Clinical Trials

1) Testosterone replacement (oral route): 6.3% with testosterone undecanoate (Study N=93) [53]

Increased estradiol level

a) Incidence: 2.6% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 2.6% with testosterone undecanoate (Study N=153) [59]

Weight increased

a) Incidence: 1.3% to 2.1% [53][59]
b) General Information

1) Led to treatment discontinuation in 1 patient in a clinical trial (Study N=138) [53]

c) Adult Clinical Trials

1) Testosterone replacement (oral route): 2.1% with testosterone undecanoate (Study N=95) [53]

2) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Gastrointestinal Effects

Testosterone

Decrease in appetite

a) Adult Clinical Trials

1) Replacement therapy (intranasal route): 1 patient [22]

Diarrhea

a) Incidence: 3% to 4% [85]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 3% to 4% [85]

Gastrointestinal hemorrhage

a) Incidence: 2% [100]
b) Adult Clinical Trials

1) Replacement therapy (transdermal route): 2% [100]

Lip swelling

a) Postmarketing

1) Has been reported during postmarketing use [23].

Nausea

a) General Information

1) May occur with injectable, topical, and intranasal forms [22][87][88][94]

b) Adult Clinical Trials

1) Replacement therapy (intranasal route): 1 patient [22]

c) Adult Postmarketing

1) Nausea has been reported [87]

Oral irritation

a) Incidence: 9.2% [108]
b) General Information
1) Irritation generally resolved in 1 to 8 days [108]
2) Tenderness generally resolved in 1 to 14 days [108]
c) Adult Clinical Trials
1) Replacement therapy (buccal route): Gum or mouth irritation, 9.2% [108]

Sore gums

a) Incidence: 3.1% [108]
b) General Information
1) Irritation generally resolved in 1 to 8 days, and tenderness generally resolved in 1 to 14 days for the buccal system [108]
c) Adult Clinical Trials
1) Replacement therapy (buccal route): Gum pain and tenderness: 3.1% [108]

Stomatitis

a) Postmarketing
1) Has been reported during postmarketing use [23]

Swollen gums

a) Incidence: 2% [108]
b) General Information
1) Irritation generally resolved in 1 to 8 days, and tenderness generally resolved in 1 to 14 days for the buccal system [108]
c) Adult Clinical Trials
1) Replacement therapy (buccal route): 2% [108]
d) Postmarketing
1) Gingival swelling has been reported during postmarketing use [23].

Taste sense altered

a) Incidence: 1% to 4.1% [25][22]
b) General Information
1) Cause of treatment discontinuation with intranasal form [22]
c) Adult Clinical Trials
1) Replacement therapy (topical route): Taste disorder, 1% vs 0% with placebo [25]
2) Replacement therapy (intranasal route): Dysgeusia, less than 3%, with treatment discontinuation in 1 patient [22]
3) Replacement therapy (buccal route): Bitter taste or taste perversion, 2% to 4.1% [108]
d) Postmarketing
1) Dysgeusia has been reported during postmarketing use [23].

Ulcer of mouth

a) Postmarketing
1) Has been reported during postmarketing use [23]

Vomiting

a) Incidence: 3% to 4% [85]
b) Adult Clinical Trials
1) Replacement therapy (topical route): 3% to 4% [85]

Xerostomia

a) Postmarketing
1) Dry mouth has been reported during postmarketing use [23].

Testosterone Cypionate

Nausea

a) Nausea may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Abdominal pain

a) Incidence: 2% [74]
b) Adult Clinical Trials
1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

Nausea

a) Incidence: 2.3% [74]
b) General Information
1) Nausea has been reported following administration of testosterone enanthate [73].
c) Adult Clinical Trials
1) Hypogonadism (subQ route): 2.3% with testosterone enanthate (n=133) [74]

Testosterone Undecanoate

Diarrhea

a) Incidence: Greater than 2% [57]
b) Adult Clinical Trials
1) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Gastric ulcer with hemorrhage

a) General Information
1) Led to discontinuation in 1.1% of patients in a clinical trial (Study N=95) [53]

Indigestion

a) Incidence: Greater than 2% [57]
b) Adult Clinical Trials
1) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Nausea

a) Incidence: Greater than 2% to 2.4% [57]
b) Adult Clinical Trials
1) Testosterone replacement (oral route): 2.4% with testosterone undecanoate (Study N=166) [57]
2) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Hematologic Effects

Testosterone

Deep venous thrombosis

a) General Information
1) Polycythemia (increases in RBC mass) may increase risk of thromboembolic events [25][22][51][85]
b) Prevention and Management
1) Evaluate for DVT if lower-limb warmth, pain, erythema, or edema develop [17][2][1][14][16][5][15][3][18]
2) Evaluate for pulmonary embolism in patients with acute shortness of breath [17][2][1][14][16][5][15][3][18]
3) Discontinue if condition suspected and initiate workup and management [17][2][1][14][16][5][15][3][18]
c) Adult Clinical Trials
1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of

treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

d) Adult Postmarketing

1) Venous thromboembolism, including DVT and PE, has been reported [17][2][1][14][16][5][15][3][18]

Erythrocytosis

a) General Information

1) Polycythemia (increases in RBC mass) may increase risk of thromboembolic events [25][22][51][85]

2) Polycythemia has been reported with injectable testosterone [94][88].

b) Prevention and Management

1) Assess hematocrit level at baseline and repeat 3 to 6 months after treatment initiation [25][51][85] and annually thereafter [25][22][51]

2) Intervention is required if hematocrit is 54% or greater during treatment [26].

3) Dose reduction or interruption may be required if condition occurs [25][22][51][85]; therapy may resume when hematocrit decreases to an acceptable level [25]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): Hematocrit increase, four subjects developed hematocrit levels above 55% from baseline levels of 48% to 51%. No hematocrit levels exceeded 58% [22]

2) Replacement therapy (topical route): Hematocrit or hemoglobin increase, 2.1% vs 0% with placebo [28]

3) Replacement therapy (topical route): Hematocrit increase, 4% to 7% [85]

4) Replacement therapy (topical route): Hematocrit or hemoglobin increase, 1% to 2% vs 0% with placebo [25][86]

d) Adult Case Reports

1) Two cases of IM testosterone-induced polycythemia were reported to have been reversed by switching to transdermal testosterone [95].

2) A report of secondary polycythemia characterized by increases in RBC, hemoglobin, hematocrit, and red cell volume with decreases in serum B12 levels and erythropoietin was documented following the use of transdermal testosterone patches (10 mg androstanolone daily) in a 73-year-old man [96].

Hematocrit - PCV - high

a) Incidence: 4% to 7% [85]

b) General Information

1) Polycythemia (increases in RBC mass) may increase risk of thromboembolic events [25][22][51][85][23].

c) Prevention and Management

1) Assess hematocrit level at baseline and repeat 3 to 6 months after treatment initiation [25][51][85] and annually thereafter [25][22][51][23].

2) Intervention is required if hematocrit is 54% or greater during treatment [26].

3) Dose reduction or interruption may be required if condition occurs [25][22][51][85]; therapy may resume when hematocrit decreases to an acceptable level [25][23].

d) Adult Clinical Trials

1) Replacement therapy (intranasal route): hematocrit increase, 4 subjects developed hematocrit levels above 55% from baseline levels of 48% to 51%; no hematocrit levels exceeded 58% [22]

2) Replacement therapy (topical route): hematocrit or hemoglobin increase, 2.1% vs 0% with placebo [28]

3) Replacement therapy (topical route): hematocrit increase, 4% to 7% [85]

4) Replacement therapy (topical route): hematocrit or hemoglobin increase, 1% to 2% vs 0% with placebo [25][86]

e) Postmarketing

1) Red blood cell increase has been reported in postmarketing use [23].

Hemorrhage

a) General Information

1) Suppression of clotting factors II, V, VII and X, and bleeding in patients receiving concomitant anticoagulant therapy have been reported [94][88].

Increased hemoglobin

a) Adult Clinical Trials

1) Replacement therapy (topical route): hematocrit or hemoglobin increase, 2.1% vs 0% with placebo [28]

2) Replacement therapy (topical route): hematocrit or hemoglobin increase, 1% to 2% vs 0% with placebo [25][86]

b) Adult Case Reports

1) Replacement therapy (topical route): Hemoglobin increases were reported in at least 2 men with 120 days of treatment [85].

Venous thromboembolism

a) General Information

1) Polycythemia (increases in RBC mass) may increase risk of thromboembolic events [25][22][51][85]

a) Transgender

1) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Prevention and Management

1) Evaluate for DVT if lower-limb warmth, pain, erythema, or edema develop [25] [22]

2) Evaluate for pulmonary embolism (PE) if acute dyspnea develops [25][22]

3) Discontinue if thromboembolic event suspected and initiate workup and management [25][22]

c) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215) -control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

d) Adult Postmarketing

1) Venous thromboembolism, including DVT and PE, has been reported with testosterone products [25][22]

Testosterone Cypionate

Deep venous thrombosis

a) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215) -control (n=909,530) population-based study; a trend of decreased

risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

Erythrocytosis

a) General Information

1) Polycythemia may occur in patients receiving testosterone cypionate [83].

2) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

b) Management

1) Intervention is required if hematocrit is 54% or greater during treatment, such as dose reduction or temporary discontinuation [26].

Hemorrhage

a) General Information

1) Suppression of clotting factors II, V, VII and X, and bleeding in patients receiving concomitant anticoagulant therapy may occur with testosterone cypionate [83].

Venous thromboembolism

a) General Information

1) Transgender

a) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

Testosterone Enanthate

Deep venous thrombosis

a) Prevention and Management

1) Evaluate patients with pain, edema, warmth, or erythema in the lower extremity for DVT and those with acute shortness of breath for pulmonary embolism [74].

2) Discontinue use if suspected and initiate appropriate work up and management [74].

b) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

c) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing use in patients using testosterone products [74].

Erythrocytosis

a) Incidence: 1.8% to 2% [74]

b) General Information

1) Polycythemia has been reported following administration of testosterone enanthate [73].

2) Mild but significant increases in mean WBC, RBC, hematocrit, and hemoglobin concentrations in 33 male subjects (aged 21 to 39 years) were reported following IM testosterone enanthate 200 mg every 3 weeks or 4 weeks for 24 weeks. Negligible changes occurred in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Although significant increases occurred in blood parameters in these individuals, clinical manifestations were not apparent [121].

3) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Prevention and Management

1) Ensure hematocrit is not elevated prior to initiating therapy [74].

2) Intervention is required if hematocrit is 54% or greater during treatment [26].

3) Interruption or discontinuation of therapy may be necessary [74].

d) Adult Clinical Trials

1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 1.8% with testosterone enanthate in pooled studies (n=283) [74]

Hematocrit - PCV - high

a) Incidence: 8.3% to 14% [74]

b) General Information

1) In clinical studies; treated resulted in mean hemotocrit increases of 3.8 +/- 3.4% at 6 months and 5.4+/- 3.4% at 1 year [74]

2) Mild but significant increases in mean WBC, RBC, hematocrit, and hemoglobin concentrations in 33 male subjects (aged 21 to 39 years) were reported following IM testosterone enanthate 200 mg every 3 weeks or 4 weeks for 24 weeks. Negligible changes occurred in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Although significant increases occurred in blood parameters in these individuals, clinical manifestations were not apparent [121].

3) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Management

1) Intervention is required if hematocrit is 54% or greater during treatment, such as dose reduction or temporary discontinuation [26].

d) Adult Clinical Trials

1) Hypogonadism (subQ route): Hematocrit increased, 14% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): Hematocrit increased, 8.3% with testosterone enanthate (n=133) [74]

3) Hypogonadism (subQ route): Hematocrit increased to 55% or greater, 4.2% with testosterone enanthate in pooled studies (n=283) [74]

Hemorrhage

a) General Information

1) Suppression of clotting factors II, V, VII and X, and bleeding in patients receiving concomitant anticoagulant therapy has been reported with testosterone enanthate [73].

Increased hemoglobin

a) General Information

1) In clinical studies, mean hemoglobin increases of 1 +/- 1.1 g/dL at 6 months and 1.1 +/- 1.4 g/dL at 1 year were reported [74]

2) Mild but significant increases in mean WBC, RBC, hematocrit, and hemoglobin concentrations in 33 male subjects (aged 21 to 39 years) were reported following

IM testosterone enanthate 200 mg every 3 weeks or 4 weeks for 24 weeks. Negligible changes occurred in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Although significant increases occurred in blood parameters in these individuals, clinical manifestations were not apparent [121].

3) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

Increased white blood cell count

a) General Information

1) Mild but significant increases in mean WBC, RBC, hematocrit, and hemoglobin concentrations in 33 male subjects (aged 21 to 39 years) were reported following IM testosterone enanthate 200 mg every 3 weeks or 4 weeks for 24 weeks. Negligible changes occurred in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Although significant increases occurred in blood parameters in these individuals, clinical manifestations were not apparent [121].

Thromboembolic disorder

a) General Information

1) Transgender

a) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Prevention and Management

1) Evaluate patients with pain, edema, warmth, or erythema in the lower extremity for DVT and those with acute shortness of breath for pulmonary embolism [74].

2) Discontinue use if suspected and initiate appropriate work up and management [74].

c) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

d) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing use in patients using testosterone products [74].

Testosterone Undecanoate

Deep venous thrombosis

a) Prevention and Management

1) Evaluate patients who experience symptoms of pain, edema, warmth, and erythema in the lower extremity for DVT [53][57][58].

2) Discontinue use and initiate appropriate workup and management if suspected [53][57][58].

b) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215) -control (n=909,530) population-based study; a trend of decreased

risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

c) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing experience [53][57][58].

Erythrocytosis

a) Incidence: Greater than 2% [57]
b) General Information

1) Hematocrit elevations, which reflect increased red blood cell mass, may increase the risk of thromboembolic events [92]

2) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Prevention and Management

1) Monitor hematocrit levels at baseline and during therapy [92].

2) Intervention is required if hematocrit is 54% or greater during treatment [26].

3) Dose interruption or discontinuation may be necessary [53][92]

d) Adult Clinical Trials

1) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

e) Postmarketing

1) Polycythemia was reported during postmarketing surveillance [92]

Hematocrit - PCV - high

a) Incidence: 1.3% to 4.8% [53][57][92]
b) General Information

1) Hematocrit elevations, which reflect increased red blood cell mass, may increase the risk of thromboembolic events [53][92][92]

2) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Prevention and Management

1) Intervention is required if hematocrit is 54% or greater during treatment [26].

2) Increases in hematocrit, reflective of increases in red blood cell mass, may necessitate lowering of the dose or permanent discontinuation of therapy [53][57][92].

d) Adult Clinical Trials

1) Testosterone replacement (Tlando(R), oral route): 4.3% with testosterone undecanoate (Study N=138) [53]

2) Testosterone replacement (Jatenzo(R), oral route): 4.8% with testosterone undecanoate (Study N=166) [57]

3) Testosterone replacement (Jatenzo(R), oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

4) Hypogonadism (IM route): 1.3% [92]

Increased hemoglobin

a) Incidence: 2% [92]
b) General Information

1) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Adult Clinical Trials

1) Hypogonadism (IM route): 2% [92]

Venous thromboembolism

a) General Information

1) Transgender

a) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with

reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Prevention and Management

1) Evaluate patients who experience symptoms of pain, edema, warmth, and erythema in the lower extremity for DVT and those who present with shortness of breath for pulmonary embolism [53][57].

2) Discontinue use and initiate appropriate workup and management if suspected [53][57].

c) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

d) Postmarketing

1) There have been postmarketing reports of venous thromboembolic events, including DVT and pulmonary embolism, in patients using testosterone replacement [53][57].

Hepatic Effects

Testosterone

Cholestatic jaundice syndrome

a) General Information

1) Cholestatic hepatitis may develop with prolonged use of high-dose of orally active 17-alpha-alkyl-androgens [23][25][22][86][87][100][94][88]

b) Prevention and Management

1) Discontinue if condition occurs [23][25][22]

c) Pediatric Case Reports

1) Fanconi anemia: Multiple hepatic tumors with cholestasis and peliosis hepatitis were reported in a 13-year-old boy following several years of androgen and corticosteroid therapy, including testosterone propionate 20 mg/day [109].

Jaundice

a) General Information

1) Jaundice may develop with prolonged use of high-dose of orally active 17-alpha-alkyl-androgens [23].

b) Prevention and Management

1) Discontinue use immediately if jaundice occurs [23].

Liver carcinoma

a) General Information

1) Hepatocellular carcinoma has been reported rarely in patients receiving long-term oral therapy with androgens in high doses; androgen withdrawal did not lead to regression of the tumors in all cases[86][87][100][88][94].

Liver function tests abnormal

a) General Information

1) Alterations in liver function tests have occurred with testosterone therapy [94] [88].

b) Postmarketing

1) Abnormal liver function tests (eg, transaminases, elevated GGTP, and bilirubin) have been reported during postmarketing surveillance of testosterone gel [87].

Neoplasm of liver

a) General Information

1) Hepatic neoplasms may develop with prolonged use of high-dose of orally active 17-alpha-alkyl-androgens [23][25][22][86][87][100][94][88].

b) Prevention and Management

1) Discontinue if condition occurs [23][25][22]

Peliosis hepatis

a) General Information

1) Life-threatening peliosis hepatitis may develop with prolonged use of high-dose of orally active 17-alpha-alkyl-androgens [23][25][22][86][87][100][94][88].

b) Prevention and Management

1) Discontinue use if condition occurs [25][22][23]

Testosterone Cypionate

Cholestatic jaundice syndrome

a) Cholestatic jaundice may occur in patients receiving testosterone cypionate [83].

Liver function tests abnormal

a) Altered liver function tests may occur in patients receiving testosterone cypionate [83].

Neoplasm of liver

a) Hepatocellular neoplasm may rarely occur in patients receiving testosterone cypionate [83].

Peliosis hepatis

a) Peliosis hepatis may rarely occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Cholestatic hepatitis

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice) [74].

b) Management

1) Promptly discontinue use if signs or symptoms of hepatic dysfunction occur [74].

Hepatotoxicity

a) Adult Case Reports

1) A 26-year-old body builder developed toxic hepatitis with hepatocellular necrosis after self-administration of stanozolol 40 mg/day, IM testosterone enanthate 500 mg twice weekly, and oral methylandrostenediol 30 mg/day for 5 weeks. On admission to the hospital, the patient's AST and ALT levels were 5870 and 10,580 international units/L, respectively. The patient's bilirubin and alkaline phosphatase were also elevated. Liver biopsy showed toxic hepatic lesions. After supportive care and within 12 weeks of discontinuation of androgenic/anabolic steroids, clinical signs and laboratory findings improved substantially [122].

Jaundice

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice) [74].

2) Cholestatic jaundice has been reported following administration of testosterone enanthate [73].

3) Jaundice is reversible with drug therapy discontinuation [73].

b) Management

1) Promptly discontinue use if signs or symptoms of hepatic dysfunction occur [74][73].

c) Adult Case Reports

1) A case of anabolic steroid-induced cholestasis was reported in a 29-year-old male bodybuilder. Following self-administered testosterone enanthate injections once weekly for 4 weeks, the patient developed pruritus and deep jaundice. These symptoms, along with weight loss, persisted for 2 months. After this time period, the patient received corticosteroids and complete resolution of jaundice occurred within 2 weeks [123].

Liver function tests abnormal

a) General Information

1) Altered liver function tests have been reported in patients receiving testosterone enanthate [73].

b) Management

1) If altered liver function tests occur, therapy should be discontinued and etiology determined [73].

Neoplasm of liver

a) General Information

1) Hepatocellular neoplasms have rarely been reported following administration of testosterone enanthate [73].

2) Long-term therapy with testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas [74][108].

3) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice) [74].

b) Management

1) Promptly discontinue use if signs or symptoms of hepatic dysfunction occur [74].

Peliosis hepatis

a) General Information

1) Peliosis hepatitis has rarely been reported following administration of testosterone enanthate [73].

2) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice) [74].

3) May be life-threatening or fatal [74]

b) Management

1) Promptly discontinue use if signs or symptoms of hepatic dysfunction occur [74].

Testosterone Undecanoate

Cholestatic hepatitis

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects including jaundice; testosterone undecanoate has not been reported to cause this adverse event [53][57].

b) Prevention and Management

1) Promptly discontinue use if suspected [53][57].

2) Advise patients to report any signs or symptoms of hepatic dysfunction [53][57].

Hepatitis, Peliosis

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects including peliosis hepatitis; testosterone undecanoate has not been reported to cause this adverse event [53][57].

2) May be life-threatening or fatal [53][57].

b) Prevention and Management

1) Promptly discontinue use if suspected [53][57].

2) Advise patients to report any signs or symptoms of hepatic dysfunction [53][57].

Jaundice

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects including jaundice; testosterone undecanoate has not been reported to cause this adverse event [53][57].

b) Prevention and Management

1) Promptly discontinue use if suspected [53][57].

2) Advise patients to report any signs or symptoms of hepatic dysfunction [53][57].

Malignant neoplasm of liver

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects including hepatic neoplasms; testosterone undecanoate has not been reported to cause this adverse event [53][57].

2) Long-term therapy with IM testosterone enanthate has produced multiple hepatic adenomas [53][57].

b) Prevention and Management

1) Promptly discontinue use if suspected [53][57].

2) Advise patients to report any signs or symptoms of hepatic dysfunction [53][57].

Immunologic Effects

Testosterone

Hypersensitivity reaction

a) General Information

1) Allergic reaction (eg, hives, lip and tongue swelling) cause of treatment discontinuation with intranasal form [22]

b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Allergic reaction was cause of treatment discontinuation in 1 patient [22]

Testosterone Cypionate

Hypersensitivity reaction

a) Hypersensitivity reactions, including anaphylactoid reactions, may occur in patients receiving testosterone cypionate [83].

Non-allergic anaphylaxis

a) Hypersensitivity reactions, including anaphylactoid reactions, may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Non-allergic anaphylaxis

a) General Information

1) Anaphylactoid reactions have rarely been reported following administration of testosterone enanthate [73].

Testosterone Undecanoate

Anaphylaxis

a) General Information

1) Anaphylaxis may occur after the first dose or with any injection during the course of therapy [59].

b) Adult Clinical Trials

1) Anaphylaxis occurred in 2 hypogonadal men who received IM testosterone undecanoate during 18 clinical trials (n=3556) [59].

c) Postmarketing

1) Episodes of anaphylaxis, including life-threatening reactions, were reported during postmarketing surveillance [59].

Hypersensitivity reaction

a) Postmarketing

1) Hypersensitivity was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Systemic lupus erythematosus

a) Postmarketing

1) Systemic lupus erythematosus was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Musculoskeletal Effects

Testosterone

Advanced bone age

a) General Information

1) May accelerate bone maturation and cause premature closure of epiphyses in pediatric patients [25][22][88]

2) Use in pediatric patients may reduce adult stature, with greatest impact among youngest children [88]

b) Pediatric Clinical Trials

1) Replacement therapy: Height stunting in adolescents has been reported with anabolic steroid use [102]

Myalgia

a) Adult Clinical Trials

1) Replacement therapy (intranasal route): Cause of treatment discontinuation in combination with arthralgia, fever, chills, and petechiae in 1 patient [22]

Pain in limb

a) Incidence: 4.3% [22]
b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Pain in extremity, 4.3% [22]

Testosterone Enanthate

Arthralgia

a) Incidence: 2% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

Backache

a) Incidence: 3.3% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 3.3% with testosterone enanthate (n=150) [74]

Increased creatine kinase level

a) Incidence: 3.3% to 3.8% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 3.3 with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 3.8% with testosterone enanthate (n=133) [74]

Testosterone Undecanoate

Musculoskeletal pain

a) Incidence: 2.1% [53]
b) Adult Clinical Trials

1) Testosterone replacement (oral route): 2.1% with testosterone undecanoate (Study N=95) [53]

Neurologic Effects

Testosterone

Amnesia

a) Incidence: Less than 1% [87]
b) Adult Clinical Trials

1) Replacement therapy (topical route): Less than 1% [87]

Cerebrovascular accident

a) General Information

1) May increase risk of major adverse cardiovascular events, such as stroke [17][2][1][14][16][5][15][3][18].

2) Risk may be increased following initiation of IM injection versus the transdermal gel [105].

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Adult Clinical Trials

1) Low serum testosterone levels: increased risk of myocardial infarction, stroke, and all-cause mortality, 29% during a median of 531 days after coronary angiography [103]

2) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with 21% increased risk of stroke compared with transdermal gels when assessed over a 1-year followup period. There was no significant difference in the risk of stroke between the transdermal gel or patch [105].

c) Adult Case Reports and Postmarketing

1) Has been reported [17][2][1][14][16][5][15][3][18]

2) A cerebrovascular accident involving the basal ganglia and internal capsule was reported in a 21-year-old man without other predisposing factors for thromboembolism [107]

Headache

a) Incidence: 1% to 6% [25][22][85][86][87][100][108]
b) General Information

1) One of the most common adverse reactions and cause of treatment withdrawal with intranasal form [22]

2) Has been reported with administration via injection, intranasal, or topical routes

[22][85][86][87][100][108]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 4.3%, with treatment withdrawal in 1 patient [22]

2) Replacement therapy (topical route): 5% to 6% [85]

3) Replacement therapy (topical route): 1% vs 0% with placebo [25][86]

4) Replacement therapy (topical route): 0% to 4% [87]

5) Replacement therapy (transdermal route): 4% [100]

6) Replacement therapy (buccal route): 3.1% [108]

Insomnia

a) Incidence: Up to 2% [25][28]

b) Adult Clinical Trials

1) Replacement therapy (topical route): 0% to 1% vs 0% with placebo [25]

2) Replacement therapy (topical route): 2% or less [28].

Paresthesia

a) Incidence: Less than 1% [87][100]

b) General Information

1) Generalized paresthesias have been reported with oral testosterone and testosterone injections [94].

c) Adult Clinical Trials

1) Replacement therapy (topical route): Less than 1% [87]

2) Replacement therapy (transdermal route): Less than 1% [100]

Testosterone Cypionate

Anxiety

a) General Information

1) Has occurred with some androgens [83]

Cerebrovascular accident

a) General Information

1) Has occurred with some androgens [82]

2) Increased risk of major adverse cardiovascular events reported in some, but not all, studies of testosterone replacement therapy in men [82]

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

Headache

a) General Information

1) Has occurred with some androgens [83]

Paresthesia

a) General Information

1) Has occurred with some androgens [83]

Testosterone Enanthate

Cerebrovascular accident

a) General Information

1) May increase risk of major adverse cardiovascular events, such as stroke [75].

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Postmarketing

1) Has been reported [75]

Headache

a) Incidence: 5.3% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 5.3% with testosterone enanthate (n=150) [74]

Insomnia

a) Incidence: 2.3% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.3% with testosterone enanthate (n=133) [74]

Paresthesia

a) Adult Clinical Trials

1) Hypogonadism (IM route): has been reported [73].

Testosterone Undecanoate

Cerebrovascular accident

a) General Information

1) May increase risk of major adverse cardiovascular events, such as stroke [53] [58].

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Postmarketing

1) Has been reported [53][57][58]

Dizziness

a) General Information

1) Led to discontinuation in 1 patient in a clinical trial (Study N=138) [53]

Headache

a) Incidence: Greater than 2% to 4.8% [53][57]
b) Adult Clinical Trials

1) Testosterone replacement (Tlando(R), oral route): 2.1% with testosterone undecanoate (Study N=95) [57]

2) Testosterone replacement (Jatenzo(R), oral route): 4.8% with testosterone undecanoate (Study N=166); led to treatment discontinuation in 1.2% of patients[57]

3) Testosterone replacement (Jatenzo(R), oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Insomnia

a) Incidence: 2% [58]
b) General Information
1) Led to treatment discontinuation in 1 patient in a clinical trial (Study N=138) [53]
c) Adult Clinical Trials
1) Hypogonadism (IM route): 2% [58]

Transient ischemic attack
a) Postmarketing
1) Has been reported [58]

Psychiatric Effects

Testosterone

Anxiety
a) Incidence: Less than 1% [87]
b) General Information
1) Anxiety has been reported with injectable and buccal testosterone [108][88][94].
c) Adult Clinical Trials
1) Replacement therapy (topical route): At least 2 out of 155 patients [85]
2) Replacement therapy (topical route): Less than 1% [87]

Depression
a) Incidence: 3% [100]
b) General Information
1) Depression has been reported with injectable testosterone [88][94].
c) Adult Clinical Trials
1) Replacement therapy (transdermal route): 3% [100]
2) Replacement therapy (buccal route): 1 of 117 patients treated for at least 6 months [108]

Dream disorder
a) Incidence: 1.3% [110]
b) Adult Clinical Trials
1) Replacement therapy (topical route): Abnormal dreams, 1.3% with testosterone gel (N=149) [110]

Hostile behavior
a) Incidence: Less than 1% [87]
b) Adult Clinical Trials
1) Replacement therapy (topical route): Hostility, less than 1% [87]

Mood swings
a) Incidence: Up to 1% [25]
b) Adult Clinical Trials
1) Replacement therapy (topical route): 0% to 1% vs 0% with placebo [25]
2) Replacement therapy (topical route): Emotional lability, 2.6% vs 0% with placebo [28]

Testosterone Cypionate

Depression
a) Depression may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Anxiety
a) Management

1) Advise patients to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes [74].

b) Adult Clinical Trials

1) Hypogonadism (IM route): has been reported [73].

Depression

a) General Information

1) Depression and suicidal ideation and behavior have been reported [74].

2) Depression leading to discontinuation occurred in 2 patients in pooled results from clinical studies (n=283) [74].

b) Management

1) Advise patients to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes [74].

c) Adult Clinical Trials

1) Hypogonadism (IM route): has been reported [73].

Suicidal thoughts

a) General Information

1) Depression and suicidal ideation and behavior have been reported [74].

2) Suicide attempts (1 complete and 1 incomplete) were reported in pooled results from clinical studies (n=283) [74].

b) Management

1) Advise patients to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes [74].

Testosterone Undecanoate

Aggressive behavior

a) Incidence: 1.3% [59]

b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Depression

a) General Information

1) Has been reported [57]

b) Prevention and Management

1) Advise patients to seek medical attention for new onset or worsening of depression, suicidal ideation or behavior, anxiety, or other mood changes [57].

Irritability

a) Incidence: 2% [59]

b) Adult Clinical Trials

1) Hypogonadism (IM route): 2% with testosterone undecanoate (Study N=153) [59]

Mood swings

a) Incidence: 2% [59]

b) Adult Clinical Trials

1) Hypogonadism (IM route): 2% with testosterone undecanoate (Study N=153) [59]

Suicidal thoughts

a) General Information

1) Has been reported [57]

b) Prevention and Management

1) Advise patients to seek medical attention for new onset or worsening of depression, suicidal ideation or behavior, anxiety, or other mood changes [57].

Renal Effects

Testosterone

Increased frequency of urination

a) Incidence: Up to 2% [28]
b) Increased frequency of urination
1) Replacement therapy (topical route): 2% or less [28]

Testosterone Enanthate

Hematuria

a) Incidence: 2% [74]
b) Adult Clinical Trials
1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

Urinary tract infectious disease

a) Incidence: 2.7% to 3% [74]
b) Adult Clinical Trials
1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]
2) Hypogonadism (subQ route): 3% with testosterone enanthate (n=133) [74]

Reproductive Effects

Testosterone

Atrophy of testis

a) Adult Clinical Trials
1) Replacement therapy (intranasal route): Testicular atrophy in 1 patient [22]
b) Adult Postmarketing
1) Reported during postmarketing surveillance of testosterone gel [87]

Azoospermia disorder

a) General Information
1) Azoospermia may occur with exogenous androgen administration [22]

Benign prostatic hyperplasia

a) Incidence: Up to 2% [28]
b) General Information
1) Patients with benign hyperplasia are at an increased risk of exacerbation with androgen treatment [23][25][22][51][22].
2) Geriatric patients are at greater risk for benign prostatic hyperplasia [22] and prostatic hypertrophy [86].
c) Prevention and Management
1) Monitor for worsening signs and symptoms [23][25][22][51].
d) Adult Clinical Trials
1) Replacement therapy (topical route): Up to 2% [28]

Breast cancer

a) Adult Case Reports
1) A 58-year-old female-to-male transsexual patient with a 25-year history of testosterone therapy was found to have breast cancer upon consultation for bilateral mastectomy. The patient had a hysterectomy previously. Preoperative mammography revealed mammary gland involution that was confirmed by ultrasonography, which showed an irregular structure in the in the left breast with a maximum diameter of 7 mm. Upon bilateral mastectomy, histology showed estrogen-receptor positive, progesterone-receptor negative, HER2 negative

invasive ductal carcinoma .The mastectomy performed on the left side included axillary lymph node dissection, and the patient received chemotherapy. A recurrence developed about 2 years later, and the patient underwent re-excision, radiotherapy, and tamoxifen therapy; the patient has been in remission since that time [115].

Drug-induced virilization

a) General Information

1) Virilization in children who were secondarily exposed to testosterone gel has been reported [25][85][87]. [87].

2) Reported signs and symptoms have included enlargement of the penis or clitoris, premature development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age [87].

3) Upon removal of the testosterone gel exposure, signs and symptoms regressed in a majority or cases. However, in a few cases, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age [87].

4) In some cases, direct contact with the application site of testosterone gel was reported, and in at least one case, exposure was suspected to be secondary to exposure to the testosterone gel user's shirt, towels, and/or sheets [87].

5) Amenorrhea, menstrual irregularities, the inhibition of gonadotropin secretion, and virilization are the most common side effects of androgen therapy in women [88].

Large prostate

a) Incidence: 11.7% [87]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 11.7% [87]

Oligozoospermia

a) General Information

1) Oligospermia may occur with high-dose androgen treatment [25][22] for prolonged periods [94][88].

2) Large doses of androgens may suppress spermatogenesis and adversely affect semen, including decreased sperm count [23].

b) Adult Postmarketing

1) Oligospermia has been reported [87].

Penile erection, Spontaneous

a) Incidence: 1% [90]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 1% with testosterone 50 mg (n=103) and 0% with testosterone 100 mg (n=149) vs 0% with placebo (n=99) [90]

Priapism

a) Pediatric Case Reports and Postmarketing

1) A case of priapism was reported in a 15-year-old boy following the administration of an IM injection of Triolandren(R), a combination of testosterone esters [116].

2) Priapism has been reported during postmarketing surveillance [87].

Prostate cancer

a) Incidence: Up to 1.2% [51][100]
b) General Information

1) Androgen treatment increases risk for prostate cancer [23][25][22][51].

2) Geriatric patients are at increased risk for prostatic carcinoma [86].

3) No significant difference was found in prostate cancer risk in a case control study comparing patients with prostate cancer (n=284) vs matched control patients without prostate cancer (n=1378) who received testosterone replacement

therapy between 2009 and 2012; the risk did not increased when analyzed by form (gel vs other forms) or timing/duration of therapy [117].

c) Prevention and Management

1) Contraindicated in patients with prostate cancer [23][25][22]

2) Evaluate patients at baseline [23], within 3 to 6 months of treatment initiation, and thereafter per screening guidelines [22].

d) Adult Clinical Trials

1) Replacement therapy (topical route): Prostatic carcinoma, 1.2% [51]

2) Replacement therapy (transdermal route): Prostatic carcinoma, less than 1% [100]

e) Adult Postmarketing

1) Replacement therapy: Two cases of prostatic adenocarcinoma and one case of chronic impotence occurred in 3 men during testosterone treatment [118]

2) Impotence (IM route): Adenocarcinoma developed in a 58-year-old man treated with testosterone 180 mg every 2 weeks [119]

Raised prostate specific antigen

a) Incidence: 1% to 11.1% [22][28][85]

b) General Information

1) One of the most common adverse reactions and cause of treatment discontinuation with intranasal form [22]

c) Prevention and Management

1) Evaluate for prostate cancer at baseline, within 3 to 6 months of treatment initiation, and thereafter per screening guidelines [22]

d) Adult Clinical Trials

1) Replacement therapy (intranasal route): 5.1% to 5.8%, with mean serum PSA level increases of 0.1 to 0.2 ng/mL; and treatment discontinuation in 1 patient [22]

2) Replacement therapy (topical route): PSA level increase, 11.1% (mean 0.14 nanograms/mL) vs 0% (mean 0.12 ng/mL) with placebo [28]

3) Replacement therapy (topical route): PSA levels increased by a significant 21.9% (between 0.19 to 0.61 nanograms/dL) from baseline in treatment-inexperienced men with baseline testosterone levels of less than 250 ng/mL; nonsignificant elevations in PSA levels occurred in men with baseline testosterone levels of 250 ng/dL or more. PSA levels significantly decreased in both groups over 12 months of treatment [120].

4) Replacement therapy (topical route): 1% to 4% [85]

5) Replacement therapy (topical route): Serum PSA levels increased by 18%, with a significant 0.26 ng/mL increase during the initial 6 months of treatment and an overall mean change from baseline of 0.11 ng/mL over 3 years. Prostate cancer was detected in 2 patients [87].

Reduced libido

a) Incidence: Up to 2% [28]

b) Adult Clinical Trials

1) Replacement therapy (topical route): 2% or less [28]

2) Replacement therapy (transdermal route): Less than 1% [100]

Testosterone Cypionate

Breast cancer

a) Adult Case Reports

1) A 58-year-old female-to-male transsexual patient with a 25-year history of testosterone therapy was found to have breast cancer upon consultation for bilateral mastectomy. The patient had a hysterectomy previously. Preoperative mammography revealed mammary gland involution that was confirmed by ultrasonography, which showed an irregular structure in the in the left breast with a maximum diameter of 7 mm. Upon bilateral mastectomy, histology showed estrogen-receptor positive, progesterone-receptor negative, HER2 negative

invasive ductal carcinoma .The mastectomy performed on the left side included axillary lymph node dissection, and the patient received chemotherapy. A recurrence developed about 2 years later, and the patient underwent re-excision, radiotherapy, and tamoxifen therapy; the patient has been in remission since that time [115].

Excessive erection

a) Excessive frequency and duration of penile erections may occur in patients receiving testosterone cypionate [83].

Increased libido

a) Increased libido may occur in patients receiving testosterone cypionate [83].

Oligozoospermia

a) Oligospermia may occur in patients receiving high doses of testosterone cypionate [83].

Prostate cancer

a) General Information

1) No significant difference was found in prostate cancer risk in a case control study comparing patients with prostate cancer (n=284) vs matched control patients without prostate cancer (n=1378) who received testosterone replacement therapy between 2009 and 2012; the risk did not increased when analyzed by form (gel vs other forms) or timing/duration of therapy [117].

Reduced libido

a) Decreased libido may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Amenorrhea

a) General Information

1) Amenorrhea has commonly been reported in female patients following administration of testosterone enanthate [73].

Breast cancer

a) Adult Case Reports

1) A 58-year-old female-to-male transsexual patient with a 25-year history of testosterone therapy was found to have breast cancer upon consultation for bilateral mastectomy. The patient had a hysterectomy previously. Preoperative mammography revealed mammary gland involution that was confirmed by ultrasonography, which showed an irregular structure in the in the left breast with a maximum diameter of 7 mm. Upon bilateral mastectomy, histology showed estrogen-receptor positive, progesterone-receptor negative, HER2 negative invasive ductal carcinoma .The mastectomy performed on the left side included axillary lymph node dissection, and the patient received chemotherapy. A recurrence developed about 2 years later, and the patient underwent re-excision, radiotherapy, and tamoxifen therapy; the patient has been in remission since that time [115].

Excessive erection

a) General Information

1) Excessive frequency and duration of penile erections has been reported following administration of testosterone enanthate [73].

Gynecomastia

a) General Information

1) Gynecomastia has been reported [74][73].

2) Symptoms may include breast pain, breast tenderness or nipple tenderness [26]

b) Management

1) If symptoms occur, a period of monitoring based on clinical judgment should be considered as breast symptoms sometimes abate [26].

Increased libido

a) General Information

1) Increased libido has been reported following administration of testosterone enanthate [73].

Oligozoospermia

a) General Information

1) Oligospermia and spermatogenesis has been reported following administration of testosterone enanthate at high doses [74][73].

Priapism

a) Adult Case Reports

1) A case of testosterone-induced priapism was documented in a 23-year-old man with hypergonadotropic hypogonadism. The patient received 250 mg testosterone enanthate IM every 14 days. Upon the fourth injection, a dose of 500 mg was administered at the patient's request. Severe priapism developed 12 hours later, which lasted until the patient presented in the emergency room 36 hours later. Complete detumescence was achieved 17 hours after a corporeal glandular shunt was performed. Two months postoperatively, the patient continued with biweekly testosterone injections at a dose of 250 mg without further incidence of priapism. These data suggest that priapism was related to a high dose of testosterone and that testosterone-induced priapism may be dose-dependent [125].

2) Severe priapism in a 20-year-old man following IM injections of testosterone enanthate 250 mg every 2 weeks has been reported. Three days after the third injection, the patient developed a painful erection that was not accompanied by sexual stimulation. Subsequent conservative therapy failed to reverse the priapism and the patient had to undergo 2 surgical procedures to achieve detumescence [126].

Prostate cancer

a) General Information

1) Patients treated with androgens may be at increased risk for prostate cancer [74].

b) Prevention

1) Evaluate for prostate cancer prior to beginning thearpy [74].

c) Adult Clinical Trials

1) No significant difference was found in prostate cancer risk in a case control study comparing patients with prostate cancer (n=284) vs matched control patients without prostate cancer (n=1378) who received testosterone replacement therapy between 2009 and 2012; the risk did not increased when analyzed by form (gel vs other forms) or timing/duration of therapy [117].

d) Adult Case Report

1) A case of prostate cancer was reported in a patient with Klinefelter syndrome who had undergone long-term testosterone replacement therapy since childhood. Intramuscular testosterone enanthate every 1 to 2 weeks was initiated at age 16 and continued for 35 years. The patient's initial prostate-specific antigen (PSA) level at age 49 was 3.6 ng/dL. The following year, his PSA level rose to 5.4 ng/dL and 6 months later, the PSA level reached 12.2 ng/dL. The rise in PSA was accompanied by a slight increase in irritative voiding symptoms and adenocarcinoma was confirmed. Radical prostatectomy was performed and the patient recovered well from surgery. Androgen replacement therapy was not reintroduced until the patient remained recurrence-free for a minimum of 1 year following surgery [127].

Prostatitis

a) Incidence: 2.7% to 3% [74]

b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 3% with testosterone enanthate (n=133) [74]

Raised prostate specific antigen

a) Incidence: 3% to 12% [74]

b) General Information

1) Defined as a increase from baseline of at least 1.4 nanogram (ng)/mL, or greater than 4 ng/mL [74]

2) Led to discontinuation in 4.6% of patients in clinical studies [74]

c) Adult Clinical Trials

1) Hypogonadism (subQ route): 12% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 3% with testosterone enanthate (n=133) [74]

Reduced libido

a) General Information

1) Decreased libido has been reported following administration of testosterone enanthate [73].

Virilization

a) General Information

1) Virilization, including inhibition of gonadotropin secretion, deepening of the voice, and enlargement of the clitoris has commonly been reported in female patients following administration of testosterone enanthate. If administered during pregnancy, virilization of the external genitalia may occur in female fetuses [73].

Testosterone Undecanoate

Benign prostatic hyperplasia

a) General Information

1) Patients treated with androgens are at an increased risk for worsening of signs and symptoms of benign prostatic hyperplasia (BPH) [53][57].

b) Prevention

1) Monitor for worsening signs or symptoms of BPH [53][57]

c) Postmarketing

1) BPH was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Breast cancer

a) Adult Case Reports

1) A 58-year-old female-to-male transsexual patient with a 25-year history of testosterone therapy was found to have breast cancer upon consultation for bilateral mastectomy. The patient had a hysterectomy previously. Preoperative mammography revealed mammary gland involution that was confirmed by ultrasonography, which showed an irregular structure in the in the left breast with a maximum diameter of 7 mm. Upon bilateral mastectomy, histology showed estrogen-receptor positive, progesterone-receptor negative, HER2 negative invasive ductal carcinoma .The mastectomy performed on the left side included axillary lymph node dissection, and the patient received chemotherapy. A recurrence developed about 2 years later, and the patient underwent re-excision, radiotherapy, and tamoxifen therapy; the patient has been in remission since that time [115].

Disorder of ejaculation

a) Incidence: 1.3% [59]

b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Disorder of prostate, Induration

a) Incidence: 1.3% [59]

b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Hypogonadism

a) Incidence: 2.6% [59]

b) Adult Clinical Trials

1) Hypogonadism (IM route): 2.6% with testosterone undecanoate (Study N=153) [59]

Large prostate

a) Adult Clinical Trials

1) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Prostate cancer

a) Incidence: 1.3% [59]
b) General Information

1) No significant difference was found in prostate cancer risk in a case control study comparing patients with prostate cancer (n=284) vs controls (n=1378) who received testosterone replacement therapy; the risk did not increased when analyzed by form (gel vs other forms) or timing or duration of therapy [117].

c) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

d) Incidence: 1.3% [59]
e) General Information

1) Patients treated with androgens are at an increased risk for prostate cancer [53][57].

f) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Raised prostate specific antigen

a) Incidence: 4.6% [59]
b) General Information

1) Mean increase in prostate specific antigen (PSA) in a clinical trial was 0.2 nanograms (ng)/mL from baseline with testosterone undecanoate (n=161); increases in serum PSA from baseline of at least 1.4 ng/mL or PSA greater than 4 ng/mL occurred in 1.9% of patients [57]

c) Adult Clinical Trials

1) Hypogonadism (IM route): 4.6% with testosterone undecanoate (Study N=153) [59]

Respiratory Effects

Testosterone

Bleeding from nose

a) Incidence: 3.8% to 6.5% [22]
b) General Information

1) One of the most common adverse reactions with intranasal form [22]

2) Symptoms usually mild to moderate [22]

c) Prevention and Management

1) Consider further evaluation or possible withdrawal if condition occurs [22]

d) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 6.5% [22]

Bronchitis

a) Incidence: 3.8% to 4.3% [22]
b) General Information

1) One of the most common adverse reactions with intranasal form [22]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 4.3% [22]

Cough

a) Incidence: Less than 3% [22]
b) Adult Clinical Trials
1) Replacement therapy (intranasal route): Less than 3% [22]

Discomfort, Nasal

a) Incidence: 3.8% to 5.9% [22]
b) General Information
1) One of the most common adverse reactions and cause of treatment discontinuation with intranasal form [22]
2) Symptoms usually mild to moderate [22]
c) Prevention and Management
1) Consider further evaluation or possible withdrawal if condition occurs [22]
d) Adult Clinical Trials
1) Replacement therapy (intranasal route): Nasal discomfort, 3.8% to 5.9%, with treatment withdrawal in 1 subject [22]

Excoriation of skin, Nasal

a) Adult Clinical Trials
1) Replacement therapy (intranasal route): 1 patient [22]

Nasal congestion

a) Incidence: Up to 3.9% [22]
b) Adult Clinical Trials
1) Replacement therapy (intranasal route): More than 2% to 3.9% [22]

Nasal discharge

a) Incidence: 3.8% to 7.8% [22]
b) General Information
1) Rhinorrhea was of the most common adverse reactions with intranasal form [22]
2) Symptoms usually mild to moderate [22]
c) Prevention and Management
1) Consider further evaluation or possible withdrawal if condition occurs [22]
d) Adult Clinical Trials
1) Replacement therapy (intranasal route): Rhinorrhea, 3.8% to 7.8% [22]

Nasal mucosa dry

a) Incidence: Up to 4.2% [22]
b) Adult Clinical Trials
1) Replacement therapy (intranasal route): More than 2% to 4.2% [22]

Nasopharyngitis

a) Incidence: 3.8% to 8.7% [22]
b) General Information
1) One of the most common adverse reactions with intranasal form [22]
2) Symptoms usually mild to moderate [22]
c) Prevention and Management
1) Consider further evaluation or possible withdrawal if condition occurs [22]
d) Adult Clinical Trials
1) Replacement therapy (intranasal route): 3.8% to 8.7% [22]

Pulmonary embolism

a) Prevention and Management
1) Evaluate for pulmonary embolism (PE) if acute dyspnea develops [25][22]
2) Discontinue if condition suspected and initiate workup and treatment [25][22]
b) Adult Clinical Trials
1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case

(n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

c) Adult Postmarketing

1) Venous thromboembolism, including DVT and PE, has been reported in postmarketing surveillance [25][22]

Sense of smell altered

a) Incidence: 5.8% [22]
b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Parosmia, 5.8% [22]

Sinusitis

a) Incidence: 3.8% [22]
b) General Information

1) One of the most common adverse reactions with intranasal form [22]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% [22]

Sleep apnea

a) General Information

1) Testosterone may contribute to sleep apnea onset, particularly in at-risk (eg, obesity or chronic lung disease) hypogonadal men [23][25][22][85][86][87].

Upper respiratory infection

a) Incidence: 3.8% to 4.3% [22]
b) General Information

1) One of the most common adverse reactions with intranasal form [22]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 4.3% [22]

Testosterone Cypionate

Pulmonary embolism

a) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

Testosterone Enanthate

Cough

a) Incidence: 2.7% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Pulmonary embolism

a) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

b) Prevention and Management

1) Evaluate patients with pain, edema, warmth, or erythema in the lower extremity for DVT and those with acute shortness of breath for pulmonary embolism [74].

2) Discontinue use if suspected and initiate appropriate work up and management [74].

c) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing use in patients using testosterone products [74].

Sleep apnea

a) Incidence: 2% [74]

b) General Information

1) Treatment with testosterone products may potentiate sleep apnea [74].

2) Increased likelihood in at risk patients (eg, obesity, chronic lung disease) [74]

c) Adult Clinical Trials

1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

d) Adult Case Reports

1) After receiving intramuscular testosterone enanthate weekly for a period of 10 months as an experimental contraceptive agent, and human chorionic gonadotropin (5000 international units) intramuscularly for 3 months, a 36-year-old moderately obese man began to experience difficulty in sleeping, daytime somnolence, and mood depression. His medical history and physical examination were unremarkable; routine hematologic and blood-chemistry studies were normal. In addition, he had received cimetidine (300 mg 3 times daily) for reflux esophagitis, and amoxapine (150 mg daily) for depression. Upper airway examination had revealed no source of obstruction; however, pulmonary function tests revealed a reduced functional residual capacity consistent with obesity as well as a mild obstructive defect. Sleep studies, testosterone levels, discontinuance of testosterone, and repeat rechallenge confirmed an association with exacerbations of clinical symptoms and testosterone administration. In comparison with normal apnea index values (less than 5 episodes of apnea lasting for more than 10 seconds per hour of sleep), his values increased to 26 and 40 following testosterone administration. Discontinuation of the drug resulted in normalization of most laboratory values (apneic index, total sleep time, free testosterone, hypoxic and hypercapnic ventilatory response, oxygen consumption) within 5 weeks. Complete reversal was achieved after 6 months [124].

Testosterone Undecanoate

Pulmonary embolism

a) Prevention and Management

1) Evaluate patients who present with shortness of breath for pulmonary embolism [53][57][92].

2) Discontinue use and initiate appropriate workup and management if suspected [53][57][58].

b) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

c) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing experience [53][57][92].

Pulmonary embolism, Oil microembolism

a) General Information

1) Symptoms such as coughing, dyspnea, hyperhidrosis, throat tightening, chest pain, dizziness, and syncope occurred during or immediately after the injection [59].

2) Although the majority of reactions lasted a few minutes and responded to supportive care, some lasted several hours and required emergency intervention and/or hospitalization [59].

3) POME reactions may occur after the first dose or with any injection during the course of therapy [59].

b) Adult Clinical Trials

1) Pulmonary oil microembolism (POME) occurred in 8 hypogonadal men (9 total events) who received IM testosterone undecanoate during 18 clinical trials (n=3556) [59].

c) Postmarketing

1) Serious POME reactions were also reported with testosterone undecanoate 1000 mg IM during postmarketing surveillance [59].

Sleep apnea

a) General Information

1) Treatment of hypogonadal men with testosterone may potentiate sleep apnea in some patients, especially those with risk factors (eg, obesity, chronic lung disease) [53][57][59].

b) Postmarketing

1) Sleep apnea syndrome was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Upper respiratory infection

a) Incidence: 3.6% [53]

b) Adult Clinical Trials

1) Testosterone replacement (oral route): 3.6% with testosterone undecanoate (Study N=138) [53]

Other

Testosterone

Death

a) General Information

1) Risk may be increased following initiation of IM injection versus the transdermal gel [105].

b) Adult Clinical Trials

1) Low serum testosterone levels (unspecified route): increased risk of myocardial infarction, stroke, and all-cause mortality, 29% [103]

2) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with 34% more deaths compared with transdermal gels when assessed over a 1-year followup period. There was no significant difference in the risk of death between the transdermal gel or patch [105].

Pain of breast

a) Incidence: 1% to 3% [87]

b) Adult Clinical Trials

1) Replacement therapy (topical route): 1% to 3% [87]

Persistent pain following procedure

a) Incidence: 4.3% [22]

b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Procedural pain, 4.3% [22]

Testosterone Cypionate

Drug abuse

a) The dependence on a combination of anabolic and androgenic steroids including testosterone cypionate was reported in a 24-year-old, noncompetitive male weight lifter. The patient met the DSM-III-R criteria for psychoactive substance dependence, and appeared depressed with some anxiety. Mild psychomotor retardation was present, and prior to medical examination the patient reported suicidal tendencies [128].

Testosterone Enanthate

Fatigue

a) Incidence: 2% to 2.3% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 2.3% with testosterone enanthate (n=133) [74]

Neoplasm of liver

a) General Information

1) Hepatocellular neoplasms have rarely been reported following administration of testosterone enanthate [73].

2) Long-term therapy with testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas [108].

Testosterone Undecanoate

Fatigue

a) Incidence: 2% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 2% with testosterone undecanoate (Study N=153) [59]

Black Box Warning

1) Testosterone

a) Topical (Gel/Jelly)

Secondary Exposure to Testosterone

Virilization has been reported in children who were secondarily exposed to testosterone gel.
Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel.
Healthcare providers should advise patients to strictly adhere to recommended instructions for use [15][5][18][3][2].

b) Topical (Solution)

Secondary Exposure to Testosterone

Virilization has been reported in children who were secondarily exposed to topical testosterone products.
Children should avoid contact with unwashed or unclothed application sites in men using testosterone topical solution.
Healthcare providers should advise patients to strictly adhere to recommended instructions for use [1].

2) Testosterone Enanthate

a) Subcutaneous (Solution)

1) Warning: Blood Pressure Increases

Testosterone enanthate can cause blood pressure (BP) increases that can increase the risk for major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, with greater risk for MACE in patients with cardiovascular risk factors or established cardiovascular disease.

Before initiating testosterone enanthate, consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled.

Starting approximately 6 weeks after initiating therapy, periodically monitor for and treat new-onset hypertension or exacerbations of pre-existing hypertension in patients on testosterone enanthate.

Re-evaluate whether the benefits of testosterone enanthate outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease while on treatment.

Due to this risk, use testosterone enanthate only for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies [74].

3) Testosterone Undecanoate

a) Intramuscular (Solution)

Serious Pulmonary Oil Microembolism (POME) Reactions and Anaphylaxis

Serious POME reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose.
Following each injection of testosterone undecanoate, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis.
Because of the risks of serious POME reactions and anaphylaxis, testosterone undecanoate is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Aveed(R) REMS Program [58].

b) Oral (Capsule)

Warning: Blood Pressure Increases

Testosterone undecanoate can cause blood pressure (BP) increases that can increase the risk of major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, with greater risk for MACE in patients with cardiovascular risk factors or established cardiovascular disease.
Before initiating testosterone undecanoate, consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled.
Starting approximately 3 weeks after initiating therapy or changing the dose, periodically monitor for and treat new-onset hypertension or exacerbations of pre-existing hypertension in patients on testosterone undecanoate.
Re-evaluate whether the benefits of testosterone undecanoate outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease while on treatment.
Due to this risk, use testosterone undecanoate only for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies [57].

REMS

No results available

Drug Interactions (single)

Drug-Drug Combinations

Alclometasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Amcinonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Anisindione

1) Interaction Effect: increased risk of bleeding
2) Summary: A number of case reports have demonstrated that coadministration of oral anticoagulants and 17-alkylated androgens (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) has resulted in a prolonged prothrombin time and hemorrhages[134][135][136][137][138]. Testosterone has been reported to suppress the clotting factors II, V, VII, and X, which may result in bleeding in patients receiving concomitant anticoagulant therapy [139].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of anabolic steroids and anisindione should be avoided when possible. If the drugs must be used together, frequent monitoring of the anticoagulant response must be maintained.
7) Probable Mechanism: unknown
8) Literature Reports

a) Anabolic steroids have been well documented to cause important interactions with dicumarol. The anabolic steroids enhance dicumarol's anticoagulant activity perhaps through reductions in clotting factor formation and increased clotting factor degradation. The 17-alpha-alkylated steroids (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) appear to be more likely to induce this reaction than the non-substituted steroids [129][130][131][132][133].

Beclomethasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Betamethasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Budesonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Bupropion

1) Interaction Effect: lowering of the seizure threshold
2) Summary: Concomitant administration of buPROPion and agents that lower seizure threshold, such as systemic steroids, should be undertaken with caution. In addition to using small initial doses and gradual dose increases, follow the dosing regimen recommendation according to each product labeling as xaximum daily dose varies by product formulation and indication[157][158][159][160][161].
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of buPROPion and systemic steroids should be used with caution. Maximum daily dose varies by product formulation and indication: 1) When coadministration of buPROPion immediate-release (Wellbutrin(R)) is required, do not exceed the total daily dose of 450 mg. Minimize the risk of seizure by giving the daily dose three times daily, and limit each single dose to 150 mg or less[157]. 2) When coadministered with buPROPion extended-release tablets (Wellbutrin XL(R)), do not exceed the total daily dose of 450 mg [158]. 3) Coadministration of sustained-release buPROPion (Wellbutrin SR(R)) should not exceed the total daily maximum of 400 mg, and should be given twice daily. Each single dose should not be higher than 200 mg to minimize high peak concentration of buPROPion [159]. 4) When administration of buPROPion extended-release or sustained-release buPROPion (Zyban(R)) is indicated for smoking cessation, the total daily dose should not exceed more than 300 mg. Give the daily dose twice daily, and limit each single dose to 150 mg or less [160][161]. Furthermore, consider using small initial doses and gradual dose increases.
7) Probable Mechanism: unknown

Ciclesonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Clobetasol

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Clobetasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Clocortolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Corticotropin

1) Interaction Effect: increased risk of edema
2) Summary: Coadministration of testosterone with corticotropin (ACTH) may enhance the formation of edema, especially in the susceptible patient with a history of cardiac or hepatic dysfunction[156].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Testosterone and corticotropin should be co-administered with caution, especially in patients with cardiac or hepatic disease.
7) Probable Mechanism: unknown

Cortisone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Cyclosporine

1) Interaction Effect: an increased risk of cycloSPORINE toxicity (renal dysfunction, cholestasis, paresthesias)
2) Summary: Concomitant administration of cycloSPORINE and anabolic steroids may result in increased cycloSPORINE blood levels and toxicity[153][154][155].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If clinically possible, avoid this combination. If these two drugs are given concomitantly, monitor circulating cycloSPORINE levels and adjust cycloSPORINE dosage as necessary; also, monitor patients for increased cycloSPORINE toxicity (renal dysfunction, neurotoxicity).
7) Probable Mechanism: decreased cycloSPORINE metabolism
8) Literature Reports

a) Concomitant administration of cycloSPORINE and anabolic steroids may result in increased cycloSPORINE blood levels and toxicity. This effect has been observed in 2 case studies with methyltestosterone and in 1 case study with danazol [150][151][152].

Dehydroepiandrosterone

1) Interaction Effect: increased risk of adverse androgenic and hepatic effects
2) Summary: Patients electing to take both dehydroepiandrosterone (DHEA) and testosterone are at increased risk for androgenic side effects. Data are conflicting on the extent that DHEA increases the testosterone-epitestosterone (T/E) ratio[174][175]. The effect appears to be dose-dependent, and at doses commonly used by body-builders (e.g. 1000 milligrams), androgenic effects are likely. Concomitant use is not advised.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and testosterone. DHEA may increase testosterone levels, increasing the incidence of adverse androgenic adverse effects such as oligospermia (in men), gynecomastia, prostatic hypertrophy (especially in elderly males), and virilization in women (deepening voice, hirsutism, acne, clitoromegaly, and menstrual irregularities). Libido may increase or decrease. Adverse hepatic effects may also occur (peliosis hepatitis, hepatic neoplasms).
7) Probable Mechanism: additive androgenic effect, since dehydroepiandrosterone appears to act as a pro-drug for testosterone
8) Literature Reports

a) Dehydroepiandrosterone (DHEA) increased the testosterone-epitestosterone (T/E) ratio in an uncontrolled study of 4 human volunteers. Two over the counter DHEA preparations were used in this study. Nature's Pride "DHEA 50 mg+" (product A) contained DHEA 50 milligrams (mg), suma 25 mg, Korean ginseng 25 mg, muira pauma 25 mg, shitake mushroom concentration 15 mg, and green tea extract 5 mg. The second product, YourLife DHEA (product B), contained DHEA 25 mg as the only active ingredient listed on the label. Neither product contained testosterone as detected by gas chromatography-mass spectrometry (GC-MS) analyses. All subjects (except subject 4) took the product once daily for 4 days at breakfast. Subject 1 (age 47) took both preparations at 3 dosage levels at different times over a 6 month period: product A 50 mg/day, product A 100 mg/day, and product B 150 mg/day for 4 days. Subjects 2 (age 61) and 3 (age 28) took product B 50 mg/day and 100 mg/day, respectively. Subject 4 (age 27) took product A 100 mg/day for 2 days. A 24-hour urine was collected on day 3 and spot urine samples were taken in the morning and evening of day 4. Subject 1 at DHEA doses of 50 mg/day, 100 mg/day, and 150 mg/day had T/E ratios of 8.1, 11.4, and 14.4, respectively, compared to a pre-dose ratio of 2.4. Pre-dose T/E ratios for subjects 2 and 3 were 1.3 and 1.7, respectively, and T/E ratios were 1.6 and 3.9, respectively after DHEA. Subject 4 had a pre-dose T/E ratio of 0.8 and a T/E ratio of 1.1 following DHEA. Ratios exceeding 6:1 are used by several organizations including the United States Military and the International Olympic Committee (IOC) as an indication

that additional tests are warranted to rule out use of exogenous physiological steroids. Manipulation of the steroid endocrine system to improve athletic performance has led some DHEA supplement providers on the internet to recommend up to 1000 mg/day [171].

b) Differences in baseline mean T/E ratios and dehydroepiandrosterone (DHEA) treatment mean ratios were not significant in 7 healthy subjects. Mean baseline T/E ratio was 0.67 (range: 0.1 to 1.2). DHEA 50 mg was taken each morning for 30 days with urinary samples collected before and two to three hours after ingestion with no voiding before collection. Individual variation was prevalent. The greatest individual variation from baseline to treatment mean T/E ratio was 1.20 to 2.11. The greatest difference from baseline mean to peak treatment mean T/E ratio was 1.2 to 3.7. A single dose of DHEA 250 mg resulted in a 40% increase in the T/E ratio relative to the pre-dose value (peak T/E ratio equal to 1.2). DHEA at this dose had a minimal effect on urine T/E ratios and would not be expected to result in a positive screen for testosterone abuse as the T/E ratio must exceed 6:1 [172].

c) Two female volunteers demonstrated three to four fold increases in plasma testosterone levels following dehydroepiandrosterone (DHEA) 100 mg administration. In subject 1, the pre-DHEA testosterone level was 0.07 mcg/100 mL compared to a maximum level of 0.28 mcg/100 mL ninety minutes after DHEA administration. In subject 2, the pre-DHEA testosterone level was 0.08 mcg/100 mL compared to a maximum level of 0.28 mcg/100 mL sixty minutes after DHEA administration. This demonstrates that in vivo conversion of DHEA to testosterone occurs in women as well as men [173].

Desonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Desoximetasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Dexamethasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase

fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Dicumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: Concomitant use of dicumarol and testosterone may result in an increased risk of bleeding. A number of case reports have demonstrated prolonged prothrombin time and hemorrhages with coadministration of oral anticoagulants and 17-alkylated androgens[141][142][146][144][147]. Testosterone has been reported to suppress the clotting factors II, V, VII, and X, which may lead to bleeding in patients receiving concomitant anticoagulant therapy [88]. If coadministration of dicoumarol and testosterone is deemed necessary, make INR determinations and increase prothrombin time monitoring, particularly when androgen treatment is initiated or discontinued [140] [88].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If the concomitant use of oral anticoagulants and testosterone is required, make INR determinations and increase monitoring of prothrombin time, particularly at androgen treatment initiation and discontinuation[140][88].
7) Probable Mechanism: modification of coagulation factor, hepatic synthesis, and competitive inhibition of plasma protein binding by testosterone
8) Literature Reports

a) Anabolic steroids have been well documented to cause important interactions with dicumarol. The anabolic steroids enhance anticoagulant activity of dicumarol perhaps through reductions in clotting factor formation and increased clotting factor degradation. The 17-alpha-alkylated steroids (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) appear to be more likely to induce this reaction than the non-substituted steroids [141][142][143][144][145].

Diflorasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Diflucortolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Difluprednate

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may

increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Dong Quai

1) Interaction Effect: increased androgenic and/or adverse effects of testosterone
2) Summary: Dong quai (Angelica dahurica) extract significantly inhibited the metabolism of testosterone in vitro[177]. The effect of dong quai on the metabolism of nifedipine in humans is unknown, as the dose used in the animal study (1 gram/kilogram) is higher than that usually used in humans. Theoretically, if dong quai similarly affects the pharmacokinetics of testosterone in humans, increased levels of testosterone may occur which may result in greater androgenic effect. It is suspected that dong quai may affect other drugs metabolized by CYP2C11, CYP3A, and CYP1A enzymes. Caution is advised.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Monitor for increased androgenic effects of testosterone (such as acne, hirsutism, behavior changes) in patients taking testosterone and dong quai concomitantly.
7) Probable Mechanism: inhibition of hepatic cytochrome P450 enzyme metabolism of testosterone
8) Literature Reports

a) Angelica dahurica (dong quai) extract 1 gram/kilogram orally significantly inhibited 2-alpha-hydroxylase, 16-alpha-hydroxylase, and 6-beta-hydroxylase activity in rat liver microsomes. 2-alpha-hydroxylase activity was inhibited from one to 24 hours after dong quai administration (p less than 0.01), with 17.2 percent to 68.7 percent of its activity remaining. 16-alpha-hydroxylase activity was inhibited from 1 to 6 hours after dong quai administration (p less than 0.01), with 28.5 percent to 39.8 percent of its activity remaining. 6-beta-hydroxylase activity was inhibited 6 hours after dong quai administration (p less than 0.05), with 70 percent of its activity remaining. Cytochrome P450 (CYP) 2C11 mediates 2-alpha- and 16-alpha-hydroxylase activity, while CYP3A and CYP1A mediate 6-beta-hydroxylase activity [176].

Flucloronide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fludrocortisone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Flumethasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Flunisolide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluocinolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluocinonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluocortin

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluocortolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluorometholone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluticasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Glimepiride

1) Interaction Effect: increased blood glucose lowering effect and increased risk of hypoglycemia
2) Summary: Exercise caution when coadministering glimepiride and androgens as this may increase the risk of hypoglycemia. If concomitant use is required, monitor more

closely for hypoglycemia. Upon discontinuation of androgens, monitor the patient for worsening of glycemic control[149].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of glimepiride and androgens may increase the risk of hypoglycemia. If concomitant use is required, monitor more closely for hypoglycemia. Upon discontinuation of androgens, monitor the patient for worsening of glycemic control[149].
7) Probable Mechanism: unknown

Halcinonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Hydrocortisone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Insulin

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Aspart, Recombinant

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in

changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Bovine

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Degludec

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Detemir

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Glargine, Recombinant

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Glulisine

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Lispro, Recombinant

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Licorice

1) Interaction Effect: decreased testosterone effectiveness
2) Summary: Licorice significantly reduced endogenous testosterone levels in healthy men and in women with polycystic ovary disease[166][167]. This may occur in clinically significant levels and may adversely affect testosterone supplementation. Licorice may inhibit conversion of androstenedione to testosterone through inhibition of 17-beta-hydroxysteroid dehydrogenase and 17,20-lyase [166][168][169]. Indirect evidence suggests that licorice may also stimulate aromatase activity and thereby increase the estradiol to testosterone ratio [170][169][167].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of licorice and testosterone. Patients reporting decreased libido or other sexual dysfunction for which testosterone supplementation is being considered should be questioned regarding licorice use and advised to discontinue licorice.
7) Probable Mechanism: inhibition of 17-beta-hydroxysteroid dehydrogenase and 17,20-lyase which catalyze the conversion of androstenedione to testosterone; increased estradiol synthesis though aromatase stimulation
8) Literature Reports

a) Licorice decreased testosterone levels in 7 healthy men (age 22 to 24 years). Subjects received licorice 7 grams daily, administered as a commercial tablet preparation (Saila, Bologna, Italy), each containing 0.5 grams of glycyrrhizic acid as confirmed by gas chromatography-mass spectrometry. Baseline testosterone levels were 740 nanograms/deciliter (ng/dL), decreasing to 414 ng/dL by day 4 (p less than 0.001), and remained significantly decreased on day 7 at 484 ng/dL (p less than 0.001). Four days after licorice discontinuation, testosterone increased to 704 ng/dL. This demonstrates that licorice inhibits 17-beta-hydroxysteroid dehydrogenase conversion of androstenedione to testosterone. A comparable increase in 17-hydroxyprogesterone occurred by day 7 with no increase in androstenedione, indicating inhibition of 17,20-lyase, which catalyzes conversion of 17-hydroxyprogesterone to androstenedione. The authors conclude that since this amount of licorice is eaten by many people, that men with decreased libido or other sexual dysfunction should be questioned regarding licorice use [164].

b) An herbal combination of peony root and licorice root reduced serum testosterone levels in 34 infertile Japanese women with polycystic ovary disease. Women received 7.5 grams of the combination for 24 weeks. At 4 weeks, serum testosterone and free testosterone levels were significantly decreased by 56.3% and 59.3%, respectively. The mean testosterone level at 4 weeks was 85.3 ng/dL compared with the baseline level of 137.1 ng/dL (p less than 0.001). At 12 and 24 weeks, mean testosterone levels remained significantly lower than pretreatment levels (p less than 0.001 and p less than 0.01, respectively). Serum testosterone levels were significantly lower after 12 weeks in patients who became pregnant after treatment versus those who did not (p less than 0.05). The estrogen to testosterone ratio increased significantly after 4 weeks (p less than 0.05). After 24 weeks, the luteinizing hormone to follicle stimulating hormone ratio was significantly reduced for the first time (p less than 0.001) [165].

Loteprednol

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Methylprednisolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Mometasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Oxyphenbutazone

1) Interaction Effect: elevated serum levels of oxyphenbutazone
2) Summary: Coadministration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone[148].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Clinicians should be aware that concomitant use of testosterone and oxyphenbutazone may result in elevated serum levels of oxyphenbutazone.
7) Probable Mechanism: unknown

Paclitaxel

1) Interaction Effect: increased paclitaxel exposure resulting in increased risk of paclitaxel toxicity
2) Summary: Testosterone, a known inhibitor of the isoenzyme CYP2C8, inhibits the metabolism of paclitaxel to its primary metabolite 6-alpha-hydroxypaclitaxel, in vitro. The pharmacokinetics of paclitaxel may also be altered in vivo in the presence of a CYP2C8 inhibitor. Caution should be exercised with the concomitant use of paclitaxel and CYP2C8 inhibitors such as testosterone[162].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for increased adverse effects due to paclitaxel toxicity including bone marrow suppression, myalgia/arthralgia, nausea/vomiting, and mucositis. Dose adjustment for either medication may be required.
7) Probable Mechanism: inhibition of CYP2C8-mediated paclitaxel metabolism by testosterone

Paclitaxel Protein-Bound

1) Interaction Effect: increased paclitaxel exposure resulting in increased risk of paclitaxel toxicity
2) Summary: Testosterone, a known inhibitor of the isoenzyme CYP2C8, inhibits the metabolism of paclitaxel to its primary metabolite 6-alpha-hydroxypaclitaxel, in vitro. The pharmacokinetics of paclitaxel may also be altered in vivo in the presence of a CYP2C8 inhibitor. Caution should be exercised with the concomitant use of paclitaxel protein-bound and CYP2C8 inhibitors such as testosterone[163].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for increased adverse effects due to paclitaxel toxicity including bone marrow suppression, myalgia/arthralgia, nausea/vomiting, and mucositis. Dose adjustment for either medication may be required.
7) Probable Mechanism: inhibition of CYP2C8-mediated paclitaxel metabolism by testosterone

Phenprocoumon

1) Interaction Effect: an increased risk of bleeding
2) Summary: Concomitant use of phenprocoumon and testosterone may result in an increased risk of bleeding. A number of case reports have demonstrated prolonged prothrombin time and hemorrhages with coadministration of oral anticoagulants and 17-alkylated androgens[141][142][146][144][147]. Testosterone has been reported to suppress the clotting factors II, V, VII, and X, which may lead to bleeding in patients receiving concomitant anticoagulant therapy [88]. If coadministration of phenprocoumon and warfarin is deemed necessary, make INR determinations and increase prothrombin time monitoring, particularly when androgen treatment is initiated or discontinued [140] [88].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If the concomitant use of oral anticoagulants and testosterone is required, make INR determinations and increase monitoring of prothrombin time, particularly at androgen treatment initiation and discontinuation[140][88].
7) Probable Mechanism: modification of coagulation factor, hepatic synthesis, and competitive inhibition of plasma protein binding
8) Literature Reports

a) Anabolic steroids have been well documented to cause important interactions with dicumarol, another anticoagulant. Anabolic steroids enhance the anticoagulant activity of dicumarol perhaps through reductions in clotting factor formation and increased clotting factor degradation. The 17-alpha-alkylated steroids (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) appear to be more likely to induce this reaction than the non-substituted steroids [141][142][143][144] [145].

Prednicarbate

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Prednisolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Prednisone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Rimexolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Triamcinolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those

with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Warfarin

1) Interaction Effect: an increased risk of bleeding
2) Summary: Concomitant use of testosterone and warfarin may result in an increased risk of bleeding. A number of case reports have demonstrated prolonged prothrombin time and hemorrhages with coadministration of oral anticoagulants and 17-alkylated androgens[141][142][146][144][147]. Testosterone has been reported to suppress the clotting factors II, V, VII, and X, which may lead to bleeding in patients on concomitant anticoagulant therapy [88]. If coadministration of testosterone and warfarin is deemed necessary, make INR determinations and increase prothrombin time monitoring, particularly when treatment with testosterone is initiated or discontinued [140][88].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If the concomitant use of oral anticoagulants and testosterone is required, make INR determinations and increase monitoring of prothrombin time, particularly at androgen treatment initiation and discontinuation[140][88].
7) Probable Mechanism: modification of coagulation factor, hepatic synthesis, and competitive inhibition of plasma protein binding by testosterone
8) Literature Reports

a) Anabolic steroids have been well documented to cause important interactions with dicumarol, another anticoagulant. Anabolic steroids enhance the anticoagulant activity of dicumarol perhaps through reductions in clotting factor formation and increased clotting factor degradation. The 17-alpha-alkylated steroids (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) appear to be more likely to induce this reaction than the non-substituted steroids [141][142][143][144][145].

b) Significant enhancement of the anticoagulant effects of warfarin was described in a 69-year-old woman following application of a vaginal ointment of testosterone propionate [141]. The mechanism of interaction is unclear.

IV Compatibility (single)

No results available

Pregnancy & Lactation

A) Teratogenicity/Effects in Pregnancy

1) Micromedex Pregnancy Rating: Contraindicated

a) Avoid use of this drug during pregnancy and prescribe an alternative. Evidence has demonstrated fetal abnormalities or risks when used during pregnancy. Advise women of childbearing potential of fetal risk.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Yes

3) Clinical Management

a) Testosterone is not indicated for use in women and should not be used in women [85][108][181][182]. Testosterone is contraindicated during pregnancy [57][74]. Advise patient of possible consequences to the fetus if pregnancy occurs during use[28], including masculinization of the

external genitalia of the female fetus. Pregnant women or those who may become pregnant should be aware of potential transfer of testosterone by men being treated with this drug [183][88].

4) Literature Reports

a) Based on animal findings and its mechanism of action, testosterone is teratogenic and can cause fetal harm when given to a pregnant woman [57][74][28][85].

b) Exposure of a female fetus to testosterone may result in varying degrees of virilization [57][74][22][85]. At least 16 cases have been reported of female offspring with virilization of genitalia after their mothers were treated with either testosterone or methyltestosterone during pregnancy [178][179]. In addition, clitoromegaly with or without labioscrotal fusion were reported in these cases. In one follow-up case, female endocrine function was normal with secondary sexual development occurring at puberty, and the internal female sex organs were also normal [180].

c) Suppressed spermatogenesis via feedback inhibition of the hypothalamic-pituitary-testicular axis may occur with treatment using large doses of exogenous androgens, including testosterone. Decreased fertility has been noted in some men receiving testosterone replacement therapy, and may be irreversible [57][74].

d) In animal developmental studies, structural impairments in male (ie, increased testicular weight, larger seminal tubular lumen diameter, and higher frequency of occluded tubule lumen) and female (ie, increased ano-genital distance, phallus development, empty scrotum, no external vagina, intrauterine growth retardation, reduced ovarian reserve, and increased ovarian follicular recruitment) offspring were observed when pregnant animals received IM testosterone during organogenesis at doses that were comparable to doses used for testosterone replacement therapy. In addition, increased pituitary weight was observed in both male and female offspring, as well as hormonal and behavioral changes. At testosterone doses that were about twice the doses used for testosterone replacement therapy, hypertension was observed in pregnant female rats and in their offspring [57][74].

B) Breastfeeding

1) World Health Organization Rating: Avoid breastfeeding.

2) Micromedex Lactation Rating: Infant risk has been demonstrated.

a) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastfeeding. An alternative to this drug should be prescribed or patients should be advised to discontinue breastfeeding.

3) Clinical Management

a) Testosterone is not indicated for use in women [57][74]. Testosterone is contraindicated in nursing women [108][182][88][181].

4) Literature Reports

a) It is not known how much testosterone transfers into human milk [85][28]. However, testosterone has been concentrated in the breast tissue of women with breast cancer [185].

5) Drug Levels in Breastmilk

a) Active Metabolites

1) dihydrotestosterone [200][205]

Monitoring

A) Testosterone

1) Therapeutic

a) Laboratory Parameters

1) Buccal

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [17]

b) Monitor morning serum testosterone 4 to 12 weeks after initiating therapy to assess therapeutic response [23].

c) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

2) Nasal Gel

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [16]

b) Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved; intranasal formulations should be measured between two to four weeks after initiation [26].

c) Monitor serum testosterone levels periodically during therapy to assess therapeutic response [22].

d) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

3) Topical Gel

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [5][15][3][2][18].

b) Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved; topical gels should be measured between two to four weeks after initiation [26].

c) Monitor serum testosterone levels periodically during therapy to ensure proper dosing [25] and assess therapeutic response [51][4].

d) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

4) Topical Solution

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [1].

b) Monitor serum testosterone levels within 2 to 8 hours and at least 14 days after initiating therapy (or dose adjustment) to assess therapeutic response [85].

c) Once therapeutic levels have been achieved, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

5) Transdermal

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [14].

b) Two weeks after therapy initiation, following system application the previous evening, evaluate the early morning serum testosterone level to assess therapeutic response [84].

c) Two weeks after switching from the 2.5, 5, and 7.5 mg/day systems to the 2, 4, and 6 mg/day systems, following system application the previous evening, assess the early morning serum testosterone level [84].

d) Once therapeutic levels have been achieved, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

2) Toxic

a) Laboratory Parameters

1) Assess serum prostate specific antigen (PSA) periodically during therapy (buccal, nasal gel, topical gel) [25][22][23][51][4]. For topical solution and transdermal system, evaluate PSA levels prior to initiating therapy, every 3 to 6 months during therapy, and in accordance with prostate cancer screening practices thereafter [84][85].

2) Monitor hematocrit levels [25] prior to initiation of therapy, at 3 to 6 months after initiation, and annually thereafter [22][23][51][4][84][85]. It is recommended that periodic monitoring of hematocrit levels should be standard practice in testosterone replacement therapy, especially in older men, due to reports linking topical testosterone with the development of polycythemia [96].

3) For topical solution, topical gel, and transdermal testosterone system, monitor hemoglobin levels prior to initiation of therapy, at 3 to 6 months after initiation, and annually thereafter [51][4][84][85].

4) Periodically monitor liver function tests [51][4][84][85].

5) Periodically monitor lipid concentrations [25][22][23][51][4][84][85], particularly after initiation of therapy [22].

6) Regularly monitor serum calcium levels in cancer patients who have an increased risk of hypercalcemia and associated hypercalciuria [25][22][23][51][4][84][85].

b) Physical Findings

1) Evaluate for prostate cancer prior to and during therapy [25][23][51][4]. In patients receiving nasal gel or transdermal testosterone treatment, evaluate for prostate cancer prior to initiating treatment, 3 to 6 months following therapy initiation, and then in accordance with prostate cancer screening practices [22][84].

2) Monitor patient for signs and symptoms of worsening benign prostatic hyperplasia [25][22][23], especially in geriatric patients [22][51][4][84][85].

B) Testosterone Cypionate

1) Therapeutic

a) Laboratory Parameters

1) Improvement in serum testosterone levels may be indicative of efficacy.

2) Measure serum testosterone in the morning on at least 2 separate days before therapy initiation to confirm hypogonadism [82].

3) Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved; testosterone cypionate should be measured no earlier than three to four cycles [26].

4) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

2) Toxic

a) Laboratory Parameters

1) Monitor hematocrit and hemoglobin levels at baseline [26] and periodically for polycythemia during long-term therapy [82][83].

b) Physical Findings

1) Monitor bone maturation and assess the bone age of the wrist and hand every 6 months in pediatric males with delayed puberty [82][83].

C) Testosterone Enanthate

1) Therapeutic

a) Laboratory Parameters

1) Improvement in serum testosterone levels may be indicative of efficacy in hypogonadal males.

2) Measure serum testosterone and confirm hypogonadism diagnosis prior to treatment initiation [74][75].

3) Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved; testosterone enanthate should be measured no earlier than three to four cycles [26].

4) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

b) Physical Findings

1) Ablation of the ovaries may indicate efficacy in women with advancing inoperable metastatic mammary cancer [75].

2) Toxic

a) Laboratory Parameters

1) Xyosted(TM)

a) Monitor hematocrit before initiating therapy and every 3 months during therapy [74].

b) Monitor PSA before initiating therapy and periodically during treatment [74].

c) Monitor lipid concentrations periodically, particularly after starting testosterone therapy [74].

d) Monitor calcium concentrations regularly in cancer patients at risk of hypercalcemia [74].

2) Delatestryl(R)

a) Monitor serum hematocrit and hemoglobin levels at baseline [26] and periodically for polycythemia during high-dose androgen therapy [75].

b) Periodically monitor lipid concentrations, particularly in patients with a history of myocardial infarction or coronary artery disease [75].

c) Monitor serum and urine calcium levels frequently in women with disseminated breast cancer [75].

b) Physical Findings

1) Xyosted(TM)

a) Assess blood pressure before initiating therapy, approximately 6 weeks after initiation, and periodically thereafter [74].

b) Monitor patients with benign prostatic hyperplasia (BPH) for worsening signs and symptoms [74]

2) Delatestryl(R)

a) Close clinical monitoring is necessary in women treated for metastatic breast carcinoma because androgen therapy occasionally appears to accelerate the disease [75].

b) Observe female patients for signs of virilization including deepening of the voice, hirsutism, acne, clitoromegaly, or menstrual irregularities [75].

c) In prepubertal males treated for delayed puberty, obtain an x-ray of the wrist and hand every 6 months to monitor bone age, the rate of bone maturation, and the effect of the drug on epiphyseal closure [75].

D) Testosterone Undecanoate

1) Therapeutic

a) Laboratory Parameters

1) Measure serum testosterone in the morning on at least 2 separate days before therapy initiation to confirm hypogonadism [57]. Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved. IM testosterone undecanoate should be tested halfway between the first two 10-week injections [26]. For oral capsules, measure serum testosterone concentrations 6 hours after the morning dose. Wait 7 days after treatment initiation or dose adjustment before checking the serum testosterone concentration [57]. Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

b) Physical Findings

1) Improvement in serum testosterone levels may be indicative of efficacy.

2) Re-evaluate whether benefits outweigh potential risks in patients who develop cardiovascular risk factors or cardiovascular disease during treatment [57].

2) Toxic

a) Laboratory Parameters

1) Monitor hemoglobin at baseline [26] and periodically during treatment [58].

2) Monitor prostatic specific antigen (PSA) periodically during treatment [57].

3) Monitor serum lipid profile periodically during treatment [57][58], particularly after starting testosterone therapy [57].

4) (Jatenzo(R)) Evaluate hematocrit prior to treatment and every 3 months during use [57]

5) (Aveed(R)) Evaluate hematocrit prior to treatment, 3 to 6 months after initiation of treatment, and annually thereafter [58].

6) Regularly monitor serum calcium concentrations in cancer patients at risk for hypercalcemia [57][58].

7) If testosterone abuse is suspected, check testosterone concentrations to ensure they are within normal limits [57].

b) Physical Findings

1) Observe patients for signs of anaphylaxis or serious pulmonary oil microembolism reactions (ie, urge to cough, dyspnea, tightening of the throat, chest pain, dizziness, or syncope) for 30 minutes after each injection [58].

2) Monitor patients with benign prostatic hyperplasia for exacerbation or worsening signs or symptoms [57][58].

3) Evaluate for prostate cancer prior to and during treatment [57][58].

4) Consider baseline cardiovascular risk prior to therapy [57].

5) Assure blood pressure is adequately controlled prior to therapy and periodically monitor for new-onset hypertension or exacerbations of pre-existing hypertension starting approximately 3 weeks after initiation of therapy [57].

6) Evaluate patients for signs or symptoms consistent with DVT or pulmonary embolism [57].

Do Not Confuse

No results available

MECHANISM OF ACTION

Mechanism of Action

A) Testosterone

1) Mechanism of Action

a) Testosterone is an endogenous androgen. Androgens are responsible for normal growth and development of male sex organs. Testosterone is involved in the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; development of male hair distribution (eg, beard, pubic, chest and axillary hair); laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution [22][28][85].

B) Testosterone Cypionate

1) Mechanism of Action

a) Testosterone is an endogenous androgen. Androgens are responsible for normal growth and development of male sex organs and maintenance of secondary sex characteristics. Testosterone is involved in the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; development of male hair distribution (eg, beard, pubic, chest and axillary hair); laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution [83].

C) Testosterone Enanthate

1) Mechanism of Action

a) Testosterone is an endogenous androgen. Androgens are responsible for normal growth and development of male sex organs and maintenance of secondary sex characteristics. Testosterone is involved in the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; development of male hair distribution (eg, beard, pubic, chest and axillary hair); laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution [74] [73].

D) Testosterone Undecanoate

1) Mechanism of Action

a) Metabolites of testosterone undecanoate, testosterone and dihydrotestosterone (DHT), modulate the normal growth and development of male sex organs (eg, prostate, seminal vesicles, penis and scrotum) and maintain male secondary sex characteristics such as facial, pubic, chest, and axillary hair, laryngeal enlargement, vocal chord thickening, and body musculature and fat distribution alterations [53][59].

PHARMACOKINETICS

Pharmacokinetics

Onset and Duration

A) Onset

1) Testosterone

a) Peak Response

1) Hypogonadism, transdermal: 3 to 24 months [186].

a) Full effect of transdermal testosterone 3 to 9 milligrams/day on bone mineral density was achieved at 24 months while full effects on lean muscle mass, erythropoiesis, prostate volume, energy, and sexual function occurred within 3 to 6 months [186].

2) Testosterone Undecanoate

a) Peak Response

1) Hypogonadism, IM: 7 days [59]

a) Serum testosterone concentrations reach maximum levels after a median of 7 days (range, 4 to 42 days) following a testosterone undecanoate 750 IM injection and then levels slowly decline [59].

2) Hypogonadism, oral: Cannot be characterized [53]

a) There is insufficient data to characterize an exposure-response relationship or time course of pharmacodynamic response of orally administered testosterone undecanoate [53].

B) Duration

1) Testosterone

a) Multiple Dose

1) Hypogonadism: 2 to 10 days (topical) [28][187][85]; 24 hours (transdermal) [84]

a) Following the last application of AndroGel(R) 1.62%, serum testosterone levels return to pretreatment levels within 48 to 72 hours [28].

b) By the fifth day after last application of AndroGel(R), serum testosterone levels return to pretreatment levels [187].

c) Testosterone serum concentrations returned to pretreatment levels 7 to 10 days following discontinuation of testosterone topical solution (administered until steady state was achieved) [85].

d) Testosterone serum concentrations returned to pretreatment levels 24 hours following the removal of the testosterone patch [84].

2) Testosterone Undecanoate

a) Single Dose

1) Hypogonadism, IM: 10 weeks [59]

a) Testosterone undecanoate 750 mg IM produces a steady state serum total testosterone level in the normal range (300 to 1000 nanograms/dL) for 10 weeks [59].

2) Hypogonadism, oral: Cannot be characterized [53]

a) There is insufficient data to characterize an exposure-response relationship or time course of pharmacodynamic response or orally administered testosterone undecanoate [53].

Drug Concentration Levels

A) Testosterone

1) Therapeutic Drug Concentration

a) Hypogonadism, Intranasal, Topical, and Transdermal: 300 to 1050 nanograms/dL (approximately normal physiologic circulating testosterone ranges) [85]

1) Following intranasal administration of testosterone gel 33 mg/day, the circulating testosterone concentrations achieved in men with hypogonadism are similar to those observed in healthy men (ie, 300 to 1050 nanogram/dL) [22].

2) Following axillary administration, testosterone topical solution delivers approximately normal physiologic circulating testosterone ranges (300 to 1050 nanograms/dL) as seen in healthy men [85].

3) Following application of testosterone 1.62% topical gel, approximately normal physiologic circulating testosterone ranges (300 to 1000 nanograms/dL) are achieved [28].

4) Transdermal testosterone delivers a continuous daily dose of testosterone resulting in normal physiologic concentrations of testosterone (300 to 1030 nanograms/dL) in healthy adult men [84].

2) Peak Concentration

a) Sublingual (solution), single-dose: 3.79 nanograms (ng)/mL (0.25 mg); 5.31 ng/mL (0.5 mg); 6.73 ng/mL (0.75 mg) [189]

1) In 16 premenopausal women, single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg yielded total testosterone mean Cmax values of 3.79 nanogram (ng)/mL (% coefficient variation (CV), 39.9), 5.31 ng/mL (%CV, 37.8), and 6.73 ng/mL (%CV, 39.6), respectively. Mean free testosterone Cmax levels following single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg were 0.021 ng/mL (%CV, 39.7), 0.032 ng/mL (%CV, 37.6), and 0.043 ng/mL (%CV, 45.7), respectively. The difference in Cmax was statistically different between all 3 doses for both total and free testosterone measurements (p less than 0.0001) [189].

b) Topical (solution), multiple-dose, hypogonadal men (30 mg to 120 mg): within normal range [85]

1) In a multicenter, open-label, efficacy study, hypogonadal men (n=155; median age, 53 years; range, 19 to 78 years) received testosterone topical solution 60 mg daily to the axilla for 15 days, then maintenance or titration upward or downward on day 45 and day 90 to 30-, 60-, 90-, or 120 mg based on serum testosterone concentration measured on day 15 and day 60, respectively. The table below describes the mean testosterone Cmax (normal serum testosterone range, 300 to 1050 nanograms/dL) in patients who completed the 120 day treatment (n=135) [85]:

Day	Testosterone topical solution dose				
	30 mg	60 mg	90 mg	120 mg	Overall (n=135)
	Cmax nanograms/dL				
Day 15		744 +/- 502 (n=135)			744 +/- 502
Day 60	491 (n=1)	898 +/- 664 (n=105)	646 +/- 382 (n=29)		840 +/- 620
Day 120	779 +/- 416 (n=3)	839 +/- 436 (n=97)	664 +/- 336 (n=25)	658 +/- 353 (n=10)	792 +/- 417
KEY: mg = milligrams; dL = deciliter.					

2) Following axillary administration of testosterone topical solution 30-, 60-, or 90-mg daily, steady-state concentrations were achieved in approximately 14 days. The mean steady-state dihydrotestosterone (DHT, active metabolite)-to-testosterone ratio remained within normal limits during treatment, ranging from 0.17 to 0.26 across all doses on days 15, 60, and 120 [85].

c) Topical (gel), multiple-dose, effect of sunscreen or moisturizing lotion (40.5 mg): 13% to 17% increase [28]

1) Application of sunscreen or moisturizing lotion increased exposure to testosterone in a randomized, 3-way crossover study of hypogonadal men (n=18). Subjects applied testosterone 1.62% gel 40.5 mg topically to the upper arms/shoulders followed in 1 hour by

sunscreen (SPF 50), moisturizing lotion, or nothing, for 7 days. The testosterone Cmax increased 13% and 17% when sunscreen and moisturizing lotion, respectively, were applied, compared with the control phase [28].

d) Transdermal, single-dose: 925 nanograms (ng)/dL (two 2.5 mg/day patches); 905 ng/dL (single 5 mg/day patch)[84]

1) In a study of 20 hypogonadal patients, average Cmax concentrations over 24 hours were 925 +/- 340 nanograms (ng)/dL, following the application of two 2.5 mg/day patches and 905 +/- 254 ng/dL following the application of a single 5 mg/day patch [84].

e) Transfer to Non-treated Women

1) Topical (solution), single-dose, transferred testosterone to nontreated subjects, 60 mg: 17% to 297% increase [85]

a) A clinical study of potential transfer of testosterone from treated men to nontreated women revealed a 17% increase in testosterone Cmax in the nontreated females. Using a 2% testosterone formulation, men (n=10) received testosterone 60 mg topically to each axilla and then covered the area with a T-shirt. Two hours after application, women rubbed their forearms on the axilla of the men for 15 minutes. The women were monitored for 72 hours after the transfer procedure. The transfer procedure led to a 17% increase in testosterone Cmax in the women compared with baseline. Another study in men who received a 1% testosterone formulation topically revealed a 297% increase in testosterone Cmax following direct skin-to-skin transfer compared with indirect (T-shirt) transfer [85].

2) Topical (gel), single-dose, transferred testosterone to nontreated subjects, 81 mg: 11% to 267% increase [28]

a) A clinical study of potential transfer of testosterone from treated men to nontreated women increased testosterone Cmax 11% in the nontreated females. Using a 1.62% testosterone gel formulation, men (n=12) received testosterone 81 mg topically to the shoulders and upper arms, then covered the area with a T-shirt. Two hours after application, women rubbed their hands, arms, and shoulders to the application site of the men for 15 minutes. The women were monitored for 24 hours after the transfer procedure. The transfer procedure led to an 11% increase in testosterone Cmax in the women compared with baseline. Another study in 8 men who received a 1.62% testosterone formulation topically revealed a 267% increase in testosterone Cmax following direct skin-to-skin transfer compared with indirect (T-shirt) transfer [28].

3) Time to Peak Concentration

a) Buccal system: 0.4 to 12 hours [192][193][194].

1) The mean peak serum testosterone level of 26.7 nanomoles/liter (nmol/liter) was reached 4.8 hours after administration of 30 milligram buccal testosterone given twice daily in 12 testosterone-deficient men with a mean age of 44.4 years. Steady state was achieved within the first 24 hours of treatment and was maintained in the normal range with a mean of 19.3 nmol/liter [192].

2) The mean maximum serum total testosterone concentrations (Cmax) are reached within 10 to 12 hours. The Cmax ranges from 910 to 970 nanograms/deciliter [193].

3) Serum concentrations of testosterone reach steady state levels after the second dose of testosterone buccal system. The mean average serum total testosterone concentrations at steady state in clinical studies ranged from 520 to 550 nanograms/deciliter [193].

4) In 6 healthy, postmenopausal women, maximum testosterone concentrations were achieved 0.6 hour after the first transbuccal dose of testosterone 2 milligrams and 0.4 hour after 2 weeks of treatment (steady state). Maximum hormone concentrations were 35.4 and 34.9 nanomole/liter, respectively [194].

b) Intranasal, gel: 40 minutes [22]

1) The Tmax is approximately 40 minutes following intranasal testosterone gel administration [22].

c) Oral, capsules: 6 hours [188].

1) To avoid the problem of endogenous levels and fluctuations of testosterone and dihydrotestosterone, 45 women were enrolled in a randomized, open-label pharmacokinetic study of oral testosterone undecanoate. Two doses each of 20, 40 and 80 milligrams (mg) were given every 12 hours to 45 healthy women without childbearing potential. Maximum

serum concentrations of testosterone after the first dose (Cmax1) of oral testosterone undecanoate 20, 40, and 80 mg were 1.82, 3.86, and 7.68 nanograms/mL, respectively. The time to each was 6, 6, and 5.5 hours, respectively. The maximum serum concentrations of testosterone after the second dose (Cmax2) at 20, 40, and 80 mg were 1.56, 2.65, and 5.20 nanograms/mL, respectively. Time to each was 5.98, 5.97, and 5.97 hours, respectively.

d) Subcutaneous, pellet: 63 days [195].

e) Sublingual (solution): 14.3 to 15.6 minutes [189]

1) In 16 premenopausal women, mean Tmax values after SL testosterone doses of 0.25 mg, 0.5 mg, and 0.75 mg were 15.6 minutes (+/- 5.4 minutes), 15.1 minutes (+/- 5.5 minutes), and 14.3 minutes (+/- 5.3 minutes), respectively. Free testosterone mean Tmax values following single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg were 15.6 minutes (+/- 5.1 minutes), 14.4 minutes (+/- 5.5 minutes), and 12.8 minutes (+/- 6.3 minutes), respectively. The differences between doses were not statistically different for total or free testosterone [189].

f) Transdermal: 2 to 6 hours, Testoderm(R) [196][191]; 4 to 12 hours, Androderm(R) [84]

1) With Testoderm(R) application, the serum testosterone concentration rises to a maximum at 2 to 4 hours [196].

2) With daily Androderm(R) application a continuous daily dose of testosterone is absorbed over 24 hours with a median Tmax of 8 hours (4 to 12 hours); corresponding Cmax is 905 to 925 nanograms (ng)/dL [84].

3) Absorption of transdermal testosterone was improved when a heat-generating 5 milligram (mg) patch was utilized. Over a 12-hour study period, the heat-generating patch reached a mean maximum serum testosterone concentration of 939 nanograms/dL at 4 hours compared to a standard 5 mg patch which achieved a maximum concentration of 635 nanograms/dL at 6 hours [191].

g) Topical gel: 4 hours [187].

1) An increase in serum testosterone was seen in all patients within 30 minutes after administration of 10 grams of testosterone 1% gel. Normal range testosterone levels (298 to 1043 nanograms/dL) were seen in 8 of 9 patients within 4 hours after initial application. Steady-state concentrations are reached on day 2 or 3. The average steady-state serum concentrations on day 30 in patients using 5 and 10 grams daily were 566 +/- 262 nanograms/dL and 792 +/- 294 nanograms/dL, respectively [187].

4) Steady State

a) Intranasal gel, multiple-dose, 33 mg/day: 421 nanogram/dL [22]

1) The average daily testosterone level was 421 +/- 116 nanogram/dL following administration of intranasal testosterone gel 33 mg/day (11 mg 3 times daily) for 90 days in hypogonadal men (N=69) [22].

b) Intranasal gel, multiple-dose, patients with allergic rhinitis, 11 mg: 21% to 24% decrease [22]

1) Patients with allergic rhinitis who received intranasal testosterone 11 mg 3 times daily for 3 doses had total serum testosterone levels that were 21% to 24% lower during a symptomatic phase than during an asymptomatic phase (N=18) [22].

c) Transdermal, single dose: 424 nanograms (ng)/dL (single 2.5 mg/day patch); 584 ng/dL (two 2.5 mg/day patches); 766 ng/dL (three 2.5 mg/day patches)[84]

1) In a study of 12 hypogonadal men with an average baseline serum testosterone concentration of 76 nanograms (ng)/dL, average morning testosterone concentrations were 424 nanograms (ng)/dL, 584 ng/dL, and 766 ng/dL at steady state following the nightly application of 1, 2, or 3 (2.5 mg/day) transdermal testosterone patches, respectively. Equivalent serum testosterone concentrations were observed following the application of two 2.5 mg/day patches compared with the application of one 5 mg/day patch in a study of 20 hypogonadal patients. Average steady state concentrations were 613 +/- 169 ng/dL following the application of two 2.5 mg/day patches and 621 +/- 176 ng/dL following the application of a single 5 mg/day patch [84].

5) Area Under the Curve

a) Oral (capsules): 10 to 76 nanograms x hours/milliliters [188].

1) Two doses each of testosterone undecanoate 20, 40, and 80 milligrams were give 12 hours apart to 45 healthy women without childbearing potential. The areas under the curve (AUC) from 0 to 12 hours for the 20, 40, and 80 mg dose were 10.3, 18.8, and 35.6 nanograms x hour/mL, respectively. The AUCs from 0 to the sampling time of the last measurable concentration after administration of the second dose were 25.8, 40.1, and 76.0 nanograms x hour/mL, respectively [188].

b) Sublingual (solution), single-dose: 194 nanograms (ng) x min/mL (0.25 mg); 266 ng x min/mL (0.5 mg); 337 ng x min/mL (0.75 mg) [189]

1) In 16 premenopausal women, single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg yielded baseline corrected total testosterone mean AUCs of 194 nanogram (ng) x min/mL (% coefficient variation (CV), 37.2), 266 ng x min/mL (%CV, 37.6), and 337 ng x min/mL (%CV, 34.7), respectively. Free testosterone AUCs following single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg were 0.95 ng x min/mL (%CV, 51.8), 1.51 ng x min/mL (%CV, 40.2), and 1.87 ng x min/mL (%CV, 47.8), respectively There was a statistically significant difference in AUC between the 3 doses for both total and free testosterone measurements (p less than 0.0001), and the increase in AUC was dose-dependent [189].

c) Topical (gel), single-dose (50 mg): 4499 to 5865 nanograms x hours/deciliter [190].

1) The area under the curve of plasma testosterone concentration versus time achieved by a single dose of topical testosterone 50 milligram gel ranged from 4499.1 to 5864.5 nanograms x hour/deciliter [190].

d) Transdermal: 6273 to 8402 nanograms x hour/dL [191].

1) The AUC of testosterone was 6273 to 8402 nanograms x hour/dL following transdermal administration. There is no accumulation of testosterone during continuous treatment [191].

2) Increased Systemic Exposure With a Heat-Generating Patch

a) The area under the curve of plasma testosterone concentration versus time achieved by a heat-generating patch was 8402 nanograms x hour/dL versus a standard 5 mg patch which achieved a value of 6273 nanograms x hour/dL [191].

3) Systemic Exposure After Showering

a) In a two-way crossover study of 16 hypogonadal males, showering 3 hours after the application of a single 4 mg/day transdermal testosterone patch did not increase the systemic exposure of testosterone compared with not showering [84].

e) Topical (solution), single-dose, transfer to nontreated subjects (60 mg): 13% to 131% increased exposure [85]

1) A clinical study of potential transfer of testosterone from treated men to nontreated women showed a 13% increase in testosterone AUC (0 to 24 hours) in the nontreated females. Using a 2% testosterone formulation, men (n=10) received testosterone 60 mg topically to each axilla and then covered the area with a T-shirt. Two hours after the application, women rubbed their forearms on the axilla of the men for 15 minutes. The women were monitored for 72 hours after the transfer procedure. The transfer procedure led to a 13% increase in testosterone AUC (0 to 24 hours) in the women compared with baseline. Another study in men who received a 1% testosterone formulation topically revealed a 131% increase in testosterone AUC (0 to 72 hours) following direct skin-to-skin transfer compared with indirect (T-shirt) transfer [85].

f) Topical (solution), single-dose, effect of showering/washing (30 mg): up to 35% decreased exposure [85]

1) The effect of showering/washing on testosterone exposure was examined in a parallel design clinical study of healthy, premenopausal women (n=12). Subjects received testosterone 30 mg topically to one axilla and either washed with soap and water 2 or 6 hours later (n=6) or did not wash (n=6). Blood samples collected over 72 hours from all subjects revealed up to a 35% decrease in testosterone AUC (0 to 72 hours) in subjects who washed compared with subjects who did not wash. Patients should not swim or wash the application site for 2 hours following administration [85].

g) Topical (solution), single-dose, effect of deodorant/antiperspirant (30 mg): up to 33% decreased exposure [85]

1) In a parallel-group, clinical study on the effects of deodorant/antiperspirant use with testosterone topical solution, the testosterone AUC decreased up to 33% when a single-dose

of testosterone 30 mg topical solution was applied to the axilla of healthy premenopausal women 2 minutes after application of deodorant/antiperspirant spray (n=6) or stick (n=6) or deodorant spray (n=6) compared with the control group (n=6) [85].

B) Testosterone Enanthate

1) Therapeutic Drug Concentration

a) SubQ: 300 to 1100 nanograms/dL (approximately normal physiologic circulating testosterone ranges) [74]

1) SubQ administration of testosterone enanthate results in approximately normal physiologic concentrations of testosterone (300 to 1100 nanograms/dL) in healthy men [74].

2) The mean average concentration (0 to 168 hours) of total testosterone was 553 +/- 127 nanograms/dL following weekly subcutaneous injections of testosterone enanthate (75 mg initially, then adjusted if needed to 50 mg or 100 mg based on total testosterone trough concentrations after 6 weeks of treatment; N=137) for 12 weeks [74].

2) Peak Concentration

a) SubQ, multiple-dose: 790 nanograms/dL [74]

1) The mean Cmax of total testosterone was 790 +/- 215 nanograms/dL following weekly subcutaneous injections of testosterone enanthate (75 mg initially, then adjusted if needed to 50 mg or 100 mg based on total testosterone trough concentrations after 6 weeks of treatment; N=137) for 12 weeks [74].

2) Following weekly administration, the mean Cmax of testosterone enanthate was 169 +/- 68 nanograms/dL at week 12 [74].

3) Time to Peak Concentration

a) IM: 24 hours [206][207]

1) The mean peak testosterone serum concentration following the administration of intramuscular testosterone enanthate 200 mg in 7 hypogonadal subjects was 1233 +/- 484 nanograms/dL 24 hours after injection; this was an increase of 1138 nanograms/dL from a basal serum level of 95 +/- 10 nanograms/dL [206].

2) The mean peak testosterone serum concentration following the administration of intramuscular testosterone enanthate 200 mg in 7 eugonadal subjects was 1965 +/- 391 nanograms/dL 6 hours after injection; this was an increase of 1486 nanograms/dL from a basal serum level of 497 +/- 63 nanograms/dL. The mean peak testosterone serum concentration following the administration of intramuscular testosterone enanthate 100 mg in 7 eugonadal subjects was 1181 +/- 204.7 nanograms/dL 24 hours after injection; this was an increase of 669 nanograms/dL from a basal serum level of 521 +/- 51.2 nanograms/dL [206].

b) SubQ: 11.9 hours [74]

1) The Cmax of total testosterone occurred at a median Tmax of 11.9 hours post-dose (range, 5.8 to 168.7 hours) following weekly subcutaneous injections of testosterone enanthate (75 mg initially, then adjusted if needed to 50 mg or 100 mg based on total testosterone trough concentrations after 6 weeks of treatment; N=137) for 12 weeks. Steady state concentrations were achieved by week 6 [74].

4) Area Under the Curve

a) SubQ, multiple-dose: 92,955 nanograms x hr/dL [74]

1) The mean AUC(0 to 168 hours) of total testosterone was 92,955 +/- 21,385 nanograms x hr/dL following weekly subcutaneous injections of testosterone enanthate (75 mg initially, then adjusted if needed to 50 mg or 100 mg based on total testosterone trough concentrations after 6 weeks of treatment; N=137) for 12 weeks [74].

C) Testosterone Undecanoate

1) Therapeutic Drug Concentration

a) Oral Route

1) Hypogonadism, oral: 476 nanograms (ng)/dL [53]

a) The average serum testosterone concentrations over 24 hours following oral administration of 225 mg was 476 ng/dL [53].

2) Hypogonadism, oral: 403 nanograms (ng)/dL [57]

a) The average daily NaF-EDTA plasma testosterone concentration was 403 +/- 128 ng/dL at the end of treatment, where the normal eugonadal range in NaF-EDTA plasma was 252 to 907 ng/dL in this study. Hypogonadal males received testosterone capsules 158 to 395 mg orally twice daily for at least 105 days [57].

b) Intramuscular Route

1) Hypogonadism, IM: 300 to 1000 nanograms/dL (750 mg) [59]

a) Testosterone undecanoate 750 mg IM produces circulating testosterone levels consistent with normal concentrations in health men (300 to 1000 nanograms/dL) [59].

2) Peak Concentration

a) Oral route, multiple doses, 225 mg twice daily: 979 to 989 nanograms (ng)/dL[53]

1) Mean Cmax serum testosterone concentrations following morning and evening doses were 979 ng/dL and 989 ng/dL, respectively, with an observed median Tmax of 5 hours [53].

b) Oral route, multiple doses, 158 to 396 mg twice daily: 1008 nanograms (ng)/dL [57]

1) The mean Cmax was 1008 +/- 581 ng/dL in a study of hypogonadal males (N=151) receiving testosterone capsules 158 to 396 mg orally twice daily for at least 105 days [57].

c) IM, single dose: 90.9 nanograms/dL [59]

1) The mean testosterone undecanoate Cmax was 90.9 +/- 68.8 nanograms/dL, achieved 4 days after a testosterone undecanoate IM injection [59].

3) Time to Peak Concentration

a) Oral Route

1) Testosterone

a) Oral route: 5 hours [53]

1) Mean Cmax serum testosterone concentrations following morning and evening doses were 979 ng/dL and 989 ng/dL, respectively, with an observed median Tmax of around 5 hours [53].

b) Intramuscular Route

1) Testosterone Undecanoate

a) IM: 4 days [59]

1) The mean testosterone undecanoate Cmax was 90.9 +/- 68.8 nanograms/dL, achieved 4 days after a testosterone undecanoate IM injection [59].

2) Testosterone

a) IM: 7 days [59]

1) Serum testosterone concentrations reach maximum levels after a median of 7 days (range, 4 to 42 days) following a testosterone undecanoate 750 IM injection and then levels slowly decline [59].

ADME

Absorption

A) Testosterone

1) Bioavailability

a) Oral: absorbed from the GI tract, oral mucosa, and skin; however, the oral route of administration is not used due to almost complete first-pass hepatic metabolism [197].

1) A significant and reproducible rise in serum testosterone was detected following the ingestion of testosterone crystals in 26 male subjects [198].

b) Subcutaneous: slow [195].

1) Following subcutaneous implantations using testosterone pellets, absorption has been reported to be complete by day 189. The daily release rate is 1.18 mg per 200 mg pellet [195].

c) Sublingual (solution): decreases with increasing doses [189]

1) In a study with 16 premenopausal women, the bioavailability decreased with increasing doses of SL testosterone. Since there was no IV standard, investigators used the lowest dose (0.25 mg) as a reference value of 100%. The bioavailability of 0.5 mg and 0.75 mg doses were calculated as 69% and 58%, respectively [189].

d) Transdermal: good [84]

1) Transdermal testosterone, administered as two 2.5 mg/day patches, resulted in an average testosterone absorption of 4 to 5 mg over 24 hours in 34 hypogonadal men when applied to the abdomen, back, thighs, or upper arms. When applied to the chest or shins the average absorption rate was 3 to 4 mg over 24 hours. Similar concentration profiles were observed for the abdomen, back, thigh, and upper arm application sites while more interindividual variability was observed when transdermal testosterone was applied to the either the chest or shins. The table below describes the mean testosterone concentration for various application sites over 24 hours following a single-dose application of two 2.5 mg/day patches [84].

Sample Time (hour)	Abdomen (nanograms/dL)	Back (nanograms/dL)	Thigh (nanograms/dL)	Upper Arm (nanograms/dL)
0	90 +/- 82	80 +/- 74	85 +/-76	81 +/- 69
3	286 +/- 201	429 +/- 252	271 +/- 201	308 +/- 226
6	476 +/- 236	608 +/- 250	489 +/- 254	468 +/- 245
9	570 +/- 234	613 +/- 214	592 +/- 251	534 +/- 204
12	575 +/- 244	588 +/- 233	594 +/- 247	527 +/- 199
24	352 +/- 164	403 +/- 174	367 +/- 161	332 +/- 124

e) Topical (gel): approximately 10% [199][187]

1) Approximately 10% of the applied testosterone gel dose is absorbed during a 24-hour period [199][187].

B) Testosterone Cypionate

1) Bioavailability

a) absorbed slowly [83]

1) Testosterone esters in oil administered IM are absorbed slowly from the lipid phase, which permits dosing every 2 to 4 weeks [83].

C) Testosterone Enanthate

1) Bioavailability

a) Absorbed slowly [73]

1) Testosterone esters in oil administered IM are absorbed slowly from the lipid phase, which permits dosing every 2 to 4 weeks [73].

D) Testosterone Undecanoate

1) Effects of Food

a) Reduced exposure when administered without food [53]

1) Administration in fasting conditions reduced exposure (AUC) by approximately 38% when compared to administration with high-fat food [53].

b) Reduced exposure when administered with a lesser amount of food [57]

1) When testosterone oral capsules were administered with a 15 g fat breakfast, there was a 25% decrease in testosterone exposure compared with a 30 g breakfast [57].

Distribution

A) Distribution Sites

1) Testosterone

a) Protein Binding

1) Testosterone-estradiol binding globulin: 98% [200][201].

a) Testosterone is bound to specific testosterone-estradiol binding globulin. The remaining 2% of testosterone remains free in plasma, and the amount of free testosterone determines its half-life [193][200][201][187].

2) Sex hormone-binding globulin: 40% [22][84][28][85]

a) Approximately 40% of testosterone is bound to sex hormone-binding globulin. Approximately 2% is free or unbound, and the remainder is bound to albumin and other proteins [22][84][28][85].

2) Testosterone Cypionate

a) Protein Binding

1) 98% [83]

a) Testosterone is 98% bound to a specific testosterone-estradiol binding globulin [83].

b) The half-life of testosterone depends on the amount of free testosterone, which is dependent of the amount of sex-hormone binding globulin in the plasma [83].

3) Testosterone Enanthate

a) Protein Binding

1) Specific testosterone-estradiol binding globulin: 98% [73]

a) Testosterone is 98% bound to a specific testosterone-estradiol binding globulin [73].

b) Approximately 40% of testosterone is bound to sex hormone-binding globulin. Approximately 2% is free or unbound, and the remainder is bound to albumin and other proteins [74].

c) The half-life of testosterone depends on the amount of free testosterone, which is dependent of the amount of sex-hormone binding globulin in the plasma [73].

4) Testosterone Undecanoate

a) Protein Binding

1) Albumin, unknown amount; Sex hormone binding hormone, 40% [53][57][59]

a) Testosterone is mostly bound to sex binding hormone (40%) and albumin; 2% of testosterone is unbound and the rest is loosely bound to albumin and other proteins [53][57][59].

B) Distribution Kinetics

1) Volume of Distribution

a) 74.9 to 122.5 L/kg [202].

1) The Vd at steady state in 2 healthy subjects following a single intramuscular 25 mg injection of testosterone propionate was reported as 74.9 and 122.5 L/kg, respectively [202].

Metabolism

A) Metabolism Sites and Kinetics

1) Testosterone

a) Liver, extensive first-pass hepatic metabolism [28][200][201][85].

1) Testosterone administered orally is not recommended [197]. Testosterone is metabolized in the liver to various 17-ketosteroids via 2 different pathways. Glucuronic and sulfuric acid conjugates of testosterone are found in urine with approximately 6% of testosterone excreted unchanged in the feces [22][28][200][201].

2) Testosterone is primarily inactivated in the liver [22][28][85].

b) Liver, transbuccal delivery of testosterone circumvents first-pass metabolism [193].

2) Testosterone Cypionate

a) Liver: primary site [83]

1) Testosterone activity depends on reduction to dihydrotestosterone in responsive

tissues [83].

2) Inactivation of testosterone happens primarily in the liver [83].

3) Testosterone Enanthate

a) Liver: Primary site [74][73]

1) Testosterone enanthate is metabolized to testosterone by ester cleavage of the enanthate group. Testosterone is metabolized to various 17-ketosteroids via 2 different pathways [74].

2) Testosterone activity depends on reduction to dihydrotestosterone in responsive tissues [73].

3) Inactivation of testosterone happens primarily in the liver [74][73].

4) Testosterone Undecanoate

a) Serum esterases (testosterone undecanoate): Primary [53]

1) Testosterone undecanoate is metabolized to active testosterone via ester cleavage of the undecanoate group [53]

b) Liver: Primary (testosterone) [53]

1) Inactivation of testosterone (the active metabolite of testosterone undecanoate) occurs primarily in the liver [53].

B) Metabolites

1) Testosterone

a) Estradiol and dihydrotestosterone (DHT): active [22][84][28][85]

1) Estradiol and dihydrotestosterone (DHT) are the major active metabolites of testosterone [22][84][28][85][200][201][187]. DHT concentration was linearly related to testosterone concentration during treatment with testosterone topical solution via axillary administration [85].

2) The average DHT:T and E2:T ratios, respectively, were 1:10 and 1:200 during steady-state pharmacokinetic studies in hypogonadal men [84].

b) Testosterone glucuronic conjugate, activity unknown [200][201].

c) Testosterone sulfuric acid conjugate, activity unknown [200][201].

1) In addition to testosterone glucuronic and sulfuric acid conjugates, 17-ketosteroid metabolites of testosterone are produced by 2 different metabolic pathways in the liver [22][85][200][201][187].

d) Testosterone-19-d3, active [202]

1) Active metabolite of testosterone propionate [202]

2) Testosterone Enanthate

a) Dihydrotestosterone (major): Active [74]

1) Dihydrotestosterone (DHT) is a major active metabolite of testosterone [74].

2) Following weekly administration of testosterone enanthate, the mean DHT/testosterone ratio was within normal range (0.07) pre-dose of week 12 [74].

b) Estradiol (major): Active [74]

1) Estradiol is a major active metabolite of testosterone [74].

c) Testosterone glucuronic conjugate: [74][73] Unknown activity

d) Testosterone sulfuric acid conjugate: [74][73] Unknown activity

e) 17-ketosteroid metabolites of testosterone: Inactive [74][73]

1) In addition to testosterone glucuronic and sulfuric acid conjugates, 17-ketosteroid metabolites of testosterone are produced by 2 different metabolic pathways in the liver [74][73]

3) Testosterone Undecanoate

a) Testosterone: Active (major) [53][57][59]

1) Testosterone undecanoate is metabolized to testosterone by ester cleavage. Testosterone is metabolized to various 17-keto steroids through 2 different pathways to estradiol and dihydrotestosterone [53][57][59].

Excretion

A) Kidney

1) Testosterone

a) Renal Clearance (rate)

1) approximately 2 L/min [202].

a) Clearance in 2 healthy male subjects following a single 25 mg intramuscular injection of testosterone propionate was reported as 2317.4 and 1958.0 mL/min, respectively [202].

b) Renal Excretion (%)

1) 90% [22][84][88][200].

a) Following an intramuscular dose of testosterone, approximately 90% is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and testosterone metabolites [22][84][28][200][88][85].

2) Testosterone Cypionate

a) Renal Excretion (%)

1) 90% [83]

a) Approximately 90% of a testosterone dose is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and it's metabolites [83].

3) Testosterone Enanthate

a) Renal Excretion (%)

1) 90%, changed [74][73]

a) Following IM administration, approximately 90% of a testosterone dose is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and it's metabolites [74][73].

4) Testosterone Undecanoate

a) 90%, as conjugated metabolites [53][59]

1) Approximately 90% of an IM testosterone dose is excreted in the urine as glucuronic and sulfuric acid conjugates or other metabolites [53][59].

B) Feces

1) Testosterone

a) 6% [22][84][28][200][88][85]

1) Approximately 6% of a IM testosterone dose is excreted in feces, mainly in the unconjugated form [22][84][28][200][88][85].

2) Testosterone Cypionate

a) 6% [83]

1) Approximately 6% of a testosterone dose is excreted in the feces; the majority as the unconjugated form [83].

3) Testosterone Enanthate

a) 6%, mostly unchanged [74][73]

1) Following IM administration, approximately 6% of a testosterone dose is excreted in the feces; the majority as the unconjugated form [74][73].

4) Testosterone Undecanoate

a) 6% [53][59]

1) Approximately 6% of an IM testosterone dose is excreted in the feces as unconjugated testosterone [53][59].

Elimination Half-life

A) Parent Compound

1) Testosterone

a) 5.7 hours, buccal [192]; 2 to 3 hours, oral [188]; 70.8 days, subQ implanted pellet[195]; 49.7 to 58.5 minutes, sublingual (solution) [189];10 to 100 minutes [22] [84][199][204][201][85]

1) The mean half life of total testosterone following SL doses of 0.25 mg, 0.5 mg, and 0.75 mg in healthy premenopausal women (n=16) was 49.8 +/- 16 minutes, 49.7 +/- 22.4 minutes, and 58.5 +/- 24.6 minutes, respectively. The calculated half-life of total testosterone was significantly different only between the 0.5 mg and 0.75 mg doses (p=0.0125). The mean half life of free testosterone following SL doses of 0.25 mg, 0.5 mg, and 0.75 mg in healthy premenopausal women (n=16) was 42.3 +/- 14.6 minutes, 55.7 +/- 27.5 minutes, and 51.1 +/- 26.4 minutes, respectively. There was no statistical difference in half-life of free testosterone between the 3 doses [189].

2) The half-life of testosterone is highly variable, ranging from 10 to 100 minutes [22] [84][28][199][204][201][85]

3) The elimination half-life of buccal testosterone 30 milligrams given twice daily for 7 days to 12 testosterone-deficient men was 5.7 hours [192].

4) Two doses each of testosterone undecanoate 20, 40, and 80 milligrams were give 12 hours apart to 45 healthy women without childbearing potential. The baseline-corrected elimination half-lives for each dose were 2.35, 2.43, and 2.58 hours, respectively [188].

5) The terminal elimination half-life for subcutaneously implanted testosterone pellets is reported to be 70.8 days. Men with larger body mass apparently have a lower half-life [195].

2) Testosterone Cypionate

a) 10 to 100 minutes [83]

1) The half-life of testosterone depends on the amount of free testosterone, which is dependent of the amount of sex-hormone binding globulin in the plasma. The half-life of testosterone is variable, and can range from 10 to 100 minutes [83].

2) The amount of free testosterone (non-protein-bound) determines its half-life. The half-life of testosterone depends upon the route of administration and which testosterone ester is used; the half-life for intramuscularly administered testosterone cypionate is approximately 8 days [200].

3) Testosterone Enanthate

a) 10 to 100 minutes [73]

1) The half-life of testosterone depends on the amount of free testosterone, which is dependent of the amount of sex-hormone binding globulin in the plasma. The half-life of testosterone is variable, and can range from 10 to 100 minutes [73].

B) Metabolites

1) Testosterone Undecanoate

a) Testosterone

1) 10 to 100 minutes [53][59]

a) There is considerable variation in the half-life of testosterone, with reports ranging from 10 to 100 minutes [53][59].

PATIENT EDUCATION

Medication Counseling

No results available

Patient Handouts

A) Testosterone (Absorbed through the skin)
Testosterone

Treats low testosterone levels.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone, or if you have breast cancer or prostate cancer.

How to Use This Medicine:
Patch

Your doctor will tell you how many patches to use, where to apply them, and how often to apply them. Do not use more patches or apply them more often than your doctor tells you to.
Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.
Wash your hands with soap and water before and after applying a patch.
Leave the patch in its sealed wrapper until you are ready to put it on. Tear the wrapper open carefully. NEVER CUT the wrapper or the patch with scissors. Do not use any patch that has been cut by accident.
The patient instructions will show the body areas where you can wear the patch. When putting on each new patch, choose a different place within these areas. Do not put the new patch on the same place you wore the last one. Be sure to remove the old patch before applying a new one.
Apply the patch to clean, dry skin with very little hair, on your back, abdomen, upper arms, or thighs. Apply the patch at about the same time every night.
Do not put the patch over burns, cuts, or irritated skin. Do not put the patch on oily or sweaty skin or on a spot that might put extra pressure on it (such as over a joint).
Bathing or swimming should not affect the patch. However, wait at least 3 hours after you apply the patch before you wash the skin area or shower or swim. Heavy exercise and sweating may cause the patch to fall off.
If the patch becomes loose, smooth it down and press it back onto your skin. If the patch comes off before 12 o'clock noon, put on a new patch, and then replace the new patch at your regular time. If the patch comes off after noon, just wait and put on a new patch at your next regular time.
Do not tape the patch to your skin.
Missed dose: If you forget to wear or change a patch, put one on as soon as you can. If it is almost time to put on your next patch, wait until then to apply a new patch and skip the one you missed. Do not apply extra patches to make up for a missed dose.
Store the patches at room temperature in a closed container, away from heat, moisture, and direct light.
Fold the used patch in half with the sticky sides together. Throw any used patch away so that children or pets cannot get to it. You will also need to throw away old patches after the expiration date has passed.
Keep the medicine in a safe place. Do not give it to anyone else, even if you have the same symptoms.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin
Blood thinner (including warfarin)
Corticosteroid (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have kidney disease, liver disease, cancer, diabetes, an enlarged prostate, heart disease, lung disease, sleep apnea, or a history of heart attack or stroke.
This medicine may cause the following problems:

Increased numbers of red blood cells
Increased risk of prostate cancer
Blood clot in your leg or lung
Increase risk of heart attack or stroke
Lower sperm count (with large doses)

The skin patch contains aluminum, which may cause skin burns if you have an MRI (magnetic resonance imaging) scan. You must remove the patch before an MRI.
This medicine is not indicated for use in women and should never be used by a pregnant woman.
This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Change in how much or how often you urinate, trouble urinating
Chest pain that may spread to your arms, jaw, back, or neck, trouble breathing, coughing up blood, unusual sweating, faintness
Chest pain, trouble breathing, or coughing up blood
Numbness or weakness on one side of your body, sudden or severe headache, problems with vision, speech, or walking
Pain, redness, or swelling in your arm or leg
Severe skin blisters, redness, swelling, or burning where the patch is applied
Swelling in your hands, ankles, or feet
Unusual bleeding or bruising

If you notice these less serious side effects, talk with your doctor:

Mild skin soreness, redness, itching, or irritation where the patch was applied
Swollen breasts

If you notice other side effects that you think are caused by this medicine, tell your doctor.
B) Testosterone (Between cheek and gum)
Testosterone

Treats low testosterone levels. Testosterone is a male hormone.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone, or if you have breast cancer or prostate cancer.

How to Use This Medicine:
Patch

Your doctor will tell you how much medicine to use. Do not use more than directed.
Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.
This medicine looks like a tablet, but it sticks to your gum like a patch. To use the patch:

Put the flat side of the patch on your fingertip. Place the patch against your gum and to the left or right of your front teeth. Gently push it up as high as it will go. Then press on the patch from the outside of your lip for at least 30 seconds. The patch should stick to your gum.
Do not chew or swallow the patch.
Each time you put in a new patch, put it on the opposite side from where you put the last one.
Keep the patch in your mouth all the time, unless you are changing patches. Check to make sure

the patch is still in place after you eat or drink, use mouthwash, or brush your teeth.
To remove a patch, use your finger to gently loosen it. Then slide it down over your teeth and take it out.
Use this medicine 2 times a day, once in the morning and once in the evening (about 12 hours apart), unless your doctor tells you differently.

Missed dose: If the patch falls off within the first 8 hours, take it out and put in a new one. Put in the next patch at the regular time. If the patch falls off after more than 8 hours, take it out and put in a new one. This will count as your next dose, and the patch can stay in place for 12 hours.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Keep the medicine in a safe place. Do not give it to anyone else, even if you have the same symptoms.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin
Blood thinner (including warfarin)
Steroid medicine (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have kidney disease, liver disease, diabetes, an enlarged prostate, heart disease, high cholesterol, sleep apnea, a history of heart attack or stroke.
This medicine may cause the following problems:

Increased risk of prostate cancer
Blood clot in your leg or lung
Possible increased risk of heart attack or stroke
Lower sperm count

This medicine is not indicated for use in women and should never be used by a pregnant woman.
This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Change in how much or how often you urinate, trouble urinating
Chest pain that may spread, trouble breathing, coughing up blood, unusual sweating, faintness
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Pain, redness, or swelling in your arm or leg
Swelling in your hands, ankles, or feet

If you notice these less serious side effects, talk with your doctor:

Gum pain, tenderness, or swelling
More erections than usual or erections that last a long time
Swollen breasts

If you notice other side effects that you think are caused by this medicine, tell your doctor.

C) Testosterone (By injection)

Testosterone

Treats low or no testosterone levels. Also treats breast cancer in women and delayed puberty in male teenagers.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. You should not receive it if you had an allergic reaction to testosterone, benzyl benzoate, refined castor oil, or sesame oil. A man should not receive this medicine if he has breast cancer, prostate cancer, or age-related hypogonadism. A woman should not receive this medicine if she is pregnant or breastfeeding.

How to Use This Medicine:
Injectable
Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as a shot into a muscle in the buttocks. Xyosted™ is given as a shot under your skin in the stomach area.
A nurse or other health provider will give you this medicine.
Xyosted™:
You may be taught how to give your medicine at home. Make sure you understand all instructions before giving yourself an injection. Do not use more medicine or use it more often than your doctor tells you to.
You will be shown the body areas where this shot can be given. Use a different body area each time you give yourself a shot. Keep track of where you give each shot to make sure you rotate body areas.
Check the liquid in the prefilled syringe or autoinjector. It should be colorless to slightly yellow. Do not use the medicine if the liquid is cloudy, discolored, or has particles in it.
Use a new needle and syringe each time you inject your medicine.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.
Missed dose: Call your doctor or pharmacist for instructions.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:
Oxyphenbutazone
Blood thinner (including warfarin)
Insulin or oral diabetes medicine
Steroid medicine (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:
It is not safe to take this medicine during pregnancy. It could harm an unborn baby. Tell your doctor right away if you become pregnant.
Tell your doctor if you have kidney disease, liver disease, lung disease, diabetes, an enlarged prostate, blood vessel or heart disease, heart failure, high cholesterol, lung disease, obesity, sleep apnea, or a history of heart attack or stroke.
This medicine may cause the following problems:
High blood pressure
Serious lung reaction called pulmonary oil embolism (may be life-threatening)
Increased risk of prostate cancer
Increased number of red blood cells
Blood clot in your leg or lung
Slow growth in children
Increased risk of heart attack or stroke

Liver problems
Changes in mood or behavior

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
This medicine may lower your sperm count (with large doses). Talk with your doctor before using this medicine if you plan to have children. Some men who use this medicine have become infertile (unable to have children).
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Change in how much or how often you urinate, trouble urinating
Chest pain, cough, trouble breathing, dizziness, tightening of your throat, unusual sweating
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Pain, redness, or swelling in your arm or leg
Swelling in your hands, ankles, or feet
Unusual mood or behavior, thoughts of killing oneself
Unusual bleeding, bruising, or weakness

If you notice these less serious side effects, talk with your doctor:

Acne, hoarse voice, facial hair growth (women)
Changes in menstrual periods
More erections than usual or erections that last a long time
Pain, redness, or swelling where the shot was given
Swollen breasts (men)

If you notice other side effects that you think are caused by this medicine, tell your doctor.
D) Testosterone (By mouth)
Testosterone Undecanoate

Treats low or no testosterone levels.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone. Male patients who have breast cancer, prostate cancer, or age-related hypogonadism should not use this medicine. This medicine is not for use in women, especially if pregnant or breastfeeding.

How to Use This Medicine:
Capsule

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.
It is best to take this medicine with food or milk.
This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.
Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin
Blood thinner (including warfarin)
Pain or cold medicine
Steroid medicine (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have liver disease, kidney disease, heart or blood vessel disease, blood disease, lung disease, diabetes, an enlarged prostate, heart failure, obesity, sleep apnea, high cholesterol, thyroid problems, or a history of heart attack or stroke.
This medicine may cause the following problems:

High blood pressure
Increased number of red blood cells
Increased risk of prostate cancer
Blood clot in your leg or lung
Increased risk of heart attack or stroke
Liver problems
Changes in mood or behavior, including thoughts of suicide

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
This medicine may lower your sperm count (with large doses). Talk with your doctor before using this medicine if you plan to have children. Some men who use this medicine have become infertile (unable to have children).
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Bone or muscle pain
Change in how much or how often you urinate, trouble urinating
Chest pain, cough, trouble breathing, tightening of your throat, unusual sweating, bluish-colored skin
Confusion, constipation, dry mouth, weight loss
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Dizziness, lightheadedness, or fainting
Numbness or weakness in your arm or leg, or on one side of your body, pain in your lower leg, sudden or severe headache, problems with vision, speech, or walking
Rapid weight gain, swelling in your hands, ankles, or feet
Unusual mood or behavior, thoughts of killing oneself
Unusual bleeding, bruising, or weakness

If you notice these less serious side effects, talk with your doctor:

Enlarged, swollen, or painful breasts in men
More erections than usual or erections that last a long time
Runny or stuffy nose, sore throat

If you notice other side effects that you think are caused by this medicine, tell your doctor.

E) Testosterone (Into the nose)

Testosterone

Treats low testosterone levels. Testosterone is a male hormone.

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone, or if you have breast cancer or prostate cancer.

How to Use This Medicine:

Gel/Jelly

Your doctor will tell you how much medicine to use. Do not use more than directed.
Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.
This medicine is for use only in the nose. Do not get any of it in your eyes or on your skin. If it does get on these areas, rinse it off right away.
To use:

Prime the pump the first time you use this medicine. To do this, hold the pump upside down over a sink, and slowly press the pump 10 times. Rinse the sink with warm water. Wipe the tip with a clean, dry tissue. The medicine is now ready to use.
If you get the medicine on your hands, wash them with warm water and soap.
Gently blow your nose to clear the nostrils.
Insert the tip of the pump into your left nostril and gently tilt it so that it touches the side of your nose. This will make sure the medicine is applied properly.
Slowly press the pump until it stops. Remove the tip from your nose.
Repeat these steps to apply the medicine into your right nostril.
After you use the pump, wipe the tip with a clean, dry tissue and put the cap back on.
Press your nostrils together just below the bridge of your nose and lightly rub them together.
Do not blow your nose or sniff for 1 hour after you use this medicine.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Keep the medicine in a safe place. Do not give it to anyone else, even if you have the same symptoms.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin
Other medicine that you use in your nose (including oxymetazoline)
Blood thinner (including warfarin)
Steroid (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have kidney disease, liver disease, diabetes, an enlarged prostate, heart disease, high cholesterol, lung disease, sleep apnea, or a history of heart attack or stroke. Also tell your doctor if you have any nose or sinus problems, including allergies or history of nose or sinus surgery or a broken nose.
This medicine may cause the following problems:

Increased risk of prostate cancer
Blood clot in your leg or lung
Possible increased risk of heart attack or stroke
Lower sperm count

This medicine is not indicated for use in women and should never be used by a pregnant woman.
This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Change in how much or how often you urinate, trouble urinating
Chest pain that may spread, trouble breathing, coughing up blood, unusual sweating, faintness
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Pain, redness, or swelling in your arm or leg
Swelling in your hands, ankles, legs, or feet

If you notice these less serious side effects, talk with your doctor:

More erections than usual or erections that last a long time
Runny or stuffy nose, sneezing, nosebleeds, or discomfort, scabbing, or dryness of your nose
Swollen breasts

If you notice other side effects that you think are caused by this medicine, tell your doctor.
F) Testosterone (On the skin)
Testosterone

Treats low testosterone levels. Testosterone is a male hormone.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone, or if you have breast cancer or prostate cancer.

How to Use This Medicine:
Gel/Jelly, Kit, Liquid

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.
This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.
Apply this medicine at the same time every day in the morning, unless your doctor tells you differently.
Apply the medicine to clean, dry, intact skin. Do not apply to skin that has a cut, scrape, or other injury.
Follow the manufacturer's directions on how to prime the pump before you use it the first time. Do not use the medicine that comes out during priming. Rinse it down the drain.
Gel:

Apply the gel only to your shoulders, upper arms, or thighs. Do not apply this medicine to your scrotum or penis.
Allow the gel to dry before you cover the area with clothing. Wait for at least 2 to 5 hours after you apply this medicine before you shower or swim.

Children and women should avoid contact with the unwashed or unclothed area where the testosterone gel has been applied. If another person accidentally gets this medicine on his or her skin, wash the area with soap and water right away.
Solution:

This medicine comes in 2 forms: a pump actuated metered dose bottle and a twist actuated metered dose bottle.
Apply an antiperspirant or deodorant spray at least 2 minutes before you apply this medicine.
Use an applicator to apply the solution to clean and dry underarms. Do not apply this medicine to any other part of your body.
Wipe any medicine that drips or runs with an applicator. Do not rub the solution with your fingers or hand.
Rinse the applicator cup with water and pat it dry with a tissue. Put the cup and cap back onto the pump actuated metered dose bottle. Put the lid back on the twist actuated metered dose bottle.
Allow the solution to dry for at least 3 minutes before you cover the area with clothing. Do not shower or swim for at least 2 hours.

Wash your hands with soap and warm water after you use this medicine.
If any medicine gets in your eyes, rinse them right away with water and call your doctor. Do not drink this medicine.
The medicine is flammable until it dries on the skin. Do not smoke or go near an open flame until the gel or solution has dried and you have covered the area with clothing.
Missed dose: Apply a dose as soon as you can. If it is almost time for your next dose, wait until then and apply a regular dose. Do not apply extra medicine to make up for a missed dose.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Keep the medicine in a safe place. Do not give it to anyone else, even if you have the same symptoms.
Throw away the empty pump, tube, or packet in a place where children and pets cannot reach it.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin, oxyphenbutazone
Blood thinner (including warfarin)
Steroid medicine (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have kidney disease, liver disease, heart disease, lung disease, blood clotting problems, diabetes, an enlarged prostate, high cholesterol, sleep apnea, or a history of heart attack or stroke.
This medicine may cause the following problems:

Increased risk of prostate cancer
Blood clot in your leg or lung
Possible increased risk of heart attack or stroke
Lower sperm count
Liver problems

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
Tell any doctor or dentist who treats you that you are using this medicine. This medicine may affect certain medical test results.
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Changes in how much or how often you urinate, trouble urinating
Chest pain that may spread, trouble breathing, coughing up blood, unusual sweating, faintness
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Pain, redness, or swelling in your arm or leg
Swelling in your hands, ankles, or feet

If you notice these less serious side effects, talk with your doctor:

More erections than usual or erections that last a long time
Swollen breasts

If you notice other side effects that you think are caused by this medicine, tell your doctor.

TOXICOLOGY

Clinical Effects

No results available

Range of Toxicity

No results available

Treatment

No results available

ABOUT

How Supplied

No results available

Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms

Testosterone
Testosterone, Micronized
Testosterone Cyp
Testosterone Cypionate
Testosterone Decanoate
Testosterone Enanthate
Testosterone Isocaproate
Testosterone Phenylpropionate
Testosterone Propionate
Testosterone Propionate, Micronized
Testosterone Undecanoate

C) Orphan Drug Status

1) Testosterone

a) This drug has one or more orphan drug designations, which may include approval or withdrawal of status; Access citation for FDA Orphan Drug Information [52]

2) Testosterone Cypionate

a) This drug has one or more orphan drug designations, which may include approval or withdrawal of status; Access citation for FDA Orphan Drug Information [52]

3) Testosterone Enanthate

a) This drug has one or more orphan drug designations, which may include approval or withdrawal of status; Access citation for FDA Orphan Drug Information [52]

D) Physicochemical Properties

1) Testosterone

a) Molecular Weight

1) 288.4 [85]; 288.42 [28]

2) Testosterone Cypionate

a) Molecular Weight

1) 412.61 [83]

b) Solubility

1) Testosterone cypionate is freely soluble in alcohol, chloroform, dioxane, ether, and vegetable oils, and is insoluble in water [83].

3) Testosterone Enanthate

a) Molecular Weight

1) 400.6 [73]

4) Testosterone Undecanoate

a) Molecular Weight

1) 456.7 [59]

Storage & Stability

A) Testosterone

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the compounding and administration of a hazardous topical drug, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator, and use eye/face and respiratory protection if not prepared in a control device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection, and if there is inhalation potential use respiratory protection [50].

b) Buccal mucosa route

1) Administration

a) The rounded side of the buccal system surface should be placed against the gum and held firmly in place with a finger over the lip for 30 seconds to ensure adhesion [23].

b) If the buccal system falls off during the first 8 hours after application, replace with a new system that should be retained until a total of 12 hours have elapsed from placement of the first system; then continue usual dosing schedule. If the buccal system falls off 8 or more hours after application, apply a new buccal system that may be retained for 12 hours; then continue usual dosing schedule [23].

c) The buccal system should not be chewed or swallowed. Remove system prior to oral care and apply a new system after [23].

c) Nasal route

1) Preparation

a) Prime the pump prior to the first use by depressing the pump 10 times, discarding initial drug delivered. Wash off the gel with warm water then wipe tip with clean, dry tissue. If the product comes into contact with hands, wash hands with soap and water [22].

2) Administration

a) Completely depress the pump 1 time in each nostril; do not apply to any other part of the body. To administer, blow nose, uncap pump, and place the finger on the actuator. Then insert pump until the finger reaches the bottom of the nose. Apply gel to lateral nasal wall and remove pump once fully depressed, wiping the tip along the inside of the lateral nostril. Press on the nostrils just below the bridge of the nose and lightly massage the applied product. Do not blow nose or sniff for 1 hour [22].

d) Topical application route

1) Axiron(R)

a) If using antiperspirant or deodorant stick, roll-on, or spray, apply these 2 minutes prior to the application of testosterone topical solution as part of a normal, consistent, daily routine [20].

b) When using for the first time, prime the pump by depressing the pump-actuated or by twisting the dose dial 3 times; discard product dispensed directly into a basin, sink, or toilet and then wash the liquid away thoroughly [20].

c) Pump actuated: After priming, depress the pump completely only 1 time each time (1 pump actuation equals 30 mg) [20].

d) Pump actuated: Apply using the applicator provided. Position the nozzle over the applicator cup and depress the pump fully once. Do not fill the cup with more than 30 mg (1 pump actuation) [20].

e) Twist actuated: After priming, completely twist (180 degree turn) the dose dial 1 time (1 twist actuation equals 30 mg). The applicator should be filled with no more than 30 mg (1 twist actuation). Dosing that requires greater than 1 twist actuation must be applied in increments of 30 mg [20]

f) Keep the applicator upright. Place it up into the axilla and wipe steadily down and up into the axilla. If the solution drips or runs, wipe it back up with the applicator cup. Do not rub the solution into the skin with fingers or hand [20].

g) Apply each morning to clean, dry, intact skin of the axilla. Do not apply to any other parts of the body. Allow each application site to dry completely prior to the next application (for higher doses) or dressing [20].

h) 30 mg, 1 pump or twist actuation: Apply once to 1 axilla only (left or right) [20].

i) 60 mg, 2 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla [20].

j) 90 mg, 3 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla. Wait for the product to dry and then apply once again 1 actuation to the left or right axilla [20].

k) 120 mg, 4 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla. Wait for the product to dry and then apply once again 1 actuation to the left axilla and 1 actuation to the right axilla [20].

l) After use, rinse the applicator under room temperature, running water, and then pat dry with a tissue. Place the applicator and cap on the bottle for storage [20].

m) Wash hands thoroughly with soap and water after applying testosterone topical solution [20].

n) Cover the application site with clothing or dressing after the solution has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [20].

o) Wait at minimum 2 hours prior to washing the application site or swimming [20].

p) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [20].

2) AndroGel(R)

a) Prime the AndroGel(R) pump by depressing the actuator 3 times while canister is in upright position. Safely discard the gel dispensed from the first 3 actuations. Priming is only necessary before the first dose [27][49].

b) Apply to clean, dry, intact skin of shoulder or upper arm that will be covered by clothing. For the 40.5 mg (2.5-g packets), squeeze a portion of the gel from the packet into the palm of hand and apply to application sites (as this size packet needs to be split between the left and right shoulder) and repeat until entire contents have been applied. The gel may be delivered from the actuator into the palm of one hand, then applied to the intended site, or may be applied directly from the pump to the intended application site [24][27][49].

c) Apply AndroGel(R) 1.62%, to the shoulder or upper arm (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt); do not apply to any other part of the body, including abdomen or genitals. Wait a minimum of 2 hours prior to washing the application site or swimming [49].

d) AndroGel(R) 1%, apply to the shoulder and upper arm and/or abdomen (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt); do not apply to genitals. Avoid swimming or showering for at least 5 hours after application [51].

e) Patients should wash hands thoroughly with soap and water immediately after applying testosterone topical gel [27][49].

f) Cover the application site with clothing or dressing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [27][49].

g) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [27][49].

h) Children and women should avoid contact with unwashed or unclothed application site [27] [49].

i) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [27][49].

j) Application recommendations for AndroGel(R) 1.62% for pump or packets are in the table below [15]:

AndroGel(R) 1.62%						
Total Dose of Testosterone	Total Pump Actuations	Pump Actuations per Upper Arm and Shoulder		Total Packets *	Gel Applications per Upper Arm and Shoulder *	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	1	1	0	One 1.25-g packet	One 1.25-g packet	0
40.5 mg	2	1	1	One 2.5-g packet	Half the contents of one 2.5-g packet	Half the contents of one 2.5-g packet
60.75 mg	3	2	1	One 1.25-g AND one 2.5-g packet	One 2.5-g packet	One 1.25-g packet
81 mg	4	2	2	Two 2.5-g packets	One 2.5-g packet	One 2.5-g packet
* Weight given as gel content of packet.						

k) Application recommendations for AndroGel(R) 1% 75-g pump are in the table below [5]:

Dosing Guidelines for the AndroGel(R) 1% 75-g Multi-Dose Pump	
Prescribed Testosterone Dose	Number of Pump Actuations
50 mg daily	4 pumps once daily
75 mg daily	6 pumps once daily
100 mg daily	8 pumps once daily

3) Fortesta(TM)

a) Prime the pump by depressing the actuator 8 times while canister is in upright position; safely discard the gel dispensed from the first 8 actuations; only necessary to prime pump before the first dose [21].

b) Apply to clean, dry, intact skin of the front and inner thighs; do not apply to genitals or other parts of the body; use one finger to apply gel [21].

c) After the application site is dry, site should be covered with clothing (with sufficient length to cover application site); wash hands thoroughly with soap and water after applying gel [21].

d) Children and women should avoid contact with unwashed or unclothed application site [21].

e) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [21].

f) If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [21].

g) Application recommendations for Fortesta(TM) are in the table below [21]:

Total Dose of Testosterone	Total Pump Actuations	Pump Actuations per Thigh	
		Thigh #1	Thigh #2
10 mg	1	1	0
20 mg	2	1	1
30 mg	3	2	1
40 mg	4	2	2
50 mg	5	3	2
60 mg	6	3	3
70 mg	7	4	3

4) Testim(R)

a) Apply to clean, dry, intact skin of shoulder or upper arm; do not apply to genitals or abdomen. Wash hands thoroughly with soap and water immediately after applying [24].

b) Do not wash application site for at least 2 hours after application. Cover the application site with clothing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [24].

c) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [24].

d) Children and women should avoid contact with unwashed or unclothed application site [24].

e) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [24].

5) Vogelxo(TM)

a) With multidose bottle, prime the pump 3 times before first use (discard any product released). Depress pump 4 times or empty entire contents of 1 unit-dose tube or packet into palm of the hand and immediately apply to clean, dry, intact skin of shoulder and upper arm. When the daily dosage is 100 mg, repeat on the opposite shoulder [25].

b) Do not apply to abdomen or genitals. Wash hands thoroughly with soap and water immediately after applying [25].

c) Do not wash site for at least 2 hours after application. Cover the application site with clothing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [25].

d) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [25].

e) Children and women should avoid contact with unwashed or unclothed application site [25].

f) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [25].

e) Transdermal route

1) Administration

a) Immediately after opening the pouch, apply the adhesive side of the Androderm(R) system to the back, abdomen, upper arm, or thigh in a clean, dry area of the skin. Press system firmly in

place, ensuring good contact with the skin, especially around the edges. Avoid application to oily, damaged, or irritated skin. Do not apply to the scrotum, and avoid bony prominences or areas of prolonged pressure during sitting or sleeping [19].

b) Avoid swimming, showering, or washing the administration site for at least 3 hours after application [19].

c) Rotate application sites, with at least 7 days between applications to the same site [19].

B) Testosterone Cypionate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Administration

a) Administer IM injection slowly and deeply into the gluteal muscle; it is not for IV injection [83].

b) If crystals formed because product was stored at lower than recommended temperatures, they can be dissolved by warming or shaking the vial [83].

C) Testosterone Enanthate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Administration

a) Administer IM injection slowly and deeply into the gluteal muscle, avoiding intravascular injection. Crystals formed during storage at lower than recommended temperatures can be dissolved by warming or shaking the vial. A wet syringe or wet needle may turn the solution cloudy but does not affect product potency [73].

c) Subcutaneous route

1) Administration

a) Xyosted(TM) is for subQ injection in the abdominal region only. Avoid IM or intravascular injection. Do not use if the liquid in the syringe is cloudy or if visible particles are present; an air bubble is normal. Do not use if the seal is broken [74].

D) Testosterone Undecanoate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Preparation

a) Carefully remove gray plastic cap from vial; leave the aluminum metal ring and crimp seal around the gray rubber stopper [63].

b) Using an 18-gauge needle at a 45-degree angle with the bevel oriented upward, inject 3 mL of air through the gray rubber stopper to create positive pressure in the vial, and then withdraw 3 mL (750 mg) of solution [64].

c) Expel any air bubbles from the syringe and change the syringe needle to a new IM needle [63].

d) .

2) Administration

a) For IM use only [63]

b) Slowly (over 60 to 90 seconds) inject IM deep into the gluteal muscle; care must be taken to avoid intravascular administration as this may lead to pulmonary oil microembolism; also avoid the superior gluteal arteries and sciatic nerve [63].

c) Discard any unused portion [63].

d) Alternate injection sites between left and right buttock between consecutive injections [63].

c) Oral route

1) Administration

a) Give with food [53][57].

E) Testosterone

1) Buccal mucosa route

a) Patch, Extended Release

1) Store at 20 to 25 degrees C (68 to 77 degrees F). Protect from heat and moisture [108].

2) Intramuscular route

a) Solution

1) Store at room temperature. Warming and rotating the vial between hands will redissolve any crystals that may have formed when stored at lower temperatures [88].

3) Nasal route

a) Gel/Jelly

1) Store at a controlled room temperature between 20 and 25 degree C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) [22].

4) Oral route

a) Capsule

1) Refrigerate between 2 and 8 degrees C before dispensing. Do not refrigerate after dispensing. The shelf life is 3 years before opening when stored between 2 and 8 degrees C and 90 days at room temperature after the container has been opened [208].

5) Topical application route

a) Gel/Jelly/Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [28][25]. Do not freeze [21].

2) Store upright at a controlled room temperature of 25 degrees C (77 degrees F); excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) [209][183].

6) Transdermal route

a) Patch, Extended Release

1) Store at 25 degrees C (77 degrees F); excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [182].

F) Testosterone Cypionate

1) Injection route

a) Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F); protect from light [83].

G) Testosterone Enanthate

1) Intramuscular route

a) Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F). If crystals form, warm and rotate vial between palms of hands to dissolve [73].

2) Subcutaneous route

a) Solution

1) Store in original carton at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F). Protect from light; do not refrigerate or freeze [74].

H) Testosterone Undecanoate

1) Intramuscular route

a) Solution

1) Store in original carton at a controlled room temperature of 25 degrees C (77 degrees F) , with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Discard any unused portion [59].

2) Oral route

a) Capsule

1) Store at a temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Store in a dry place and protect from moisture [57].

b) Capsule, Liquid Filled

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [53].

Trade Names

No results available

Regulatory Status

No results available

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