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Gonadotropin-Releasing Hormone Analogs and Antagonists

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

Number: 0501

Commercial CPB | Medicare CPB (0501m.html)

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Last Review
02/15/2023
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Brand Selection for Medically Necessary Indications

Prostate Cancer Indication Only

As defined in Aetna commercial policies, health care services are not medically necessary when they are more costly than alternative services that are at least as likely to produce equivalent therapeutic or diagnostic results. Camcevi (leuprolide mesylate), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin), and Zoladex (goserelin) are

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more costly to Aetna than other gonadotropin-releasing hormone analogs and antagonists for certain indications. There is a lack of reliable evidence that Camcevi (leuprolide mesylate), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin), and Zoladex (goserelin) are superior to the lower cost gonadotropin-releasing hormone analogs and antagonists, Eligard (leuprolide acetate) and Firmagon (degarelix), for the medically necessary indication of prostate cancer. Therefore, Aetna considers Camcevi (leuprolide mesylate), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin), and Zoladex (goserelin) to be medically necessary only for members who have a contraindication, intolerance or ineffective response to the available equivalent alternative gonadotropin-releasing hormone analogs and antagonists, Eligard (leuprolide acetate) and Firmagon (degarelix) for prostate cancer.

Policy

Note: Requires Precertification:

Precertification of cetrorelix acetate (Cetrotide), degarelix (Firmagon), ganirelix acetate (Ganirelix AC), goserelin acetate implant (Zoladex), leuprolide acetate (Eligard), leuprolide acetate, 7.5 mg (Lupron Depot), leuprolide mesylate (Camcevi), and triptorelin (Trelstar) is required of all Aetna participating providers and members in applicable plan designs. For precertification, call (866) 752-7021 (Commercial), (866) 503-0857 (Medicare), or fax (888) 267-3277.

Cetrorelix Acetate (Cetrotide) and Ganirelix Acetate (e.g., Fyremadel)

I. *Criteria for Initial Approval*

Aetna considers cetrorelix acetate or ganirelix medically necessary for the inhibition of premature LH surges in members undergoing ovulation induction or assisted reproductive technology (ART).

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational or Not Medically Necessary, and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of cetrorelix acetate or ganirelix therapy medically necessary for all members (including new members) requesting authorization for continuation of therapy who meet all initial authorization criteria.

Note: Coverage of GnRH antagonists for this indication is limited to plans that cover advanced reproductive technologies. Please check benefit plan descriptions for details.

Degarelix (Firmagon)

I. *Criteria for Initial Approval*

Aetna considers degarelix (Firmagon) medically necessary for the treatment of prostate cancer.

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational or Not Medically Necessary, and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of degarelix (Firmagon) therapy medically necessary in members requesting reauthorization who are experiencing clinical benefit to therapy (e.g., serum testosterone less than 50 ng/dL) and who have not experienced an unacceptable toxicity.

Goserelin (Zoladex)

I. *Criteria for Initial Approval*

Aetna considers goserelin (Zoladex) medically necessary for *any* of the following indications:

A. Breast cancer - for treatment of hormone receptor-positive breast cancer; *or*
B. Prostate cancer - for treatment of prostate cancer; *or*
C. Endometriosis - total of 6 months of treatment for endometriosis; *or*
D. Endometrial - thinning agent:

1. For endometrial thinning (2 doses) prior to endometrial ablation or resection for dysfunctional uterine bleeding; *or*
2. Total of 6 months of treatment for chronic anovulatory uterine bleeding with severe anemia; *or*

E. Gender dysphoria

1. Pubertal hormonal suppression in an adolescent member when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member has reached Tanner stage 2 of puberty or greater; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*
   e. The member has been informed of fertility preservation options; *and*
   f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

2. Gender transition when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*

b. The member will receive Zoladex concomitantly with gender-affirming hormones; *and*
c. The member's comorbid conditions are reasonably controlled; *and*
d. The member has been educated on any contraindications and side effects to therapy; *and*
e. The member has been informed of fertility preservation options; *and*
f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

F. Preservation of ovarian function when the member is premenopausal and undergoing chemotherapy; *or*
G. Prevention of recurrent menstrual related attacks in members with acute porphyria when the requested medication is prescribed by or in consultation with a physician experienced in the management of porphyrias; *or*
H. Uterine leiomyomata (fibroids) - total of 3 months of treament prior to surgery.

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational or Not Medically Necessary, and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of goserelin therapy medically necessary in members requesting reauthorization who meet *any* of the following criteria:

A. Breast cancer - are experiencing clinical benefit to therapy and who have not experienced an unacceptable toxicity; *or*
B. Prostate cancer - are experiencing clinical benefit to therapy (e.g., serum testosterone less than 50 ng/dL) and who have not experienced an unacceptable toxicity; or

C. Gender dysphoria -

1. For continued treatment for pubertal hormonal suppression in adolescent members requesting reauthorization when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member has previously reached Tanner stage 2 of puberty or greater; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*
   e. Before the start of therapy, the member has been informed of fertility preservation options; *and*
   f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

2. For continued treatment for gender transition in members requesting reauthorization when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member will receive Zoladex concomitantly with gender-affirming hormones; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*
   e. Before the start of therapy, the member has been informed of fertility preservation options; *and*
   f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has

collaborated care with a mental health care provider for members less than 18 years of age.

D. All members (including new members) requesting authorization for continuation of therapy for the specified indications below must meet all initial authorization criteria:

1. Endometriosis;
2. Endometrial-thinning agent;
3. Preservation of ovarian function;
4. Prevention of recurrent menstrual related attacks in acute porphyria;
5. Uterine leiomyomata (fibroids).

Histrelin (Supprelin LA)

I. *Criteria for Initial Approval*

Aetna considers histrelin acetate subcutaneous implant (Supprelin LA) medically necessary for the following indications:

A. Central precocious puberty (CPP) in a female member when *all* of the following criteria are met:

1. Intracranial tumor has been evaluated by appropriate lab tests and diagnostic imaging, such as computed tomography (CT scan), magnetic resonance imaging (MRI), or ultrasound; *and*
2. The diagnosis of CPP has been confirmed by a pubertal response to a gonadotropin releasing hormone (GnRH) agonist test or a pubertal level of a third-generation luteinizing hormone (LH) assay; *and*
3. The assessment of bone age versus chronological age supports the diagnosis of CPP; *and*
4. The member was less than 8 years of age at the onset of secondary sexual characteristics;

B. Central precocious puberty (CPP) in a male member when *all* of the following criteria are met:

1. Intracranial tumor has been evaluated by appropriate lab tests and diagnostic imaging, such as CT scan, MRI, or ultrasound; *and*
2. The diagnosis of CPP has been confirmed by a pubertal response to a GnRH agonist test or a pubertal level of a third-generation LH assay; *and*
3. The assessment of bone age versus chronological age supports the diagnosis of CPP; *and*
4. The member was less than 9 years of age at the onset of secondary sexual characteristics;

C. Gender dysphoria

1. For pubertal hormonal suppression in an adolescent member when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member has reached Tanner stage 2 of puberty or greater; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*
   e. The member has been informed of fertility preservation options; *and*
   f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

2. For gender transition when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member will receive Supprelin LA concomitantly with gender-affirming hormones; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*

d. The member has been educated on any contraindications and side effects to therapy; *and*

e. The member has been informed of fertility preservation options; *and*

f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

D. Preservation of ovarian function when the member is premenopausal and undergoing chemotherapy;

E. Prevention of recurrent menstrual related attacks in members with acute porphyria when the requested medication is prescribed by or in consultation with a physician experienced in the management of porphyrias.

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational or Not Medically Necessary, and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of Supprelin LA therapy medically necessary for the following indications when criteria are met:

A. Central precocious puberty (CPP)

1. CPP in a female member if the member is currently less than 12 years of age and the member meets *both* of the following:

a. The member is currently receiving the requested medication through a previously authorized pharmacy or medical benefit; *and*

b. The member is not experiencing treatment failure such as clinical pubertal progression, lack of growth deceleration, and continued excessive bone age advancement;

2. CPP in a male member if the member is currently less than 13 years of age and the member meets *both* of the following:

   a. The member is currently receiving the requested medication through a previously authorized pharmacy or medical benefit; *and*
   b. The member is not experiencing treatment failure such as clinical pubertal progression, lack of growth deceleration, and continued excessive bone age advancement;

B. Gender dysphoria

1. For continued treatment for pubertal hormonal suppression in adolescent members when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member has previously reached Tanner stage 2 of puberty or greater; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*
   e. Before the start of therapy, the member has been informed of fertility preservation options; *and*
   f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

2. For continued treatment for gender transition in members when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*

b. The member will receive Supprelin LA concomitantly with gender-affirming hormones; *and*
c. The member's comorbid conditions are reasonably controlled; *and*
d. The member has been educated on any contraindications and side effects to therapy; *and*
e. Before the start of therapy, the member has been informed of fertility preservation options; *and*
f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age;

C. All other indications when all members (including new members) meet all initial selection criteria.

Leuprolide Acetate (Subcutaneous Injection)

I. *Criteria for Initial Approval*

Aetna considers leuprolide acetate subcutaneous injection medically necessary for the following indications:

A. Central precocious puberty (CPP) in a female member when *all* of the following criteria are met:

1. Intracranial tumor has been evaluated by appropriate lab tests and diagnostic imaging, such as computed tomography (CT scan), magnetic resonance imaging (MRI), or ultrasound; *and*
2. The diagnosis of CPP has been confirmed by a pubertal response to a gonadotropin releasing hormone (GnRH) agonist test or a pubertal level of a third-generation luteinizing hormone (LH) assay; *and*
3. The assessment of bone age versus chronological age supports the diagnosis of CPP; *and*
4. The member was less than 8 years of age at the onset of secondary sexual characteristics;

B. Central precocious puberty (CPP) in a male member when *all* of the following criteria are met:

1. Intracranial tumor has been evaluated by appropriate lab tests and diagnostic imaging, such as CT scan, MRI, or ultrasound; *and*
2. The diagnosis of CPP has been confirmed by a pubertal response to a GnRH agonist test or a pubertal level of a third generation LH assay; *and*
3. The assessment of bone age versus chronological age supports the diagnosis of CPP; *and*
4. The member was less than 9 years of age at the onset of secondary sexual characteristics;

C. Stimulation test for CPP diagnosis - one dose for use as a stimulation test to confirm the diagnosis of CPP;

D. Advancing puberty and growth failure in a pediatric member when leuprolide acetate is used in combination with growth hormone;

E. Prostate cancer treatment;

F. Salivary gland tumors - for treatment of recurrent salivary gland tumors as a single agent when the tumor is androgen receptor positive;

G. Inhibition of premature luteinizing hormone (LH) surge in a member undergoing ovulation induction or assisted reproductive technology (ART);

H. Oocyte maturation and ovulation trigger - in a member undergoing ovulation induction or assisted reproductive technology (ART).

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational or Not Medically Necessary, and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of leuprolide acetate subcutaneous injection therapy medically necessary for the following indications:

A. Central precocious puberty (CPP)

1. CPP in a female member if the member is currently less than 12 years of age and the member meets *both* of the following:

   a. The member is currently receiving the requested medication through a previously authorized pharmacy or medical benefit; *and*
   b. The member is not experiencing treatment failure such as clinical pubertal progression, lack of growth deceleration, and continued excessive bone age advancement;

2. CPP in a male member if the member is currently less than 13 years of age and the member meets *both* of the following:

   a. The member is currently receiving the requested medication through a previously authorized pharmacy or medical benefit; *and*
   b. The member is not experiencing treatment failure such as clinical pubertal progression, lack of growth deceleration, and continued excessive bone age advancement;

B. Salivary gland tumors - for members who are experiencing clinical benefit to therapy and who have not experienced an unacceptable toxicity;
C. Prostate cancer - for members who are experiencing clinical benefit to therapy (e.g., serum testosterone less than 50 ng/dL) and who have not experienced an unacceptable toxicity;
D. All members (including new members) with the specified indications below must meet all initial selection criteria:

1. Stimulation test for CPP diagnosis
2. Advancing puberty and growth failure
3. Inhibition of premature LH surge
4. Oocyte maturation and ovulation trigger.

Leuprolide Acetate (Eligard)

I. *Criteria for Initial Approval*

Aetna considers leuprolide acetate subcutaneous injection (Eligard) medically necessary for the following indications:

A. Prostate cancer treatment;
B. Gender dysphoria

1. For pubertal hormonal suppression in an adolescent member when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member has reached Tanner stage 2 of puberty or greater; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*
   e. The member has been informed of fertility preservation options; *and*
   f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age;

2. For gender transition when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member will receive Eligard concomitantly with gender-affirming hormones; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*

e. The member has been informed of fertility preservation options; *and*

f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age;

C. Salivary gland tumors - treatment of recurrent salivary gland tumors as a single agent when the tumor is androgen receptor positive.

Aetna considers all other indications as experimental and investigational.

II. *Continuation of Therapy*

Aetna considers continuation of leuprolide acetate subcutaneous injection (Eligard) therapy medically necessary in members requesting reauthorization for the following indications when criteria are met:

A. Salivary gland tumors - and experiencing clinical benefit to therapy and who have not experienced an unacceptable toxicity;

B. Prostate cancer - and experiencing clinical benefit to therapy (e.g., serum testosterone less than 50 ng/dL) and who have not experienced an unacceptable toxicity;

C. Gender dysphoria -

1. For continued treatment for pubertal hormonal suppression in adolescent members requesting reauthorization when *all* of the following criteria are met:

a. The member has a diagnosis of gender dysphoria; *and*

b. The member has previously reached Tanner stage 2 of puberty or greater; *and*

c. The member's comorbid conditions are reasonably controlled; *and*

d. The member has been educated on any contraindications and side effects to therapy; *and*
e. Before the start of therapy, the member has been informed of fertility preservation options; *and*
f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

2. For continued treatment for gender transition in members requesting reauthorization when *all* of the following criteria are met:

a. The member has a diagnosis of gender dysphoria; *and*
b. The member will receive Eligard concomitantly with gender-affirming hormones; *and*
c. The member's comorbid conditions are reasonably controlled; *and*
d. The member has been educated on any contraindications and side effects to therapy; *and*
e. Before the start of therapy, the member has been informed of fertility preservation options; *and*
f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age.

Leuprolide Acetate (Fensolvi)

I. *Criteria for Initial Approval*

Aetna considers leuprolide acetate subcutaneous injection (Fensolvi) medically necessary for the following indications:

A. Central precocious puberty (CPP) in a female member when *all* of the following criteria are met:

1. Intracranial tumor has been evaluated by appropriate lab tests and diagnostic imaging, such as computed tomography (CT scan), magnetic resonance imaging (MRI), or ultrasound; *and*
2. The diagnosis of CPP has been confirmed by a pubertal response to a gonadotropin releasing hormone (GnRH) agonist test or a pubertal level of a third generation luteinizing hormone (LH) assay; *and*
3. The assessment of bone age versus chronological age supports the diagnosis of CPP; *and*
4. The member was less than 8 years of age at the onset of secondary sexual characteristics;

B. Central precocious puberty (CPP) in a male member when *all* of the following criteria are met:

1. Intracranial tumor has been evaluated by appropriate lab tests and diagnostic imaging, such as CT scan, MRI, or ultrasound; *and*
2. The diagnosis of CPP has been confirmed by a pubertal response to a GnRH agonist test or a pubertal level of a third generation LH assay; *and*
3. The assessment of bone age versus chronological age supports the diagnosis of CPP; *and*
4. The member was less than 9 years of age at the onset of secondary sexual characteristics;

C. Gender dysphoria

1. For pubertal hormonal suppression in an adolescent member when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria *and*
   b. The member has reached Tanner stage 2 of puberty or greater; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*

e. The member has been informed of fertility preservation options; *and*

f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

2. For gender transition when *all* of the following criteria are met:

a. The member has a diagnosis of gender dysphoria; *and*

b. The member will receive Fensolvi concomitantly with gender-affirming hormones; *and*

c. The member's comorbid conditions are reasonably controlled; *and*

d. The member has been educated on any contraindications and side effects to therapy; *and*

e. The member has been informed of fertility preservation options; *and*

f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age.

Aetna considers all other indications as experimental and investigational.

II. *Continuation of Therapy*

Aetna considers continuation of leuprolide acetate subcutaneous injection (Fensolvi) therapy medically necessary for the following indications:

A. Central precocious puberty (CPP)

1. CPP in a female member if the member is currently less than 12 years of age and the member meets *both* of the following:

   a. The member is currently receiving the requested medication through a previously authorized pharmacy or medical benefit; *and*
   b. The member is not experiencing treatment failure such as clinical pubertal progression, lack of growth deceleration, and continued excessive bone age advancement;

2. CPP in male member if the member is currently less than 13 years of age and the member meets *both* of the following:

   a. The member is currently receiving the requested medication through a previously authorized pharmacy or medical benefit; *and*
   b. The member is not experiencing treatment failure such as clinical pubertal progression, lack of growth deceleration, and continued excessive bone age advancement;

B. Gender dysphoria

1. For continued treatment for pubertal hormonal suppression in adolescent members when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member has previously reached Tanner stage 2 of puberty or greater; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*
   e. Before the start of therapy, the member has been informed of fertility preservation options; and
   f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender

youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

2. For continued treatment for gender transition in members when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member will receive Fensolvi concomitantly with gender-affirming hormones; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*
   e. Before the start of therapy, the member has been informed of fertility preservation options; *and*
   f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age.

Leuprolide Acetate for Depot Suspension (Lupron Depot: 3.75 mg, 3-Month 11.25 mg)

I. *Criteria for Initial Approval*

Aetna considers Lupron Depot 3.75 mg or 3-month 11.25 mg intramuscular injection medically necessary for the following indications when applicable criteria are met:

A. Endometriosis - for initial treatment of endometriosis;
B. Uterine leiomyomata (fibroids) - initial treatment when *either* of the following criteria is met:

   1. Member has anemia due to uterine leiomyomata; *or*
   2. Lupron Dept will be used prior to surgery for uterine leiomyomata;

C. Breast cancer - for treatment of hormone receptor-positive breast cancer;

D. Ovarian cancer - for treatment of persistent disease or recurrence of *any* of the following types of ovarian cancer when used as a single agent:

1. Epithelial ovarian cancer;
2. Fallopian tube cancer;
3. Primary peritoneal cancer;
4. Grade 1 endometrioid carcinoma;
5. Low-grade serous carcinoma;
6. Carcinosarcoma (malignant mixed Müllerian tumors);
7. Mucinous carcinoma of the ovary;
8. Clear cell carcinoma of the ovary;

E. Salivary gland tumors - for treatment of recurrent salivary gland tumors when the tumor is androgen receptor positive;

F. Gender dysphoria

1. For pubertal hormonal suppression in an adolescent member when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member has reached Tanner stage 2 of puberty or greater; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*
   e. The member has been informed of fertility preservation options; *and*
   f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

2. For gender transition when *all* of the following criteria are met:

a. The member has a diagnosis of gender dysphoria; *and*
b. The member will receive Lupron Depot concomitantly with gender-affirming hormones; *and*
c. The member's comorbid conditions are reasonably controlled; *and*
d. The member has been educated on any contraindications and side effects to therapy; *and*
e. The member has been informed of fertility preservation options; *and*
f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

G. Preservation of ovarian function in members with cancer when the member is premenopausal and undergoing chemotherapy;
H. Prevention of recurrent menstrual related attacks in members with acute porphyria when the requested medication is prescribed by or in consultation with a physician experienced in the management of porphyrias.

Aetna considers all other indications as experimental and investigational.

II. *Continuation of Therapy*

Aetna considers continuation of Lupron Depot 3.75 mg or 3-month 11.25 mg intramuscular injection therapy medically necessary for the following indications when criteria are met:

A. Endometriosis - for retreatment of endometriosis (for a lifetime maximum of 12 months total) when *all* of the following criteria are met:

1. The member has had a recurrence of symptoms; *and*

2. The member has a bone mineral density within normal limits;

B. Uterine leiomyomata (fibroids) - for a lifetime maximum of 6 months total) when *either* of the following criteria is met:

1. Member has anemia due to uterine leiomyomata; *or*
2. Lupron Depot will be used prior to surgery for uterine leiomyomata;

C. Breast cancer and ovarian cancer when there is no evidence of unacceptable toxicity or disease progression while on the current regimen;

D. Salivary gland tumors when there is no evidence of unacceptable toxicity or disease progression while on the current regimen;

E. Gender dysphoria

1. For continued treatment for pubertal hormonal suppression in adolescent members when *all* of the following criteria are met:

a. The member has a diagnosis of gender dysphoria; *and*
b. The member has previously reached Tanner stage 2 of puberty or greater; *and*
c. The member's comorbid conditions are reasonably controlled; *and*
d. The member has been educated on any contraindications and side effects to therapy; *and*
e. Before the start of therapy, the member has been informed of fertility preservation options; *and*
f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

2. For continued treatment for gender transition in members when *all* of the following criteria are met:

a. The member has a diagnosis of gender dysphoria; *and*
b. The member will receive Lupron Depot concomitantly with gender-affirming hormones; *and*
c. The member's comorbid conditions are reasonably controlled; *and*
d. The member has been educated on any contraindications and side effects to therapy; *and*
e. Before the start of therapy, the member has been informed of fertility preservation options; *and*
f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age;

F. All members (including new members) with the specified indication below must meet *all* initial selection criteria:

1. Preservation of ovarian function in members with cancer; *and*
2. Prevention of recurrent menstrual related attacks in acute porphyria.

Leuprolide Acetate for Depot Suspension (Lupron Depot: 1-Month 7.5 mg, 3-Month 22.5 mg, 4-Month 30 mg, 6-Month 45 mg)

I. *Criteria for Initial Approval*

Aetna considers Lupron Depot 1-Month 7.5 mg, 3-Month 22.5 mg, 4-Month 30 mg, or 6-Month 45 mg intramuscular injection, medically necessary for the following indications when applicable criteria are met:

A. Prostate cancer treatment;
B. Gender dysphoria

1. For pubertal hormonal suppression in an adolescent member when *all* of the following criteria are met:

a. The member has a diagnosis of gender dysphoria; *and*
b. The member has reached Tanner stage 2 of puberty or greater; *and*
c. The member's comorbid conditions are reasonably controlled; *and*
d. The member has been educated on any contraindications and side effects to therapy; *and*
e. The member has been informed of fertility preservation options; *and*
f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

2. For gender transition when all of the following criteria are met:

a. The member has a diagnosis of gender dysphoria; *and*
b. The member will receive Lupron Depot concomitantly with gender-affirming hormones; *and*
c. The member's comorbid conditions are reasonably controlled; *and*
d. The member has been educated on any contraindications and side effects to therapy; *and*
e. The member has been informed of fertility preservation options; *and*
f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

C. Ovarian cancer - for treatment of malignant sex cord-stromal tumors (granulosa cell tumors) as a single agent;
D. Recurrent salivary gland tumors as a single agent when the tumor is androgen receptor positive.

Aetna considers all other indications as experimental and investigational.

II. *Continuation of Therapy*

Aetna considers continuation of Lupron Depot 1-Month 7.5 mg, 3-Month 22.5 mg, 4-Month 30 mg, or 6-Month 45 mg therapy medically necessary for members requesting reauthorization for the following indications when criteria are met:

A. Prostate cancer - for members experiencing clinical benefit to therapy (e.g., serum testosterone less than 50 ng/dL) and who have not experienced an unacceptable toxicity;
B. Gender dysphoria -

1. For continued treatment for pubertal hormonal suppression in adolescent members requesting reauthorization when *all* of the following criteria are met:

a. The member has a diagnosis of gender dysphoria; *and*
b. The member has previously reached Tanner stage 2 of puberty or greater; *and*
c. The member's comorbid conditions are reasonably controlled; *and*
d. The member has been educated on any contraindications and side effects to therapy; *and*
e. Before the start of therapy, the member has been informed of fertility preservation options; *and*
f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

2. For continued treatment for gender transition in members requesting reauthorization when *all* of the following criteria are met:

a. The member has a diagnosis of gender dysphoria; *and*

b. The member will receive Lupron Depot concomitantly with gender-affirming hormones; *and*
c. The member's comorbid conditions are reasonably controlled; *and*
d. The member has been educated on any contraindications and side effects to therapy; and
e. Before the start of therapy, the member has been informed of fertility preservation options; *and*
f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age;

C. Ovarian cancer - malignant sex cord-stromal tumors (granulosa cell tumors) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen;
D. Salivary gland tumors - for members who are experiencing clinical benefit to therapy and who have not experienced an unacceptable toxicity.

Leuprolide Acetate for Depot Suspension-Pediatric (Lupron Depot-PED)

I. *Criteria for Initial Approval*

Aetna considers Lupron Depot-PED medically necessary for the following indications:

A. Central precocious puberty (CPP) in a female member when *all* of the following criteria are met:

1. Intracranial tumor has been evaluated by appropriate lab tests and diagnostic imaging, such as computed tomography (CT scan), magnetic resonance imaging (MRI), or ultrasound; *and*
2. The diagnosis of CPP has been confirmed by a pubertal response to a gonadotropin releasing hormone (GnRH)

agonist test or a pubertal level of a third-generation luteinizing hormone (LH) assay; *and*

3. The assessment of bone age versus chronological age supports the diagnosis of CPP; *and*
4. The member was less than 8 years of age at the onset of secondary sexual characteristics;

B. Central precocious puberty (CPP) in a male member when *all* of the following criteria are met:

1. Intracranial tumor has been evaluated by appropriate lab tests and diagnostic imaging, such as CT scan, MRI, or ultrasound; *and*
2. The diagnosis of CPP has been confirmed by a pubertal response to a GnRH agonist test or a pubertal level of a third generation LH assay; *and*
3. The assessment of bone age versus chronological age supports the diagnosis of CPP; *and*
4. The member was less than 9 years of age at the onset of secondary sexual characteristics;

C. Gender dysphoria

1. For pubertal hormonal suppression in an adolescent member when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member has reached Tanner stage 2 of puberty or greater; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*
   e. The member has been informed of fertility preservation options; *and*
   f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has

collaborated care with a mental health care provider for members less than 18 years of age; *or*

2. For gender transition when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member will receive Lupron Depot-PED concomitantly with gender-affirming hormones; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*
   e. The member has been informed of fertility preservation options; *and*
   f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age.

Aetna considers all other indications as experimental and investigational.

II. *Continuation of Therapy*

Aetna considers continuation of Lupron Depot-PED therapy medically necessary for the following indications:

A. Central precocious puberty (CPP)

1. CPP in a female member if the member is currently less than 12 years of age and the member meets *both* of the following:

   a. The member is currently receiving the requested medication through a previously authorized pharmacy or medical benefit; *and*
   b. The member is not experiencing treatment failure such as clinical pubertal progression, lack of growth

deceleration, and continued excessive bone age advancement;

2. CPP in a male member if the member is currently less than 13 years of age and the member meets *both* of the following:

   a. The member is currently receiving the requested medication through a previously authorized pharmacy or medical benefit; *and*
   b. The member is not experiencing treatment failure such as clinical pubertal progression, lack of growth deceleration, and continued excessive bone age advancement;

B. Gender dysphoria - all members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

C. Gender dysphoria -

1. For continued treatment for pubertal hormonal suppression in adolescent members when *all* of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member has previously reached Tanner stage 2 of puberty or greater; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*
   e. Before the start of therapy, the member has been informed of fertility preservation options; *and*
   f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

2. For continued treatment for gender transition in members when all of the following criteria are met:

   a. The member has a diagnosis of gender dysphoria; *and*
   b. The member will receive Lupron Depot-PED concomitantly with gender-affirming hormones; *and*
   c. The member's comorbid conditions are reasonably controlled; *and*
   d. The member has been educated on any contraindications and side effects to therapy; *and*
   e. Before the start of therapy, the member has been informed of fertility preservation options; *and*
   f. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age.

Leuprolide Acetate for Depot Suspension / Norethindrone Acetate (Lupaneta Pack)

I. *Criteria for Initial Approval*

Aetna considers the Lupaneta Pack medically necessary for initial treatment of endometriosis.

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational or Not Medically Necessary, and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of Lupaneta Pack therapy (for a lifetime maximum of 12 months total) medically necessary for retreatment of endometriosis when *all* of the following criteria are met:

A. The member has had a recurrence of symptoms; *and*

B. The member has a bone mineral density within normal limits.

Leuprolide Mesylate (Camcevi)

I. *Criteria for Initial Approval*

Aetna considers leuprolide mesylate (Camcevi) subcutaneous injection medically necessary for the treatment of prostate cancer.

Aetna considers all other indications as experimental and investigational.

II. *Continuation of Therapy*

Aetna considers continued leuprolide mesylate (Camcevi) therapy medically necessary for members with prostate cancer who are experiencing clinical benefit to therapy (e.g. serum testosterone less than 50 ng/dL) and who have not experienced an unacceptable toxicity.

Triptorelin (Trelstar; Triptodur)

I. *Trelstar (triptorelin)*

A. Criteria for Initial Approval

Aetna considers triptorelin (Trelstar) medically necessary for the following indications:

1. Prostate cancer treatment;
2. Preservation of ovarian function when member is premenopausal and undergoing chemotherapy;
3. Breast cancer - ovarian suppression: for ovarian suppression in premenopausal members with hormone-receptor positive breast cancer at higher risk for recurrence (e.g., young age, high-grade tumor, lymph-node involvement) when used in combination with endocrine therapy.

4. Gender dysphoria

a. For pubertal hormonal suppression in an adolescent member when *all* of the following criteria are met:

i. The member has a diagnosis of gender dysphoria; *and*
ii. The member has reached Tanner stage 2 of puberty or greater; *and*
iii. The member's comorbid conditions are reasonably controlled; *and*
iv. The member has been educated on any contraindications and side effects to therapy; *and*
v. The member has been informed of fertility preservation options; *and*
vi. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

b. For gender transition when *all* of the following criteria are met:

i. The member has a diagnosis of gender dysphoria; *and*
ii. The member will receive Trelstar concomitantly with gender-affirming hormones; *and*
iii. The member's comorbid conditions are reasonably controlled; *and*
iv. The member has been educated on any contraindications and side effects to therapy; *and*
v. The member has been informed of fertility preservation options; *and*
vi. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist,

family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age.

Aetna considers all other indications as experimental and investigational.

B. Continuation of Therapy

Aetna considers continuation of Trelstar therapy medically necessary in all members (including new members) requesting reauthorization when the member meets the following criteria:

1. Prostate cancer - for members who are experiencing clinical benefit to therapy (e.g., serum testosterone less than 50 ng/dL) and who have not experienced an unacceptable toxicity;
2. Breast cancer - ovarian suppression: up to 5 years total for members requesting reauthorization who were premenopausal at diagnosis and are still undergoing treatment with endocrine therapy;
3. Gender dysphoria -

   a. For continued treatment for pubertal hormonal suppression in adolescent members requesting reauthorization when *all* of the following criteria are met:

      i. The member has a diagnosis of gender dysphoria; *and*
      ii. The member has previously reached Tanner stage 2 of puberty or greater; *and*
      iii. The member's comorbid conditions are reasonably controlled; *and*
      iv. The member has been educated on any contraindications and side effects to therapy; *and*
      v. Before the start of therapy, the member has been informed of fertility preservation options; *and*

vi. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

b. For continued treatment for gender transition in members requesting reauthorization when *all* of the following criteria are met:

i. The member has a diagnosis of gender dysphoria; *and*
ii. The member will receive Trelstar concomitantly with gender-affirming hormones; *and*
iii. The member's comorbid conditions are reasonably controlled; *and*
iv. The member has been educated on any contraindications and side effects to therapy; *and*
v. Before the start of therapy, the member has been informed of fertility preservation options; *and*
vi. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age.

II. *Triptodur (triptorelin)*

A. Criteria for Initial Approval

Aetna considers triptorelin extended-release injectable suspension (Triptodur) medically necessary for the following indications:

1. Central precocious puberty (CPP) in a female member when *all* of the following criteria are met:

a. Intracranial tumor has been evaluated by appropriate lab tests and diagnostic imaging, such as computed tomography (CT scan), magnetic resonance imaging (MRI), or ultrasound; *and*
b. The diagnosis of CPP has been confirmed by a pubertal response to a gonadotropin releasing hormone (GnRH) agonist test or a pubertal level of a third generation luteinizing hormone (LH) assay; *and*
c. The assessment of bone age versus chronological age supports the diagnosis of CPP; *and*
d. The member was less than 8 years of age at the onset of secondary sexual characteristics;

2. Central precocious puberty (CPP) in a male member when *all* of the following criteria are met:

a. Intracranial tumor has been evaluated by appropriate lab tests and diagnostic imaging, such as CT scan, MRI, or ultrasound; *and*
b. The diagnosis of CPP has been confirmed by a pubertal response to a GnRH agonist test or a pubertal level of a third generation LH assay; *and*
c. The assessment of bone age versus chronological age supports the diagnosis of CPP; *and*
d. The member was less than 9 years of age at the onset of secondary sexual characteristics;

3. Gender dysphoria

a. For pubertal hormonal suppression in an adolescent member when *all* of the following criteria are met:

i. The member has a diagnosis of gender dysphoria; *and*
ii. The member has reached Tanner stage 2 of puberty or greater; *and*
iii. The member's comorbid conditions are reasonably controlled; *and*
iv. The member has been educated on any contraindications and side effects to therapy; *and*

v. The member has been informed of fertility preservation options; *and*

vi. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

b. For gender transition when *all* of the following criteria are met:

i. The member has a diagnosis of gender dysphoria; *and*

ii. The member will receive Triptodur concomitantly with gender-affirming hormones; *and*

iii. The member's comorbid conditions are reasonably controlled; *and*

iv. The member has been educated on any contraindications and side effects to therapy; *and*

v. The member has been informed of fertility preservation options; *and*

vi. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

4. Preservation of ovarian function when the member is premenopausal and undergoing chemotherapy;
5. For prevention of recurrent menstrual related attacks in members with acute porphyria when the requested medication is prescribed by or in consultation with a physician experienced in the management of porphyrias.

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational or Not Medically Necessary, and

Background sections).

B. Continuation of Therapy

Aetna considers continued treatment with continuation of Triptodur therapy medically necessary in members requesting reauthorization for the following indications when criteria are met:

1. Central precocious puberty (CPP)

   a. CPP in a female member if the member is currently less than 12 years of age and the member meets *both* of the following:

      i. The member is currently receiving the requested medication through a previously authorized pharmacy or medical benefit; *and*
      ii. The member is not experiencing treatment failure such as clinical pubertal progression, lack of growth deceleration, and continued excessive bone age advancement;

   b. CPP in a male member if the member is currently less than 13 years of age and the member meets *both* of the following:

      i. The member is currently receiving the requested medication through a previously authorized pharmacy or medical benefit; *and*
      ii. The member is not experiencing treatment failure such as clinical pubertal progression, lack of growth deceleration, and continued excessive bone age advancement;

2. Gender dysphoria -

   a. For continued treatment for pubertal hormonal suppression in adolescent members when *all* of the following criteria are met:

i. The member has a diagnosis of gender dysphoria; *and*

ii. The member has previously reached Tanner stage 2 of puberty or greater; *and*

iii. The member's comorbid conditions are reasonably controlled; *and*

iv. The member has been educated on any contraindications and side effects to therapy; *and*

v. Before the start of therapy, the member has been informed of fertility preservation options; *and*

vi. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age; *or*

b. For continued treatment for gender transition in members when all of the following criteria are met:

i. The member has a diagnosis of gender dysphoria; *and*

ii. The member will receive Triptodur concomitantly with gender-affirming hormones; *and*

iii. The member's comorbid conditions are reasonably controlled; *and*

iv. The member has been educated on any contraindications and side effects to therapy; *and*

v. Before the start of therapy, the member has been informed of fertility preservation options; *and*

vi. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist) that has collaborated care with a mental health care provider for members less than 18 years of age;

3. All other indications for all members (including new members) who meet all initial selection criteria.

Related Policies

For nafarelin acetate (Synarel), see Specialty Pharmacy Clinical Policy Bulletin:
Synarel 2984-A, 3157-A, 3158-A Supplemental Specialty PA (https://www.aetna.com/products/rxnonmedicare/data/2022/Synarel_2984-A,_3157-A,_3158-A_Supplemental_Specialty_PA_P2021a.html)

See also:

- CPB 0327 - Infertility (../300_399/0327.html)
- CPB 0345 - Implantable Hormone Pellets (../300_399/0345.html)

Dosage and Administration

Below includes dosing recommendations as per the FDA-approved prescribing information. Please see full prescribing information for dose modification and monitoring recommendations.

Camcevi

Camcevi is supplied as a kit with a pre-filled, single-dose, sterile syringe for subcutaneous injection. Each pre-filled syringe delivers 42 mg leuprolide (equivalent to approximately 48 mg leuprolide mesylate). Camcevi must be administered by a healthcare provider.

For advanced prostate cancer, the recommended dose of Camcevi is 42 mg administered subcutaneously once every 6 months.

Source: Foresee Pharmaceuticals, 2021a

Cetrotide

Cetrotide (cetrorelix acetate for injection) is supplied as 0.25 mg in a carton of one packaged tray, for subcutaneous use. Cetrotide can be self-administered after appropriate instructions by healthcare provider.

Ovarian stimulation therapy with gonadotropins (FSH, hMG) is started on cycle Day 2 or 3. The dose of gonadotropins should be adjusted according to individual response. Cetrotide (cetrorelix acetate for injection) may be administered subcutaneously either once daily (0.25 mg dose) or once (3 mg dose) during the early- to mid-follicular phase.

See full Prescribing Information for additional dosage and administration detail.

Source: EMD Serono, May 2018

Eligard

Eligard (leuprolide acetate injectable suspension) is supplied in the following strengths: 7.5 mg, 22.5 mg, 30 mg, and 45 mg, for subcutaneous use.

For the palliative treatment of advanced prostate cancer. The recommended dosages include:

- 7.5 mg subcutaneously every month
- 22.5 mg subcutaneously every 3 months
- 30 mg subcutaneously every 4 months
- 45 mg subcutaneously every 6 months.

Source: Tolmar Pharmaceuticals, 2019

Fensolvi

Fensolvi (leuprolide acetate injectable suspension) is available as a 45 mg subcutaneous injection. Fensolvi must be administered by a healthcare professional.

For Central Precocious Puberty (CPP), the recommended dosage is 45 mg subcutaneously every 6 months.

Source: Tolmar Pharmaceuticals, 2020.

Firmagon

Firmagon (degarelix for injection) is supplied as the following for subcutanous use only and is to be administered by a healthcare professional:

- Firmagon (240 mg): Two single-dose vials each delivering 120 mg of degarelix in a lyophilized powder for reconstitution supplied with diluent in two prefilled syringes; or
- Firmagon (80 mg): One single-dose vial delivering 80 mg of degarelix in a lyophilized powder for reconstitution supplied with diluent in one prefilled syringe.

Advanced prostate cancer: The recommended starting dose is 240 mg given as two subcutaneous injections of 120 mg each at a concentration of 40 mg/mL. The first maintenance dose should be given 28 days after the starting dose: 80 mg given as one subcutaneous injection at a concentration of 20 mg/mL.

Source: Ferring Pharmaceuticals, 2020

Ganirelix Acetate

After initiating FSH therapy on Day 2 or 3 of the cycle, Ganirelix Acetate Injection 250 mcg may be administered subcutaneously once daily during the mid to late portion of the follicular phase.

Source: Merck, 2020

Leuprolide Acetate (generic; Lupron brand discontinued)

Leuprolide acetate injection is a sterile solution supplied in a 2.8 mL multiple-dose vial.

The recommended dosage for the palliative treatment of advanced prostatic cancer is 1 mg (0.2 mL or 20 unit mark) administered as a single daily subcutaneous injection.

Source: Sandoz, 2021

Lupaneta Pack

Lupaneta Pack contains leuprolide acetate, a gonadotropin-releasing hormone (GnRH) agonist and norethindrone acetate, a progestin, indicated for initial management of the painful symptoms of endometriosis and management of recurrence of symptoms.

Leuprolide acetate for depot suspension 3.75 mg given by a healthcare provider as a single intramuscular injection every month for up to six injections (6 months of therapy).

- Norethindrone acetate 5 mg tablets taken orally by the individual once per day for up to 6 months.
- If endometriosis symptoms recur after initial course of therapy, consider retreatment for up to another six months.

Leuprolide acetate for depot suspension 11.25 mg given by a healthcare provider as a single intramuscular injection every 3 months for up to two injections (6 months of therapy).

- Norethindrone acetate 5 mg tablets taken orally by the individual once per day for up to 6 months.
- If endometriosis symptoms recur after initial course of therapy, consider retreatment for up to another six months.

Source:AbbVie Inc, 2015

Lupron Depot 1-Month 3.75 mg, 3-Month 11.25 mg

Lupron Depot (leuprolide acetate for depot suspension) is available as depot suspension for injection as 3.75 mg or 11.25 mg lyophilized powder for reconstitution in a dual-chamber syringe. The 3.75 mg for 1-month administration has different release characteristics than 11.25 mg for 3-month administration and is dosed differently

Endometriosis: Initial, 3.75 mg intramuscular (IM) depot injection monthly with or without norethindrone acetate 5 mg orally daily for 6 months. Treatment of symptom recurrence, 3.75 mg IM monthly with norethindrone acetate 5 mg orally daily for 6 months; assess bone

mineral density before retreatment; additional treatment after a single retreatment course is not recommended. Initial, 11.25 mg IM depot injection once every 3 months for 1 or 2 doses with or without norethindrone acetate 5 mg orally daily. Treatment of symptom recurrence, 11.25 mg IM once every 3 months for 1 or 2 doses with norethindrone acetate 5 mg orally daily; MAX 12 months total treatment; assess bone mineral density before retreatment; use without add-back therapy with norethindrone is not recommended; additional treatment after a single retreatment course is not recommended.

Uterine Leiomyomata (Fibroids): 3.75 mg IM depot injection once monthly for up to 3 months with concomitant iron therapy; symptoms will recur after therapy discontinuation, if additional treatment is considered, evaluate bone mineral density before therapy re-initiation. Recommended dose of Lupron Depot 11.25 mg is one IM 3-month depot injection with concomitant iron therapy.

Source: AbbVie 2020, 2021

Lupron Depot: 1-Month 7.5 mg, 3-Month 22.5 mg, 4-Month 30 mg, 6-Month 45 mg

Lupron Depot (leuprolide acetate for depot suspension) is available as depot suspension as 7.5 mg, 22.5 mg, 30 mg, and 45 mg injections in a kit with prefilled dual chamber syringe, which must be administered under the supervision of a physician.

Palliative treatment of advanced prostate cancer:

Due to different release characteristics, the dosage strengths are not additive and must be selected based upon the desired dosing schedule.

- Lupron Depot 7.5 mg for 1-month administration, given as a single intramuscular injection every 4 weeks.
- Lupron Depot 22.5 mg for 3-month administration, given as a single intramuscular injection every 12 weeks.
- Lupron Depot 30 mg for 4-month administration, given as a single intramuscular injection every 16 weeks.

- Lupron Depot 45 mg for 6-month administration, given as a single intramuscular injection every 24 weeks.

Source: AbbVie, 2019

Lupron Depot-PED

Lupron Depot-PED (leuprolide acetate for depot suspension-pediatric) is administered as a single intramuscular injection and must be administered by a healthcare professional.

Central Precocious Puberty (CPP): The starting dose 7.5 mg, 11.25 mg, or 15 mg for 1-month administration is based on the child's weight. The doses are either 11.25 mg or 30 mg for 3-month administration.

Source: AbbVie, 2021

Supprelin LA

Supprelin LA is an implant that contains 50 mg histrelin acetate for subcutaneous use. Each implant delivers approximately 65 mcg histrelin acetate per day over 12 months.

For Central precocious Puberty (CPP), the recommended dose of Supprelin LA is one implant every 12 months. The implant is inserted subcutaneously in the inner aspect of the upper arm and provides continuous release of histrelin for 12 months of hormonal therapy.

Source: Endo Pharmaceuticals, 2019

Trelstar

Trelstar (triptorelin) is administered as a single intramuscular injection in either buttock. Due to different release characteristics, the dosage strengths are not additive and must be selected based upon the desired dosing schedule. Must be administered under the supervison of a physician.

- 3.75 mg every 4 weeks

- 11.25 mg every 12 weeks
- 22.5 mg every 24 weeks.

Source: Verity, 2021

Triptodur

Triptodur (triptorelin) is available for extended-release injectable suspension as 22.5 mg of triptorelin as a powder cake for reconstitution with the co-packaged 2 mL of diluent (sterile water) for injection. Must be administered by a healthcare provider.

Central precocious puberty (CPP): The recommended does of Triptodur as a single intramuscular injection is 22.5 mg once every 24 weeks

Source: Arbor Pharmaceuticals, 2018

Zoladex

Zoladex (goserelin) is supplied as a 3.6 mg and 10.8 mg implant administered subcutaneously under the supervision of a physician.

Stage B2-C Prostatic Carcinoma, Prostatic Carcinoma, Endometriosis, Endometrial Thinning, and Advanced Breast Cancer

- Zoladex, at a dose of 3.6 mg, should be administered subcutaneously every 28 days into the anterior abdominal wall below the navel line using an aseptic technique under the supervision of a physician.
- Stage B2-C Prostatic Carcinoma: When Zoladex is given in combination with radiotherapy and flutamide for persons with Stage T2b-T4 (Stage B2-C) prostatic carcinoma, treatment should be started 8 weeks prior to initiating radiotherapy and should continue during radiation therapy. A treatment regimen using one Zoladex 3.6 mg depot 8 weeks before radiotherapy, followed in 28 days by one Zoladex 10.8 mg depot, can be administered. Alternatively, four injections of 3.6 mg depot can be administered at 28-day intervals, two depots preceding and two during radiotherapy.

- For the management of advanced prostate cancer, Zoladex is intended for long-term administration unless clinically inappropriate.
- For the management of endometriosis, the recommended duration of administration is 6 months. Currently, there are no clinical data on the effect of treatment of benign gynecological conditions with Zoladex for periods in excess of 6 months. Retreatment cannot be recommended for the management of endometriosis since safety data for retreatment are not available.
- For use as an endometrial-thinning agent prior to endometrial ablation, the dosing recommendation is one or two depots (with each depot given four weeks apart). When one depot is administered, surgery should be performed at four weeks. When two depots are administered, surgery should be performed within two to four weeks following administration of the second depot.
- For the management of advanced breast cancer, Zoladex is intended for long-term administration unless clinically inappropriate.

Stage B2-C Prostatic Carcinoma and Prostatic Carcinoma

- Zoladex, at a dose of 10.8 mg, should be administered subcutaneously every 12 weeks into the anterior abdominal wall below the navel line using an aseptic technique under the supervision of a physician.
- Stage B2-C Prostatic Carcinoma: When Zoladex is given in combination with radiotherapy and flutamide for persons with Stage T2b-T4 (Stage B2-C) prostatic carcinoma, treatment should be started 8 weeks prior to initiating radiotherapy and should continue during radiation therapy. A treatment regimen using one Zoladex 3.6 mg depot, followed in 28 days by one Zoladex 10.8 mg depot, should be administered.
- For the management of advanced prostate cancer, Zoladex is intended for long-term administration unless clinically inappropriate.

Source: TerSera Therapeutics, 2020a, 2020b

Experimental and Investigational or Not Medically Necessary

Cetrorelix acetate (Cetrotide) and Ganirelix acetate

Aetna considers all other indications experimental and investigational, including for use in males (including but not limited to any type of male infertility).

Degarelix (Firmagon)

Aetna considers degarelix contraindicated and considered not medically necessary for members with hypersensitivity to degarelix.

Aetna considers degarelix experimental and investigational for all other indications (e.g., benign prostatic hyperplasia and colon cancer, and for use in in-vitro fertilization, (not an all-inclusive list)) because of insufficient evidence in the peer-reviewed literature.

Goserelin (Zoladex)

Aetna considers goserelin 10.8 mg strength unproven and not medically necessary for diagnoses other than prostate cancer, breast cancer, and gender dysphoria (if applicable).

Aetna considers goserelin experimental and investigational for all other indications, including the following (not an all-inclusive list) because its effectiveness for these indications has not been established:

- Chronic pelvic pain
- Pancreatic cancer
- Preservation of testicular function during chemotherapy.

For use of goserelin in infertility, see CPB 0327 - Infertility (../300_399/0327.html)

Histrelin (Vantas; Supprelin LA)

Aetna considers histrelin acetate implants experimental and investigational for all other indications (e.g., precocious puberty due to adrenal hyperplasia; (not an all-inclusive list) because there is insufficient evidence in the peer-reviewed literature.

Leuprolide Acetate

Aetna considers leuprolide experimental and investigational for all other indications, including any of the following conditions (not an all-inclusive list), because limited information has been published and further research including randomized, controlled trials is required to determine its efficacy:

- ACTH-dependent Cushing syndrome
- Alzheimer's disease
- Amenorrhea induction prior to bone marrow transplant
- Angiomyxoma
- Autoimmune progesterone dermatitis of pregnancy
- Benign metastasizing leiomyoma (BML)
- Benign prostatic hyperplasia
- Borderline leiomyosarcoma
- Catamenial pneumothorax
- Disseminated cellular leiomyoma / leiomyomatosis
- Endometrial cancer (including endometrial stromal sarcoma)
- Epilepsy
- Hyperandrogenism
- Irritable bowel syndrome
- Juvenile idiopathic arthritis
- Menorrhagia (metromenorrhagia, metrorrhagia, menometrorrhagia)
- Menstrual migraines
- Multiple sclerosis
- Myeloma
- Osteosarcoma
- Parotid gland cancer
- Perineal leiomyoma
- Polycystic ovarian disease

- Porphyria cutanea tarda
- Precocious pubarche alone, or pseudoprecocious puberty (gonadotropin independent precocious puberty)
- Premature ovarian failure
- Preservation (suppression) of ovarian function during chemotherapy (except when member meets medical necessity for Lupron Depot 3.75 mg or 3-month 11.25 mg intramuscular injection)
- Preservation (suppression) of testicular function during chemotherapy
- Sickle cell anemia-associated priapism
- Spinal cord injury
- Stuttering
- Testicular cancer
- Uterine cancer.

Leuprolide Acetate / Norethindrone Acetate (Lupaneta Pack)

Lupaneta Pack is considered experimental and investigational for all other indications including the following (not an all-inclusive list):

- Abnormal uterine bleeding
- concomitant use with other LHRH agents.

Lupaneta Pack is considered not medically necessary for persons with the following contraindications to its use:

- Females who are pregnant or lactating
- Persons with a known or history of breast or other hormone-sensitive cancer
- Persons with thrombotic or thromboembolic disorders
- Persons with liver tumors or liver disease.

Triptorelin (Trelstar; Triptodur)

Aetna considers triptorelin experimental and investigational for fibrocystic breast disease and all other indications because of insufficient evidence in the peer-reviewed literature.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description
Leuprolide acetate:	
Other CPT codes related to the CPB:	
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
HCPCS codes covered if selection criteria are met:	
J9218	Leuprolide acetate, per 1 mg
J9219	Leuprolide acetate implant, 65 mg
Other HCPCS codes related to the CPB:	
84402	Testosterone; free
84403	Testosterone; total
ICD-10 codes covered if selection criteria are met:	
C08.0 - C08.9	Malignant neoplasm of other and unspecified major salivary glands
C61	Malignant neoplasm of prostate
E22.8	Other hyperfunction of pituitary gland [central precocious puberty]
E30.1 - E30.8	Precocious puberty and other disorders of puberty
E80.21	Acute intermittent (hepatic) porphyria
N97.0 - N97.9	Female infertility
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
C07	Malignant neoplasm of parotid gland
C49.0 - C49.9	Malignant neoplasm of other collective and soft tissue [borderline leiomyosacroma]
C55	Malignant neoplasm of uterus, part unspecified
C62.00 - C62.92	Malignant neoplasm of testis

Code	Code Description
C90.00 - C90.02	Multiple myeloma
C90.30	Solitary plasmacytoma not having achieved remission [solitary myeloma]
D25.0 - D25.9	Leiomyoma of uterus [disseminated cellular leiomyoma / leiomyomatosis] [perineal leiomyoma]
D37.030 - D37.039	Neoplasm of uncertain behavior of the major salivary glands
D47.Z9	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue [solitary myeloma]
D48.1	Neoplasm of uncertain behavior of connective and other soft tissue [angiomyxoma]
D57.00 - D57.819	Sickle-cell disorders
E28.310 - E28.319	Primary ovarian failure [premature ovarian failure]
E80.1	Porphyria cutanea tarda
F98.5	Adult onset fluency disorder [stuttering]
G35	Multiple sclerosis
G43.821 - G43.839	Menstrual migraine
J93.12	Secondary spontaneous pneumothorax [catamenial pneumothorax]
K58.0 - K58.9	Irritable bowel syndrome
M08.40 - M08.48	Pauciarticular juvenile rheumatoid arthritis
N40.0 - N40.1	Enlarged prostate [benign]
N48.30 - N48.39	Priapism
N80.8	Other endometriosis [catamenial pneumothorax]
N92.1 - N93.9, N95.0	Excessive, frequent or irregular menstruation

Code	Code Description
S14.0xxA - S14.159S	Injury of nerves and spinal cord at neck level [spinal cord injury]
S24.101A - S24.159S	Injury of nerves and spinal cord at thorax level [spinal cord injury]
S34.01xA - S34.139S	Injury of lumbar and sacral spinal cord and nerves at abdomen, lower back and pelvis level [spinal cord injury]
Lupron Depot:	
HCPCS codes covered if selection criteria are met:	
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg
J1954	Injection, leuprolide acetate for depot suspension (lutrate), 7.5 mg
J9217	Leuprolide acetate (for depot suspension), 7.5 mg
Other HCPCS codes related to the CPB:	
84402	Testosterone; free
84403	Testosterone; total
ICD-10 codes covered if selection criteria are met:	
C08.0 - C08.9	Malignant neoplasm of other and unspecified major salivary glands
C50.011 - C50.929	Malignant neoplasm of breast
C54.0 – C54.9	Malignant neoplasm of corpus uteri
C56.1 - C56.9	Malignant neoplasm of ovary
C61	Malignant neoplasm of prostate
D05.00 - D05.92	Carcinoma in situ of breast
D07.0	Carcinoma in situ of endometrium
D07.5	Carcinoma in situ of prostate
D25.0 - D25.9	Leiomyoma of uterus [disseminated cellular leiomyoma / leiomyomatosis] [not covered for Leuprolide]
D39.10 – D39.12	Neoplasm of uncertain behavior of ovary [granulosa cell tumors]
E22.8	Other hyperfunction of pituitary gland [central precocious puberty]

Code	Code Description
E30.1 - E30.8	Precocious puberty and other disorders of puberty
F64.0 - F64.9	Gender identity disorders
N80.00 - N80.03, N80.A0 - N80.D9	Endometriosis
Z51.11	Encounter for antineoplastic chemotherapy [when used for the prevention of heavy uterine bleeding in pre-menopausal women during chemotherapy]
Z87.890	Personal history of sex reassignment
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
C07	Malignant neoplasm of parotid gland
D48.1	Neoplasm of uncertain behavior of connective and other soft tissue [angiomyxoma]
Leuprolide acetate for depot suspension-Pediatric (Lupron Depot-PED):	
HCPCS codes covered if selection criteria are met:	
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg
ICD-10 codes covered if selection criteria are met:	
E22.8	Other hyperfunction of pituitary gland [central precocious puberty]
E30.1 - E30.8	Precocious puberty and other disorders of puberty
F64.0 - F64.9	Gender identity disorders
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
D25.0 - D25.9	Leiomyoma of uterus [disseminated cellular leiomyoma / leiomyomatosis]
D48.1	Neoplasm of uncertain behavior of connective and other soft tissue [angiomyxoma]
Eligard:	
HCPCS codes covered if selection criteria are met:	
J9217	Leuprolide acetate (for depot suspension), 7.5 mg
Other HCPCS codes related to the CPB:	
84402	Testosterone; free
84403	Testosterone; total

Code	Code Description
ICD-10 codes covered if selection criteria are met:	
C08.0 - C08.9	Malignant neoplasm of other and unspecified major salivary glands
C61	Malignant neoplasm of prostate
D07.5	Carcinoma in situ of prostate
F64.0 - F64.9	Gender identity disorders
Z87.890	Personal history of sex reassignment
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
C07	Malignant neoplasm of parotid gland
D25.0 - D25.9	Leiomyoma of uterus [disseminated cellular leiomyoma / leiomyomatosis]
D48.1	Neoplasm of uncertain behavior of connective and other soft tissue [angiomyxoma]
Goserelin (Zoladex):	
Other CPT codes related to the CPB:	
58353	Endometrial ablation, thermal, without hysteroscopic guidance
58356	Endometrial cryoablation with ultrasonic guidance, including endometrial curettage, when performed
58563	Hysteroscopy, surgical; with endometrial ablation (eg, endometrial resection, electrosurgical ablation, thermoablation)
HCPCS codes covered if selection criteria are met:	
J9202	Goserelin acetate implant, per 3.6 mg
Other HCPCS codes related to the CPB:	
84402	Testosterone; free
84403	Testosterone; total
ICD-10 codes covered if selection criteria are met:	
C50.011 - C50.929	Malignant neoplasm of breast
C61	Malignant neoplasm of prostate
D05.00 - D05.92	Carcinoma in situ of breast
D07.5	Carcinoma in situ of prostate
D25.0 - D25.9	Leiomyoma of uterus

Code	Code Description
D64.89	Other specified anemias [chronic anovulatory uterine bleeding with severe anemia]
F64.0 - F64.9	Gender identity disorders
N80.00 - N80.03, N80.A0 - N80.D9	Endometriosis
N93.8	Other specified abnormal uterine and vaginal bleeding [chronic anovulatory uterine bleeding with severe anemia] [Dysfunctional uterine bleeding]
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
C25.0 - C25.9	Malignant neoplasm of pancreas
R10.2	Pelvic and perineal pain
R10.30	Lower abdominal pain, unspecified [chronic pelvic pain]
Supprelin LA histrelin acetate subcutaneous implant:	
CPT codes covered if selection criteria are met:	
11980	Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin)
HCPCS codes covered if selection criteria are met:	
J9226	Histrelin implant (Supprelin LA), 50 mg
ICD-10 codes covered if selection criteria are met:	
E22.8	Other hyperfunction of pituitary gland [central precocious puberty]
F64.0 - F64.9	Gender identity disorders
Z51.11	Encounter for antineoplastic chemotherapy [when used for the prevention of heavy uterine bleeding in pre-menopausal women during chemotherapy]
ICD-10 codes not covered for indications listed in the CPB:	
E25.0 - E25.9	Hyperaldosteronism [precocious puberty due to adrenal hyperplasia]
E27.8	Other specified disorders of adrenal glands
E30.1 - E30.8	Precocious puberty and other disorders of puberty
E35	Disorders of endocrine glands in diseases classified elsewhere

Code	Code Description
Triptorelin (Trelstar; Triptodur):	
Other CPT codes related to the CPB:	
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
HCPCS codes covered if selection criteria are met:	
J3315	Injection, triptorelin pamoate, 3.75 mg
Other HCPCS codes related to the CPB:	
84402	Testosterone; free
84403	Testosterone; total
ICD-10 codes covered if selection criteria are met:	
C50.011 - C50.929	Malignant neoplasm of breast
C61	Malignant neoplasm of prostate
E22.8	Other hyperfunction of pituitary gland [central precocious puberty]
E30.1 - E30.8	Precocious puberty [true central]
F64.0 - F64.9	Gender identity disorders
N80.00 - N80.03, N80.A0 - N80.D9	Endometriosis
N85.01	Benign endometrial hyperplasia
Z51.11	Encounter for antineoplastic chemotherapy [including premenopausal women undergoing chemotherapy]
Z87.890	Personal history of sex reassignment
ICD-10 codes not covered for indications listed in the CPB:	
C81.00 - C81.99	Hodgkin lymphoma [for suppression of ovarian function]
N60.11 - N60.19	Diffuse cystic mastopathy [fibrocystic breast disease]
Triptorelin extended-release (Triptodur):	
Other CPT codes related to the CPB:	
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular

Code	Code Description
HCPCS codes covered if selection criteria are met:	
J3316	Injection, triptorelin, extended-release, 3.75 mg
ICD-10 codes covered if selection criteria are met:	
E22.8	Other hyperfunction of pituitary gland [central precocious puberty]
F64.0 - F64.9	Gender identity disorders
Z51.11	Encounter for antineoplastic chemotherapy [when used for the prevention of heavy uterine bleeding in pre-menopausal women during chemotherapy]
Degarelix:	
Other CPT codes related to the CPB:	
58970	Follicle puncture for oocyte retrieval, any method
58974	Embryo transfer, intrauterine
58976	Gamete, zygote, or embryo intrafallopian transfer, any method
HCPCS codes covered if selection criteria are met:	
J9155	Injection, degarelix, 1 mg
ICD-10 codes covered if selection criteria are met:	
C61	Malignant neoplasm of prostate
ICD-10 codes not covered for indications listed in the CPB:	
C18.0 - C18.9	Malignant neoplasm of colon
N40.0 - N40.1	Enlarged prostate without/with lower urinary tract symptoms
T50.995A - T50.995S	Adverse effect of other drugs, medicaments and biological substances [contraindicated and considered not medically necessary for persons with hypersensitivity to degarelix]
Z31.83	Encounter for assisted reproductive fertility procedure cycle [in-vitro fertilization]
Lupaneta Pack:	
HCPCS codes covered if selection criteria are met:	
Lupaneta Pack - no specific code	
ICD-10 codes covered if selection criteria are met:	
N80.00 - N80.03, N80.A0 - N80.D9	Endometriosis

Code	Code Description
Leuprolide acetate (Fensolvi):	
HCPCS codes covered if selection criteria are met:	
J1951	Injection, leuprolide acetate for depot suspension (fensolvi), 0.25 mg
ICD-10 codes covered if selection criteria are met:	
E22.8	Central precocious puberty
F64.0	Gender dysphoria in adolescents and adults
Cetrorelix acetate (Cetrotide) and Ganirelix (Gonadotropin releasing hormone antagonists):	
HCPCS codes covered if selection criteria are met:	
Cetrorelix acetate (Cetrotide), Fyremadel - no specific code	
S0132	Injection, ganirelix acetate, 250 mcg
ICD-10 codes covered if selection criteria are met:	
N97.0 - N97.9	Female infertility [inhibition of premature LH surges in members undergoing ovulation induction or assisted reproductive technology (ART)]
ICD-10 codes not covered for indications listed in the CPB:	
N46.021 - N46.9	Male infertility
Leuprolide mesylate (Camcevi):	
Other CPT codes related to the CPB:	
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
96401	Chemotherapy administration, subcutaneous or intramuscular; non-hormonal anti-neoplastic
HCPCS codes covered if selection criteria are met:	
J1952	Leuprolide injectable, camcevi, 1 mg
ICD-10 codes covered if selection criteria are met:	
C61	Malignant neoplasm of prostate

Background

Abarelix (Plenaxis)

Plenaxis (abarelix) is a GnRH antagonist approved by the FDA in November 2003. It is indicated for the treatment of the symptoms of men with advanced prostate cancer who can not take other hormone therapies and who have refused surgical castration. Plenaxis is marketed under a voluntary risk management program agreed to and administered by the sponsor that will restrict the use of Plenaxis to patients with advanced prostate cancer, who have no alternative therapy, because of an increased risk of serious, and potentially life-threatening, allergic reactions associated with its use.

In a phase III clinical study (n = 269), McLeod and colleagues (2001) evaluated the levels of testosterone and other hormones in men with prostate cancer treated with abarelix versus leuprolide. The authors concluded that treatment with abarelix produced a higher percentage of patients who avoided a testosterone surge and had a more rapid time to testosterone suppression with a higher rate of medical castration 1 day after treatment and greater reductions in testosterone, LH, FSH, and dihydrotestosterone during the first 2 weeks of treatment compared with leuprolide. The achievement and maintenance of castration was comparable between the two groups.

In another phase III clinical trial (n = 255), Trachtenberg et al (2002) reported that abarelix as monotherapy achieved medical castration significantly more rapidly than combination therapy (LHRH agonist and a non-steroidal anti-androgen) and avoided the testosterone surge characteristic of agonist therapy. Both treatments were equally effective in reducing serum PSA, and achieving and maintaining castrate levels of testosterone.

Koch et al (2003) stated that abarelix provided a safe and effective medical alternative to surgical castration in symptomatic patients (n = 81) with advanced prostate cancer without the risk of the clinical flare associated with LHRH agonists.

In June 2006, the manufacturer of abarelix voluntarily discontinued its sale and distribution due to a significantly reduced demand for the product. The drug was no longer be available after August 31, 2006.

Cetrorelix Acetate and Ganirelix Acetate

U.S. Food and Drug Administration (FDA)-Approved Indications

- Cetrotide, Fyremadel, and ganirelix are indicated for the inhibition of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian stimulation.

Cetrotide (cetrorelix acetate for injection) is a synthetic decapeptide with gonadotropinreleasing hormone (GnRH) antagonistic activity. GnRH induces the production and release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the gonadotrophic cells of the anterior pituitary. Due to a positive estradiol (E2) feedback at midcycle, GnRH liberation is enhanced resulting in an LH-surge. This LHsurge induces the ovulation of the dominant follicle, resumption of oocyte meiosis and subsequently luteinization as indicated by rising progesterone levels (EMD Serono, 2018).

Cetrotide is contraindicated in persons with a hypersensitivity to cetroelix acetate, extrinsic peptide hormones or mannitol, known hypersensitivity to GnRH or any other GnRH analogs, known or suspected pregnancy, and lactation, and severe renal impairment.

Ganirelix acetate Injection is a synthetic decapeptide with high antagonistic activity against naturally occurring gonadotropin-releasing hormone (GnRH). Ganirelix Acetate acts by competitively blocking the GnRH receptors on the pituitary gonadotroph and subsequent transduction pathway. It induces a rapid, reversible suppression of gonadotropin secretion. The suppression of pituitary LH secretion by Ganirelix Acetate is more pronounced than that of FSH. An initial release of endogenous gonadotropins has not been detected with Ganirelix acetate, which is consistent with an antagonist effect. Upon discontinuation of Ganirelix Acetate, pituitary LH and FSH levels are fully recovered within 48 hours (Merck, 2020).

Ganirelix acetate is contraindicated in persons with known hypersensitivity to ganirelix acetate or to any of its componenets including dry natural rubber/latex, known hypersensitivity to GnRH or any other GnRH analog, and known or supspected pregnancy (Merck, 2020).

Degarelix (Firmagon)

U.S. Food and Drug Administration (FDA)-Approved Indications

- Firmagon is indicated for the treatment of advanced prostate cancer.

Compendial Uses

- Prostate cancer

Degarelix is available as Firmagon (Ferring Pharmaceuticals, Inc.). Degarelix is a GnRH receptor antagonist. Degarelix binds reversibly to the pituitary GnRH receptors, thereby reducing the release of gonadotropins (luteinizing hormone and follicle-stimulating hormone) and consequently testosterone. In men, the level of testosterone is reduced to a level typically seen in surgically castrated men.

On December 29, 2008, the FDA approved degarelix, a GnRH receptor inhibitor, for the treatment of patients with advanced prostate cancer. The effectiveness of degarelix was established in a clinical trial in which patients with prostate cancer received either degarelix or leuprolide.

Long-term androgen deprivation therapy prolongs the QT interval. Consider risks and benefits especially when used concomitantly with other medications known to prolong the QT interval.

Do not administer degarelix intravenously.

Degarelix should not be used with other LHRH agonists.

Use with caution in patients with creatinine clearance (Clcr) <50 mL/minute.

Hypersensitivity reactions, including anaphylaxis, urticaria and angioedema, have been reported post-marketing with Firmagon (degarelix). In case of a serious hypersensitivity reaction, discontinue Firmagon (degarelix) immediately if the injection has not been completed, and manage as clinically indicated. Patients with a known history of serious hypersensitivity reactions to Firmagon (degarelix) should not be re-challenged with Firmagon (degarelix).

Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist analog. It can be anticipated that long periods of medical castration in men will have effects on bone density.

There is an increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving GnRH agonists for the treatment of prostate cancer.

Firmagon (degarelix) should not be utilized in persons with known hypersensitivity to degarelix, mannitol, or any of the excipients in the formulations.

Degarelix is not indicated in women and may lead to fetal harm if given during pregnancy (pregnancy category X).

The safety and efficacy of degarelix in pediatric patients less than 18 years old has not been established.

In a 12-month, comparative, randomized, open-label, parallel-group phase III study, Klotz et al (2008) assessed the safety and effectiveness of degarelix versus leuprolide for achieving and maintaining testosterone suppression in a 1-year phase III trial involving patients with prostate cancer. A total of 610 patients with adenocarcinoma of the prostate (any stage; median age of 72 years; median testosterone of 3.93 ng/ml, median PSA level of 19.0 ng/ml) were randomized and received study treatment. Androgen-deprivation therapy was indicated (neoadjuvant hormonal treatment was excluded) according to the investigator's assessment. Three dosing regimens were evaluated: a starting dose of 240 mg of degarelix subcutaneous (SC) for 1 month, followed by SC maintenance doses of 80 mg or 160 mg monthly, or IM leuprolide doses

of 7.5 mg monthly. Therapy was maintained for the 12-month study. Both the intent-to-treat (ITT) and per protocol populations were analyzed. The primary endpoint of the trial was suppression of testosterone to less than or equal to 0.5 ng/ml at all monthly measurements from day 28 to day 364, thus defining the treatment response. This was achieved by 97.2 %, 98.3 % and 96.4 % of patients in the degarelix 240/80 mg, degarelix 240/160 mg and leuprolide groups, respectively (ITT population). At 3 days after starting treatment, testosterone levels were less than or equal to 0.5 ng/ml in 96.1 % and 95.5 % of patients in the degarelix 240/80 mg and 240/160 mg groups, respectively, and in none in the leuprolide group. The median PSA levels at 14 and 28 days were significantly lower in the degarelix groups than in the leuprolide group ($p < 0.001$). The hormonal side-effect profiles of the 3 treatment groups were similar to previously reported effects for androgen-deprivation therapy. The SC degarelix injection was associated with a higher rate of injection-site reactions than with the IM leuprolide injection (40 % versus less than 1 %; $p < 0.001$, respectively). There were additional differences between the degarelix and leuprolide groups for urinary tract infections (3 % versus 9 %. $p < 0.01$, respectively), arthralgia (4 % versus 9 %, $p < 0.05$, respectively) and chills (4 % versus 0 %, $p < 0.01$, respectively). There were no systemic allergic reactions. The authors concluded that degarelix was not inferior to leuprolide at maintaining low testosterone levels over a 1-year treatment period. Degarelix induced testosterone and PSA suppression significantly faster than leuprolide; PSA suppression was also maintained throughout the study. Degarelix represents an effective therapy for inducing and maintaining androgen deprivation for up to 1 year in patients with prostate cancer, and has a different mechanism of action from traditional GnRH agonists. Its immediate onset of action achieves a more rapid suppression of testosterone and PSA than leuprolide. Furthermore, there is no need for anti-androgen supplements to prevent the possibility of clinical "flare". The findings of Klotz et al (2008) are in agreement with those of Gittelman et al (2008) as well as Van Poppel et al (2008).

In a phase 3, 1-year, multi-center, randomized, open-label study, Tombal et al (2010) compared the safety and effectiveness of degarelix at 240 mg for 1 month, and then 80 mg monthly (240/80mg); degarelix at 240 mg for 1 month, and then 160 mg monthly; and leuprolide at 7.5 mg/month. Overall, 610 patients with histologically confirmed prostate cancer (all

stages), for whom androgen deprivation therapy was indicated, were included. The primary endpoint of this trial has been reported previously; the protocolled and exploratory subgroup analyses reported in this paper focus on degarelix at 240/80 mg (dose approved by the FDA and the European Medicine Evaluation Association for the treatment of patients with hormone-naive advanced prostate cancer). Prostate-specific antigen progression-free survival (2 consecutive increases in PSA of 50 % compared with nadir and greater than or equal to 5 ng/ml on 2 consecutive measurements at least 2 weeks apart or death) and change in PSA were reviewed. Effects of baseline disease stage (localized, locally advanced, and metastatic) and PSA level (less than 10, 10 to 20, greater than 20 to 50, and greater than 50 ng/ml) were analysed. Patients receiving degarelix showed a significantly lower risk of PSA progression or death compared with leuprolide (p = 0.05). Prostate-specific antigen recurrences occurred mainly in patients with advanced disease and exclusively in those with baseline PSA greater than 20 ng/ml. Patients with PSA greater than 20 ng/ml had a significantly longer time to PSA recurrence with degarelix (p = 0.04). The relatively low number of patients in each subgroup is a limitation of this study. The authors concluded that these findings generate the hypothesis that degarelix at 240/80 mg offers improved PSA control compared with leuprolide. Prostate-specific antigen recurrences occurred almost exclusively in patients with metastatic prostate cancer or high baseline PSA during this 1-year study. The authors stated that further studies are needed to confirm these findings.

Ghiringhelli and colleagues (2013) noted that FSH receptor was recently found to be selectively expressed by endothelial cells on tumor-associated blood vessels in a wide range of human cancers. In this context, these researchers hypothesized that degarelix may have anti-angiogenic effects via its capacity to block FSH production. These investigators reported the case of a patient with metastatic colon cancer exhibiting tumor progression after failure of all conventional chemotherapeutic regimens. The addition of degarelix to the last chemotherapeutic regimen was proposed as compassionate treatment. Degarelix induced a rapid decrease in FSH level. This treatment induced radiological stabilization and carcino-embryonic antigen stabilization during 1 year. Contrast-enhanced ultrasonography demonstrated reduction of tumor vasculature. The authors stated that this case

represented the first report of an anti-tumoral effect of degarelix in metastatic colon cancer and suggested an anti-angiogenic property of this drug. The clinical value of degarelix in the treatment of colon cancer needs to be ascertained in well-designed RCTs.

Degarelix for Use in In-Vitro Fertilization

In a proof-of-concept clinical trial, Papanikolaou and colleagues (2018) examined the efficacy of a single-dose, long-acting GnRH antagonist (degarelix) IVF protocol. The efficacy of a single-dose, long-acting antagonist, degarelix, was explored initially in healthy donors and subsequently in infertile patients. In the 1st part, 5 healthy oocyte donors underwent ovarian stimulation with this new protocol: in the late luteal phase, at day 24, a bolus injection of degarelix was administered subcutaneously to control the LH surge in the follicular phase. Ovarian stimulation with gonadotropins was initiated subsequently from day 7 to day 10. End-points were first to inhibit the LH surge later in the follicular phase and, second, to retrieve mature oocytes for IVF. In the 2nd part, 5 infertile women received the same bolus injection of degarelix administered during the luteal phase at day 24. Different gonadotropin starting days (day 2 through day 8) were tested in order to observe possible differences in ovarian stimulation. In these infertile patients, fresh embryo transfers were performed to assess the pregnancy efficacy of this protocol on pregnancy outcomes and to address any possible negative effects on endometrium receptivity. In the 1st part of the study, all donors were effectively down-regulated with a single luteal dose of 0.5 ml of degarelix for up to 22 days until the final oocyte maturation triggering day. Mature oocytes were retrieved after 36 hours from all patients and all produced 2 to 7 blastocysts. In the 2nd part, all 5 infertile patients achieved sufficient LH down-regulation and completed ovarian stimulation without any LH surge. All patients (except 1 with freeze all strategy) had blastocysts transferred and pregnancy occurred in 3 out of 5 women. The authors concluded that this proof of concept study indicated that using a single luteal phase antagonist protocol could potentially combine the benefits of both antagonist and agonist protocols. For example, this approach could combine the flexibility of programming and homogenized follicular cohort benefits of the long agonist protocol with the near eradication of ovarian hyper-stimulation syndrome (OHSS) and the patient friendliness of the short antagonist protocol; this novel

approach appeared to offer a promising alternative to the long-established GnRH agonist regimens for all IVF couples. Moreover, they stated that this new long antagonist protocol could be used in oocyte donors to facilitate synchronization with the acceptor without risking OHSS. They also noted that a single-dose of antagonist can facilitate the hormone replacement protocol for frozen embryos, which is becoming increasingly popular, particularly after the freeze-all strategy; however, further RCTs are needed to confirm this novel concept prior to its universal implementation in IVF practice.

The authors stated that the drawbacks of this study were that it had a small population and had no comparative control group, preventing extrapolation of the findings to a larger scale IVF population. Moreover, the cost of degarelix was relatively higher; in Greece 1 vial of 80 mg degarelix costs 100 Euros whereas 5 vials of ganirelix or cetrorelix cost approximately 50 Euros. This might be sorted out in the future by the drug companies if they develop lower dose vials only for use in IVF as it happened with GnRH agonists years ago for endometriosis, IVF, and prostate cancer.

Cetrorelix (Cerotide) and ganirelix are the two FDA-approved gonadotropin-releasing hormone (GnRH) antagonists indicated for inhibiting premature leuteinizing hormone (LH) surges in women undergoing controlled ovarian hyperstimulation with FSH and HCG, followed by subsequent assisted insemination or reproductive technology (ART) procedures. Ganirelix was the first GnRH antagonist FDA-approved in the United States in 1999, followed by cetrorelix FDA approval in August 2000.

Goserelin (Zoladex)

U.S. Food and Drug Administration (FDA)-Approved Indications

- Prostate cancer
  - For use in combination with flutamide for the management of locally confined stage T2b-T4 (Stage B2-C) carcinoma of the prostate. Treatment with Zoladex and flutamide should start 8

weeks prior to initiating radiation therapy and continue during radiation therapy.
- In the palliative treatment of advanced carcinoma of the prostate

- Endometriosis - for the management of endometriosis, including pain relief and reduction of endometriotic lesions for the duration of therapy. Experience with Zoladex for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months (Zoladex 3.6 mg strength only)
- Endometrial thinning - for use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding (Zoladex 3.6 mg strength only)
- Advanced breast cancer - for use in the palliative treatment of advanced breast cancer in pre-and perimenopausal women

Compendial Uses

- Breast cancer
- Prostate cancer
- Gender dysphoria (also known as gender non-conforming or transgender persons)
- Preservation of ovarian function
- Prevention of recurrent menstrual related attacks in acute porphyria
- Uterine leiomyomata (fibroids)
- Treatment of chronic anovulatory uterine bleeding with severe anemia

Goserelin is available as Zoladex (TerSera Therapeutics). Goserelin is a GnRH (also known as gonadorelin and LHRH) analog, which is indicated in certain conditions requiring suppression of estrogen or testosterone secretion. Zoladex (goserelin) is a synthetic analog of luteinizing hormone releasing hormone (LHRH) also known as gonadotropin releasing hormone (GnRH). In males and premenopausal females, LHRH is released from the hypothalamus in intervals of approximately every 90 minutes. LHRH binds to the LHRH receptors on the pituitary gland

resulting in the release of LH and Follicle Stimulating Hormone (FSH). In response to LH stimulation in males, the Leydig cells of the testes produce testosterone.

In response to LH stimulation in females, the ovaries secrete estrogens. Zoladex (goserelin) stimulates LH receptors continuously which results in a down regulation of LH receptors leading to decreased estrogen and testosterone secretion.

Goserelin has been studied for the treatment of uterine leiomyomata (fibroids). Clinical studies have demonstrated the benefit of leuprolide in reducing vascular and surgical complications secondary to obstructive fibroid size. In tests, GnRH agonists have effectively reduced the fibroid size, but their use was accompanied by a rapid re-growth following discontinuation. Therefore, the literature states that goserelin therapy does not prevent or replace the eventual need for surgery. If used as a pre-operative adjunct, the literature recommends short-term treatment (6 months or less).

Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist analog. It can be anticipated that long periods of medical castration in men will have effects on bone density.

There is an increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving GnRH agonists for the treatment of prostate cancer.

The 10.8 mg dose of Zoladex is contraindicated in pregnancy. The 3.6 mg dose of Zoladex is contraindicated in pregnancy unless used for treatment of advanced breast cancer.

Zoladex should not be utilized in persons with a known hypersensitivity to goserelin products, luteinizing hormone releasing hormone (LHRH), or LHRH analogues.

Zoladex should not be used concomitantly with other LHRH agents.

Zoladex should not be used in abnormal vaginal bleeding of unknown etiology.

The safety and efficacy of Zoladex in pediatric patients less than 18 years old has not been established.

The most common, clinically significant adverse reactions occurring in greater than 10% of men include hot flashes, sexual dysfunction, decreased erections and lower urinary tract symptoms. Tumor flare can occur on the initiation of Zoladex therapy.

In a prospective pilot study (n = 5), Franke et al (2005) explored the effects of goserelin acetate in women with Hodgkin's disease (HD) receiving chemotherapy while taking a continuous combined estrogen-progestin preparation as add-back on the prevention of premature ovarian failure (POF). Pre-menopausal women with HD received goserelin and add-back until polychemotherapy was completed. Every 4 weeks during treatment and thereafter, a hormonal profile (follicle-stimulating hormone (FSH), LH, 17beta-estradiol, progesterone and inhibin B) was measured until resumption of menstruation or the development of a hyper-gonadotropic state (2 x FSH greater than 30 U/l). All patients reached pre-pubertal status during treatment. Following cessation of goserelin therapy, 1 patient developed a hyper-gonadotropic state and 4 patients resumed menstruation. One of those patients became pregnant and delivered a healthy son. These investigators concluded that the effectiveness of GnRH agonist plus add-back on the prevention of POF during polychemotherapy in women with HD needs further elucidation in randomized controlled trials (RCTs).

Del Mastro et al (2006) noted that standard methods to prevent chemotherapy-induced early menopause in young, breast cancer patients are unavailable to date. Pre-clinical data has suggested that LHRH analogs given during treatment can decrease the gonado-toxicity induced by chemotherapy. In a phase II clinical trial, these investigators evaluated the activity of such a method in young, breast cancer patients undergoing adjuvant chemotherapy. Pre-menopausal patients received goserelin 3.6 mg every 4 weeks before and during chemotherapy. According to 2-stage optimal phase II Simon design, treatment was considered clinically interesting if it was able to prevent menopause in 19 out of 29 patients of

the study population. The resumption of ovarian function was defined by a resumption of menstrual activity or by a FSH value less than or equal to 40 IU/l within 12 months after the last cycle of chemotherapy. A total of 30 patients were enrolled and 29 were evaluable. Median age was 38 years (range of 29 to 47 years). All but 1 patient received CEF regimen (cyclophosphamide, epirubicin, 5-fluorouracil). Resumption of menstrual activity was observed in 21 patients (72 %; 95 % confidence interval [CI]: 52 to 87 %) and a FSH value less than or equal to 40 IU/l in 24 patients (83 %; 95 % CI: 63 to 93 %). Menses resumption was observed in 16 out of 17 patients (94 %) with age less than 40 years and in 5 out of 12 patients (42 %) with age 40 years or over. These researchers concluded that goserelin given before and during chemotherapy may prevent premature menopause in the majority of patients. However, the different success rate by age indicates the need of a prospective evidence of the effectiveness of such a strategy.

In a prospective RCT, Badawy et al (2009) examined if GnRHa administration before and during combination chemotherapy for breast cancer could preserve post-treatment ovarian function in young women or not. A total of 80 patients with unilateral adenocarcinoma of the breast and with no metastasis who had undergone modified radical mastectomy or breast-conserving surgery plus full axillary lymph node dissection were included in the study. Patients were assigned randomly to receive combined GnRHa and chemotherapy or chemotherapy alone. One woman in each group dropped out. Main outcome measures included return of spontaneous menstruation and ovulation as well as hormonal changes (FSH, LH, E(2), P) during and after the course of treatment. In the study group, 89.6 % resumed menses and 69.2 % resumed spontaneous ovulation within 3 to 8 months of termination of the GnRHa/chemotherapy co-treatment; 11.4 % experienced hyper-gonadotrophic amenorrhea and ovarian failure 8 months after treatment. In the control group (chemotherapy without GnRHa), 33.3 % resumed menses and 25.6 % resumed normal ovarian activity. The median FSH and LH concentrations, 6 months after completion of the GnRHa/chemotherapy cotreatment group, were significantly less than the control group. During the GnRHa/chemotherapy co-treatment the concentrations of FSH, LH, and P decreased to almost pre-pubertal levels. However, within 1 to 3 months after the last GnRHa injection, an increase in LH and FSH concentrations was detected, followed several

weeks later in by an increase in P concentrations to within normal levels. The authors concluded that administration of GnRHa before and during combination chemotherapy for breast cancer may preserve post-treatment ovarian function in women less than 40 years. Moreover, they stated that long-term studies are needed.

In a systematic review, Clowse et al (2009) examined if administration of GnRHa during chemotherapy is protective of ovarian function and fertility. These investigators searched the English-language literature (1966 to April 2007) using Medline and meeting abstracts and included studies that reported an association between GnRHa and ovarian preservation in women receiving chemotherapy. Studies without a control group were excluded. Ovarian preservation was defined as the resumption of menstrual cycles and a pre-menopausal FSH after chemotherapy. Fertility was determined by a woman's ability to become pregnant. These researchers estimated the summary relative risk (RR) and associated 95 % CI using a random-effects model. A total of 9 studies included 366 women -- 3 studies included women with autoimmune disease receiving cyclophosphamide; 6 studies included women with hematologic malignancy receiving combination chemotherapy. In total, 178 women were treated with GnRHa during chemotherapy, 93 % of whom maintained ovarian function. Of the 188 women not treated with GnRHa, 48 % maintained ovarian function. The use of a GnRHa during chemotherapy was associated with a 68 % increase in the rate of preserved ovarian function compared with women not receiving a GnRHa (summary RR = 1.68, 95 % CI: 1.34 to 2.1). Among the GnRHa-treated women, 22 % achieved pregnancy following treatment compared with 14 % of women without GnRHa therapy (summary RR = 1.65, CI: 1.03 to 2.6). The authors concluded that based on the available studies, GnRHa appear to improve ovarian function and the ability to achieve pregnancy following chemotherapy. Several RCTs are underway to define the role and mechanism of GnRHa in ovarian function preservation.

Moore et al (2015) randomly assigned 257 premenopausal women with operable hormone-receptor-negative breast cancer to receive standard chemotherapy with the GnRH agonist goserelin (goserelin group) or standard chemotherapy without goserelin (chemotherapy-alone group). For patients randomly assigned to the goserelin group, goserelin at a dose of 3.6 mg was administered subcutaneously every 4 weeks

beginning 1 week before the initial chemotherapy dose and was continued to within 2 weeks before or after the final chemotherapy dose. The primary study end-point was the rate of ovarian failure at 2 years, with ovarian failure defined as the absence of menses in the preceding 6 months and levels of follicle-stimulating hormone (FSH) in the post-menopausal range. Rates were compared with the use of conditional logistic regression. Secondary end-points included pregnancy outcomes and disease-free and overall survival. At baseline, 218 patients were eligible and could be evaluated. Among 135 with complete primary end-point data, the ovarian failure rate was 8 % in the goserelin group and 22 % in the chemotherapy-alone group (odds ratio, 0.30; 95 % CI: 0.09 to 0.97; 2-sided p = 0.04). Owing to missing primary end-point data, sensitivity analyses were performed, and the results were consistent with the main findings. Missing data did not differ according to treatment group or according to the stratification factors of age and planned chemotherapy regimen. Among the 218 patients who could be evaluated, pregnancy occurred in more women in the goserelin group than in the chemotherapy-alone group (21 % versus 11 %, p = 0.03); women in the goserelin group also had improved disease-free survival (p = 0.04) and overall survival (p = 0.05). The investigators concluded that, although missing data weaken interpretation of the findings, administration of goserelin with chemotherapy appeared to protect against ovarian failure, reducing the risk of early menopause and improving prospects for fertility. Commenting on this study, Rebener (2015) stated that these findings are reassuring and suggest that a GnRH agonist could be provided to premenopausal women undergoing chemotherapy. The editorialist stated that, although the results should be reproducible in women treated for other cancers, no confirmatory data exist; also, the utility of this approach in young women with hormone-receptor-positive breast cancer remains to be shown.

Rebener (2014) stated that, while the results of the study by Moore et al are encouraging and the only reported downside of goserelin (which is not FDA approved for ovarian suppression in breast cancer patients) was the development of menopausal symptoms (e.g., hot flashes, accelerated bone loss), it's worth noting that results of many prior studies have been inconsistent -- and in this study population, between-group pregnancy rates were of borderline statistical significance. The author stated that only further studies will answer the questions of whether these findings

persist in larger studies and whether they pertain only to women with receptor-negative breast cancer. The editorialist stated that the benefits of preventing ovarian failure with its consequent vasomotor symptoms, dyspareunia, and rapid bone loss are well established, and this study adds to the growing evidence supporting the efficacy of GnRH agonists during chemotherapy.

Del Mastro et al (2014) conducted a systematic review and metaanalysis of randomized trials evaluating the efficacy of GnRH analogues (GnRHa), given before and during chemotherapy, in the prevention of POF in pre-menopausal cancer patients. Studies were retrieved by searching PubMed, Web of Knowledge database and the proceedings of major conferences. The investigators calculated Odds Ratios (OR) and 95 % CIs for POF from each trial and obtained pooled estimates through the random effects model as suggested by DerSimonian and Laird. A total of 9 studies were included in the meta-analysis with 225 events of POF occurring in 765 analyzed patients. The authors stated that pooled OR estimate indicates a highly significant reduction in the risk of POF (OR = 0.43; 95 % CI: 0.22 to 0.84; p = 0.013) in patients receiving GnRHa. There was statistically significant heterogeneity among studies (I(2) = 55.8 %; p = 0.012). The authors said that there was no evidence of publication bias. Subgroups analyses showed that the protective effect of GnRHa against POF was similar in subgroups of patients defined by age and timing of POF assessment, while it was present in breast cancer but unclear in ovarian cancer and lymphoma patients. The authors stated that their pooled analysis of randomized studies shows that the temporary ovarian suppression induced by GnRHa significantly reduces the risk of chemotherapy-induced POF in young cancer patients.

In a Cochrane review, Cheong et al (2014) evaluated the safety and effectiveness of non-surgical interventions for women with chronic pelvic pain. These investigators searched the Menstrual Disorders and Subfertility Group Specialised Register. They also searched (from inception to February 5, 2014) AMED, CENTRAL, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS; and hand-searched sources such as citation lists, trial registers and conference proceedings. Randomized controlled trials on non-surgical management of chronic pelvic pain were eligible for inclusion. These investigators included studies of women with a diagnosis of pelvic congestion syndrome or adhesions but excluded

those with pain known to be caused by endometriosis, primary dysmenorrhea (period pain), active chronic pelvic inflammatory disease or irritable bowel syndrome. These researchers considered studies of any non-surgical intervention, including lifestyle, physical, medical and psychological treatments. Study selection, quality assessment and data extraction were performed independently by 2 review authors. Meta-analysis was performed using the Peto odds ratio (Peto OR) for dichotomous outcomes and the mean difference (MD) for continuous outcomes, with 95 % CIs. The primary outcome measure was pain relief, and secondary outcome measures were psychological outcomes, quality of life, requirement for analgesia and adverse effects. The quality of the evidence was assessed by using GRADE methods. A total of 21 RCTs were identified that involved non-surgical management of chronic pelvic pain: 13 trials were included in the review, and 8 were excluded. The studies included a total of 750 women -- 406 women in the intervention groups and 344 in the control groups. Included studies had high attrition rates, and investigators often did not blind adequately or did not clearly describe randomization procedures. Progestogen (medroxyprogesterone acetate (MPA)) was more effective than placebo at the end of treatment in terms of the number of women achieving a greater than 50 % reduction in visual analog scale (VAS) pain score immediately after treatment (Peto OR 3.00, 95 % CI: 1.70 to 5.31, 2 studies, n = 204, I(2) = 22 %, moderate-quality evidence). Evidence of benefit was maintained up to 9 months after treatment (Peto OR 2.09, 95 % CI: 1.18 to 3.71, 2 studies, n = 204, I(2) = 0 %, moderate-quality evidence). Women treated with progestogen reported more adverse effects (e.g., weight gain, bloatedness) than those given placebo (high-quality evidence). The estimated effect of lofexidine on pain outcomes when compared with placebo was compatible with benefit and harm (Peto OR 0.42, 95 % CI: 0.11 to 1.61, 1 study, 39 women, low-quality evidence). Women in the lofexidine group reported more adverse effects (including drowsiness and dry mouth) than women given placebo (moderate-quality evidence). Head-to-head comparisons showed that women taking goserelin had greater improvement in pelvic pain score (MD 3, 95 % CI: 2.08 to 3.92, 1 study, n = 47, moderate-quality evidence) at 1 year than those taking progestogen. Women taking gabapentin had a lower VAS pain score than those taking amitriptyline (MD -1.50, 95 % CI: -2.06 to -0.94, n = 40, low-quality evidence). Study authors reported that no statistically significant difference was observed in the rate of adverse effects among

women taking gabapentin compared with women given amitriptyline. The study comparing goserelin versus progestogen did not report on adverse effects. Women who underwent reassurance ultrasound scans and received counseling were more likely to report improved pain than those treated with a standard "wait and see" policy (Peto OR 6.77, 95 % CI: 2.83 to 16.19, n = 90, low-quality evidence). Significantly more women who had writing therapy as a disclosure reported improvement in pain than those in the non-disclosure group (Peto OR 4.47, 95 % CI: 1.41 to 14.13, n = 48, very low-quality evidence). No difference between groups in pain outcomes was noted when other psychological therapies were compared with standard care or placebo (quality of evidence ranged from very low to low). Studies did not report on adverse effects. Distension of painful pelvic structures was more effective for pain when compared with counseling (MD 35.8, 95 % CI: 23.08 to 48.52 on a 0 to 100 scale, 1 study, n = 48, moderate-quality evidence). No difference in pain levels was observed when magnetic therapy was compared with use of a control magnet (very low-quality evidence). Studies did not report on adverse effects. The results of studies examining psychological and complementary therapies could not be combined to yield meaningful results. The authors concluded that evidence of moderate quality supported progestogen as an option for chronic pelvic pain, with efficacy reported during treatment. In practice, this option may be most acceptable among women unconcerned about progestogenic adverse effects (e.g., weight gain, bloatedness -- the most common adverse effects). Although some evidence suggested possible benefit of goserelin when compared with progestogen, gabapentin as compared with amitriptyline, ultrasound versus "wait and see'" and writing therapy versus non-disclosure, the quality of evidence is generally low, and evidence is drawn from single studies. They stated that given the prevalence and healthcare costs associated with chronic pelvic pain in women, RCTs of other medical, lifestyle and psychological interventions are urgently needed.

West and Hillier (1994) conducted a study to determine the effectiveness of ovarian suppression by a goserelin GnRH agonist analogue in 32 women with prospectively confirmed severe premenstrual tension. The design was a randomized, double-blind study comparing goserelin 3.6 mg with placebo, both given as a monthly s.c. injection for 3 months. Self-assessment was by daily visual analogue scales (VAS) for anxiety and

depression, daily quantitative symptom rating for breast discomfort, swelling, irritability, tension, depression and by monthly Hospital Anxiety and Depression (HAD) scales. Of the 16 women in each group, 15 completed active and 12 completed placebo therapy. Median symptom scores for whole cycles showed a significant reduction of breast discomfort and swelling during active treatment, with no significant improvement in psychological symptoms. Analysis by cycle phase showed that for individual subjects, pre-treatment differences in VAS scores for anxiety and depression were abolished in a significantly greater proportion of actively treated cycles. Within-group comparisons showed a marked placebo effect and, comparing the two groups, differences reached significance only during treatment cycle 1 and the first post-treatment cycle for anxiety with no significant differences for depression. It was concluded that while suppression of ovarian activity with a gonadotrophin-releasing hormone analogue dampens down cyclical mood swings, it has a more marked effect on the physical components of the premenstrual syndrome. Results reconfirm the positive role of placebo in the management of this condition.

Leather, et al. (1999) conducted a study aimed to determine if the addition of daily low-dose oral estrogen with a cyclical progestogen given to young women using a goserelin depot gonadotropin-releasing hormone (GnRH) analog implant for the treatment of their premenstrual syndrome (PMS) would affect the clinical outcome. In a double-blind placebo-controlled study in a specialist premenstrual syndrome clinic setting, 60 women aged between 20 and 45 years were randomized to one of three treatment groups: Group A (placebo implant four weekly + placebo tablets daily), Group B (goserelin 3.6 mg implant four weekly + estradiol valerate 2 mg daily with norethisterone 5 mg from days 21-28 of a 28-day cycle) or Group C (goserelin 3.6 mg implant four weekly + placebo tablets daily). Differences between PMS scores at 2, 4 and 6 months were compared with pretreatment values. There was a significant improvement in PMS scores in Group C (Zoladex + placebo) after 2, 4 and 6 months of treatment when compared to pretreatment values and Group A (placebo + placebo). The addition of a low-dose oral estrogen with a cyclical progestogen to GnRH analog treatment (Group B) resulted in a less dramatic response when compared to pretreatment values and no significant improvement when compared to Group A (placebo + placebo) at 2, 4 and 6 months of treatment. The authors concluded that the

addition of a low-dose oral estrogen with a cyclical progestogen to depot GnRH analog therapy in the treatment of PMS reduces the clinical response.

Guidelines from the British and Irish Porphyria Network on clinical management of acute attacks of porphyria and their complications (Stein, et al., 2012) state that, in women with recurrent pre-menstrual attacks of porphyria, goserelin acetate 3.6 mg (Zoladex) can be administered to prevent ovulation. The implant is given by subcutaneous injection into the anterior abdominal wall every 28 days, with the first injection being given during the first few days of the menstrual cycle. The guidelines warn that administration of gonadotrophin releasing hormone analogues may induce a hormone surge that can trigger an acute attack. Side effects include depression, hot flushes, reduced libido, osteoporosis and other menopausal symptoms. These can be reduced by use of a low dose estrogen patch. The guidelines state that regular gynecological review, and annual bone density determinations should be arranged, and that treatment with gonadotrophin releasing hormone analogues should be reviewed after one year.

Histrelin Acetate (Supprelin LA)

U.S. Food and Drug Administration (FDA)-Approved Indications for Supprelin LA

- Supprelin LA is indicated for the treatment of children with central precocious puberty (CPP).

Compendial Uses for Supprelin LA

- Gender dysphoria (also known as gender non-conforming or transgender persons)
- Preservation of ovarian function
- Prevention of recurrent menstrual related attacks in acute porphyria

Histrelin, an LH-releasing hormone (LH-RH) agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses. Continuous administration of histrelin causes a reversible down-

regulation of the GnRH receptors in the pituitary gland and desensitization of the pituitary gonadotropes. These inhibitory effects result in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. These decreases occur within 2 to 4 weeks after initiation of treatment.

The histrelin implant is designed to provide continuous subcutaneous release of histrelin at a rate of 50 to 60 mcg/day (Vantas) or approximately histrelin 65 mcg per day (Supprelin LA) over 12 months.

Supprelin LA is a GnRH agonist and an inhibitor of gonadotropin secretion when given continuously. Both animal and human studies indicate that following an initial stimulatory phase, chronic, subcutaneous administration of histrelin acetate desensitizes responsiveness of the pituitary gonadotropin which, in turn causes a reduction in ovarian and testicular steroidogenesis. In humans, administration of histrelin acetate results in an initial increase in circulating levels of LH and FSH, leading to a transient increase in concentration of gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females). However, continuous administration of histrelin acetate causes a reversible down-regulation of the GnRH receptors in the pituitary gland and desensitization of the pituitary gonadotropes. These inhibitory effects result in decreased levels of LH and FSH (Endo Pharmaceuticals, 2019).

Supprelin LA carries the following warnings and precautions:

- Initial Agonistic Action: Initial transient increases of estradiol and/or testosterone may cause a temporary worsening of symptoms
- Psychiatric events have been reported in patients taking GnRH agonists. Events include emotional lability, such as crying, irritability, impatience, anger, and aggression.
- Convulsions have been observed in patients receiving GnRH agonists with or without a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions.

The most common adverse reaction of Supprelin LA use is implant site reaction (51.1%), including complications related to the insertion or removal of the implant, and adverse events related to suppression of endogenous sex steroid secretion may occur. Supprelin LA is contraindicated in pregnance.
Supprelin (histrelin acetate) LA is not interchangeable with Vantas (histrelin acetate), which also contains 50mg of histrelin acetate per implant but is indicated for the palliative treatment of advanced prostate cancer.

Children with central precocious puberty (neurogenic or idiopathic) have an early onset of secondary sexual characteristics (earlier than 8 years of age in females and 9 years of age in males). They also show a significantly advanced bone age, which can result in diminished adult height attainment. Supprelin LA was approved by the FDA for the treatment of children with central precocious puberty based on the results of a single-arm, open-label study involving 36 patients ranging in age from 4 to 11 years. The primary endpoint of the study was hormonal suppression below pubertal levels by month 3 with continued suppression upon GnRH challenge. All patients in the study were suppressed within the first month of treatment.

Prior to initiation of treatment, a clinical diagnosis of central precocious puberty should be confirmed by measurement of blood concentrations of total sex steroids, LH and FSH following stimulation with a GnRH analog, and assessment of bone age versus chronological age. Baseline evaluations should include height and weight measurements, diagnostic imaging of the brain (to rule out intra-cranial tumor), pelvic/testicular/adrenal ultrasound (to rule out steroid secreting tumors), human chorionic gonadotropin levels (to rule out chorionic gonadotropin secreting tumor), and adrenal steroids to exclude congenital adrenal hyperplasia.

During treatment, LH, FSH and estradiol or testosterone should be monitored at 1 month post implantation then every six months thereafter. Additionally, height (for calculation of height velocity) and bone age should be assessed every six-to-12 months.

Supprelin LA should be removed after 12 months of therapy. At the time an implant is removed, another implant may be inserted to continue therapy. Discontinuation of Supprelin LA should be considered at the discretion of the physician and at the appropriate time point for the onset of puberty (approximately 11 years for females and 12 years for males).

Supprelin LA (histrelin acetate) implants are sterile non-biodegradable, diffusion-controlled, HYDRON polymer reservoirs containing histrelin acetate, and designed to deliver approximately 65 mcg histrelin acetate per day over 12 months.

The safety and effectiveness of Supprelin LA in persons less than two years old has not been established.

Supprelin LA should not be used in women who are pregnant or lactating.

Supprelin LA should not be used concomitantly with other LHRH agents.

Vantas was approved by the FDA for the palliative treatment of advanced prostate cancer. The FDA approval was based upon an open-label, multi-center study evaluating 138 patients with advanced prostate cancer and mean baseline serum levels of 388.3 ng/dL for testosterone and 83.6 ng/mL for prostate-specific antigen (PSA). Patients were treated with a single histrelin acetate implant and were evaluated for at least 60 weeks. Of the 138 patients, 37 had Jewett stage C disease, 29 had stage D disease, and 72 had an elevated or rising serum PSA after definitive therapy for localized disease. Ninety percent of patients were 65 years of age or older. Efficacy was determined by the number of patients who attained the criterion level of chemical castration (defined as serum testosterone 50 ng/dL or less) at week 4 and maintained this level through week 52. The study found that all evaluable patients (n = 134) attained chemical castration after 4 weeks of treatment. A statistically significant low mean testosterone level of less than 16 ng/dL ($p < 0.0001$) was achieved by week 4, and testosterone levels maintained below 20 ng/dL through week 52 of the study. The investigators reported that all patients experienced a decrease in PSA levels after they began treatment with histrelin implant. By week 24, 93 % of patients (n = 103) experienced a decrease in serum PSA to within normal limits.

Lopez and colleagues (2018) identified national trends in the utilization of histrelin acetate implants among transgender children in the United States. These investigators analyzed demographic, diagnostic and treatment data from 2004 to 2016 on the use of histrelin acetate reported to the Pediatric Health Information System (PHIS) to determine the temporal trends in its use for transgender-related billing diagnoses, e.g. "gender identity disorder". Demographic and payer status data on this patient population were also collected. Between 2004 and 2016, the annual number of implants placed for a transgender-related diagnosis increased from 0 to 63. The average age for placement was 14 years. Compared to natal females, natal males were more likely to receive implants (57 versus 46) and more likely to have implants placed at an older age (62 % of natal males versus 50 % of natal females were greater than or equal to 13 years; $p < 0.04$). The majority of children were White non-Hispanic (White: 60, minority: 21). When compared to the distribution of patients treated for precocious puberty (White: 1,428, minority: 1,421), White non-Hispanic patients were more likely to be treated with a histrelin acetate implant for a transgender-related diagnosis than minority patients ($p < 0.001$). This disparity was present even among minority patients with commercial insurance ($p < 0.001$). The authors concluded that utilization of histrelin acetate implants among transgender children has increased dramatically. Compared to natal females, natal males were more likely to receive implants and also more likely to receive implants at an older age. Treated transgender patients were more likely to be White when compared to the larger cohort of patients being treated with histrelin acetate for central precocious puberty (CPP), thus identifying a potential racial disparity in access to medically appropriate transgender care.

Swendiman and associates (2018) performed the largest review of the safety and clinical management practices of histrelin implantation in children. These investigators carried out a retrospective cohort study including all patients (age less than or equal to 20) that underwent histrelin implant insertion, replacement, or removal by a single surgeon at a large pediatric tertiary care center (2008 to 2017). Data analyzed included patient demographics, procedure details, and complications. A total of 377 patients, with a mean age of 9.3 ± 2.4 years, underwent 866 unique procedures (352 insertions, 329 replacements, and 185 removals) for a diagnosis of either central precocious puberty (343 patients, 821

cases) or gender identity disorder (34 patients, 45 cases). There were 271 (72 %) female patients, 72 (19 %) male patients, and 34 (9 %) children in gender transition. Procedures were performed in 3 settings: 415 (47.9 %) in the out-patient clinic, 401 (46.3 %) in a sedation unit, and 50 (5.8 %) in the operating room. The preferred setting shifted over time to more clinic-based procedures (9.4 % versus 62.9 % in the first 5 versus second 5 years, respectively). Complications were rare (1 % of cases). The authors concluded that histrelin implantation in the pediatric population was safe, with minimal morbidity. Implantation and removal in the clinic setting were appropriate for the majority of patients. Level of evidence = IV.

Furthermore, UpToDate reviews on "Transgender men: Evaluation and management" (Tangpricha and Safer, 2019a), "Transgender women: Evaluation and management" (Tangpricha and Safer, 2019b) and "Management of transgender and gender-diverse children and adolescents" (Olson-Kennedy and Forcier, 2019) do not mention histrelin as a therapeutic option.

In September 2021, Endo Pharmaceuticals made a business decion to discontinue the manufacture of Vantas (FDA, 2021).

Leuprolide Acetate Injection and Leuprolide Acetate for Depot Suspension

U.S. Food and Drug Administration (FDA)-Approved Indications

- Leuprolide Acetate Injection (solution for subcutaneous use)

  Leuprolide acetate is indicated in the palliative treatment of advanced prostate cancer.

- Eligard (suspension for subcutaneous use)

  Palliative treatment of advanced prostate cancer

- Fensolvi (suspension for subcutaneous use)

  Fensolvi is indicated for the treatment of pediatric patients 2 years of age and older with central precocious puberty (CPP).

- Lupron Depot 3.75 mg, 11.25 mg (depot suspension for intramuscular use)

  - Endometriosis

    Lupron Depot 3.75 mg and Lupron Depot-3 Month 11.25 mg are indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Lupron Depot 3.75 mg monthly and Lupron Depot-3 Month 11.25 mg with norethindrone acetate 5 mg daily are also indicated for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms.

    Use of norethindrone acetate in combination with Lupron Depot 3.75 mg is referred to as add-back therapy, and is intended to reduce the loss of bone mineral density (BMD) and reduce vasomotor symptoms associated with use of Lupron Depot 3.75 mg.

  - Uterine Leiomyomata (Fibroids)

    When used concomitantly with iron therapy, Lupron Depot 3.75 mg and Lupron Depot-3 Month 11.25 mg are indicated for preoperative hematologic improvement of patients with anemia caused by fibroids for whom three months of hormonal suppression is deemed necessary. The clinician may wish to consider a one-month trial period on iron alone, as some patients will respond to iron alone. Lupron Depot may be added if the response to iron alone is considered inadequate.

    Limitations of Use:

    For endometriosis: the total duration of therapy with Lupron Depot 3.75 mg and 11.25mg plus add-back therapy should not exceed 12 months due to concerns about adverse impact on bone mineral density.

For uterine leiomyomata: Lupron Depot 3.75 mg and 11.25mg are not indicated for combination use with norethindrone acetate add-back therapy for the preoperative hematologic improvement of women with anemia caused by heavy menstrual bleeding due to fibroids.

- Lupron Depot 7.5 mg, 22.5 mg, 30 mg, 45 mg (depot suspension for intramuscular use)

  Leuprolide acetate for depot suspension: Lupron Depot 1-Month 7.5 mg, Lupron Depot 3-Month 22.5 mg, Lupron Depot 4-Month 30 mg, and Lupron Depot 6-Month 45 mg are indicated in the palliative treatment of advanced prostate cancer.

- Lupron Depot-PED (depot suspension for intramuscular use)

  Lupron Depot-PED is indicated for the treatment of children with central precocious puberty (CPP).

Compendial Uses

- Leuprolide Acetate Injection (solution for subcutaneous use)

  - Central precocious puberty (CPP)
  - Use as a stimulation test to confirm the diagnosis of CPP
  - Use in combination with growth hormone for children with growth failure and advancing puberty
  - Prostate cancer
  - Inhibition of premature luteinizing hormone (LH) surges in women undergoing assisted reproductive technology
  - Androgen receptor positive salivary gland tumors
  - Triggering of oocyte maturation and ovulation in assisted reproductive technology cycle.

- Eligard (suspension for subcutaneous use)

  - Prostate cancer
  - Recurrent androgen receptor positive salivary gland tumors
  - Gender dysphoria (also known as gender non-conforming or transgender persons)

- Fensolvi (suspension for subcutaneous use)

  Gender dysphoria (also known as gender non-conforming or transgender persons)

- Lupron Depot 3.75 mg, 11.25 mg (depot suspension for intramuscular use)

  - Breast cancer
  - Ovarian cancer - epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer, and less common ovarian cancers [grade 1 endometrioid carcinoma, low-grade serous carcinoma, carcinosarcoma (malignant mixed Müullerian tumors), mucinous carcinoma of the ovary, or clear cell carcinoma of the ovary]
  - Recurrent androgen receptor positive salivary gland tumors
  - Gender dysphoria (also known as gender non-conforming or transgender persons)
  - Preservation of ovarian function in patients with cancer
  - Prevention of recurrent menstrual related attacks in acute porphyria

- Lupron Depot 7.5 mg, 22.5 mg, 30 mg, 45 mg (depot suspension for intramuscular use)

  - Prostate cancer
  - Ovarian cancer - Malignant sex cord-stromal tumors
  - Recurrent androgen receptor positive salivary gland tumors
  - Gender dysphoria (also known as gender non-conforming or transgender persons)

- Lupron Depot-PED (depot suspension for intramuscular use)

  Gender dysphoria (also known as gender non-conforming or transgender persons)

Leuprolide acetate is a gonadotropin-releasing hormone (GnRH) agonist, which may be indicated for treatment of certain conditions, which are hormonally regulated.

Leuprolide acetate is a synthetic analog of luteinizing hormone releasing hormone (LHRH). It acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. In humans, administration of leuprolide results in an initial increase in circulating luteinizing hormone (LH) and follicle stimulating hormone (FSH) leading to transient increases in gonadal steroids. However, continuous administration of leuprolide results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In premenopausal females, estrogen levels are reduced to postmenopausal levels. These decreases occur within two-to-four weeks after initiation of therapy. This effect is reversible upon discontinuation of drug therapy. Leuprolide acetate is not active when given orally.

Leuprolide acetate injection is available in various formulations such as an aqueous solution or injectable suspension intended for subcutanous use, and long-acting, slow-release formulation (depot suspension) for intramuscular use.

Luprolide acetate (Eligard), administered as a subcutaneous injection, carries the following warnings and precautions:

- Tumor Flare: Transient increase in serum levels of testosterone during treatment may result in worsening of symptoms or onset of new signs and symptoms during the first few weeks of treatment, including bone pain, neuropathy, hematuria, bladder outlet obstruction, ureteral obstruction, or spinal cord compression.
- Hyperglycemia and diabetes: Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH analogs.
- Cardiovascular diseases: Increased risk of myocardial infarction, sudden cardiac death and stroke has been reported in men.
- Effect on QT/QTc Interval: Androgen deprivation therapy may prolong the QT interval. Consider risks and benefits.
- Embryo-Fetal Toxicity: May cause fetal harm.
- Convulsions have been observed in patients with or without a history of predisposing factors.

Luprolide acetate (Fensolvi), administered as a subcutaneous injection, carries the following warnings and precautions:

- Initial Rise of Gonadotropins and Sex Steroid Levels: During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the initial stimulatory effect of the drug. Therefore, an increase in clinical signs and symptoms of puberty including vaginal bleeding may be observed during the first weeks of therapy or after subsequent doses.
- Psychiatric events have been reported in patients taking GnRH agonists. Events include emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms.
- Convulsions have been observed in patients with or without a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions.

Leuprolide acetate for depot suspension (Lupron Depot-PED), administered as an intramuscular injection, carries the following warnings and precautions:

- An increase in clinical signs and symptoms of puberty may be observed during the first 2-4 weeks of therapy since gonadotropins and sex steroids rise above baseline because of the initial stimulatory effect of the drug before being suppressed.
- Psychiatric events have been reported in patients taking GnRH agonists. Events include emotional lability, such as crying, irritability, impatience, anger, and aggression.
- Convulsions have been observed in patients with or without a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions.

Leuprolide acetate is not recommended in pregnancy and is considered contraindicated and listed as a category X for Lupron Depot-PED. Safe use of leuprolide acetate in pregnancy has not been established in clinical studies. It is not known whether leuprolide acetate is excreted in human milk, thus, should not be used by nursing mothers.

Adverse events related to suppression of endogenous sex steroid secretion and injection site reactions including abscess may occur with Lupron Depot-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month administration. In clinical studies for Lupron Depot-PED 11.25 mg or 30 mg for 3-month administration, the most frequent (≥2 patients) adverse reactions included injection site pain, weight increased, headache, mood altered, and injection site swelling (AbbVie, 2020).

The safety and effectiveness of Eligard in pediatric patients have not been established. For Lupron Depot-PED, safety and effectiveness in pediatric patients below the age of 2 years have not been established, thus, the use of Lupron Depot-PED in children under 2 years is not recommended.

Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a gonadotropin-releasing hormone (GnRH) agonist analog. It can be anticipated that long periods of medical castration in men will have effects on bone density.

On May 01, 2020, the U.S. Food and Drug Administration (FDA) approved leuprolide acetate (Fensolvi) injectable suspension for subcutaneous use for the treatment of pediatric patients aged 2 years and older with central precocious puberty (CPP). Fensolvi is designed to deliver 45 mg of leuprolide acetate, a GnRH agnosist, at a controlled rate over a six-month therapeutic period. Fensolvi must be administered by a healthcare professional. Response to Fensolvi is monitored with a GnRH agonist stimulation test, basal serum luteinizing hormone (LH) levels or serum concentration of sex steroid levels at 1 to 2 months following initiation of therapy and as needed to confirm adequate suppression of pituitary gonadotropins, sex steroids, and progression of secondary sexual characteristics. Height is measured every 3 to 6 months and bone age is monitored periodically.

The efficacy of Fensolvi was evaluated in an uncontrolled, open-label, single arm clinical trial in which 64 pediatric patients (62 females and 2 males, naïve to previous GnRH agonist treatment) with CPP received at least one dose of Fensolvi at a dosing interval of 24 weeks and were observed for 12 months. The mean age was 7.5 years (range 4 to 9

years) at the start of treatment. In pediatric patients with CPP, Fensolvi reduced stimulated and basal gonadotropins to prepubertal levels. Suppression of peak stimulated LH concentrations to <4 IU/L was achieved in 87% of pediatric patients by month 6 and in 86% of patients by month 12. In addition, the study demonstrated that leuprolide acetate suppressed sex hormones to pre-pubertal levels, and stopped or reversed the progression of clinical signs of puberty. Suppression of estradiol or testosterone concentration to prepubertal levels at the 6-month assessment was achieved in 97% and 100% of patients, respectively. Suppression of estradiol or testosterone was maintained at the 12-month assessment with 98% (55/56 females) and 50% (1/2 males) maintaining suppression. Fensolvi arrested or reversed progression of clinical signs of puberty with reductions in growth velocity and bone age. Mean growth velocity decreased from 8.9 ± 13.1 cm/yr at 1 month to 6.9 ± 3.1 cm/yr at 6 months and to 6.4 ± 1.9 cm/yr at 12 months. Eight female patients out of 62 did not meet the primary efficacy criteria for LH <4 IU/L at 6 months. In four of the eight patients, the LH level at 6 months was between 4.2 and 4.8 IU/L. The remaining four patients had LH levels >5 IU/L. However, post stimulation estradiol was suppressed to prepubertal levels (<20 pg/mL) in seven of the eight patients at month 6 and was maintained through month 12.

Leuprolide may be indicated in advanced cancer (palliative treatment) in patients who have inoperable prostate tumor, or refuse orchiectomy. The available literature suggests combined therapy with leuprolide and an anti-androgen (e.g., megestrol, flutamide) appears to produce additive effects and to be more effective than leuprolide therapy alone in the treatment of advanced prostate cancer. According to established guidelines, recommended dosing of leuprolide for palliative treatment of advanced prostate cancer is 1 mg given subcutaneously daily. According to established guidelines, if patient is receiving leuprolide acetate suspension (Lupron depot) dosing is 7.5 mg IM once-monthly.

Leuprolide has been used in the treatment of true (central) precocious puberty, defined as sexual maturation less than age 8 in girls, and sexual maturation less than age 9 in boys. The available literature suggests tumors should be ruled out by lab tests, CT, MRI, or ultrasound. Leuprolide is not indicated for precocious pubarche alone or pseudoprecocious puberty (gonadotropin-independent precocious

puberty). According to established guidelines, recommended starting doses are: Lupron Depot Ped: 0.3 mg/kg every 4 weeks (minimum 7.5 mg), or Lupron injection: 50 mcg/kg daily. Doses may be titrated upwards in order to achieve hormonal down-regulation.

Studies of leuprolide for endometriosis indicate that 6 months is an appropriate length for therapy. Because of lack of safety data with long-term use, and because of concerns expressed in the available literature regarding effects on bone density, treatment after 6 months is typically not recommended. According to established guidelines, recommended dosing of leuprolide for endometriosis is 3.75 mg as a single monthly intra-muscular (IM) injection.

Leuprolide has been studied for the treatment of uterine fibroids (leiomyoma uteri), as a pre-operative adjunct to surgical treatment. Clinical studies have demonstrated the benefit of leuprolide in reducing vascular and surgical complications secondary to obstructive fibroid size. In tests, gonadotropin-releasing hormone (GnRH) agonists have effectively reduced the fibroid size, but their use was accompanied by a rapid re-growth following discontinuation. The available literature states leuprolide therapy does not prevent or replace the eventual need for surgery. If used as a pre-operative adjunct, the available literature states short-term treatment only is recommended (i.e., 1 to 3 months).

Leuprolide also has been shown to be an effective pre-operative adjunct to decrease endometrial thickness prior to endometrial ablation. If used as a pre-operative adjunct, short-term treatment only (i.e., 1 to 2 months) is indicated.

Leuprolide is used in conjunction with urofollitropin or menotropins in patients with infertility. It has been used to suppress LH production in patients with documented premature luteinizing hormone (LH) surge. In addition, it has been used in "super-ovulation" regimens associated with in-vitro fertilization. Treatment of infertility may be subject to limitations under some benefit plans. Some HMO contracts, with or without a separate infertility benefit such as the Advanced Reproductive Technology (ART) Rider, specifically exclude injectable infertility drugs.

Leuprolide has been shown to be useful in the treatment of metastatic breast cancer in pre-menopausal patients whose disease has progressed or recurred despite a 3 or more months trial of tamoxifen.

Leuprolide has been used as treatment for various other conditions (e.g., polycystic ovarian disease, hypermenorrhea, pre-menstrual syndrome, paraphilias, and endometrial cancer). At this time limited information has been published to show efficacy for conditions other than those mentioned in the clinical criteria above. Further research with randomized, controlled trials is required to determine efficacy in these other conditions.

The American Society of Clinical Oncology's recommendations on fertility preservation in cancer patients (Lee et al, 2006) stated that sperm and embryo cryo-preservation are considered standard practice. On the other hand, the use of GnRH analogs or antagonists for testicular or ovarian suppression is considered investigational. ASCO guidelines state: "At this time, since there is insufficient evidence regarding the safety and effectiveness of GnRH analogs and other means of ovarian suppression on female fertility preservation, women interested in ovarian suppression for this purpose are encouraged to participate in clinical trials." The guidelines also noted that there is insufficient evidence of the effectiveness of GnRH analogues in preventing chemotherapy-induced gonadal damage in men: "The efficacy of gonadoprotection through hormonal manipulations has only been evaluated in very small studies in cancer patients."

In a review of the literature, Sonmezer and Oktay (2006) explained that there are a limited number of prospective studies of GnRH analogues in preventing chemotherapy-induced gonadal damage, "which are flawed because of short-term follow-up and/or because of lack of control subjects." The review notes that "[i]n addition to the lack of consistent support from clinical studies, there is currently no biological explanation for who GnRHa [GnRH analogues] can affect ovarian reserve." The authors concluded that "[i]n the absence of a prospective randomized study with sufficient power, we do not rely on ovarian suppression as an effective means of fertility preservation."

Leuprolide has been employed as a therapeutic option for individuals with paraphilia who have failed pharmacotherapies such as cyproterone acetate (CPA), medroxyprogesterone acetate (MPA), and selective serotonin reuptake inhibitors (SSRIs). Leuprolide is thought to decrease sexual drive in men afflicted with paraphilias by decreasing testosterone production. Briken et al (2003) stated that in addition to psychotherapy, pharmacotherapy is an important treatment option for paraphilias, especially in sexual offenders. They noted that research has showed that LH-releasing hormone (LHRH) agonists may offer a new treatment option for treatment of paraphilic patients. These investigators performed a literature review on the use of LHRH agonist a new treatment option for treatment of paraphilic patients. They found 4 case reports, 1 case-control study, 7 open uncontrolled studies, and 1 study comparing patients receiving CPA with those receiving LHRH agonist treatment in forensic hospitals. In total, the studies reported on a sample of 118 treated patients with different forms of paraphilias -- sadism, pedophilia, exhibitionism, voyeurism. Nearly all of the studies used self-reports to measure the effects of medication. Duration of follow-up was between 6 months and 7 years and revealed that there were no relapses if patients remained under treatment. Patients previously treated with other agents like CPA, MPA, or SSRIs reported better effects when taking LHRH agonists. The authors concluded that although there is a need for further research, LHRH agonists offer a treatment option for patients with severe paraphilia. Furthermore, in a review on medications that may alter behaviors of sex-offenders, Scober and colleagues (2006) stated that therapeutic drugs include LHRH inhibitors (e.g., leuprolide acetate, CPA, and triptorelin), synthetic estrogens (e.g., diethylstilbestrol), and progesterones (e.g., MPA).

Leuprolide has also been tried for the treatment of seizures (Akaboshi and Takeshita, 2000) as well as Alzheimer's disease (Casadesus et al, 2006). However, there is currently insufficient evidence to support its use for these indications.

Available evidence on the effectiveness of leuprolide for the treatment of endometrial stromal sarcoma is limited to case reports. Guidelines on systemic therapy for uterine sarcoma from Cancer Care Ontario included no recommendation for the use of leuprolide in uterine stromal sarcomas

(Kanjeekal et al, 2004). Furthermore, the National Cancer Institute's PDQ on uterine sarcoma (2008) did not include leuprolide or GnRH analogs as treatment options for uterine sarcoma.

Quaas and Ginsburg (2007) provided a systematic review on prevention and treatment of uterine bleeding in the setting of hematologic malignancy. These researchers performed MEDLINE, PubMed, EMBASE and Cochrane searches with the terms uterine bleeding, uterine hemorrhage, hematologic malignancy. All identified literature sources were included in the review. The identified literature is largely comprised of case series and pilot studies. No evidence-based protocols for gynecologists and hematologists are available. The majority of the identified literature centers on menstrual suppression with GnRH agonists in hematologic malignancy, although no randomized trials could be identified. Review of the identified literature suggests that medical prevention with GnRH agonist therapy is highly effective for prevention of uterine bleeding in hematologic malignancy. With respect to treatment of acute uterine bleeding in the setting of hematologic malignancy, medical therapy can be used and is successful in the majority of patients, according to the identified studies. Surgical treatment should be used expeditiously if medical treatment options fail to control acute bleeding. Empiric prevention and treatment algorithms for the discussed clinical settings are proposed. The authors stated that more research is necessary on the topic, with the goal to develop evidence-based guidelines for gynecology and hematology-oncology care providers. Close cooperation between the specialties may improve morbidity and mortality associated with uterine bleeding in hematological malignancy in the future.

Hembree and colleagues (2009) formulated practice guidelines for endocrine treatment of transsexual persons. This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence, which was low or very low. Committees and members of the Endocrine Society, European Society of Endocrinology, European Society for Paediatric Endocrinology, Lawson Wilkins Pediatric Endocrine Society, and World Professional Association for Transgender Health commented on preliminary drafts of these guidelines. The authors concluded that

transsexual persons seeking to develop the physical characteristics of the desired gender require a safe, effective hormone regimen that will (i) suppress endogenous hormone secretion determined by the person's genetic/biologic sex and (ii) maintain sex hormone levels within the normal range for the person's desired gender. A mental health professional (MHP) must recommend endocrine treatment and participate in ongoing care throughout the endocrine transition and decision for surgical sex re-assignment. The endocrinologist must confirm the diagnostic criteria the MHP used to make these recommendations. Because a diagnosis of transsexualism in a prepubertal child can not be made with certainty, the authors do not recommend endocrine treatment of prepubertal children. They recommended treating transsexual adolescents (Tanner stage 2) by suppressing puberty with GnRH analogs until age 16 years old, after which cross-sex hormones may be given. They suggested suppressing endogenous sex hormones, maintaining physiologic levels of gender-appropriate sex hormones and monitoring for known risks in adult transsexual persons.

An UpToDate review on "Heavy or irregular uterine bleeding during chemotherapy" (Milbourne, 2013) states that "We suggest inducing amenorrhea with a GnRH agonist [e.g., leuprolide acetate] in premenopausal women at risk of chemotherapy induced thrombocytopenia

UpToDate reviews on "Treatment of locally advanced, recurrent, or metastatic endometrial cancer" (Campos and Miller, 2013) and "Overview of endometrial carcinoma" (Plaxe and Mundt, 2013) do not mention leuprolide as a therapeutic option. Also, the 2013 NCCN's Drugs and Biologics Compendium does not list uterine cancer as an indication of leuprolide acetate.

UpToDate reviews on "Malignant salivary gland tumors: Treatment of recurrent and metastatic disease" (Laurie, 2013) and "Salivary gland tumors: Treatment of locoregional disease" (Lydiatt and Quivey, 2013) do NOT mention the use of leuprolide as a therapeutic option. Also, the 2013 NCCN's Drugs and Biologics Compendium does not list parotid carcinoma as a recommended indication of leuprolide acetate.

Leuprolide for Angiomyxoma

Ribiero, et al. (2015) stated that analogs of GnRH have been used in some few cases of premenopausal women with angiomyxoma of the vulva, but this tumor can regrowth once the therapy is discontinued. The authors noted that preoperative reduction of tumors using analogs of GnRH can increase the chances of complete excision and reduce the radicality of the surgical procedure.

In a case-report, Schwartz et al (2014) described the results of hormonal therapy in the management of a patient with recurrent aggressive angiomyxoma (AAM) and proposed a management strategy for AAM based on (i) the estrogen receptor (ER) and progestin receptor contents of the tumor, (ii) the extent of disease based on magnetic resonance imaging findings, and (iii) the patient's menopausal status. The chart of a patient with multiple pelvic recurrences of AAM managed surgically during a 16-year period followed by hormonal therapy was reviewed, and a literature search of pelvic, vaginal, and vulva AAM was performed. The patient presented in this report experienced 7 recurrences of AAM managed surgically during a 16-year period. She then was placed on leuprolide acetate for 3 monthly cycles, but the tumor recurred 6 months after the leuprolide acetate was discontinued. The patient was placed back on monthly leuprolide acetate for 5 years and has remained free of disease for more than 2 years after discontinuing the leuprolide acetate. A literature review suggested a role for hormonal therapy in the management of AAM based on the presence of ER/progestin receptor, the extent of the disease, and the menopausal status of the patient. Gonadotropin-releasing hormone analogs have been successfully used in pre-menopausal women as neoadjuvant therapy before surgery for previously untreated or recurrent disease, as adjuvant therapy after the initial surgical resection or after the resection of recurrent disease, and as the definitive treatment of AAM. Aromatase inhibitors may play a role in the treatment of ER-positive AAM occurring in post-menopausal women. The authors concluded that AAM can be an extremely hormonally sensitive tumor. Hormonal therapy may have a significant role in the treatment of patients with extensive or recurrent AAM that is ER positive. The selection of hormonal agents used for treating AAM can be based on the patient's menopausal status.

Damodaran et al (2017) noted that AAM is a rare benign mesenchymal stromal tumor, characterized by locally infiltrative nature and a tendency for recurrence. Only a few cases of penile involvement have been reported in the literature so far. These investigators reported a case of AAM involving the penile in a 62-year old obese, diabetic male patient. He presented with obstructive lower urinary tract symptoms (LUTS) and diffuse enlargement of the penis and scrotum. He was managed with excision, reduction scrotoplasty, internal urethrotomy, followed by leuprolide therapy for prevention of recurrence. He was followed-up for 20 months without recurrence and obstructive symptoms.

An UpToDate review on "Umbilical cord abnormalities: Prenatal diagnosis and management" (Sepulveda, 2020) states that "Angiomyxomas are extremely rare and arise from proliferation of the primitive angiogenic mesenchyme of the cord. The term angiomyxoma is based on the prominent myxoid material contained within the tumor ... Tumor growth could cause umbilical vessel compression; therefore, the author serially monitors tumor growth and Doppler flow in the umbilical vessels. The frequency depends on the size and growth rate of the tumor. In the third trimester, nonstress testing is also performed. In case of abnormal Doppler waveforms in the umbilical vessels, percutaneous aspiration of the cyst or prompt delivery should be considered; this decision depends on the gestational age". This review does not mention leuprolide as a therapeutic option.

Leuprolide for the Treatment of Acute Intermittent Porphyria

An UpToDate reviews on "Acute intermittent porphyria: Management" (Sood and Anderson, 2020) states that "frequently recurring attacks confined to the luteal phase of the menstrual cycle can be prevented with a gonadotropin-releasing hormone (GnRH) analogue to suppress ovulation. If treatment is effective after several months, additional therapies should be included to prevent bone loss. Options include low-dose estradiol, preferably by the transdermal route; a bisphosphonate; or switching to a low-dose estrogen-progestin contraceptive".

Leuprolide for the Treatment of Benign Metastasizing Leiomyoma

In a case-series study, Lewis and colleagues (2013) evaluated novel hormonal therapies in patients with unresectable benign metastasizing leiomyoma (BML) disease. A total of 5 subjects with the diagnosis of BML based on imaging and/or histopathologic diagnosis were included in this study; 4 patients were treated with single or combination therapy of leuprolide acetate and/or an aromatase inhibitor; 1 patient was treated with an anti-progestin (CDB-2914). Response to therapy was measured by tumor burden on cross-sectional imaging employing RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 guidelines; 4 patients treated with single or combination therapy of leuprolide acetate and/or an aromatase inhibitor demonstrated stable disease (SD) with reduction in tumor burden. The 5th patient treated with anti-progestin (CDB-2914) had degeneration of her tumor, progression of its size, and an improvement in symptoms. The authors concluded that hormone treatment with GnRH agonist and/or aromatase inhibition may be a therapeutic option to reduce tumor burden in unresectable BML disease or for those patients who wish to avoid surgical intervention. RECIST 1.1 guidelines, while traditionally used to evaluate tumor response to cancer therapeutics, may be useful in evaluating BML tumor burden response to hormone therapy.

The authors stated that this study was limited by the fact that 2 of their cases lack histopathologic confirmation of distant metastases (Cases 2 and 3). While these patients lacked histologic diagnosis, the available radiologic evidence supported the diagnosis of BML. The combination of new findings of lung nodules in relatively healthy women with a prior history of uterine surgery for leiomyomas strongly supported the diagnosis of BML, and did not require the patient to undergo the risks associated with pulmonary biopsies. In the cases reviewed here, pulmonary nodules also stabilized or regressed with therapy. In 1 patient, histologic diagnosis may have been associated with significant morbidity, given close proximity of lung nodules to the heart (Case 1). Another case demonstrated the reported close pathogenesis between intravenous leiomyomatosis (IVL) and BML, as the patient presented with an inferior vena cava/cardiac tumor consistent with intravenous leiomyomatosis as well as pulmonary lesions consistent with BML (Case 4). These researchers stated that the findings of this case-series study suggested

that hormonal therapy may be used in the treatment of BML, specifically by employing synergistic combinations with individual dosing. One patient who received high-dose anastrozole at 5 mg/daily (Case 4) instead of traditional dosing at 1 mg/daily, for example, illustrated that higher doses may be critical in obtaining disease regression in BML patients. Initial studies on anastrozole found doses of 1-mg and 10-mg equipotent in suppressing estradiol levels, but a recent study found large variations in drug metabolism and drug effect, indicating that anastrozole therapy might need to be individualized. In 3 of these patients (Case 1, 2, 3), these investigators found that more frequent dosing of Lupron (3.75 mg/3 weeks) than the standard regimen of Lupron (3.75 mg/4 weeks) was necessary for effective disease stabilization. These findings were consistent with the results of other authors who demonstrated variability in response to standard doses of Lupron, and ultimately adjusted frequency of dosing based on end organ response by measuring sex steroid levels. In this case-series study, specific doses and combinations of medications were effective for some patients and not for others. They stated that future hormonal treatments of BML could involve monitoring of therapy response with serum sex-steroids levels, and adjusting doses/frequency as needed.

Leuprolide for the Treatment of Borderline Leiomyosarcoma

An UpToDate reviews on "Treatment and prognosis of uterine leiomyosarcoma" (Hensley and Leitao, 2021) does not mention leuprolide as a therapeutic option.

Leuprolide for the Treatment of Disseminated Cellular Leiomyoma / Leiomyomatosis

D'Anna et al (1994) noted that it has been amply demonstrated that uterine leiomyoma possess estrogen receptors. On the basis of this presupposition, it is considered logical to use GnRH-agonists which, by reducing the level of estrogen, also reduce the volume of the leiomyoma, although to a varying extent. The maximum reduction which can be obtained occurs, according to published data, between 3 and 6 months of treatment, attaining mean values of approximately 50 %. In the author's experience the treatment period was shortened even further by administering only 2 vials of leuprolide depot each month to women who

subsequently underwent hysterectomy. The sample group comprised 30 women with uterine leiomyomatosis, of whom 15 were treated with a gonadotropin-releasing hormone agonist (GnRH-a) and 15 with placebo. The reduction of uterine volume was evaluated by echography and was found to be 40 % in the treated group, whereas no change was detected in the "placebo-group".

In a prospective, randomized study, Watanabe and Nakamura (1995) compared the effects of 2 different doses of a monthly depot injection of a GnRH-a on uterine cavity area in patients with uterine leiomyomata. A total of 36 pre-menopausal women, 25 to 52 years of age, with uterine leiomyomata were enrolled in this trial. Leuprolide acetate (LA) depot, 1.88 or 3.75 mg, was administered SC every 4 weeks for 24 weeks. Uterine cavity area before and after treatment was assessed by hysterosalpingography. The 1.88- and 3.75-mg LA depots significantly reduced uterine cavity area by 40.8 % and 40.2 %, respectively. No significant difference was observed between the 2 groups. The authors concluded that monthly injection of 1.88 or 3.75 mg LA depots appeared to reduce uterine cavity area to a similar extent in patients with uterine leiomyomata.

Tresukosol et al (1995) stated that intravascular leiomyomatosis is an uncommon uterine tumor characterized by grossly visible intravascular proliferation of benign smooth muscle. Based on its role in reducing the size of leiomyomas, leuprolide acetate was given as induction therapy for extensive inoperable intravascular leiomyomatosis. In this case report, a 44-year old woman, gravida 1, para 1-0-0-1, presented in July 1992 with abnormal uterine bleeding. Pelvic examination and ultrasonography (US) revealed the presence of a large irregular pelvic mass. At laparotomy, uterine and bilateral adnexal masses were noted extending up to the pelvic inlet and into the broad and infundibulo-pelvic ligaments. This tumor was not resectable. Based on histologic and immuno-peroxidase studies, the lesion was interpreted as a plexiform epithelioid smooth-muscle tumor of uncertain malignant potential. Leuprolide acetate depot therapy (7.5 mg every 4 weeks) was begun in September 1992 and continued for a total of 20 months. Maximal tumor regression was achieved after 9 months. Subsequent re-exploration at 20 months revealed a resectable tumor. Resection was accomplished successfully, leaving no apparent residual disease. The authors concluded that

leuprolide acetate induced tumor regression and rendered debulking surgery feasible in a patient with previously unresectable, widespread, retroperitoneal intravascular leiomyomatosis. Primary hormone therapy may provide alternative therapeutic options for certain cases of intravascular leiomyomatosis.

Burgos et al (2013) noted that Alport syndrome with diffuse leiomyomatosis (ASDL) is a complex combination that doesn't have a specific course of treatment. In this case report, these researchers presented the findings of a 44-year old woman with ASDL and detailed her treatment. The patient presented at the emergency room (ER) with symptoms of anemia, bronchial asthma, and abnormal uterine bleeding (AUB). She had diffused myomas in different areas of her body, including the esophagus and genital tract. She was treated by a multi-disciplinary team that included members from the hematology/oncology, pulmonary, interventional radiology, anesthesia, surgery, and gynecology services. A physician from interventional radiology performed an embolization of the uterine arteries to treat the patient's AUB. Surgery was carried out in May 2011 to remove the esophageal leiomyomas to improve her pulmonary function. Surgery included a distal esophagectomy, a proximal gastrostomy, and the resection of the leiomyomatous mass. In order to shrink the tumor in her genito-pelvic region so that it could be extirpated with the highest likelihood of success, the patient was treated with leuprolide acetate (3.75 mg/month for 4 months). In May 2012, the patient had a total abdominal hysterectomy (TAH), with a bilateral salpingo-ophorectomy (BSO), the excision of a leiomyoma, and a posterior colporrhaphy.

Akinseye et al (2020) reported the findings of a 54-year old woman with recently diagnosed multiple cardiac thrombi and pulmonary embolism that was treated with thrombolytics and anti-coagulants. She presented again with worsening dyspnea and was found to have persistent large cardiac thrombi on echocardiogram. Surgical findings revealed a single right atrial mass originating from inferior vena cava and extending into the pulmonary artery. The mass was successfully removed. Final pathology revealed a benign smooth muscle and vascular mass with estrogen and progesterone receptor positivity favoring uterine intravenous leiomyoma. She was discharged on warfarin and leuprolide therapy. This diagnosis

requires a high index of suspicion, especially in a middle-aged woman with right atrial mass and history of an existing leiomyoma, hysterectomy or myomectomy.

Yang et al (2020) stated that leiomyomatosis peritonealis disseminate (LPD) is a rare benign lesion primarily consisting of smooth muscle cells, which mostly affects pre-menopausal women. These researchers reported 3 women with LPD (age of 40 to 48 years) admitted for pelvic masses. All 3 LPD cases received laparoscopic uterine fibroid morcellation at 3, 8, and 14 years ago, respectively. Two cases were admitted for pelvic masses; 1 case was admitted for recurrent fibroids with pollakiuria. LPD was considered in 2 cases pre-operation according to imaging examination, and 1 of them received ultrasound (US)-guided biopsy of the lesion in the right lobe of the liver. One case was considered as recurrent fibroids pre-operation. After surgery, all cases were pathologically diagnosed as LPD consisting of benign smooth muscle cells. A total abdominal hysterectomy, salpingo-oophorectomy, and debulking was performed for all 3 cases. Intra-operative exploration revealed that the fibroids distributed in the mesentery (3 cases), broad ligament (1 case), omentum (1 case), liver (1 case), and rectus abdominis (1 case). No recurrence was found during post-operative follow-up (5 to 12 months). The authors concluded that pre-operative diagnosis of LPD was presented as a challenge due to non-specific clinical manifestations. Its diagnosis mainly depends on histopathologic evaluation. Surgery is still the primary treatment for LPD. For patients without reproductive desire, total abdominal hysterectomy, salpingo-oophorectomy, and debulking can be performed, and the affected tissue should be removed as much as possible based on the risk assessment. Again, this study did not provide any clinical data regarding the use of leuprolide for the management of patients with LPD.

Furthermore, UpToDate reviews on “Uterine fibroids (leiomyomas): Variants and smooth muscle tumors of uncertain malignant potential” (Stewart et al, 2020) and “Hereditary leiomyomatosis and renal cell cancer (HLRCC)” (Cowen, 2020) do not mention leuprolide as a management / therapeutic option.

Leuprolide for the Treatment of Endometrial Stromal Sarcoma

National Comprehensive Cancer Network's clinical practice guideline on "Uterine neoplasms" (Version 1.2021) does not provide a recommendation for leuprolide in low-grade endometrial stromal sarcomas.

Leuprolide for the Treatment of Perineal Leiomyoma

von-Waagner and colleagues (2014) reported on the case of a 40-year-old woman who presented with a large perineal mass with no rectal or vaginal involvement. Imaging could not rule out malignancy. She underwent wide surgical excision. Histological analysis revealed a large, atypical leiomyoma, measuring 24 × 12 × 8 cm. Follow-up after 2 years showed no recurrence; and she has been asymptomatic since surgery. This was the largest perineal leiomyoma reported so far. The authors concluded that giant perineal leiomyomas are uncommon tumors that can grow to large dimensions and are usually observed in young female patients. Imaging is helpful in characterizing and determining the extent of these tumors. Complete resection is recommended; and the local recurrence is rare. Leuprolide was not mentioned as a therapeutic option.

Furthermore, National Comprehensive Cancer Network's Drugs & Biologics Compendium (2022) does not list perineal leiomyoma as a recommended indication of leuprolide acetate for depot suspension.

Leuprolide Mesylate (Camcevi)

U.S. Food and Drug Administration (FDA)-Approved Indication

- Camcevi is indicated for the treatment of adult patients with advanced prostate cancer.

Compendial Use

- Prostate cancer

Camcevi (Forsee Pharmaceuticals Co. Ltd.) is supplied as a kit with a pre-filled, single-dose, sterile syringe for subcutaneous injection. Each pre-filled syringe delivers 42 mg leuprolide (equivalent to approximately

48 mg leuprolide mesylate). Leuprolide, a GnRH agonist, acts as an inhibitor of gonadotropin secretion. Subcutaneous administration of single daily doses of leuprolide result in an initial increase in circulating levels of LH and FSH, leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males). However, continuous daily administration of leuprolide results in decreased levels of LH and FSH. In males, testosterone is reduced to below castration levels. These decreases generally occur within 2 to 4 weeks after initiation of treatment, and castration levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to 5 years (Foresee Pharmaceuticals, 2021a).

Camcevi is contraindicated for persons with a hypersensitivity to GnRH, GnRH agonist analogs, or any of the components of Camcevi. The label includes the following warnings and precautions:

- Tumor Flare: Transient worsening of bone pain, uretral obstruction, spinal cord compression, or the occurrence of additional signs and symptoms of prostate cancer may develop during the first few weeks of treatment;
- Hyperglycemia and Diabetes: Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists;
- Cardiovascular Diseases: Increased risk of myocardial infarction, sudden cardiac death, and stroke has been reported in men receiving GnRH agonists;
- QT/QTc Prolongation: Androgen deprivation therapy may prolong the QT interval;
- Convulsions;
- Embryo-Fetal Toxicity: may cause fetal harm.

The most common (>10%) adverse reactions include hot flash, hypertension, injection site reactions, upper respiratory tract infections, musculoskeletal pain, fatigue, and pain in extremity.

In May 2021, the FDA approved the New Drug Application (NDA) for Camcevi 42 mg, a ready-to-use 6-month subcutaneous depot formulation of leuprolide mesylate, as a treatment for advanced prostate cancer. FDA approval was based on an open label, single arm, multinational, Phase 3

study evaluating the efficacy of Camcevi in 137 patients with advanced prostate carcinoma who had a baseline morning serum testosterone level greater than 150 ng/dL and Eastern Cooperative Oncology Group performance status of 2 or less. Camcevi was administered subcutaneously at a dose of 42 mg initially on Day 0 and on Week 24. The major efficacy outcome measure was medical castration rate, defined as achieving and maintaining serum testosterone suppression to 50 ng/dL or less by Week 4 through Week 48 of treatment. Following the first injection of Camcevi, serum testosterone levels were suppressed to 50 ng/dL or less by Week 4 in 98.5% of the patients; and from Week 4 through Week 48 in 97.0% of patients. In conclusion, the primary efficacy endpoint was successfully achieved in 97% of patients, with mean testosterone concentration suppressed below castrate levels to 17.6 ng/dL on Day 28 (Foresee Pharmaceuticals, 2021a, 2021b).

Lupaneta Pack

U.S. Food and Drug Administration (FDA)-Approved Indications

- Lupaneta Pack is indicated for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms.

  Limitations of Use:

  Duration of use is limited due to concerns about adverse impact on bone mineral density. The initial treatment course of Lupaneta Pack is limited to six months. A single retreatment course of not more than six months may be administered after the initial course of treatment if symptoms recur. Use of Lupaneta Pack for longer than a total of 12 months is not recommended.

Lupaneta Pack contains leuprolide acetate, a gonadotropin-releasing hormone (GnRH) agonist and norethindrone acetate, a progestin. Leuprolide acetate for depot suspension is a long-acting GnRH analog. A single injection of leuprolide acetate for depot suspension results in an initial elevation followed by a prolonged suppression of pituitary gonadotropins. Repeated dosing at quarterly intervals results in decreased secretion of gonadal steroids; consequently, tissues and

functions that depend on gonadal steroids for their maintenance become quiescent. This effect is reversible on discontinuation of drug therapy. Leuprolide acetate is not active when given orally. Norethindrone acetate induces secretory changes in an estrogen-primed endometrium (AbbVie, 2015).

Endometriosis is defined as the presence of normal endometrial mucosa (glands and stroma) abnormally grows in locations other than the uterine cavity. About one third of women with endometriosis remain asymptomatic while some women with endometriosis have some degree of pelvic pain. Treatment options for symptomatic endometriosis include oral contraceptives, nonsteroidal anti-inflammatory drugs, high-dose progestins, androgenic agents and GnRH agonists.

Several GnRH agonists including leuprolide acetate have been shown to be effective in reducing the pelvic pain associated with endometriosis, often when other medical therapies are failed. However, treatment with GnRH agonist is associated with hypoestrogenic side effects, including progressive bone loss and vasomotor symptoms, such as hot flashes and headache and vaginal dryness. The use of hormonal add-back therapy can alleviate the hypoestrogenic symptoms associated with a GnRH agonist, while preserving therapeutic efficacy.

Lupaneta Pack is a kit consisting of the co-packaging of two previously FDA-approved drugs including leuprolide acetate for depot suspension for intramuscular use and norethindrone acetate tablets for oral use. It is indicated for the management of initial and recurrent painful symptoms of endometriosis.

Leuprolide acetate, a gonadotropin-releasing hormone (GnRH), inhibits the production of estrogen through negative feedback of pituitary gonadotropins resulting in decreasing endometrial implants and symptoms of endometriosis such as pelvic pain.

Norethindrone acetate, a progestin, is used to decrease the hypoestrogenic effects associated with leuprolide acetate and possibly mitigate bone mineral density loss. Norethindrone acetate is a progestin that has both estrogenic and androgenic properties and is effective as an

add-back regimen without estrogen supplementation. Norethindrone add-back therapy has been shown beneficial effects on bone mineral density and vasomotor symptoms associated with GnRH agonist therapy.

There have been postmarketing reports of convulsions in patients on leuprolide acetate (e.g. Lupron Depot) therapy. These included patients with and without concurrent medications and comorbid conditions.

The most common adverse reactions for leuprolide acetate for depot suspension (>10%) include hot flashes/sweats, headache/migraine, depression/emotional lability, nausea/vomiting, nervousness/anxiety, insomnia, pain, acne, asthenia, vaginitis, weight gain, constipation/diarrhea. The most common adverse reaction for progestins include breakthrough bleeding and spotting (AbbVie, 2015).

Lupaneta Pack (leuprolide acetate and norethindrone acetate) should not be utilized in persons with known hypersensitivity to Lupron (leuprolide acetate), gonadotropin releasing hormone (GnRH), GnRH analogs, or any of the excipients in the formulations.

Lupaneta Pack should be discontinued if there is a sudden partial or complete loss of vision or sudden onset of proptosis, diplopia, or migraine.

Observe patients with history of depression and Lupaneta Pack should be discontinued if the depression recurs to a serious degree.

Triptorelin (Trelstar, Triptodur)

U.S. Food and Drug Administration (FDA)-Approved Indications

- Trelstar

  Trelstar is indicated for the palliative treatment of advanced prostate cancer.

- Triptodur

Triptodur is indicated for the treatment of pediatric patients 2 years of age and older with central precocious puberty (CPP).

Compendial Uses

- Trelstar
  - Prostate cancer
  - Preservation of ovarian function
  - Breast cancer – ovarian suppression
  - Gender dysphoria (also known as gender non-conforming or transgender persons)
- Triptodur
  - Gender dysphoria (also known as gender non-conforming or transgender persons)
  - Preservation of ovarian function
  - Prevention of recurrent menstrual related attacks in acute porphyria

Triptorelin is a gonadotropin-releasing hormone (GnRH) agonist which results in sustained decrease in LH and FSH secretion after continuous administration. Triptorelin is available as Triptodur (Arbor Pharmaceuticals, LLC) and Trelstar (Verity Pharmaceuticals); however, they are FDA approved for different indications.

Triptorelin (Triptodur) carries the following warnings and precautions:

- Initial rise of gonadotropins and sex steroid levels: An increase in clinical signs and symptoms of puberty may be observed during the first 2-4 weeks of therapy since gonadotropins and sex steroids rise above baseline because of the initial stimulatory effect of the drug.
- Psychiatric events have been reported in patients taking GnRH agonists. Events include emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms.

- Convulsions have been observed in patients with or without a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions.

In clinical trials for Triptodur, the most common adverse reactions (≥4.5%) are injection site reactions, menstrual (vaginal) bleeding, hot flush, headache, cough, and infections (bronchitis, gastroenteritis, influenza, nasopharyngitis, otitis externa, pharyngitis, sinusitis, and upper respiratory tract infection).
Trelstar, Trelstar Depot and Trelstar LA were approved by the FDA for the palliative treatment of advanced prostate cancer. It offers an alternative treatment for prostate cancer when orchiectomy or estrogen administration is either not indicated or unacceptable to the patient.

Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist analog. It can be anticipated that long periods of medical castration in men will have effects on bone density.

Trelstar should not be used in known cases of hypersensitivity to triptorelin, gonadotropin releasing hormone (GnRH), GnRH analogs, or any of the excipients in the formulations.

Trelstar should not be used concomitantly with other LHRH agents.

Arriagada et al (2005) evaluated the role of ovarian suppression in patients with early breast cancer previously treated with local surgery and adjuvant chemotherapy. A total of 926 pre-menopausal patients with completely resected breast cancer and either axillary node involvement or histological grade 2 or 3 tumors were randomized after surgery to adjuvant chemotherapy alone (control arm) or adjuvant chemotherapy plus ovarian suppression (ovarian suppression arm). Ovarian suppression was obtained by either radiation-induced ovarian ablation or triptorelin for 3 years. The analyses were performed with Cox models stratified by center. Median follow-up was 9.5 years. Mean age was 43 years. Ninety per cent of patients had histologically proven positive axillary nodes, 63 % positive hormonal receptors and 77 % had received

an anthracycline-based chemotherapy regimen. Ovarian suppression was by radiation-induced ovarian ablation (45 % of patients) or with triptorelin (48 %). At the time of randomization, all patients had regular menses or their FSH and estradiol levels indicated a pre-menopausal status. The 10-year disease-free survival rates were 49 % (95 % CI: 44 % to 54 %) in both arms (p = 0.51). The 10-year overall survival rates were 66 % (95 % CI: 61 % to 70 %) for the ovarian suppression arm and 68 % (95 % CI: 63 % to 73 %) for the control arm (p = 0.19). There were no variations in the treatment effect according to age, hormonal receptor status or ovarian suppression modality. However, in patients less than 40 years of age and with estrogen receptor-positive tumors, ovarian suppression significantly decreased the risk of recurrence (p = 0.01). The authors concluded that the results of this trial, after at least 10 years of follow-up, do not favor the use of ovarian suppression after adjuvant chemotherapy. They stated that the potential beneficial effect in younger women with hormone-dependent tumors should be further assessed.

Jannuzzo et al (2009) noted that LHRH agonists (e.g., triptorelin) reduce ovarian estrogen production in pre-menopausal women with hormone-sensitive breast cancer. Aromatase inhibitors (e.g., exemestane) inhibit extra-ovarian production of estrogen and may further reduce circulating estrogens when combined with an LHRH agonist. These researchers examined the effects of estrogen suppression in pre-menopausal women following 8 weeks of treatment with exemestane and triptorelin versus triptorelin alone. Healthy pre-menopausal women were randomized to receive 3.75 mg triptorelin (T) on days 1 and 29 with 25 mg exemestane (EX) or matched placebo once-daily for 8 weeks, from day 1 to day 56. The primary objective was to evaluate the effect of T +/- EX on estradiol (E(2)) suppression by comparing the AUC (days 36 to 57) for the 2 treatments. Secondary objectives included evaluation of estrone (E(1)), LH, and FSH suppression; effects of EX on the T-induced gonadotrophin and estrogen flare; pharmacokinetics (PK); and safety. A total of 28 subjects (14 in each arm) were evaluable for efficacy and PK. Mean plasma estrogen levels (AUC (days 36 to 57)) were significantly lower for subjects who received T + EX than for subjects who received T alone (20.6 versus 54.0 pg d/ml [-62 %; p < 0.05], and 38.9 versus 198.0 pg d/ml [-80 %; p < 0.01] for E(2) and E(1), respectively). Co-administration of EX did not affect the initial flare or subsequent suppression of LH and FSH following the first dose of T, or the PK of T. Both treatments were

well-tolerated. The authors concluded that co-administration of T and EX resulted in greater estrogen suppression than when T was given alone. They noted that these findings could translate into improved clinical outcomes for pre-menopausal breast cancer patients receiving LHRH agonists.

Francis et al (2015) noted that suppression of ovarian estrogen production reduces the recurrence of hormone-receptor-positive early breast cancer in premenopausal women, but its value when added to tamoxifen is uncertain. These investigators randomly assigned 3,066 premenopausal women, stratified according to prior receipt or non-receipt of chemotherapy, to receive 5 years of tamoxifen, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression. The primary analysis tested the hypothesis that tamoxifen plus ovarian suppression (triptorelin was used in 80.7 % of the patients) would improve disease-free survival, as compared with tamoxifen alone. In the primary analysis, 46.7 % of the patients had not received chemotherapy previously, and 53.3 % had received chemotherapy and remained premenopausal. After a median follow-up of 67 months, the estimated disease-free survival rate at 5 years was 86.6 % in the tamoxifen-ovarian suppression group and 84.7 % in the tamoxifen group (hazard ratio for disease recurrence, second invasive cancer, or death, 0.83; 95 % confidence interval [CI]: 0.66 to 1.04; p = 0.10). Multi-variable allowance for prognostic factors suggested a greater treatment effect with tamoxifen plus ovarian suppression than with tamoxifen alone (hazard ratio, 0.78; 95 % CI: 0.62 to 0.98). Most recurrences occurred in patients who had received prior chemotherapy, among whom the rate of freedom from breast cancer at 5 years was 82.5 % in the tamoxifen-ovarian suppression group and 78.0 % in the tamoxifen group (hazard ratio for recurrence, 0.78; 95 % CI: 0.60 to 1.02). At 5 years, the rate of freedom from breast cancer was 85.7 % in the exemestane-ovarian suppression group (hazard ratio for recurrence versus tamoxifen, 0.65; 95 % CI: 0.49 to 0.87). the authors concluded that adding ovarian suppression to tamoxifen did not provide a significant benefit in the overall study population. However, for women who were at sufficient risk for recurrence to warrant adjuvant chemotherapy and who remained premenopausal, the addition of ovarian suppression improved disease outcomes. Further improvement was seen with the use of exemestane plus ovarian suppression.

The authors also noted that "Any benefit from ovarian suppression must be weighed against the adverse effects. Adding ovarian suppression to tamoxifen resulted in increased adverse events -- most notably, menopausal symptoms, depression, and adverse events with possible long-term health implications such as hypertension, diabetes, and osteoporosis. When exemestane is combined with ovarian suppression, adverse sexual, musculoskeletal, and bone-density effects are more frequent than with tamoxifen plus ovarian suppression. Longer follow-up is required, because SOFT is currently underpowered, and the overall survival analysis is premature after 5% of patients have died".

In a systematic review and meta-analysis, Bedaiwy and associates (2011) examined if GnRHa co-treatment with chemotherapy provides better reproductive outcomes for women at risk of POF as a side-effect of gonadotoxic chemotherapy. Electronic and manual searches (e.g., MEDLINE, EMBASE, CENTRAL) up to January 2010 were performed to identify RCTs comparing GnRH co-treatment with chemotherapy alone in pre-menopausal women. Main outcome measures included incidence of POF after treatment, incidence of women with resumption of ovulation, POF after an initial normal cycle, normal cycles but abnormal markers of ovarian reserve, spontaneous occurrence of pregnancy after treatment, and time to re-establishment of menstruation; data were also extracted to allow for an intention-to-treat analysis. A total of 28 RCTs were identified, but only 6 met the inclusion criteria. Data were only available for the incidence of women with new onset of POF, resumption of ovulation, and occurrence of pregnancy. The incidence of POF or resumption of ovulation both demonstrated a statistically significant difference in favor of the GnRH co-treatment. The occurrence of spontaneous pregnancy showed no statistically significant difference between GnRH co-treatment and the control groups. The authors concluded that evidence from RCTs suggests a potential benefit of GnRH co-treatment with chemotherapy in pre-menopausal women, with higher rates of spontaneous resumption of menses and ovulation but not improvement in pregnancy rates. Data relating to study quality and possible bias for the majority of the outcomes in this review were not available, denoting possible selective reporting of trial data.

Del Mastro et al (2011) examined the effect of the temporary ovarian suppression obtained by administering triptorelin during chemotherapy on the incidence of early menopause in young patients with breast cancer undergoing adjuvant or neoadjuvant chemotherapy. The PROMISE-GIM6 (Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients-Gruppo Italiano Mammella 6) study, a parallel, randomized, open-label, phase III superiority trial, was conducted at 16 sites in Italy and enrolled 281 patients between October 2003 and January 2008. Patients were pre-menopausal women with stage I through III breast cancer who were candidates for adjuvant or neoadjuvant chemotherapy. Assuming a 60 % rate of early menopause in the group treated with chemotherapy alone, it was estimated that 280 patients had to be enrolled to detect a 20 % absolute reduction in early menopause in the group treated with chemotherapy plus triptorelin. The intention-to-treat analysis was performed by including all randomized patients and using imputed values for missing data. Before beginning chemotherapy, patients were randomly allocated to receive chemotherapy alone or combined with triptorelin. Triptorelin was administered intramuscularly at a dose of 3.75 mg at least 1 week before the start of chemotherapy and then every 4 weeks for the duration of chemotherapy. Main outcome measure was incidence of early menopause (defined as no resumption of menstrual activity and post-menopausal levels of FSH and estradiol 1 year after the last cycle of chemotherapy). The clinical and tumor characteristics of the 133 patients randomized to chemotherapy alone and the 148 patients randomized to chemotherapy plus triptorelin were similar. Twelve months after the last cycle of chemotherapy (last follow-up, August 18, 2009), the rate of early menopause was 25.9 % in the chemotherapy-alone group and 8.9 % in the chemotherapy plus triptorelin group, an absolute difference of -17 % (95 % CI: -26 % to -7.9 %; $p < 0.001$). The odds ratio for treatment-related early menopause was 0.28 (95 % CI: 0.14 to 0.59; $p < 0.001$). The authors concluded that the use of triptorelin-induced temporary ovarian suppression during chemotherapy in pre-menopausal patients with early-stage breast cancer reduced the occurrence of chemotherapy-induced early menopause.

In an editorial that accompanied the afore-mentioned study, Rugo and Rosen (2011) noted that GnRH agonist therapy to suppress ovarian function during chemotherapy is an additional treatment that can potentially expand fertility possibilities in patients with hormone-

insensitive disease. On the other hand, they stated that the use of GnRH agonists concomitant with chemotherapy can not be recommended as a standard treatment and should be approached with caution in women with hormone-sensitive disease.

In a prospective randomized trial, Munster et al (2012) evaluated the effectiveness of triptorelin to preserve ovarian function in women treated with chemotherapy for early-stage breast cancer. Pre-menopausal women age 44 years or younger were randomly assigned to receive either triptorelin or no triptorelin during (neo)adjuvant chemotherapy and were further stratified by age (less than 35, 35 to 39, greater than 39 years), estrogen receptor status, and chemotherapy regimen. Objectives included the resumption of menses and serial monitoring of FSH and inhibin A and B levels. Targeted for 124 patients with a planned 5-year follow-up, the trial was stopped for futility after 49 patients were enrolled (median age of 39 years; range of 21 to 43 years); 47 patients were treated according to assigned groups with 4 cycles of adriamycin plus cyclophosphamide alone or followed by 4 cycles of paclitaxel or 6 cycles of fluorouracil, epirubicin, and cyclophosphamide. Menstruation resumed in 19 (90 %) of 21 patients in the control group and in 23 (88 %) of 26 in the triptorelin group ($p = 0.36$). Menses returned after a median of 5.8 months (range of 1 to 19 months) after completion of chemotherapy in the triptorelin versus 5.0 months (range of 0 to 28 months) in the control arm ($p = 0.58$). Two patients (aged 26 and 35 years at random assignment) in the control group had spontaneous pregnancies with term deliveries. Follicle-stimulating hormone and inhibin B levels correlated with menstrual status. The authors concluded that when stratified for age, estrogen receptor status, and treatment regimen, amenorrhea rates on triptorelin were comparable to those seen in the control group. Thus, these findings indicated that the use of GnRH agonists in pre-menopausal patients treated with contemporary neoadjuvant chemotherapy does not offer a benefit in preserving ovarian function compared with patients not treated with GnRH, and it should not be recommended.

Commenting on the study by Munster et al, Partridge (2012) stated that "the role of ovarian suppression through chemotherapy remains uncertain for prevention of premature menopause. The value of this strategy is especially unclear for fertility preservation because of the lack of rigorous data from any study to show that actual fertility outcomes are improved

with GnRH treatment throughout chemotherapy. Given the current level of evidence, women who are interested in future fertility and the providers who are assisting them in these often difficult decisions should not rely on GnRH agonist treatment during chemotherapy for preservation of menstrual and ovarian function or fertility".

Endocrine Society Guidelines on endocrine therapy of transsexual persons (Hembree, et al., 2009) recommend the use of gonadotropin analogues. For female-to-male transsexual persons, the guidelines state that gonadotropin-releasing hormone analogues or depot medroxyprogesterone may also be used to stop menses prior to testosterone treatment and to reduce estrogens to levels found in biological males. For male to female transsexual persons, the guidelines states that estrogens may be used with or without antiandrogens or a GnRH agonist. The guidelines discuss a study by Dittrich, et al., which reported a series of 60 male to female transsexual persons who used monthly the GnRH agonist goserelin acetate in combination with estrogen, and found this regimen to be effective in reducing testosterone levels with low incidence of adverse reactions.

Triptorelin for Suppression of Ovarian Function in Pre-Menopausal Women with Hodgkin's Lymphoma

National Comprehensive Cancer Network Drugs & Biologics Compendium (NCCN, 2021) does not list preservation of ovarian function or Hodgkin lymphoma as recommended indications of triptorelin.

Benign Prostatic Hyperplasia

Sakai et al (2015) noted that degarelix is a GnRH receptor (GnRHR) antagonist approved for use in patients with prostate cancer (PCa) who need androgen deprivation therapy. The slowing of prostate cell growth is a common goal shared by PCa and benign prostatic hyperplasia (BPH) patients, and the effect of degarelix on BPH cells has not yet been investigated. These researchers evaluated the direct effect of degarelix on human BPH primary cell growth. Gene expression studies performed with BPH (n = 11), stage 0 (n = 15), and PCa (n = 65) human specimens demonstrated the presence of GNRHR1 and GNRHR2 and their respective endogenous peptide ligands. BPH-isolated epithelial and

stromal cells were either cultured alone or co-cultured (1:4 or 4:1 ratio of epithelial to stromal cells) and subsequently treated with increasing concentrations of degarelix. Degarelix treatment induced a decrease in cell viability and cell proliferation rates, which occurred in parallel to an increase in apoptosis. Both epithelial and stromal BPH cells were sensitive to degarelix treatment and, interestingly, degarelix was also effective when the cells were growing in a co-culture microenvironment. In contrast to degarelix, the GnRHR agonists, leuprolide and goserelin, exerted no effect on the viability of BPH epithelial or stromal cells. The authors concluded that (i) prostate tissues express GNRHR and are a potential target for degarelix; and (ii) degarelix directly inhibits BPH cell growth through a decrease in cell proliferation and an increase in apoptosis.

Furthermore, an UpToDate review on "Medical treatment of benign prostatic hyperplasia" (Cunningham and Kadmon, 2016) does not mention degarelix as a therapeutic option.

Gonadotropin-Releasing Hormone Analogs for Girls with Gender Dysphoria

Joseph and associates (2019) noted that more young individuals with gender dysphoria (GD) are undergoing hormonal intervention starting with GnRHa treatment. The impact on bone density is unclear, with guidelines mentioning that bone mineral density (BMD) should be monitored without suggesting when. These investigators examined a cohort of adolescents from a single center to examine if there were any clinically significant changes in BMD and bone mineral apparent density (BMAD) while on GnRHa therapy. They carried out a retrospective review of 70 subjects aged 12 to 14 years, referred to a national center for the management of GD (2011 to 2016) who had yearly dual energy X-ray absorptiometry (DXA) scans. BMAD scores were calculated from available data. Two analyses were carried out, a complete longitudinal analysis (n = 31) where patients had scans over a 2-year treatment period, and a larger cohort over the 1st treatment year (n = 70) to extend the observation of rapid changes in lumbar spine BMD when puberty was blocked. At baseline trans-boys had lower BMD measures than trans-girls. Although there was a significant fall in hip and lumbar spine BMD and lumbar spine BMAD Z-scores, there was no significant change in the absolute values of

hip or spine BMD or lumbar spine BMAD after 1 year on GnRHa and a lower fall in BMD/BMAD Z-scores in the longitudinal group in the 2nd year. The authors concluded that these findings suggested that reference ranges may need to be re-defined for this select patient cohort; and long-term BMD recovery studies on sex hormone treatment are needed.

Schagen and colleagues (2020) stated that hormonal interventions in adolescents with GD may have adverse effects, such as reduced bone mineral accrual. In a prospective, observational study, these researchers described bone mass development in adolescents with GD treated with GnRHa, subsequently combined with gender-affirming hormones. A total of 51 trans-girls and 70 trans-boys receiving GnRHa and 36 trans-girls and 42 trans-boys receiving GnRHa and gender-affirming hormones, subdivided into early- and late-pubertal groups. Main outcome measures included BMAD, age- and sex-specific BMAD z-scores, and serum bone markers. At the start of GnRHa treatment, mean areal BMD (aBMD) and BMAD values were within the normal range in all groups. In trans-girls, the mean z-scores were well below the population mean. During 2 years of GnRHa treatment, BMAD stabilized or showed a small decrease, whereas z-scores decreased in all groups. During 3 years of combined administration of GnRHa and gender-affirming hormones, a significant increase of BMAD was found; z-scores normalized in trans-boys but remained below zero in trans-girls. In trans-girls and early pubertal trans-boys, all bone markers decreased during GnRHa treatment. The authors concluded that treatment with GnRHa resulted in a stabilization and maintenance of previously achieved bone mass in the lumbar spine but a small decrease in BMAD of the femoral neck of the non-dominant hip. Gender-affirming hormone treatment increased bone accretion and normalized the age- and sex-specific BMAD z-scores in trans-boys. Trans-girls had lower BMAD z-scores, especially the late-pubertal group, but as z-scores were already lower at baseline, this may be due to other factors than the endocrine treatment, such as lifestyle factors. The consequences of lower BMD for long-term bone health in these individuals remains unclear. Moreover, these researchers stated that future studies should examine peak bone mass in those who started treatment as adolescents and evaluate clinically important outcomes such as fracture risk in this population.

Multiple Sclerosis

Guzman-Soto and colleagues (2016) noted that recent findings have shown that GnRH administration in an animal model of multiple sclerosis (experimental autoimmune encephalomyelitis, EAE) improves clinical signs of locomotion. These researchers examined if the administration of the synthetic analog of GnRH, leuprolide acetate (LA) -- besides its effects on clinical signs of locomotion -- also has an effect on the activation/expression levels of molecular markers of EAE, namely transcription nuclear factor (NF)-κB and the pro-inflammatory cytokines IL-1β, IL-17A, IL-23 and TNF-α. EAE spinal cords were collected from control and LA-administered rats. Lumbar sections were processed at 4 different time points during the course of the disease to analyze NF-κB activation by chemiluminescent Western blot, and during the EAE recovery phase to evaluate pro-inflammatory cytokine levels by quantitative real-time PCR. It was found that LA administration to EAE rats promoted a significant reduction of NF-κB activation during the course of the disease and also decreased the mRNA expression levels of the pro-inflammatory cytokines IL-1β, IL-17A and TNF-α in the EAE recovery phase; both effects were consistent with the decrease in the severity of clinical signs of locomotion induced by the treatment. The authors concluded that LA caused a reduction in the severity of locomotor activity, as well as in the activation of NF-κB and the number of pro-inflammatory markers in rats with EAE. They stated that these findings suggested the use of this agonist as a potential therapeutic approach for multiple sclerosis.

Ovarian Preservation During Chemotherapy

The American College of Rheumatology's guidelines on "Screening, treatment, and management of lupus" (2012) failed to achieve consensus on the use of leuprolide for fertility preservation.

Park et al (2014)examined the effects of a GnRH agonist (GnRHa) depot (leuprolide) in women with gynecologic cancer receiving chemotherapy while taking a continuous add-back on the prevention of premature ovarian failure. A total of 14 pre-menopausal patients with gynecological malignancies who had undergone conservation of ovaries surgery received a GnRH-a depot plus add-back until chemotherapy was

completed; 4 weeks thereafter, a hormonal profile (FSH) was measured. The mean FSH level was 15.8 IU/L. All patients exhibited a restoration of ovarian failure during follow-up; 1 patient became pregnant during the follow-up period. The authors concluded that in the short-term, GnRHa appeared to protect ovarian function and ability to achieve pregnancy following chemotherapy. They stated that the result of this study needs further elucidation in a large randomized controlled trial (RCT).

Kim et al (2014) determined the impact of concurrent use of GnRHa on relapse-free and overall survival, and established the oncologic safety of ovarian protection with GnRHa. Pre-menopausal women aged between 20 and 40 years who received adjuvant chemotherapy for breast cancer from January 2002 to April 2012 were classified into 2 groups: (i) treatment with GnRHa for ovarian protection during chemotherapy, (ii) without ovarian protection. A propensity score matching strategy was used to create matched sets of 2 groups with age, pathologic stage, hormone receptor, and Her2 status. A total of 101 patients treated with concurrent GnRHa during chemotherapy were compared with 335 propensity score-matched patients. Among them, 81.2 % were younger than 35 years and 58.4 % were hormone responsive. Survival analysis using stratified Cox regression showed that women treated with concurrent GnRHa had better recurrence-free survival (adjusted hazard ratio [HR] 0.21, p = 0.009; unadjusted HR 0.33, p = 0.034). The authors concluded that ovarian protection using GnRHa can be safely considered for young women with breast cancer in terms of oncologic outcomes. Moreover, they stated that further studies are needed to evaluate the long-term outcomes of concurrent GnRHa use with chemotherapy.

In a systematic review and meta-analysis, Vitek and associates (2014) examined if concurrent use of GnRHa with chemotherapy preserves ovarian function in women with breast cancer who did not use tamoxifen. Pre-menopausal women with breast cancer treated with chemotherapy who did not receive tamoxifen were included in this analysis. Main outcome measures were OR of resumption of menses 1 year or more after chemotherapy. Searches were conducted in PubMed, Scopus, Cochrane Trials Register, and the National Research Register through March 2014, and all randomized trials that reported resumption of menses 1 year or more after GnRHa with chemotherapy or chemotherapy

alone among women with breast cancer who did not receive tamoxifen were included. A total of 4 studies were analyzed in the meta-analysis and included 252 patients (GnRHa with chemotherapy, n = 131; chemotherapy alone, n = 121). There was no significant difference in the rate of return of menses between the 2 groups (OR, 1.47; 95 % CI: 0.60 to3.62). Heterogeneity among the trials was not significant (I2 = 16.6 %). The authors concluded that concurrent GnRHa with chemotherapy may not preserve ovarian function in women with breast cancer; furthermore, randomized data were limited regarding fertility after concurrent use of GnRHa with chemotherapy.

Bildik et al (2015) stated that RCTs of the co-administration of GnRHa with adjuvant chemotherapy to preserve ovarian function have shown contradictory results. This fact, together with the lack of a proven molecular mechanism of action for ovarian protection with GnRHa places this approach as a fertility preservation strategy under scrutiny. These researchers provided in-vitro evidence for or against the role of GnRHa in the prevention of chemotherapy-induced damage in human ovary. This translational research study of ex-vivo and in-vitro models of human ovary and granulosa cells was conducted in a university hospital between 2013 and 2015. Ovarian cortical pieces (n = 15, age of 14 to 37 years) and mitotic non-luteinized (COV434 and HGrC1) and non-mitotic luteinized human granulosa cells (HLGC) expressing GnRH receptor were used for the experiments. The samples were treated with cyclophosphamide, cisplatin, paclitaxel, 5-FU, or TAC combination regimen (docetaxel, adriamycin and cyclophosphamide) with and without GnRHa leuprolide acetate for 24 hours. DNA damage, apoptosis, follicle reserve, hormone markers of ovarian function and reserve (estradiol (E2), progesterone (P) and anti-mullerian hormone (AMH)) and the expression of anti-apoptotic genes (bcl-2, bcl-xL, bcl-2L2, Mcl-1, BIRC-2 and XIAP) were compared among control, chemotherapy and chemotherapy + GnRHa groups. The greatest magnitude of cytotoxicity was observed in the samples treated with cyclophosphamide, cisplatin and TAC regimen. Exposure to these drugs resulted in DNA damage, apoptosis and massive follicle loss along with a concurrent decline in the steroidogenic activity of the samples. Co-administration of GnRHa and chemotherapy agents stimulated its receptors and raised intracellular cAMP levels. But it neither activated anti-apoptotic pathways nor prevented follicle loss, DNA damage and apoptosis induced by these drugs. The authors concluded that GnRHa

treatment with chemotherapy did not prevent or ameliorate ovarian damage and follicle loss in-vitro. They stated that these data can be useful when consulting a young patient who may wish to receive GnRH treatment with chemotherapy to protect her ovaries from chemotherapy-induced damage.

Elgindy and colleagues (2015) examined if GnRH analog administration during chemotherapy can protect against development of ovarian toxicity. MEDLINE (1966 to present), EMBASE (1980 to present), Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov were searched through March 2015 using the phrases: "gonadotropin-releasing hormone", "chemotherapy" and "premature ovarian failure". Hand-search on conference abstracts, SCOPUS, and ISI Web of Science were also searched. Published English-language RCTs comparing resumption of ovarian function between GnRH analogs plus chemotherapy with chemotherapy without GnRH analogs were included. Studies including women with pelvic metastases or recent history of receiving chemotherapy were excluded. Accordingly, 10 eligible trials (907 women) were analyzed. The primary outcome was the proportion of women with resumed ovarian function (defined as resumption of menstruation, prevention of chemotherapy-induced ovarian failure, or both) at the longest follow-up after the end of chemotherapy. Secondary outcomes were evaluating ovarian reserve parameters and pregnancy. Risk ratio was used to integrate qualitative results and MD was used for quantitative data. Gonadotropin-releasing hormone analog co-treatment did not significantly increase ovarian function resumption (320/468 [68.4 %] in GnRH analog arm and 263/439 [59.9 %] in the chemotherapy alone arm; risk ratio 1.12, 95 % CI: 0.99 to 1.27). No protective effect existed after subgroup analyses (type of malignancy [p = 0.31], age [p = 0.14], and GnRH analog type [p = 0.44]). These researchers noted that GnRH analogs did not protect any of ovarian reserve parameters, whether FSH (MD -2.63, 95 % CI: -7.33 to 2.07), antral follicle count (MD 1.66, 95 % CI: -0.69 to 4.01), or AMH (MD 0.31, 95 % CI: -0.41 to 1.03). Spontaneous pregnancy was also comparable (RR 1.63, 95 % CI: 0.94 to 2.82). The authors concluded that GnRHa administration during chemotherapy did not appear to protect the ovaries from gonadal toxicity. It is not a reliable method for fertility preservation.

Spinal Cord Injury

Diaz Galindo and colleagues (2015) stated that GnRH and its synthetic analog LA, a GnRH agonist, have neurotrophic properties. These researchers examined if administration of LA can improve locomotor behavior, gait, micturition reflex, spinal cord morphology and the amount of microglia in the lesion epicenter after spinal cord injury (SCI) in rats. Rats with spinal cord compression injury were administered LA or saline solution for 5 weeks. At the 5th week, LA-treated rats showed locomotor activity recovery by 38 %, had improvement in kinematic gait and exhibited voiding reflex recovery by 60 %, as compared with the 1st week. In contrast, saline solution-treated rats showed locomotor activity recovery only by 7 %, but voiding reflex did not recover. More importantly, LA treatment reduced microglial immunological reaction and induced a trend towards greater area of white and gray matter in the spinal cord. The authors concluded that LA has great potential to repair SCI.

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Leuprolide Acetate / Norethindrone Acetate (Lupaneta Pack)

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