# GONADOTROPIN RELEASING HORMONE ANALOGS

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## INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Drug Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Drug Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

## BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

Treatment for gender dysphoria is sometimes referred to as: gender identity disorder treatment, sex transformation surgery, sex change, sex reversal, gender change, transsexual surgery, transgender surgery and sex or gender reassignment. These terms are used interchangeably throughout this document, and, for purposes of this document, are intended to have the same meaning.

### Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be

removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

## COVERAGE RATIONALE

Please refer to the Oncology Medication Clinical Coverage Policy for updated information based on the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium® (NCCN Compendium®) for oncology indications.

This policy refers to the following gonadotropin releasing hormone analog (GnRH analog) drug products:
- Firmagon (degarelix)
- Lupaneta Pack (leuprolide acetate injection & norethindrone acetate tablets)
- Lupron Depot (leuprolide acetate)
- Lupron Depot-Ped (leuprolide acetate)
- Supprelin LA (histrelin acetate)
- Trelstar (triptorelin pamoate)
- Triptodur (triptorelin)
- Vantas (histrelin acetate)
- Zoladex (goserelin acetate)

For the coverage criteria below, in absence of specified drug products, the term "GnRH analogs" will be used in this policy where the coverage criteria apply to all products listed above.

**Covered Indications**

**I. Central precocious puberty** (Lupron Depot-Ped, Supprelin LA, Triptodur)

**Lupron Depot-Ped, Supprelin LA, and Triptodur are proven for the treatment of central precocious puberty.**

**Lupron Depot-Ped, Supprelin LA, and Triptodur are medically necessary for the treatment of central precocious puberty when all of the following criteria are met:**
A. Diagnosis of central precocious puberty (idiopathic or neurogenic); **and**
B. Onset of secondary sexual characteristics in one of the following:
   1. Females ≤ 8 years of age; **or**
   2. Males ≤ 9 years of age;

   **and**
C. Confirmation of diagnosis as defined by **one** of the following:
   1. Pubertal basal level of luteinizing hormone (based on laboratory reference ranges); **or**
   2. A pubertal luteinizing hormone response to a GnRH stimulation test; **or**
   3. Bone age advanced one year beyond the chronological age.

Lupron Depot-Ped, Supprelin LA, or Triptodur treatment should be discontinued at the appropriate age of onset of puberty at the discretion of the physician. Give consideration to discontinuing treatment before 11 years of age in girls and 12 years of age in boys.

**II. Endometriosis** (Lupaneta Pack, Lupron Depot, Zoladex)

**Lupaneta Pack, Lupron Depot, and Zoladex are proven for the treatment of endometriosis or suspected endometriosis.**

**Lupaneta Pack, Lupron Depot, and Zoladex are medically necessary for the treatment of endometriosis when all of the following criteria are met:**
A. For **initial therapy**, **all** of the following:
   1. Diagnosis of endometriosis or endometriosis is suspected; **and**
   2. **One** of the following:
      a. Contraindication, intolerance, or failure of initial treatment with **both** of the following:
         i. Oral contraceptives or depot medroxyprogesterone (e.g., Depot Provera); **and**
         ii. Non-steroidal anti-inflammatory drugs (NSAIDs);

         **or**
      b. Patient has had surgical ablation to prevent recurrence;

      **and**
   3. Initial treatment course is limited to a maximum of 6 months.

B. For **retreatment**, **all** of the following (Lupaneta Pack and Lupron Depot **ONLY**):
   1. Diagnosis of endometriosis or suspected endometriosis; **and**
   2. Recurrence of symptoms following an initial course of therapy; **and**
   3. Concurrently to be used with add-back therapy (e.g., progestin, estrogen, or bone sparing agents); **and**
   4. Duration of both the initial and recurrent course of therapies is no longer than 12 months total.

Zoladex is not recommended for the retreatment of endometriosis, per FDA labelling.

The prescribing information for Lupron Depot and Zoladex state that the duration of initial treatment for endometriosis should be limited to 6 months.

For Lupaneta Pack, 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.

For Lupron Depot, for recurrence of symptoms, the prescriber should consider the impact to bone mineral density prior to retreatment. Leuprolide must be used in combination with add back therapy (e.g., norethindrone acetate) for 6 months; greater than one retreatment period is not recommended. Lupron Depot monotherapy is not recommended for retreatment.

For Zoladex, there is no clinical data on the effect of treatment of benign gynecological conditions with Zoladex for periods in excess of 6 months. Retreatment with Zoladex cannot be recommended for the management of endometriosis.

**III. Endometrial thinning/dysfunctional uterine bleeding** (Zoladex)

**Zoladex is proven for endometrial thinning prior to endometrial ablation for dysfunctional uterine bleeding.**

**Zoladex is medically necessary for endometrial thinning when all of the following criteria are met:**
A. For use prior to endometrial ablation; **and**
B. Other causes of symptoms or bleeding are ruled out; **and**
C. Patient is to receive Zoladex 3.6mg implant; **and**
D. Course of therapy is a maximum of two depots.

**IV. Fertility preservation**

**GnRH analogs are proven and medically necessary for the treatment of fertility preservation when both of the following criteria are met:**
A. For use in pre-menopausal women; **and**
B. Patient is receiving a cytotoxic agent that is associated with causing primary ovarian insufficiency (premature ovarian failure) [e.g., Cytoxan (cyclophosphamide), procarbazine, vinblastine, cisplatin].

GnRH therapy should be discontinued upon the completion of cytotoxic treatment.

**V. Uterine leiomyomata (fibroids)** (Lupron Depot)

**Lupron Depot is proven for the treatment of uterine leiomyomata (fibroids).**

**Lupron Depot is medically necessary for the treatment of uterine leiomyomata when one of the following criteria is met:**
A. **All** of the following:
   1. For the treatment of uterine leiomyomata related anemia; **and**
   2. Patient did not respond to iron therapy of one month duration; **and**
   3. For use prior to surgery;

   **or**
B. For use prior to surgery to reduce the size of fibroids to facilitate a surgical procedure (e.g., myomectomy, hysterectomy).

The recommended duration of therapy for the treatment of uterine leiomyomata is ≤ 3 months.[13]

**VI. Gender dysphoria in adolescents**

**GnRH analogs may be covered for the treatment of Gender Dysphoria when all of the following criteria are met:**

A. For **initial therapy**, submission of medical records (e.g., chart notes, laboratory values) documenting all the following:
   1. Diagnosis of gender dysphoria, according to the current DSM (i.e., DSM-5) criteria, by a mental health professional with expertise in child and adolescent psychiatry; **and**
   2. Medication is prescribed by or in consultation with a pediatric endocrinologist or by a physician working in a multidisciplinary clinic for transgender youth;
      **and**
   3. Patient has experienced puberty development to at least Tanner stage 2 (stage 2 through 4); **and**
   4. **One** of the following laboratory tests, based upon the laboratory reference range, confirming:
      a. Pubertal levels of estradiol in females; **or**
      b. Pubertal levels of testosterone in males; **or**
      c. Pubertal basal level of luteinizing hormone (based on laboratory reference ranges); **or**
      d. A pubertal luteinizing hormone response to a GnRH stimulation test;
      **and**
   5. A letter from the prescriber and/or formal documentation stating all of the following:
      a. Patient has experienced pubertal changes that have resulted in an increase of their gender dysphoria that has significantly impaired psychological or social functioning; **and**
      b. Coexisting psychiatric and medical comorbidities or social problems that may interfere with the diagnostic procedures or treatment have been addressed or removed; **and**
      c. **Both** of the following:
         iii. Current enrollment, attendance, and active participation in psychological and social support treatment program; **and**
         iv. Patient will continue enrollment, attendance and active participation in psychological and social support throughout the course of treatment;
         **and**
      d. Patient demonstrates knowledge and understanding of the expected outcomes of treatment and related transgender therapies; **and**
      e. Initial authorization will be for no longer than 12 months.

B. For **continuation therapy**, submission of medical records (e.g., chart notes, laboratory values) documenting all the following:
   1. Documentation of LH suppression using a GnRH stimulation test
   2. Documented diagnosis of gender dysphoria, according to the current DSM (i.e., DSM-5) criteria, by a mental health professional with expertise in child and adolescent psychiatry; **and**
   3. Medication is prescribed by or in consultation with a pediatric endocrinologist or by a physician working in a multidisciplinary clinic for transgender youth; **and**
   4. A letter from the prescriber and/or formal documentation stating **all** of the following:
      a. Patient continues to meet their individual goals of therapy for gender dysphoria; **and**
      b. Patient continues to have a strong affinity for the desired (opposite of natal) gender; **and**
      c. Discontinuation of treatment and subsequent pubertal development would interfere with or impair psychological functioning and well-being; **and**
      d. Coexisting psychiatric and medical comorbidities or social problems that may interfere with treatment continue to be addressed or removed; **and**
      e. **Both** of the following:
         i. Current enrollment, attendance, and active participation in psychological and social support treatment program; **and**
         ii. Patient will continue enrollment, attendance and active participation in psychological and social support throughout the course of treatment;
         **and**
      f. Patient demonstrates knowledge and understanding of the expected outcomes of treatment and related transgender therapies; **and**
      g. Reauthorization will be for no longer than 12 months.

**VII. Adjunct for Gender-Affirming Hormonal Therapy for Transgender Adults**

**GnRH analogs may be covered for adjunct treatment in transgender adults when all of the following criteria are met:**

A. For **initial therapy**, submission of medical records (e.g., chart notes, laboratory values) documenting all the following:

1. Diagnosis of gender dysphoria, according to the current DSM (i.e., DSM-5) criteria, by a mental health professional; **and**
2. Medication is prescribed by or in consultation with an endocrinologist or a medical provider knowledgeable in transgender hormone therapy; **and**
3. Gonads (i.e., testes, ovaries) have not been removed and are functional (e.g., hormone producing); **and**
4. Patient is currently receiving hormonal therapy (e.g., testosterone, estrogens, progesterones) to achieve the desired (e.g., non-natal) gender; **and**
5. **One** of the following:
   a. Hormonal and/or anti-hormone (e.g., anti-androgen) therapy is not sufficient to suppress and/or overcome natal secondary sex characteristics or gonadotropins (e.g., menses, testosterone); **or**
   b. History of failure, contraindication, or intolerance to hormonal and/or antihormonal therapy at the required strengths for suppression due to increased risk of comorbid disease (e.g., thromboembolism, liver dysfuntion, cardiovascular disease, type 2 diabetes, etc.);

   **and**
6. A letter from the prescriber and/or formal documentation stating all of the following:
   a. Transgender patient has identified goals of gender-affirming hormone therapy; **and**
   b. Coexisting psychiatric and medical comorbidities or social problems that may interfere with the diagnostic procedures or treatment have been addressed or removed; **and**
   c. **Both** of the following:
      i. Current enrollment, attendance, and active participation in psychological and social support treatment program; **and**
      ii. Patient will continue enrollment, attendance and active participation in psychological and social support throughout the course of treatment;

      **and**
   d. Patient demonstrates knowledge and understanding of the expected outcomes of treatment and related transgender therapies; **and**
   e. Initial authorization will be for no longer than 12 months.

B. For **continuation therapy**, submission of medical records (e.g., chart notes, laboratory values) documenting all the following:
1. Documented diagnosis of gender dysphoria, according to the current DSM (i.e., DSM-5) criteria, by a mental health professional; **and**
2. Medication is prescribed by or in consultation with an endocrinologist or a medical provider knowledgeable in transgender hormone therapy; **and**
3. Gonads (i.e., testes, ovaries) are intact; **and**
4. Patient is currently receiving hormonal therapy (e.g., testosterone, estrogens, progesterones) to achieve the desired (e.g., non-natal) gender; **and**
5. **One** of the following:
   a. Hormonal and/or anti-hormone (e.g., anti-androgen) therapy alone is not sufficient to suppress natal secondary sex characteristics or gonadotropins (e.g., menses, testosterone); **or**
   b. History of failure, contraindication, or intolerance to hormonal and/or antihormonal therapy at the required strengths for suppression due to increased risk of comorbid disease (e.g., thromboembolism, liver dysfuntion, cardiovascular disease, type 2 diabetes, etc.);

   **and**
6. A letter from the prescriber and/or formal documentation stating all of the following:
   a. Transgender patient continues to meet goals of gender-affirming hormone therapy; **and**
   b. Coexisting psychiatric and medical comorbidities or social problems that may interfere with the diagnostic procedures or treatment continue to be addressed or removed; **and**
   c. **Both** of the following:
      i. Current enrollment, attendance, and active participation in psychological and social support treatment program; **and**
      ii. Patient will continue enrollment, attendance and active participation in psychological and social support throughout the course of treatment;

      **and**
   d. Patient demonstrates knowledge and understanding of the expected outcomes of treatment and related transgender therapies; **and**
   e. Reauthorization will be for no longer than 12 months.

**Note**: Clinical evidence supporting the use of GnRH analogs for the treatment of gender dysphoria and transgender individuals is limited and lacks long-term safety data. Statistically robust randomized controlled trials are needed to address the issue of whether the benefits outweigh the clinical risk in its use.

**DISCLAIMER**: This Medical Benefit Drug Policy does not constitute medical advice. UnitedHealthcare does not make decisions about the kind of care a member should or should not receive. Health care professionals are solely responsible for the care they deliver.

## U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Firmagon is a gonadotropin releasing hormone (GnRH) receptor antagonist indicated for treatment of patients with advanced prostate cancer.

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
- Management of recurrence of symptoms[38]

Lupron Depot-Ped, Supprelin LA, and Triptodur are GnRH agonists indicated for the treatment of children with central precocious puberty (CPP).[1,28,37]

Lupron Depot is a GnRH agonist indicated for:[2]
- Management of endometriosis, including pain relief and reduction of endometriotic lesions (3.75 mg for 1-month administration, 11.25mg for 3-month administration) with duration of initial treatment or retreatment not to exceed 6 months
- Initial management of endometriosis and for management of recurrence of symptoms (3.75 mg monthly with norethindrone acetate 5 mg daily) with duration of initial treatment or retreatment not to exceed 6 months
- Preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata (3.75 mg concomitantly with iron therapy) with recommended duration of therapy up to 3 months
- Palliative treatment of advanced prostate cancer (22.5 mg for 3-month administration, 30 mg for 4-month administration, and 45 mg for 6-month administration)*

Trelstar and Vantas are GnRH agonists indicated for the palliative treatment of advanced prostate cancer.[29,30]*

Zoladex is a GnRH agonist indication for:[31]
- 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.*
- Palliative treatment of advanced carcinoma of the prostate.*
- 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
- Use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding.
- Use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.*

*This statement is provided for information only. Oncology indications for GnRH analogs are listed in the NCCN Drugs & Biologics Compendium.

The prescribing information for the GnRH analogs contain warnings associated with their use:[2]
- Tumor flare – transient worsening of symptoms due to increases of testosterone above baseline during the first weeks of treatment. Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first weeks of therapy.
- Convulsions have been reported 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.
- Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH analogs. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH analog and manage with current practice for treatment of hyperglycemia or diabetes.
- Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH analogs in men. Patients receiving a GnRH analog should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.
- Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected.

- For Lupron Depot: Monitor serum levels of testosterone following injection of LUPRON DEPOT 7.5 mg for 1-month administration, 22.5 mg for 3-month administration, 30 mg for 4-month administration, or 45 mg for 6-month administration. In the majority of patients, testosterone levels increased above baseline, and then declined thereafter to castrate levels (< 50 ng/dL) within four weeks.
- Injection site injury and vascular injury including pain, hematoma, hemorrhage and hemorrhagic shock, requiring blood transfusions and surgical intervention, have been reported with GnRH analogs. Extra care should be taken when administering to patients with a low BMI and/or to patients receiving full anticoagulation

## BACKGROUND

**Firmagon** (degarelix) is a GnRH receptor antagonist. It binds reversibly to the pituitary gonadotropin releasing hormone (GnRH) receptors, thereby reducing the release of gonadotropins and consequently gonadal steroids.[27]

**Lupron, Lupaneta Pack** (leuprolide acetate) is a synthetic nonapeptide analog of naturally occurring GnRH which acts as a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses. Consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent.[13]

**Supprelin LA** and **Vantas** (histrelin acetate) are GnRH agonists and an inhibitor of gonadotropin secretion when given continuously, in turn causes a reduction in ovarian and testicular steroidogenesis.[28, 30]

**Trelstar** (triptorelin pamoate), **Triptodur** (triptorelin), and **Zoladex** (goserelin acetate) are synthetic decapeptide analog agonists of GnRH, which inhibit gonadotropin secretion when given continuously in therapeutic doses.[29, 31,37]

## APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

| HCPCS Code | Description |
|---|---|
| J1950 | Injection, leuprolide acetate (for depot suspension), per 3.75 mg |
| J3315 | Injection, triptorelin pamoate, 3.75 mg |
| J3316 | Injection, triptorelin, extended-release, 3.75 mg |
| J3490 | Unclassified drug – used for Triptodur until a code is assigned. |
| J9155 | Injection, degarelix, 1 mg |
| J9202 | Goserelin acetate implant, per 3.6 mg |
| J9217 | Leuprolide acetate (for depot suspension), 7.5 mg |
| J9225 | Histrelin implant (Vantas), 50 mg |
| J9226 | Histrelin implant (Supprelin LA), 50 mg |

| ICD-10 Diagnosis Code | Description |
|---|---|
| D25.0 | Submucous leiomyoma of uterus |
| D25.1 | Intramural leiomyoma of uterus |
| D25.2 | Subserosal leiomyoma of uterus |
| D25.9 | Leiomyoma of uterus, unspecified |
| E22.8 | Other hyperfunction of pituitary gland |
| E30.1 | Precocious puberty |
| E30.8 | Other disorders of puberty |
| F64.0 | Transsexualism |
| F64.1 | Dual role transvestism |
| F64.2 | Gender identity disorder of childhood |
| F64.8 | Other gender identity disorders |
| F64.9 | Gender identity disorder, unspecified |

| ICD-10 Diagnosis Code | Description |
|---|---|
| N80.0 | Endometriosis of uterus |
| N80.1 | Endometriosis of ovary |
| N80.2 | Endometriosis of fallopian tube |
| N80.3 | Endometriosis of pelvic peritoneum |
| N80.4 | Endometriosis of rectovaginal septum and vagina |
| N80.5 | Endometriosis of intestine |
| N80.6 | Endometriosis in cutaneous scar |
| N80.8 | Other endometriosis |
| N80.9 | Endometriosis, unspecified |
| N93.8 | Other specified abnormal uterine and vaginal bleeding |
| Z31.62 | Encounter for fertility preservation counseling |
| Z31.84 | Encounter for fertility preservation procedure |
| Z87.890 | Personal history of sex reassignment |

## CLINICAL EVIDENCE

**Central Precocious Puberty**

Lupron Depot-Ped is indicated for the treatment of central precocious puberty (CPP).[1]

A phase III, open-label, multicenter extension study was designed to assess the long term (36 month) hypothalamic-pituitary-gonadal axis suppression and safety of leuprolide acetate 3-month depot 11.25mg and 30mg in children with CPP, for 36 months was performed. Seventy-two patients with CPP who completed the preceding study and showed maintenance of LH suppression were included.17,18 All eligible subjects had documented LH suppression as evidenced by peak-stimulated LH < 4 mIU/mL after 6 months of treatment and demonstrated suppression of physical signs of puberty (regression or no progression of breast development in girls or of testicular volume and genital staging in boys). Subjects received up to 12 intramuscular injections of the same treatment they were previously assigned in the lead-in study. No dose adjustments were permitted during the treatment period. The main outcome measures were peak-stimulated LH, estradiol, testosterone, growth rate, pubertal progression, and adverse events. Twenty-nine of 34 subjects in the 11.25mg group and 36 of 38 subjects in the 30mg group had LH values < 4 mIU/mL after day 1 at all time points. All seven subjects who escaped LH suppression at any time still maintained sex steroid concentrations at prepubertal levels and showed no signs of pubertal progression. Adverse events were comparable between groups, with injection site pain being the most common (26.4% overall). No adverse event led to discontinuation of study drug. The safety profile over 36 months was comparable to that observed during the 6-month pivotal study.

**Endometriosis**

Leuprolide acetate is indicated for the management of endometriosis, including pain relief and reduction of endometriotic lesions. Leuprolide acetate, concomitantly with norethindrone acetate 5 mg daily, is also indicated for the initial management of endometriosis and management of recurrence of symptoms.[2,38]

The Pelvic Pain Study Group evaluated and compared the safety and efficacy of leuprolide versus placebo in managing chronic pelvic pain in women with clinically suspected endometriosis.[3] Women ages 18 to 45 years with moderate to severe pelvic pain of at least 6 months' duration underwent extensive, noninvasive diagnostic testing and laboratory evaluation. Those with clinically suspected endometriosis were randomized to double-blind treatment with either depot leuprolide 3.75 mg or placebo IM every 4 weeks for 12 weeks. Of 100 women randomized, 95 completed the study: 49 in the leuprolide group and 46 in the placebo group. Post-treatment laparoscopic examination confirmed endometriosis in 78% of patients in the depot leuprolide group and 87% of the placebo group. Women in the leuprolide group had clinically and statistically significant ($p \leq 0.001$) mean improvements from baseline after 12 weeks of therapy in all pain measures. These mean improvements were significantly greater ($p \leq 0.001$) than those in the placebo group. At 12 weeks, mean decreases in physician-rated scores (on a 4 point scale) for dysmenorrhea, pelvic pain, and pelvic tenderness were 1.7, 1.0, and 0.8 points greater, respectively, in the leuprolide group than in the placebo group. Depot leuprolide was effective and safe for treating patients with chronic pelvic pain and clinically suspected endometriosis, confirming the potential of its empiric use in these patients.

The Lupron Study Group evaluated the safety and efficacy of leuprolide acetate for depot suspension 3.75 mg versus placebo in the treatment of pain associated with endometriosis.[4] In a randomized, double-blind, multicenter study involving 52 patients, dysmenorrhea, pelvic pain, and pelvic tenderness all responded significantly to leuprolide acetate compared to placebo. Menses were suppressed in all of the subjects in the leuprolide acetate treatment group. Estradiol decreased significantly to menopausal levels in the leuprolide acetate group. Although there were small to

moderate changes in a variety of laboratory parameters, these were not clinically significant. The most common adverse event was vasodilatation, occurring significantly more frequently in the leuprolide acetate group.

**Uterine Leiomyomata (Fibroids)**

Leuprolide acetate, concomitantly with iron therapy, is indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata.[2] Leuprolide acetate may also be used preoperatively to reduce the size of uterine fibroids to allow for a vaginal procedure (e.g., myomectomy, hysterectomy).[5-9]

Stovall et al. conducted a phase III, stratified, randomized, double-blind, placebo-controlled, parallel-group, 12-week multicenter study to determine the effectiveness of leuprolide acetate depot plus iron compared with iron alone in the preoperative treatment of anemia due to prolonged or excessive bleeding associated with uterine leiomyomas.[6] Study participants had hemoglobin levels of 10.2 g/dL or less and/or hematocrit values of 30% or less. Subjects were entered into one of two strata based on their pre-study hematocrit level: stratum A, hematocrit less than or equal to 28%, and stratum B, hematocrit greater than 28%. Of the 309 patients entered into the study, 265 were evaluated. Patients within each stratum were randomized to one of three treatment arms: leuprolide acetate depot 7.5 mg (n=99), leuprolide acetate depot 3.75 mg (n=89), or placebo (n=77). All patients received iron orally. Response was defined as a hemoglobin level of 12 g/dL or more and a hematocrit value of 36% or greater. A significantly greater number of patients in both leuprolide acetate groups (combined strata) responded to therapy than did those in the placebo group: 74% in each leuprolide acetate group versus 46% in the placebo group ($p<0.001$). Gonadotropin-releasing hormone agonist-treated patients had a significant reduction in uterine and myoma volume when compared with the placebo group ($p<0.01$). Hot flashes and vaginitis were reported significantly more often ($p<0.001$) in the leuprolide acetate-treated groups than in the placebo group. Both dosages of GnRH agonist plus iron were more effective than iron alone in treating the anemia of patients with uterine leiomyomas, in reducing uterine-myoma volume, and in alleviating bleeding and other leiomyoma-related symptoms.

In a randomized, double-blind, placebo-controlled multicenter study involving 13 investigative centers, Friedman et al. evaluated efficacy and safety parameters in women (n=128) with leiomyomata uteri treated with the GnRH agonist leuprolide acetate.[7] Study participants received either leuprolide acetate depot 3.75 mg (n=63) or placebo (n=65) by intramuscular (IM) injection every 4 weeks for 24 weeks. Of the 128 patients enrolled in the study, 124 were eligible for efficacy analysis. Patients were seen every 4 weeks for 24 weeks, and those confirmed by unblinding at the end of the study to have received leuprolide acetate were followed under a separate, no-treatment protocol for one year. While mean uterine volume decreased by 36% at 12 weeks and 45% at 24 weeks of leuprolide therapy, patients treated with placebo had increased in mean uterine volume of 16% at 12 weeks and 5% at 24 weeks. Seventy-seven percent of leuprolide-treated patients had a more than 25% reduction in uterine volume, compared with 9% of placebo-treated controls. Mean uterine volume returned to pre-treatment size 24 weeks after cessation of leuprolide treatment. The majority of patients had resolution or improvement of their fibroid-related symptoms after 24 weeks of leuprolide treatment. Of 38 leuprolide-treated patients presenting with menorrhagia, 37 (97%) had resolution of this symptom at the time of the final visit. Although 95% of women treated with leuprolide acetate experienced some side effects related to hypoestrogenism, only five patients (8%) terminated treatment prematurely. The authors concluded that leuprolide acetate depot treatment of leiomyomata uteri is safe and causes significant but temporary reductions in uterine size and fibroid-related symptoms.

Stovall et al. conducted a randomized trial in 50 premenopausal patients to evaluate leuprolide acetate before hysterectomy as treatment for symptomatic uterine leiomyomas which were the size of 14 to 18 weeks' gestation.[8] Subjects were randomized into two groups to determine whether preoperative gonadotropin-releasing hormone agonist would increase the feasibility of vaginal rather than abdominal hysterectomy. The control group (group A; n = 25) did not receive preoperative leuprolide acetate and underwent immediate hysterectomy, but patients in Group B (n = 25) received 2 months of leuprolide acetate before undergoing hysterectomy. Patients in the two groups were similar with respect to age, gravidity, parity, pretreatment uterine size, and hemoglobin and hematocrit levels. After GnRH therapy, patients in group B had an increase in hemoglobin levels (10.75 to 12.12 gm/dL, $p<0.05$), a reduction in uterine size from 15.7 to 11.2 weeks' mean gestational size as determined by pelvic examination ($p<0.05$), and a decrease in uterine volume (1086.7 to 723.4 mL, $p<0.05$). Patients in group B also were more likely to undergo vaginal hysterectomy (76.0% vs 16%) and had shorter hospitalizations (5.2 vs 3.8 days, $p<0.05$). The authors concluded that the administration of leuprolide acetate for 2 months followed by vaginal hysterectomy is preferable to abdominal hysterectomy in selected patients with uterine leiomyomas.

Friedman et al. enrolled thirty-eight premenopausal women with uterine leiomyomata in a randomized, double-blind, placebo-controlled study evaluating the efficacy of depot leuprolide acetate (LA) in decreasing uterine volume.[9] Subjects received intramuscular (IM) depot LA 3.75 mg every 4 weeks for 24 weeks (group A, n=18) or IM placebo with the same injection schedule (group B, n=20). The study groups were well-matched for age, weight, and pretreatment uterine volume. Patients were seen at 4-week intervals during the treatment period and assessed once more at 3 months after cessation of therapy. Group A patients had a mean reduction in pretreatment uterine volume from 505 ± 93 cu cm to 305 ± 57 cu cm after 12 weeks ($p<0.05$ versus pretreatment) and 307 ± 57 cu cm after 24

weeks of therapy (p<0.05 versus pretreatment). At 3 months after cessation of therapy, the mean uterine volume in group A had increased to 446± 92 cu cm (p<0.05 versus week 24). Group B patients had no significant change in uterine volume over the 24-week treatment period. These results suggest that depot LA therapy may significantly decrease uterine volume in patients with leiomyomata and may be useful as a preoperative adjuvant for hysterectomy and myomectomy.

**Fertility Preservation**

NCCN oncology guidelines for Breast Cancer (V2.2018) report that randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea. Additionally noted is that smaller historical experiences in women with ER-positive breast cancer have reported conflicting results regarding the protective effect of GnRH agonist on fertility.[19]

The NCCN oncology guidelines for adolescents and young adults (V2.2018) state that fertility preservation should be an essential part in the management of adolescent and young adults with cancer who are at any risk for infertility due to cancer treatments.[20] Providers should discuss with their patients the risks for infertility due to cancer and its therapy, fertility preservation, and contraception prior to the start of therapy. Men are at risk for azoospermia following therapy, which may or may not resolve over time. Women are at risk for premature ovarian failure due to chemotherapy. For men, options include the use of a sperm bank. For females, oocyte or embryo cryopreservation, oophoropexy, and menstrual suppression are possibilities. The guidelines state that menstrual suppression is inconclusive whether this would protect the ovaries. Randomized trials that have evaluated the role of menstrual suppression with gonadotropin-releasing hormone agonists to preserve ovarian function during chemotherapy have provided conflicting reports. Medroxyprogesterone, oral contraceptives, or gonadotropin-releasing hormone agonists may be used in protocols that are predicted to cause prolonged thrombocytopenia and present a risk for menorrhagia.[20]

Ovarian toxicity of chemotherapy treatments involve the prevention of cell division and adverse effects on DNA function within the ovarian cells.[25,26] Alkylating agents are overall more toxic to the ovaries than platinum-based therapies and antimetabolites. These effects are age dependent, with older individuals being associated with greater impact, probably due to an overall smaller follicular reserve at the beginning of treatment. Different chemotherapy regimens and cytotoxic agents carry different risks for primary ovarian insufficiency. The table below lists the cytotoxic medications that carry a high or intermediate degree of risk of ovarian toxicity when administered.

| Cytotoxic Drugs with High or Intermediate Risk of Ovarian Toxicity[25,26] | | |
|---|---|---|
| High risk of ovarian toxicity | Busulfan<br>Carmustine<br>Cyclophosphamide<br>Dacarbazine<br>Procarbazine | Ifosfamide<br>Lomustine<br>Melphalan |
| Intermediate risk of ovarian toxicity | Cisplatinum<br>Cytarabine | Etoposide<br>Vinblastine |

A single-center, prospective, randomized study investigated the efficacy of leuprolide acetate in premenopausal patients with breast cancer on ovarian function protection against chemotherapy-induced genotoxicity.[21] Premenopausal women aged 18 to 45 years with stage I – III breast cancer were eligible for this study. All patients received primary surgical therapy, but needed to have no history of prior chemotherapy or hormone therapy, in addition to other criteria. FSH, estradiol, and menstrual activity were measured throughout the trial. Patients were randomly allocated to receive chemotherapy only (n=94) or chemotherapy plus leuprolide acetate (LA, 3.75 mg, n=89). Serum estrogen level was measured 2 weeks after injection. If ovarian suppression was confirmed, patients started to receive chemotherapy, otherwise treatment was not started until ovarian suppression was proved. During chemotherapy, patients were given LA at the same dosage every 4 weeks. All patients received cyclophosphamide-doxorubicin-based chemotherapy with some patients receiving additional adjuvant therapy. For those patients experiencing early menopause, 27 patients (28.7%) in the chemotherapy only group and 15 patients (16.9%) in the chemotherapy plus LA group had early menopause (p<0.01). Paclitaxel treatment significantly affected the risk of developing early menopause (0.01 < P < 0.05). Patients with cyclophosphamide, doxorubicin, and paclitaxel had a significantly lower occurrence of early menopause in chemotherapy plus LA group (0.01 < P < 0.05). Resumption of menses was reported by 39 patients in chemotherapy only group and 53 patients in chemotherapy plus LA group (0.01 < P < 0.05). Premenopausal level of FSH and estrogen without resumption of menses was observed in seven patients in chemotherapy only group and 14 patients in the LA group (p > 0.05). Per the author's definition of effective treatment, ovarian suppression with LA effectively preserved the ovarian function after chemotherapy (P < 0.01) The median time to resume menstruation was 9.2 months in the LA group, while no median time was reached with the chemotherapy only group. The mean estrogen levels were significantly decreased in both groups relatively to

the values at study entry. At 12 months, these levels were not significantly different between the two groups. In contrast, mean values of FSH were significantly elevated in both groups relative to the values at study entry, but significantly higher in the chemotherapy only group at 12 months after the end of treatment ($P < 0.05$). The authors conclude that LA treatment simultaneously with cyclophosphamide-doxorubicin-based chemotherapy reduced the risk of developing premature menopause in premenopausal women with breast cancer.

Somers et al., conducted a cohort study to evaluate the effectiveness of depot leuprolide acetate (LA), a synthetic gonadotropin-releasing hormone analog (GnRH-a), for protection against premature ovarian failure (POF) during cyclophosphamide (CYC) therapy in premenopausal patients diagnosed with systemic lupus erythematosus (SLE).[23] Patients were eligible for this study if they had a diagnosis consistent with lupus or if they satisfied the American College of Rheumatology (ACR) criteria for SLE, were women of reproductive age, and had an exacerbation of disease activity requiring treatment with at least 6 monthly boluses of CYC. Patients were excluded from this analysis if they were age ≥35 years at the beginning of CYC treatment or if they were found at baseline to have symptoms consistent with ovarian failure based on gynecologic evaluation. All study participants underwent a standardized IVCYC protocol for the treatment of severe manifestations of SLE. Participation in the GnRH-a protocol was offered to consecutive female SLE patients in whom CYC treatment was initiated. Depot LA was administered by injection once per month at a dose of 3.75 mg throughout the course of CYC treatment. In patients who did not achieve satisfactory disease control, LA administration was continued throughout CYC therapy. In order to avoid CYC exposure during the initial surge of estrogen, the GnRH-a injection was timed to occur at least 10 days prior to the subsequent monthly bolus of CYC. Controls were randomly selected female SLE patients in the Michigan Lupus Cohort who had participated in the IVCYC protocol and fulfilled the above eligibility criteria, but who had not received GnRH-a. Controls were randomly selected female SLE patients in the Michigan Lupus Cohort who had participated in the IVCYC protocol and fulfilled the above eligibility criteria, but who had not received GnRH-a. The minimum period of follow-up was 3.0 years unless ovarian failure developed sooner. The analysis was based on a total of 287.1 person-years at risk for POF, including 186.9 person-years among controls (median 10.3 years at risk for POF, range 0.8–16.7 years) and 100.2 person-years among GnRH-a–treated patients (median 4.6 years at risk for POF, range 0.6–9.3 years). At follow-up, ovarian failure had developed in 1 of 20 GnRH-a–treated patients (5%) compared with 6 of 20 controls (30%). Based on a matched pairs analysis, the odds of ovarian failure were significantly lower in the GnRH-a–treated group (OR 0.09, $P < 0.05$). The single GnRH-a–treated patient who developed ovarian failure was older (28.2 years) and received a higher cumulative CYC dose (33.5 gm) than the corresponding mean values for the population (24.4 years and 12.9 gm). Accounting for time at risk for ovarian failure, Kaplan-Meier survival estimates showed greater cumulative preservation of ovarian function in the GnRH-a–treated group than in controls ($P = 0.04$). The median time to onset of ovarian failure was 4.3 years (interquartile range 1.2–5.7). Based on Cox regression, the hazard of developing ovarian failure within 10 years of CYC initiation in the GnRH-a–treated group was less than one-tenth that in the control group (hazard ratio 0.09, 95% confidence internal 0.01–0.8). Although it is not known how many of the women attempted conception subsequent to CYC therapy, 3 of 20 control patients (15%) and 7 of 20 GnRH-a–treated patients (35%) had successful pregnancies following treatment. There was no statistically significant difference in adverse events potentially attributable to the study protocol, including dysfunctional uterine bleeding, deep venous thrombosis, or new ischemic cardiac events during the treatment period. The authors acknowledged that their study is limited because it was not a randomized controlled trial, however, they matched controls to account for known confounders. The authors concluded that treatment with a depot GnRH-a during CYC therapy was associated with a significant reduction in the future incidence of ovarian failure among women with severe SLE.

A systematic review and meta-analysis of studies assessing the efficacy of GnRH agonists in reducing chemotherapy induced ovarian failure in cancer or systemic lupus erythematosus (SLE) identified sixteen trials, four SLE and twelve cancer. The meta-analysis revealed that GnRH agonists are effective in reducing amenorrhea rates in all patients (RR .26, 95% CI 0.14-0.49). Pregnancy rate was also higher in the GnRH agonist arms. This advantage, however, was shown only in the observational trials, not in randomized trials. The authors concluded that GnRH agonists appear to improve menstruation resumption, but larger, prospective, randomized trials are needed to further evaluate the role of GnRH agonists in preventing chemotherapy induced ovarian failure.[24]

**Gender Dysphoria in Adolescents**

Costa et al, published the results of a longitudinal study involving 201 adolescents with gender dysphoria (GD), comparing treatment modalities involving psychological support, puberty suppression with GnRH analogs, or both.[35] Patients' global functioning were evaluated every 6 months from the first visit. Patients completed the Utrecht Gender Dysphoria Scale (UGDS), a self-report measure of GD-related discomfort, and the Children's Global Assessment Scale (CGAS) to assess the psychosocial functioning of adolescents. The authors hypothesized that subjects would have poor general functioning at baseline, an improvement after psychological support, and a further improvement after beginning puberty suppression. The 201 adolescents participating in the study completed the diagnostic procedure (about 6 months) and continued to participate in follow-up evaluations. All patients were eligible for puberty suppression with GnRH analogs per WPATH guidelines, however, some were immediately eligible, and some were delayed eligible, who continued to receive psychological support without medication, until the patient was ready to make a decision to continue therapy. GD adolescents' CGAS at baseline (Time 0, $M = 57.7 \pm 12.3$) revealed a score

suggestive of "variable functioning with sporadic difficulties or symptoms in several but not all social areas" (range 50–59). Natal men had a significantly lower functioning than natal women at baseline ($P = 0.03$). GD adolescents' CGAS scores at baseline were significantly lower ($t = 7.4$, $P < 0.001$) than that found in a sample of children/adolescents without observed psychological/psychiatric symptoms (N = 169, 67.1 ± 12). GD adolescents' psychosocial functioning was increasingly higher at each of the following evaluations. In particular, CGAS scores were significantly higher after 6 months of psychological support (Time 0 vs. Time 1, P < 0.001). Also there was a further significant improvement 18 months from baseline (Time 1 vs. Time 3, P = 0.02). Delayed eligible GD adolescents, who received only psychological support for the entire duration of the study, had a significantly better psychosocial functioning after six months of psychological support (Time 0 vs. Time 1, P = 0.05). The delayed eligible group, however, continued to score lower than a sample of children/adolescents without observed psychological/psychiatric symptoms, even after 18 months of psychological support (Time 3, t = 2.0, P = 0.04). The immediately eligible group, who at baseline had a higher, but not significantly different psychosocial functioning than the delayed eligible group, did not show any significant improvement after 6 months of psychological support. However, immediately eligible adolescents had a significantly higher psychosocial functioning after 12 months of puberty suppression compared with when they had received only psychological support (Time 1 vs. Time 3 P = 0.001). Also, their CGAS scores after 12 months of puberty suppression (Time 3) coincided with those found in a sample of children/adolescents without observed psychological/psychiatric symptoms (t = 0.01, P = 0.99). The authors concluded that psychological support and puberty suppression were both associated with an improved global psychosocial functioning in GD adolescents. Both these interventions may be considered effective in the clinical management of psychosocial functioning difficulties in GD adolescents.

In 2014, de Vries et al, published the results of a small, longitudinal study, that followed 55 patients with gender dysphoria (GD), to evaluate the psychological functioning, objective and subjective well-being through 3 time points during the patient therapy: 1) Before start of puberty suppression with GnRH analogs (mean age 13.6 years, T0), 2) when cross-sex hormones (CSH) are introduced (mean age 16.7 years, T1), and at least 1 year after gender reassignment surgery (GSR) (mean age 20.7 years, T2). Throughout the course of puberty suppression therapy, GD and body image difficulties persisted (at T0 and T1) and remitted after the administration of CSH and GRS (at T2). Transwomen reported more satisfaction over time with primary sex characteristics than transmen and a continuous improvement in satisfaction with secondary and neutral sex characteristics. Transmen reported more dissatisfaction with secondary and neutral sex characteristics at T1 than T0, but improvement in both from T1 to T2. At T2, the patients were slightly more likely to live with parents (67% vs 63%), than the Dutch population, and more likely, when studying, to be pursuing higher education (58% vs 31%). Families of GD patients were supportive of the transitioning process: 95% of mothers, 80% of fathers, and 87% of siblings. Most (79%) young adults reported having 3 or more friends, were satisfied with their male (82%) and female peers (88%), and almost all (95%) had received support from friends regarding their gender reassignment. After their GRS, many participants (89%) reported having been never or seldom called names or harassed. The majority (71%) had experienced social transitioning as easy. None of the participants reported regret during puberty suppression, CSH treatment, or after GRS. Satisfaction with appearance in the new gender was high, and at T2 no one reported being treated by others as someone of their assigned gender. All young adults reported they were very or fairly satisfied with their surgeries. The authors concluded that their clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons, including puberty suppression, followed by cross-sex hormones and gender reassignment surgery, provides gender dysphoric youth who seek gender reassignment from early puberty on, the opportunity to develop into well-functioning young adults.

## Technology Assessments

### *Proven*

### Endometriosis

A 2014 Cochrane review was published as an overview of reports on interventions for pain relief and subfertility in pre-menopausal women with clinically diagnosed endometriosis.[5,15] The objective was to summarize the evidence from Cochrane systematic reviews on treatment options for women with pain or subfertility associated with endometriosis. Seventeen systematic reviews published in The Cochrane Library were included. All the reviews were high quality. The quality of the evidence for specific comparisons ranged from very low to moderate. The authors concluded that for women with pain and endometriosis, suppression of menstrual cycles with gonadotropin-releasing hormone (GnRH) analogues, the levonorgestrel-releasing intrauterine system (LNG-IUD) and danazol were beneficial interventions. Laparoscopic treatment of endometriosis and excision of endometriomata were also associated with improvements in pain. The evidence on NSAIDs was inconclusive. There was no evidence of benefit with post-surgical medical treatment. In women with endometriosis undergoing assisted reproduction, three months of treatment with GnRH agonist improved pregnancy rates. Excisional surgery improved spontaneous pregnancy rates in the nine to 12 months after surgery compared to ablative surgery. Laparoscopic surgery improved live birth and pregnancy rates compared to diagnostic laparoscopy alone. There was no evidence that medical treatment improved clinical pregnancy rates. Evidence on harms was scanty, but GnRH analogues, danazol and depot progestogens were associated with higher rates than other interventions.

**Uterine Leiomyomata (Fibroids)**

A 2011 Cochrane review was published evaluative the efficacy and safety of GnRH analogues given before or in parallel to chemotherapy to prevent chemotherapy-related ovarian damage in premenopausal women with malignant or non-malignant conditions.[16] The authors concluded that the use of GnRH agonists should be considered in women of reproductive age receiving chemotherapy. Intramuscular or subcutaneous GnRH analogues seem to be effective in protecting ovaries during chemotherapy and should be given before or during treatment, although no significant difference in pregnancy rates was seen.

***Other***

**Hormone Therapy for the Treatment of Gender Dysphoria**

Hayes compiled a Medical Technology Directory on hormone therapy for the treatment of gender dysphoria dated May 19, 2014, and updated April 18, 2017.[14,41] Hayes assigned a rating of:

- C, For hormone therapy to treat GD in adults for whom a qualified mental health professional has made a formal diagnosis of GD and a recommendation for hormone therapy and who do not have any medical contraindications to endocrine therapy. This Rating reflects the reporting of some positive evidence but serious limitations in the evidence of both effectiveness and safety. Also of concern is the fact that the magnitude of suggested benefit was typically small, which diminishes confidence in a true treatment effect.
- D2, no proven benefit and/or not safe, for pubertal suppression therapy or cross-sex hormone therapy in adolescents. This rating was based upon insufficient published evidence to assess safety and/or impact on health outcomes or patient management.

**Professional Societies**

***Proven***

**Fertility Preservation**

In 2018, the American Society of Clinical Oncology (ASCO) released an update to their clinical practice guideline regarding fertility preservation for adults and children with cancer.[22,40]
The following recommendations and conclusions were published:

According to the guidelines, there is conflicting evidence to recommend gonadotrophin-releasing hormone agonists (GnRHa) and other methods of ovarian suppression. The guidelines state: "The panel recognizes that, when proven fertility preservation methods such as oocyte, embryo, or ovarian tissue cryopreservation are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency.

**Endometriosis**

In 2010 (reaffirmed in 2018),the American College of Obstetricians and Gynecologists (ACOG) released a practice bulletin that discusses the management of endometriosis.[10]
The following recommendations and conclusions were published:

- After an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives and non-steroidal anti-inflammatory drugs (NSAIDs), empiric therapy with a 3-month course of a GnRH agonist is appropriate.
- When relief of pain from treatment with a GnRH agonist supports continued therapy, the addition of add-back therapy reduces or eliminates GnRH agonist-induced bone mineral loss and provides symptomatic relief without reducing the efficacy of pain relief.
- Medical suppressive therapy improves pain symptoms; however, recurrence rates are high after the medication is discontinued.
- There is significant short-term improvement in pain after conservative surgical treatment; however, as with medical management, there is also a significant rate of pain recurrence.
- Medical suppressive therapies such as oral contraceptives (OCs) or gonadotropin-releasing hormone (GnRH) agonists for endometriosis-associated infertility are ineffective.
- Surgical management of endometriosis-related infertility does improve pregnancy rates, but the magnitude of improvement is unclear.
- In patients with known endometriosis and dysmenorrhea, OCs and oral norethindrone or depot medroxyprogesterone acetate (DMPA) are effective compared with placebo and are equivalent to other more costly regimens.
- Long-term (at least 24 months) OC use is effective in reducing endometrioma recurrence as well as a reduction in the frequency and severity of dysmenorrhea.
- In patients with normal ovaries, a hysterectomy with ovarian conservation and removal of the endometriotic lesions should be considered.

**Uterine Leiomyomata (Fibroids)**

In 2008 (reaffirmed in 2016), the American College of Obstetricians and Gynecologists (ACOG) released a practice bulletin that discusses alternatives to hysterectomy in the management of leiomyomas.[11] The following recommendations and conclusions are based upon good and consistent scientific evidence (Level A):

- GnRH agonists have been shown to improve hematologic parameters, shorten hospital stay, and decrease blood loss, operating time, and post-operative pain when given for 2-3 months preoperatively.
- The benefits of preoperative use of GnRH agonists should be weighed against their cost and side effects for individual patients.

***Other***

**Gender Dysphoria in Adolescents/Transgender Adults**

In the 2017 update to the 2009 Endocrine Society clinical practice guidelines for the endocrine treatment of transsexual persons,the guidelines recommend:[32, 39]

Treatment of adolescents:

- Adolescents fulfilling diagnostic criteria and treatment for Gender Dysphoria (GD)/gender incongruence (GI) and are requesting treatment, should initially undergo treatment to suppress pubertal development.
- Clinicians begin pubertal hormone suppresion after girls and boys first exhibit physical changes of puberty.
- GnRH analogs are used to suppress pubertal hormones.
- Initiating treatment using a gradually increasing dose schedule after a multidisciplinary team has confirmed the persistence of GD and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years.
- Monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment.

Hormonal therapy for transgender adults:

- Clinicians confirm the diagnostic criteria of GD/GI and the criteria for the endocrine phase of gender transition before beginning treatment.
- Clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment.
- Clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender.
- Endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment.

In 2012, the World Professional Association for Transgender Health (WPATH), an advocacy group, published *Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People, 7th Version.* This publication suggested the following criteria for the use of puberty-suppressing hormones in adolescents with gender dysphoria:[33]

In order for adolescents to receive puberty-suppressing hormones, the following minimum criteria must be met:

- The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed);
- Gender dysphoria emerged or worsened with the onset of puberty;
- Any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment;
- The adolescent has given informed consent and, particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process.

WPATH also presented regimens, monitoring and risks for puberty suppression in adolescents with gender dysphoria.[33]

For puberty suppression, adolescents with male genitalia should be treated with GnRH analogues, which stop luteinizing hormone secretion and therefore testosterone secretion. Adolescents with female genitalia should be treated with GnRH analogues, which stop the production of estrogens and progesterone.

During pubertal suppression, an adolescent’s physical development should be carefully monitored—preferably by a pediatric endocrinologist—so that any necessary interventions can occur (e.g., to establish an adequate gender appropriate height, to improve iatrogenic low bone mineral density)

Early use of puberty-suppressing hormones may avert negative social and emotional consequences of gender dysphoria more effectively than their later use would. Intervention in early adolescence should be managed with pediatric endocrinological advice, when available. Adolescents with male genitalia who start GnRH analogues early in

puberty should be informed that this could result in insufficient penile tissue for penile inversion vaginoplasty techniques (alternative techniques, such as the use of a skin graft or colon tissue, are available).

Neither puberty suppression nor allowing puberty to occur is a neutral act. On the one hand, functioning in later life can be compromised by the development of irreversible secondary sex characteristics during puberty and by years spent experiencing intense gender dysphoria. On the other hand, there are concerns about negative physical side effects of GnRH analogue use (e.g., on bone development and height). Although the very first results of this approach (as assessed for adolescents followed over 10 years) are promising, the long-term effects can only be determined when the earliest-treated patients reach the appropriate age.

WPATH also recommended the use of GnRH analogues as part of anti-hormone regimens to help minimize the doses of cross sex hormones needed, and thereby reducing the risks associated with high-dose exogenous hormone therapy.

In May 2013, the American Psychiatric Association published an update to their Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5). The DSM-5 provided updated diagnostic criteria for gender dysphoria for both children and adults. The new criteria are as follows:[34]

**I. Gender Dysphoria in Adolescents**

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1):
   1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).
   2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
   3. A strong preference for cross-gender roles in make-believe play or fantasy play.
   4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
   5. A strong preference for playmates of the other gender.
   6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
   7. A strong dislike of one's sexual anatomy.
   8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

*Specify* if:

- **With a disorder of sex development** (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).
- **Coding note:** Code the disorder of sex development as well as gender dysphoria.

**II. Gender Dysphoria in Adolescents and Adults**

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:
   1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
   2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
   3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
   4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
   5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
   6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

*Specify* if:

- **With a disorder of sex development** (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).
- **Coding note:** Code the disorder of sex development as well as gender dysphoria.

*Specify* if:

- **Post-transition:** The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen—namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

## CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for FIRMAGON® (degarelix for injection). Local Coverage Determinations (LCDs) do not exist at this time.

Medicare does not have NCDs for Lupaneta Pack (leuprolide acetate injection & norethindrone acetate tablets), Lupron Depot (leuprolide acetate), Lupron Depot-Ped (leuprolide acetate), Supprelin LA (histrelin acetate), Trelstar (triptorelin pamoate), Triptodur (triptorelin), Vantas (histrelin acetate) and Zoladex (goserelin acetate). LCDs exist, see the LCDs for Luteinizing Hormone-Releasing Hormone (LHRH) Analogs.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals. (Accessed August 22, 2018)

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## POLICY HISTORY/REVISION INFORMATION

| Date | Action/Description |
|---|---|
| 01/01/2019 | Updated list of applicable HCPCS codes to reflect annual code edits; added J3316. Policy 2018D0038I archived. |
| 11/01/2018 | Annual review. Added Lupaneta to the drug policy. Added coverage criteria for transgender therapy. Approved by the National Pharmacy & Therapeutics Committee on 10/17/2018. Policy 2017D0038H archived. |
| 11/01/2017 | Annual review. Added Triptodur to the drug policy. Updated criteria for endometriosis. Updated clinical evidence, CMS statement, and references. Approved by the National Pharmacy & Therapeutics Committee on 08/18/2017. Policy 2017D0038G archived. |
| 01/01/2017 | Updated drug policy. Changed "Proven" to "May be covered" for all covered indications. Added disclaimer. Updated clinical evidence. Approved by the National Pharmacy & Therapeutics Committee on 08/19/2016. Policy 2016D0038F archived. |
| | Annual review. Renamed drug policy. Added all GnRH analogs into drug policy for non-oncology uses. Updated Coverage Rationale to include indications and criteria for endometrial thinning and gender dysphoria. Updated coverage rationale for endometriosis fertility preservation. Updated CMS, Background, US FDA, Clinical Evidence, References, J Codes, ICD-9 and ICD-10 codes. Approved by the National Pharmacy & Therapeutics Committee on 05/20/2016. |
| 02/01/2016 | Added E22.8. Policy 2015D0038E archived. |
| 12/01/2015 | Updated Policy. Updated criteria for fertility preservation for patients receiving cytotoxic therapy that is associated with primary ovarian sufficiency. Approved by the National Pharmacy & Therapeutics Committee on 09/04/2015. Policy 2015D0038D archived. |
| 10/01/2015 | Updated Applicable Codes for ICD-10 transition. Policy 2014D0038C archived. |
| | Annual review of policy. Added fertility preservation in patients undergoing chemotherapy as a proven use. Added luteinizing hormone response for CPP. Added EHB language to Benefit Considerations. Clinical evidence and references updated. Updated ICD-9 and ICD-10 codes, respectively. Approved by the National Pharmacy & Therapeutics Committee on 07/14/2015. |
| 09/01/2014 | Annual review of policy. Added duration of therapy statements for CPP, endometriosis, and uterine leiomyomata. Listed puberty suppression in patients with gender identity disorder as an unproven use. Clinical evidence and references updated. Approved by the National Pharmacy & Therapeutics Committee on 07/08/2014. Policy 2013D0038B archived. |
| 07/01/2013 | Annual review of policy. Added medical necessity criteria. Removed infertility from the list of proven uses. Clinical evidence and references updated. Removed code J9218. Updated ICD-9 codes (removed 628.0 and 628.1) and associated ICD-10 codes. Approved by the National Pharmacy & Therapeutics Committee on 05/21/2013. Policy 2012D0038A archived. |
| 11/14/2012 | New policy 2012D0038A. Approved by the National Pharmacy & Therapeutics Committee on 04/10/2012. |