This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee

**Drug:** degarelix (Firmagon), goserelin (Zoladex), histrelin acetate (Supprelin LA), histrelin acetate (Supprelin LA implant), histrelin acetate (Vantas Implant), leuprolide acetate (Eligard), leuprolide acetate (Lupron Depot), leuprolide acetate (Lupron Depot Ped), leuprolide acetate and norethindrone (Lupaneta Pack), nafarelin acetate (Synarel nasal spray), triptorelin pamoate (Trelstar, Trelstar Depot, Trelstar LA)

**Class:** Gonadotropin Releasing Hormone (GnRH) Analogs

**Line of Business:** Non-Medicare

**Effective Date:** February 17, 2016

**Policy/Criteria:**

1. **Endometriosis:**

   *Lupron Depot* (leuprolide acetate), *Lupaneta Pack* (leuprolide acetate and norethindrone), *Synarel* (nafarelin acetate nasal spray), *Zoladex* (goserelin)

   Medication is considered medically necessary and will be initially authorized for 6 months if the following criteria are met:

   a. Documented inadequate response or clinically significant adverse effects to a continuous or extended-cycle oral contraceptive (e.g. Camrese 3 month dose pack, Quasense 3 month dose pack)
   b. Confirmed diagnosis of endometriosis and prescribed by an OB-GYN specialist
   c. Age 18 or older
   d. **Formulary Position:** Zoladex is the preferred product for treatment of endometriosis

2. **Prostate Cancer:**

   *Eligard* (leuprolide acetate), *Firmagon* (degarelix), *leuprolide acetate immediate release*,
   *Lupron Depot* (leuprolide acetate), *Trelstar*, *Trelstar Depot/LA* (triptorelin pamoate),
   *Vantas* (histrelin acetate implant), *Zoladex* (goserelin)

   Medication is considered medically necessary and will be initially authorized for 12 months if the following criteria are met:

   a. Treatment of advanced prostate cancer
   b. Prescribed by an oncologist or urologist
c. Requests dispensed at pharmacy: Eligard, Trelstar, Trelstar Depot/LA and Zoladex are the preferred products for treatment of prostate cancer
d. Lupron administered at medical office (e.g. J code) will be approved for treatment of prostate cancer, if criteria are met (2a-2b).

3. Breast Cancer:

**goserelin (Zoladex), leuprolide acetate (Lupron Depot)**
Medication is considered medically necessary and will be initially authorized for 12 months if the following criteria are met:
   a. Confirmed diagnosis of advanced breast cancer in pre- and perimenopausal women and prescribed by an oncologist
   b. **Formulary Position:** Zoladex is the preferred product for treatment of breast cancer

4. Uterine leiomyomata (fibroids):

**leuprolide acetate (Lupron Depot)**
Medication is considered medically necessary and will be initially authorized for 3 months if the following criteria are met:
   a. Confirmed diagnosis of uterine leiomyomata (fibroids) and prescribed by an OB-GYN specialist
   b. Age 18 or older

5. Ovarian Cancer:

**leuprolide acetate (Lupron Depot)**
Medication is considered medically necessary and will be initially authorized for 12 months if the following criteria are met:
   a. Confirmed diagnosis of ovarian cancer in pre-menopausal women, including fallopian tube cancer and primary peritoneal cancer and prescribed by an oncologist

6. Central Precocious Puberty:

**leuprolide acetate (Lupron Depot Ped), Supprelin LA (histrelin acetate implant), Synarel (nafarelin intranasal)**
Medication is considered medically necessary and will be initially authorized for 12 months if the following criteria are met:
   a. Confirmed diagnosis of central precocious puberty
   b. Prescribed by a pediatrician or endocrinologist
   c. Onset of secondary sexual characteristics in one of the following:
      1) Females ≤ 8 years of age
      2) Males ≤ 9 years of age
**Clinical Justification:**

**Comparison of FDA-Approved Indications and Off-Label Uses**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer, advanced, palliative treatment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Prostate cancer, stage B2 to C, in combination with an antiandrogen and radiotherapy</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer, advanced, palliative treatment</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Off-label</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial thinning</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine leiomyomata (fibroids)</td>
<td>Off-label</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Off-label</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Precocious Puberty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Supprelin LA</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

**Dosing and Administration**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zoladex (goserelin)</strong></td>
<td></td>
</tr>
<tr>
<td>3.6mg SQ every month</td>
<td>• Administer implant by inserting the needle at a 30 to 45 degree angle into the anterior wall below the navel line</td>
</tr>
<tr>
<td>10.8mg SQ every 3 months</td>
<td>• Use caution due to the proximity of underlying inferior epigastric artery and its branches</td>
</tr>
<tr>
<td></td>
<td>• Insert the needle with the bevel facing up, until the protective sleeve touches the patient’s skin</td>
</tr>
<tr>
<td></td>
<td>• Depress the plunger until you hear a “CLICK.”</td>
</tr>
</tbody>
</table>
click ensures the SafeSystem has been activated and depot has been deposited in the correct location

- Do not penetrate into muscle or peritoneum
- If a large vessel is penetrated, blood will be visualized in the syringe chamber. Withdraw needle and inject elsewhere with a new syringe.
- Implant may be detected by ultrasound if removal is required.
- Use extra care when administering goserelin to patients with a low BMI and/or to patients receiving full dose anticoagulation.
- Monitor for signs/symptoms of abdominal hemorrhage

| Lupron Depot (leuprolide) | Provided in a prefilled dual chamber syringe  
| 3.75mg IM every month  
| 7.5mg IM every month  
| 22.5mg IM every 3 months  
| 30mg IM every 4 months  |
|-------------------------|---------------------------------------------------------------|
| Eligard (leuprolide)    | Allow product to come to room temperature  
| 7.5mg SQ every month    |
| 22.5mg SQ every 3 months|
| 30mg SQ every 4 months  |
| 45mg SQ every 6 months  |
|-------------------------|---------------------------------------------------------------|
| Vantas (histrelin)      | Surgically inserted                                            |
| 50mg implant surgically inserted every 12 months |
|-------------------------|---------------------------------------------------------------|
| Lupaneta Pack (leuprolide and norethindrone) | Follow the mixing procedure as directed  
| 3.75mg IM every month by healthcare provider; norethindrone 5mg po once daily for up to 6 months  
<p>| 11.25mg IM every 3 months administered by healthcare provider; norethindrone 5mg po once daily for up to 6 months |
|-------------------------|---------------------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Firmagon (degarelix)</th>
<th>Reconstitute and mix as directed</th>
</tr>
</thead>
</table>
Loading dose: 240mg
Maintenance: 80mg SQ every 28 days

- Subcutaneous injection in the abdominal region

### Synarel (nafarelin)

- Intranasal spray
- One spray (200 mcg) into 1 nostril each morning and 1 spray (200 mcg) into the other nostril each evening starting between days 2 and 4 of menstrual cycle
- If regular menstruation persists after 2 months of therapy, may increase dose to 2 sprays in the morning and evening. Total duration of therapy should not exceed 6 months.

### Trelstar (triptorelin)

- Reconstituted the Trelstar vial as directed
- Administer the intramuscular injection into the buttock; alternate injection sites. Administer immediately after reconstitution

#### Clinical Management Guidelines: Management of Endometriosis 2010

- Evidence suggests that pain associated with endometriosis can be reduced with the use of a variety of medications (progestins, danazol, combined oral contraceptives (OCs), NSAIDS and Gonadotropin-releasing hormone (GnRH) agonists).
- In a 2-year prospective study of women with endometriosis-associated dysmenorrhea that was not responsive to cyclic combined OCs, continuous combined OC administration was found to provide significant pain reduction from baseline.
- GnRH agonists are highly effective in reducing the pain syndromes associated with endometriosis. However, they are not superior to other methods such as combined OCs as first-line therapy.
- GnRH agonists may have significant side effects, including hot flushes, vaginal dryness and osteopenia. Osteopenia has shown to be reversible with short-term use, but may not be with long-term use or use of multiple cycles.
- As with other suppressive therapy, recurrence of symptoms is common after the medication is discontinued. The recurrence rate at 5-year follow-up, after discontinuing GnRH agonist treatment, ranges from 53% to as high as 73% in women with advanced disease.
- There may be an option for prolonged use of the GnRH agonist for up to 1 year if add-back therapy is used.
Androgen deprivation therapy (ADT) is administered as primary systemic therapy in advanced disease or as neoadjuvant, concomitant, adjuvant therapy in combination with radiation in localized or locally advanced prostate cancers.

- LHRH agonist or antagonist (medical castration) and bilateral orchiectomy (surgical castration) are equally effective.
- Combined androgen blockage (medical or surgical castration combined with an antiandrogen) provides modest to no benefit over castration alone in patients with metastatic disease.
- Antiandrogen therapy should precede or be co-administered with LHRH agonist and be continued in combination for at least 7 days for patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone.
- Antiandrogen monotherapy appears to be less effective than medical or surgical castration and is not recommended.
- Patients who do not achieve suppression of serum testosterone (less than 50ng/dL) with medical or surgical castration can be considered for additional hormonal manipulations (with estrogen, anti-androgens, LHRH antagonists, or steroids), although the clinical benefit remains uncertain. The optimal level of serum testosterone to effect “castration” has yet to be determined.

The U.S. Food and Drug Administration Safety Information: February 2015

- Injection site injury and vascular injury including pain, hematoma, hemorrhage and hemorrhagic shock, requiring blood transfusions and surgical intervention, have been reported with Zoladex. Extra care should be taken when administering Zoladex to patients with low BMI and/or to patients receiving full dose anticoagulation.

The U.S. Food and Drug Administration Safety Information: July 2013

- Postmarketing reports of convulsions have been observed in patients on Lupron Depot therapy. These included patients with a history of seizure, cerebrovascular disorders, central nervous anomalies of tumors, and in patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs.


- Hormone therapy with tamoxifen or other agents including aromatase inhibitors (such as exemestane, anastrozole and letrozole), leuprolide acetate or megestrol acetate continues to be a viable therapeutic option for patients who cannot tolerate or have not responded to cytotoxic regimens.
• Note that bevacizumab or leuprolide may be considered for patients with recurrent granulosa cell tumors


• In premenopausal women, endocrine therapies include selective ER modulators (tamoxifen or toremifene); LHRH agonists (goserelin and leuprolide); surgical or radiotherapeutic oophorectomy; progestin (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol).
• For most premenopausal patients the use of ovarian suppression or ablation in combination with endocrine therapy for postmenopausal women is appropriate.
• Ovarian suppression utilizes luteinizing hormone-releasing hormone (LHRH) agonists that result in suppression of luteinizing hormone (LH) and release of follicle-stimulating hormone (FSH) from the pituitary and reduction in ovarian estrogen production.
• Available LHRH agonists in the United States include goserelin and leuprolide and, when used for ovarian suppression, both agents should be given as monthly injections as the 3-month depots do not reliably suppress estrogen levels in all patients.

References