Leuprolide acetate, LUPRON DEPOT®, LUPRON DEPOT-PED® (leuprolide acetate)
Pharmacy Coverage Policy

Reviewed Date: 03/08/2014
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Reviewer Initials: KH
Effective Date: 06/15/2014
Policy type: PA with QL, QL only
Program type: Standard
Specialty: Yes
Line of Business: Commercial

<table>
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<th>Brand Name</th>
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<td>GnRH agonist</td>
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<td>leuprolide acetate for depot suspension</td>
<td>214050102564**</td>
<td>GnRH agonist</td>
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<td>214050102064**</td>
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<td>Lupron Depot-PED</td>
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<td>GnRH agonist</td>
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CRITERIA FOR COVERAGE/NONCOVERAGE

Leuprolide acetate, LUPRON® (leuprolide acetate), and LUPRON DEPOT® (leuprolide acetate) will be considered for coverage under the pharmacy benefit program when the following criteria are met:

Prostate Cancer (1 mg/0.2 mL solution for injection and 7.5 mg 1-month, 22.5 mg 3-month, 30 mg 4-month, & 45 mg 6-month depots only)
- Patient has a diagnosis of advanced or metastatic prostate cancer

Endometriosis (3.75 mg 1-month & 11.25 mg 3-month depots only)
- In patients with childbearing potential, pregnancy has been excluded and patient will be using nonhormonal contraception during and for 12 weeks after therapy AND
- Patient is not breastfeeding AND
- Patient does not have undiagnosed abnormal vaginal bleeding

Initial Course
- Patient has a diagnosis of endometriosis AND
- Patient has had an inadequate pain control response or patient has an intolerance or contraindication to one of the following:
  - Danazol (six month trial) OR
  - Combination [estrogen/progesterone] oral contraceptives (six month trial) OR
  - Progestins (six month trial)

Retreatment Course
- Patient has a diagnosis of endometriosis AND
- Patient is experiencing recurrence of symptoms after an initial course of therapy (6 months) with leuprolide acetate AND

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- Norethindrone acetate 5 mg daily will be co-administered

**Uterine Leiomyomata (Fibroids)** (3.75 mg 1-month & 11.25 mg 3-month depots only)
- Patient is 18 years of age or older **AND**
- In patients with childbearing potential, pregnancy has been excluded and patient will be using nonhormonal contraception during and for 12 weeks after therapy **AND**
- Patient is not breastfeeding **AND**
- Patient does not have undiagnosed abnormal vaginal bleeding **AND**
- Patient has a diagnosis of anemia due to uterine leiomyomata (fibroids) **AND**
- Patient is preoperative **AND**
- Patient has tried and had an inadequate response to 1 month of monotherapy with iron **AND**
- Patient will be receiving concomitant iron therapy while on leuprolide

**Central Precocious Puberty (CPP)** (1 mg/0.2 mL solution for injection; 7.5 mg, 11.25 mg, & 15 mg 1-month depot-ped; 11.25 mg 3-month depot-ped; 30 mg 3-month depot-ped)
- Medication will be used for GnRH analog stimulation testing to confirm diagnosis of CPP (1mg/0.2 mL solution for injection ONLY)
  **OR**
- Patient has a diagnosis of central precocious puberty **AND**
  - Patient had an early onset of secondary sexual characteristics:
    - Male: earlier than 9 years of age
    - Female: earlier than 8 years of age
  **AND**
- Patient has advanced bone age of at least one year compared with chronological age **AND**
- Patient has undergone gonadotropin-releasing hormone agonist (GnRHa) testing **AND** Peak luteinizing hormone (LH) level above pre-pubertal range
  **OR**
- Patient has a random LH level in the pubertal range **AND**
- Patient had the following diagnostic evaluations to rule out tumors, when suspected:
  - Diagnostic imaging of the brain (MRI or CT scan) (in patients with symptoms suggestive of a brain tumor or in those 6 years of age or younger)
  - Pelvic/testicular/adrenal ultrasound (if steroid levels suggest suspicion)
  - Adrenal steroids to rule out congenital adrenal hyperplasia (when pubarche precedes thelarche or gonadarche)
  **AND**
- Medication is prescribed by or in consultation with a pediatric endocrinologist

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Leuprolide acetate is subject to a quantity limit as follows:

<table>
<thead>
<tr>
<th>Strength</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.75 mg depot</td>
<td>1 injection every 28 days (1 month)</td>
</tr>
<tr>
<td>7.5 mg depot</td>
<td>1 injection every 28 days (1 month)</td>
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<tr>
<td>7.5 mg depot-ped</td>
<td>1 injection every 28 days (1 month)</td>
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<tr>
<td>11.25 mg depot</td>
<td>1 injection every 84 days (3 months)</td>
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<tr>
<td>11.25 mg depot-ped (1-month)</td>
<td>1 injection every 28 days (1 month)</td>
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<tr>
<td>11.25 mg depot-ped (3-month)</td>
<td>1 injection every 84 days (3 months)</td>
</tr>
<tr>
<td>15 mg depot-ped</td>
<td>1 injection every 84 days (3 months)</td>
</tr>
<tr>
<td>22.5 mg depot</td>
<td>1 injection every 84 days (3 months)</td>
</tr>
<tr>
<td>30 mg depot</td>
<td>1 injection every 112 days (4 months)</td>
</tr>
<tr>
<td>30 mg depot-ped</td>
<td>1 injection every 84 days (3 months)</td>
</tr>
<tr>
<td>45 mg depot</td>
<td>1 injection every 168 days (6 months)</td>
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</tbody>
</table>

Re-Authorization
Authorization for continued use for prostate cancer shall be reviewed at least every 12 months to confirm that current coverage policy criteria are met.

Authorization for endometriosis shall be approved for 6 months initially provided the current coverage policy criteria are met. An additional 6 months of therapy for retreatment shall be approved provided the current coverage policy criteria are met (for a maximum of 12 months total).

Authorization for continued use for uterine fibroids shall be reviewed at least every 3 months to confirm that current coverage policy criteria are met.

Authorization for continued use for central precocious puberty shall be reviewed at least every twelve months to confirm the following:
- Consideration for discontinuation of therapy at age 11 for females and age 12 for males.
- LH levels have been suppressed to pre-pubertal levels

Off label uses for oncology drugs are approvable if considered medically acceptable as described in the Supporting Information section. (Does not apply to Lupron Depot-PED formulations)

Leuprolide acetate, LUPRON® (leuprolide acetate), and LUPRON DEPOT® (leuprolide acetate) is considered experimental/investigational for conditions not listed in this coverage policy section.

SUPPORTING INFORMATION

FDA Approved Indications (Leuprolide prescribing information, 2011; Lupron Depot prescribing information, 2013; Lupron Depot-Ped prescribing information; 2013.)
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Leuprolide 1 mg/0.2 mL solution for injection, Lupon Depot (leuprolide acetate) 7.5 mg 1-month, Lupon Depot (leuprolide acetate) 22.5 mg 3-month, Lupon Depot (leuprolide acetate) 30 mg 4-month, & Lupon Depot (leuprolide acetate) 45 mg 6-month
• Palliative treatment of advanced prostate cancer

Lupon Depot (leuprolide acetate) 3.75 mg 1-month & Lupon Depot (leuprolide acetate) 11.25 mg 3-month
• Management of endometriosis, including pain relief and reduction of endometriotic lesions. Leuprolide acetate with norethindrone acetate 5 mg daily is also indicated for initial management of endometriosis and for management of recurrence of symptoms. Duration of initial treatment should be limited to 6 months.
• Anemia caused by uterine fibroids for preoperative hematologic improvement concomitantly with iron therapy. Recommended duration of therapy is up to three months. Experienced with leuprolide acetate in females has been limited to women 18 years of age and older.

Leuprolide acetate 1 mg/0.2 mL solution for injection, Lupon Depot-PED (leuprolide acetate) 7.5 mg, 11.25 mg, & 15 mg 1-month, Lupon Depot-PED (leuprolide acetate) 11.25 mg & 30 mg 3-month depot
• Treatment of children with central precocious puberty.

Place in Therapy
Prostate Cancer
The choice of initial treatment of prostate cancer is influenced by estimated life expectancy, comorbid features, adverse events associated with therapy, probability of cure and patient preference (NCCN Guidelines for Prostate Cancer, 2014). Initial therapy for clinically localized disease includes active surveillance, radical prostatectomy or radiotherapy. Androgen deprivation therapy (ADT) is commonly used in the treatment of prostate cancer. ADT can be accomplished either with surgical castration (via orchectomy) or medical castration (gonadotropin-releasing hormone agonists [GnRH, LHRH] or antagonists), which are equally effective. GnRH agonists are associated with an initial flare of testosterone. In those with metastatic disease, antiandrogen therapy should be initiated before or alongside the GnRH agonist for a minimum of 7 days to alleviate potential symptoms of flare. ADT can be used with radiation therapy in localized or locally advanced prostate cancer and as primary systemic therapy in advanced disease. The NCCN compendia further defines place in therapy for leuprolide (NCCN Compendia, 2014).

Endometriosis
• According to the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on the management of endometriosis, 2010:
  o When relief of pain from treatment with GnRH agonists 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.
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- After an appropriate pre-treatment evaluation and failure of initial treatment with oral contraceptives and nonsteroidal anti-inflammatory drugs (NSAIDS), empiric therapy with a three-month course of a GnRH agonist is appropriate.
- GnRH agonists are effective but not superior to other agents, such as oral contraceptives, in reducing pain syndromes associated with endometriosis.

Uterine Leiomyomata (Fibroids)
- According to an ACOG practice bulletin reviewing alternatives to hysterectomy in the management of leiomyomas (ACOG, 2008), GnRH agonists have been shown to improve hematologic parameters, shorten hospital stay, and decrease blood loss, operating time, and postoperative pain when given for 2 to 3 months preoperatively [Level A – based on good and consistent scientific evidence].
- The clinician may wish to consider a one-month trial period on iron alone as some of the patients will respond to iron alone. Leuprolide may be added if the response to iron alone is considered inadequate.

Central Precocious Puberty (CPP)
- Leuprolide 1mg/0.2 mL solution for injection can be used for GnRH analog stimulation testing to confirm diagnosis of CPP (Carel, 2009).
- Normal age for the onset of puberty ranges from 8 to 13 years in girls and 9.5 to 13.5 years for boys (Carel, 2008). CPP is defined as early onset of secondary sexual characteristics associated with pubertal pituitary gonadotropin activation. It may show a significantly advanced bone age than can result in diminished adult height (Carel, 2009).
- The standard treatment of CPP involves the use of GnRH analogs (Carel, 2009).
- According to a consensus statement on the use of GnRH analogs in children (Carel, 2009), girls with onset of progressive CPP before 6 years of age benefit most in terms of height from GnRH agonists. The decision to initiate therapy in girls with onset after the age of 6 should be individualized. Treatment should be considered for all boys with onset of progressive CPP before 9 years of age who have compromised height potential. The use of GnRH agonists solely to influence the psychosocial consequences of CPP or to delay menarche should be considered carefully given the absence of convincing data. Depot preparations are preferred because of improved adherence.
- 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 may be observed (Lupron Depot-PED prescribing information, 2011).
- Factors that can influence the decision to stop GnRHa treatment depend on the primary goals of therapy, including maximizing height, synchronizing puberty with peers, ameliorating psychosocial distress, and facilitating care of the developmentally delayed child (Carel, 2009).
- Prior to the initiation of treatment, a clinical diagnosis of CPP should be confirmed by measurement of blood concentrations of luteinizing hormone (LH) (Houk, 2009). Patients with CPP have a random LH level in the pubertal range. Literature suggests that a single basal LH measurement is adequate to diagnosis in most but not all girls with CPP.
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- Gonadotropin-releasing hormone agonist (GnRHa) testing is another diagnostic option. Patients with CPP have a peak LH level above the pre-pubertal range.
- In addition, bone age versus chronological age should be assessed (Supprelin LA prescribing information, 2013). Patients should have advanced bone age of at least one year compared with chronological age.
- Baseline evaluations should include height and weight measurements, diagnostic imaging of the brain which is only necessary in patients 6 years or younger or patients with symptoms suggestive of a brain tumor, pelvic/testicular/adrenal ultrasound (to rule out steroid-secretting tumors), and adrenal steroids to exclude congenital adrenal hyperplasia when pubarche precedes thelarche or gonadarche. Our external pediatric endocrinologist recommended removing the hCG level criteria altogether as this is not necessary in all boys.

Safety Concerns
- Leuprolide acetate is contraindicated in patients with known hypersensitivity to GnRH, GnRH agonist analogs or any of the components of the product (Micromedex, 2014).
- Leuprolide acetate is also contraindicated in women who (1) have undiagnosed abnormal vaginal bleeding; (2) are breast-feeding; and (3) are or may become pregnant while receiving the drug. Leuprolide can cause fetal harm when administered to a pregnant woman (pregnancy category X rating in patients with endometriosis and endometrial thinning). There is an increased risk for pregnancy loss and fetal mortality due to expected hormone changes that occur with leuprolide treatment. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.
- When used monthly at the recommended dose, leuprolide usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking leuprolide. Therefore, female patients should use non-hormonal methods of contraception.
- Osteopenia associated with leuprolide therapy may occur (Pierce, 2000). Studies show that osteopenia can be reversible with short-term use, but may not be with long-term use or multiple cycles.

Dosage Information
- The quantity limits in the coverage policy are based on how the drug was dosed in clinical trials (which is weekly rather than monthly) (Ling, 1999; Clinical Pharmacology, 2014).
- Duration of initial treatment or retreatment for endometriosis should be limited to 6 months each due to potential negative effects on bone mineral density (Lupron 3.75 mg prescribing information, 2013).
- Literature suggests that leuprolide may be considered for long-term treatment for uterine leiomyomata (Nakayama, 1999).
- See Appendix for specific dosing information.

Additional Relevant Information

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For CPP, leuprolide acetate should be discontinued at the appropriate age of onset of puberty (11 years of age in girls and 12 years of age in boys) at the discretion of the physician (Lupron Depot-PED prescribing information, 2013).

Experience with Lupron Depot (leuprolide acetate) has been limited to women 18 years of age or older for the treatment of uterine fibroids (Lupron Depot 3.75 mg 1-month prescribing Information, 2013; Lupron Depot 11.25 mg 3-month prescribing Information, 2013).

Off label uses for oncology drugs are approvable if considered medically acceptable in one or more of the following compendia (i.e., Micromedex DrugDex, Lexi-Comp (AHFS), Clinical Pharmacology, and NCCN.) A use is identified by a compendium as medically accepted if the:

- Indication is a Category 1 or 2A in NCCN,
- Indication is a Class I, Class IIA or Class IIB in DrugDex,
- Narrative text in Lexi-Comp or Clinical Pharmacology is supportive; or
- The use is supported by clinical research in 1 or more peer-reviewed medical journals as specified in the Compendial SOP document.
REFERENCES


Lupron Depot (leuprolide acetate for depot suspension) 22.5 mg 3-month, 30 mg 4-month, & 45 mg 6-month prescribing Information. Abbott Laboratories. North Chicago, IL. July 2013.


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