This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit 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.

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 for oncology indications.

This policy refers to the following leuprolide acetate drug products:
- Lupron Depot
- Lupron Depot-Ped
Intramuscular injection of leuprolide acetate is proven for:

1. Central precocious puberty

   **Additional information to support medical necessity review where applicable:**
   Leuprolide acetate is medically necessary for the treatment of central precocious puberty when all of the following criteria are met:1,12
   
   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
      2) Males ≤ 9 years of age
   AND
   
   C. Confirmation of diagnosis as defined by one of the following:
      1) A pubertal response to a GnRH stimulation test
      2) Bone age advanced one year beyond the chronological age
   
   The leuprolide acetate label states that treatment should be discontinued at the appropriate age of onset of puberty at the discretion of the physician.1 Give consideration to discontinuing treatment before 11 years of age in girls and 12 years of age in boys.13

2. Endometriosis

   **Additional information to support medical necessity review where applicable:**
   Leuprolide acetate is medically necessary for the treatment of endometriosis when both of the following criteria are met:2,10,12
   
   A. Diagnosis of endometriosis
   AND
   
   B. One of the following:
      1) Contraindication, intolerance, or failure of initial treatment with oral contraceptives and non-steroidal anti-inflammatory drugs (NSAIDs). Refer to Benefit Considerations for specific state guidance.
      2) Patient has had surgical ablation to prevent recurrence
   
   The leuprolide acetate label states that the duration of initial treatment or retreatment for endometriosis should be limited to 6 months.2 For recurrence of symptoms, leuprolide may be used in combination with norethindrone acetate for 6 months; greater than one retreatment period is not recommended. Leuprolide monotherapy is not recommended for retreatment.13

3. Uterine leiomyomata (fibroids)

   **Additional information to support medical necessity review where applicable:**
   Leuprolide acetate is medically necessary for the treatment of uterine leiomyomata when one of the following criteria is met:5,9,11,12
   
   A. All of the following:
      1) For the treatment of anemia
      AND
      2) Anemia is caused by uterine leiomyomata
      AND
      3) Patient did not respond to iron therapy of one month duration. Refer to Benefit Considerations for specific state guidance.
      AND
      4) 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. 

Injectable leuprolide acetate is unproven for puberty suppression in patients with gender identity disorder due to the lack of long-term safety data. Statistically robust randomized controlled trials are needed to address the issue of whether the benefits outweigh the substantial inherent clinical risk in its use.

**Centers for Medicare and Medicaid Services (CMS):**
Medicare does not have a National Coverage Determination (NCD) for Lupron. Local Coverage Determinations (LCDs) do exist. Refer to 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 (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf.

(Accessed May 1, 2014)

**BENEFIT CONSIDERATIONS**

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit 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.

The State of New Jersey prohibits requiring failed prior therapy or intolerance to therapy as a requirement for coverage.

**BACKGROUND**

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH) 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.

**CLINICAL EVIDENCE**

**Proven Uses:**
**Central Precocious Puberty**
Leuprolide acetate is indicated for the treatment of central precocious puberty (CPP). An open-label study of monthly leuprolide acetate IM injections for the treatment of CPP enrolled 55 subjects (49 female, 6 male, mean age 7 ± 2 years) naïve to previous GnRH agonist therapy. Patients were treated until they reached an age appropriate for entry into puberty (mean duration 4 ± 2 years) and a subset of 40 patients (35 female, 5 male) was then monitored post-treatment. During the treatment period, leuprolide acetate was shown to suppress gonadotropins and sex steroids (estrogen and testosterone) to prepubertal levels. Peak stimulated luteinizing hormone (LH) levels decreased from a mean baseline of 35 mIU/mL to less than 1.75 mIU/mL in 96% of all patients. Peak stimulated luteinizing hormone (LH) levels decreased from a mean baseline of 35 mIU/mL to less than 1.75 mIU/mL in 96% of all patients.

Leuprolide Acetate Policy: Drug Policy (Effective 09/01/2014)

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subjects by week 4 and continued throughout the 5-year treatment period. In boys (n=6), stimulated testosterone levels decreased from a mean baseline of 347.7 ng/dL and remained at levels less than 25.3 ng/dL throughout treatment. In girls, stimulated estradiol levels decreased from a mean baseline of 15.1 pg/mL to 5 pg/mL by week 4 and continued throughout treatment. Suppression of breast development ranged from 66.7% to 90.6% in girls, and suppression of genitalia development ranged from 60% to 100% in boys during the study period. For all subjects, the height standard deviation score decreased from a mean baseline of 1.6 to 0.7, and the mean ratio of bone age to chronological age decreased from a mean baseline of 1.5 to 1.1 at the end of the treatment period. At 6 months post-treatment, return to pubertal levels of LH occurred in 87.9% or subjects, as well as increase in breast development in 66.7% of girls and increase in genitalia development in 80% of boys. Mean age of regular menses onset was 12.9 years, with a mean onset of approximately 1.5 years after stopping leuprolide acetate.

In an open-label study of 84 subjects (76 female, 8 male, age range 1 to 11 years) with central precocious puberty, children were randomized to receive either 11.25 mg or 30 mg leuprolide acetate IM once every 3 months. Each group had an equal number of treatment-naïve patients who had pubertal luteinizing hormone (LH) levels and patients previously treated with GnRH agonist therapy who had prepubertal LH levels at the time of study entry. Patients were assessed at months 2, 3, and 6 of therapy. Suppression of peak stimulated LH levels to < 4 mIU/mL by month 6 of therapy occurred in 78.6% (95% confidence interval (CI), 63.2% to 89.7%) and 95.2% (95% CI, 83.8% to 99.4%) of patients receiving 11.25 mg and 30 mg, respectively. Suppression of sex steroids (estradiol or testosterone) to prepubertal levels occurred in 93% (39/42) of patients receiving 11.25 mg and in 100% (42/42) of patients receiving the 30 mg dose. Clinical suppression of puberty at 6 months of leuprolide acetate treatment was observed in 90.6% and 82.4% of girls receiving 11.25 mg and 30 mg, respectively; while clinical suppression of puberty was observed in 50% (1/2) and 40% (2/5) of boys receiving 11.25 mg and 30 mg, respectively. The mean ratio of bone age to chronological age at month 6 of treatment decreased in 87.9% (29/33) and 75% (30/40) of patients receiving 11.25 mg and 30 mg, respectively.

**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.

In controlled clinical studies, leuprolide acetate IM 3.75 mg/month was shown to be comparable to danazol 800 mg/day in relieving symptoms of endometriosis (pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and inducing laparoscopic improvement. The clinical significance of a decrease in endometriotic lesions is not known and laparoscopic staging does not necessarily correlate with severity of symptoms. Leuprolide induced amenorrhea in 74% and 98% of patients after 1 and 2 months of treatment, respectively. In patients who did not become pregnant, normal menstrual cycles resumed in 95% of patients by the third post-treatment month.

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. 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 (ps0.001) mean improvements from baseline after 12 weeks of therapy in all pain measures. These mean improvements were significantly greater (ps0.001) 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. 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.

In two clinical studies of 12 months duration, concurrent hormone therapy with norethindrone 5 mg daily was shown to be effective in significantly reducing loss of bone mineral density (BMD) associated with leuprolide acetate therapy without compromising its efficacy in relieving the symptoms of endometriosis. In one controlled, randomized, double-blinded study of 106 women, 51 were treated with leuprolide acetate alone and 55 received combination therapy of leuprolide acetate and norethindrone. The second open-label study of 136 women, all who received combination therapy, confirmed the reduction in loss of BMD that was observed in the first study. Suppression of menses was maintained throughout treatment in 84% and 73% of patients receiving combo therapy in the controlled and open label studies, respectively. Menses resumption after treatment with leuprolide acetate and norethindrone occurred at a median time of 8 weeks in the study participants.

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

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. 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. 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. 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. 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.

**Technology Assessments**

Leuprolide Acetate Policy: Drug Policy (Effective 09/01/2014)

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A 2001 Cochrane review was published evaluating pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Authors conclude that:

- The use of GnRH analogues for 3 to 4 months prior to fibroid surgery reduces both uterine volume and fibroid size.
- GnRH analogues are beneficial in the correction of pre-operative iron deficiency anemia, if present, and reduce intra-operative blood loss.
- If uterine size is such that a mid-line incision is planned, this can be avoided in many women with the use of GnRH analogues.
- For patients undergoing hysterectomy, a vaginal procedure is more likely following the use of GnRH analogues.

Hayes compiled a Medical Technology Directory on hormone therapy for the treatment of gender dysphoria dated May 19, 2014. Hayes assigned a rating of D2, no proven benefit and/or not safe, for pubertal suppression 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**

In 2010, the American College of Obstetricians and Gynecologists (ACOG) released a practice bulletin that discusses the management of endometriosis. 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 uncertain.
- 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.

In 2008, the American College of Obstetricians and Gynecologists (ACOG) released a practice bulletin that discusses alternatives to hysterectomy in the management of leiomyomas. 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.
Lupron Depot-Ped (leuprolide acetate) is a gonadotropin releasing hormone (GnRH) agonist indicated for the treatment of children with central precocious puberty (CPP).1

Lupron Depot (leuprolide acetate) is a gonadotropin releasing hormone (GnRH) agonist indicated for:2

- management of endometriosis, including pain relief and reduction of endometriotic lesions (3.75 mg) 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)*

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

### APPLICABLE CODES

The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document.

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**ICD-10 Codes (Preview Draft)**

In preparation for the transition from ICD-9 to ICD-10 medical coding on October 1, 2015*, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated.
to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. *The effective date for ICD-10 code set implementation is subject to change.*

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### POLICY HISTORY/REVISION INFORMATION

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