DRUG POLICY

Lupron® Depot / Lupron® Depot-Ped (leuprolide acetate)

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INSTRUCTIONS FOR USE
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® (NCCN Compendium®) for oncology indications.

This policy refers to the following leuprolide acetate drug products:
- Lupron Depot
- Lupron Depot-Ped

Lupron Depot is **proven** for:

1. **Central precocious puberty**

Additional information to support medical necessity review where applicable:
Lupron Depot 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 luteinizing hormone response to a GnRH stimulation test
(2) Bone age advanced one year beyond the chronological age

The Lupron Depot 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:
Lupron Depot 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).
(2) Patient has had surgical ablation to prevent recurrence

The Lupron Depot 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. Lupron Depot monotherapy is not recommended for retreatment.[13]

3. **Uterine leiomyomata (fibroids)**

Additional information to support medical necessity review where applicable:
Lupron Depot 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.
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.[13]

4. **Fertility preservation**

Additional information to support medical necessity review where applicable:
Lupron Depot is **medically necessary** for fertility preservation when the following criteria are met:

a. **Both** of the following:
   (1) For use in pre-menopausal women
   AND
   (2) Patient is receiving a cytotoxic agent that is associated with causing primary ovarian insufficiency (premature ovarian failure) [e.g., Cytoxan (cyclophosphamide), procarbazine, vinblastine, cisplatin][25,26]

Lupron Depot therapy should be discontinued upon the completion of cytotoxic treatment.

Unproven:
Lupron Depot is **unproven and not medically necessary** 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 or for Luteinizing Hormone-Releasing Hormone (LHRH) Analogs. 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 19, 2015)

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.

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 (such as maternity benefits), 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 guideline, it is important to refer to the enrollee's specific plan document to determine benefit coverage.

BACKGROUND

Lupron 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.[13]

CLINICAL EVIDENCE

Proven:

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.

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.[1] 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 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.[17] 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.[2]

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 (V2.2015) 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 (V2.2015) 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 Carmustine Cyclophosphamide Dacarbazine Ifosfamide Lomustine Melphalan

	Procarbazine
Intermediate risk of ovarian toxicity	Cisplatinum Cytarabine Etoposide 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]

Technology Assessments

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.

Gender Identity Disorder
Hayes compiled a Medical Technology Directory on hormone therapy for the treatment of gender dysphoria dated May 19, 2014.[14] 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
Fertility Preservation
In 2013, 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]
The following recommendations and conclusions were published:

Currently, there is insufficient evidence regarding the effectiveness of GnRHa and other means of ovarian suppression in fertility preservation. GnRHa should not be relied upon as a fertility preservation method. However, GnRHa may have other medical benefits such as a reduction of vaginal bleeding when patients have low platelet counts as a result of chemotherapy. This benefit must be weighed against other possible risks such as bone loss, hot flashes, and potential interference with response to chemotherapy in estrogen-sensitive cancers. Women interested in this method should participate in clinical trials, because current data do not support it. In true emergency or rare or extreme circumstances where proven options are not available, providers may consider GnRHa an option, preferably as part of a clinical trial.

Endometriosis
In 2010, 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, 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.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Lupron Depot-Ped is a gonadotropin releasing hormone (GnRH) agonist indicated for the treatment of children with central precocious puberty (CPP).[1]

Lupron Depot is a gonadotropin releasing hormone (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)*

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

- The prescribing information for Lupron Depot contains warnings associated with its use:[2] Tumor flare – transient worsening of symptoms due to increases of testosterone to approximately 50% 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 agonists. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist 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 agonists in men. Patients receiving a

GnRH agonist 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.
- 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.

APPLICABLE CODES

The Current Procedural Terminology (CPT®) codes and/or Healthcare Common Procedure Coding System (HCPCS) codes listed in this policy are for reference purposes only. Listing of a service 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 enrollee specific benefit 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 claims payment. Other policies and coverage determination guidelines may apply. This list of codes may not be all inclusive.

HCPCS Code	Description
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg
J9217	Leuprolide acetate (for depot suspension), 7.5 mg

ICD-9 Codes (Discontinued 10/01/15)
The following list of codes is provided for reference purposes only. Effective October 1, 2015, the Centers for Medicare & Medicaid Services (CMS) implemented ICD-10-CM (diagnoses) and ICD-10-PCS (inpatient procedures), replacing the ICD-9-CM diagnosis and procedure code sets.
ICD-9 codes will not be accepted for services provided on or after October 1, 2015.

ICD-9 Code (Discontinued 10/1/15)	Description
218.0	Submucous leiomyoma of uterus
218.1	Intramural leiomyoma of uterus
218.2	Subserous leiomyoma of uterus
218.9	Leiomyoma of uterus, unspecified
259.1	Sexual development and puberty, not elsewhere classified
617.0	Endometriosis of uterus
617.1	Endometriosis of ovary
617.2	Endometriosis of fallopian tube
617.3	Endometriosis of pelvic peritoneum
617.4	Endometriosis of rectovaginal septum and vagina
617.5	Endometriosis of intestine
617.6	Endometriosis in scar of skin
617.8	Endometriosis of other specified sites
617.9	Endometriosis, site unspecified
V26.42	Procreative management; Encounter for fertility preservation counseling
V26.82	Procreative management; Encounter for fertility preservation procedure.
V58.11	Encounter for antineoplastic chemotherapy

V87.41	Personal history of antineoplastic chemotherapy

ICD-10 Codes (Effective 10/1/15)
ICD-10-CM (diagnoses) and ICD-10-PCS (inpatient procedures) must be used to report services provided on or after October 1, 2015.

ICD-10 codes will not be accepted for services provided prior to October 1, 2015.

ICD-10 Diagnosis Code (Effective 10/1/15)	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
E23.0	Hypopituitarism
E30.1	Precocious puberty
E30.8	Other disorders of puberty
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
Z31.62	Encounter for fertility preservation counseling
Z31.84	Encounter for fertility preservation procedure
Z51.11	Encounter for antineoplastic chemotherapy
Z92.21	Personal history of antineoplastic chemotherapy

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
2/1/2016	Added E22.8. Policy 2015D0038E archived.
12/1/2015	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 9/4/2015. Policy 2015D0038D archived.
10/1/2015	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 7/14/2015.
9/1/2014	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 7/8/2014. Policy 2013D0038B archived.
7/1/2013	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 5/21/2013. Policy 2012D0038A archived.
11/14/2012	New policy 2012D0038A. Approved by the National Pharmacy & Therapeutics Committee on 4/10/2012.