Policy Number	RX501.041
Policy Effective Date	08/15/2025

Gonadotropin-Releasing Hormone (GnRH) Agonists and Antagonists

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Related Policies (if applicable)
SUR717.001: Gender Assignment Surgery and Gender Reassignment Surgery with Related Services
RX502.061: Oncology Medications

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses

as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

EXCEPTION: Effective for policies issued after January 1, 2019, **Illinois** law (215 ILCS 5/356z.29) requires coverage and reimbursement for standard fertility preservation services when a necessary medical treatment may directly or indirectly cause iatrogenic infertility to a member. "Standard fertility preservation services" means procedures based upon current evidence-based standards of care established by the American Society for Reproductive Medicine, the American Society for Clinical Oncology, or other national medical associations that follow current evidence-based standards of care.

EXCEPTION: For policies issued or renewed on or after January 1, 2024, **Montana** law (Senate Bill 516, Section 2-18-704) requires medically necessary coverage of standard fertility preservation services for individuals diagnosed with cancer, and the standard of care involves medical treatment that may directly or indirectly cause iatrogenic infertility. For the purposes of this mandate, iatrogenic infertility means an impairment of fertility caused directly or indirectly by surgery, chemotherapy, radiation, or other medical treatment; medical treatment that may directly or indirectly cause iatrogenic infertility means treatment with a potential side effect of impaired fertility, as established by a national association of practitioners of reproductive medicine or clinical oncology; and standard fertility preservation services means procedures consistent with established medical practices and professional guidelines published by a national association for practitioners of reproductive medicine or clinical oncology.

EXCEPTION: For policies delivered, issued for delivery or renewed on or after January 1, 2024, **Texas** law (TIC Chapter 1366, Subchapter C, §§1366.101 – 1366.103), mandates coverage of fertility preservation services to an individual who will receive a medically necessary treatment for cancer, including surgery, chemotherapy, or radiation, that the American Society of Clinical Oncology or the American Society for Reproductive Medicine has established that may directly or indirectly cause impaired fertility. The fertility preservation services as described by this mandate must be standard procedures to preserve fertility consistent with established medical practices or professional guidelines published by the American Society of Clinical Oncology or the American Society for Reproductive Medicine. For the purposes of this mandate, fertility preservation services means the collection and preservation of sperm, unfertilized oocytes and ovarian tissue, and does **NOT** include the storage of such unfertilized genetic materials.

Coverage

This medical policy does NOT address Gender Reassignment Services (Transgender Services). This medical policy IS NOT TO BE USED for Gender Reassignment Services. Refer to SUR717.001, Gender Assignment Surgery and Gender Reassignment Surgery with Related Services.

NOTE 1: This medical policy does NOT address oncologic indications. This medical policy IS NOT TO BE USED for oncologic indications. Refer to RX502.061 Oncology Medications for oncologic indications.

NOTE 2: Carefully check the member's benefit plan, summary plan description or contract for language specific to infertility services. IF infertility services are determined to be eligible for member benefits, then the following services that are listed as medically necessary should be considered for benefit coverage.

Special Comment: This policy **addresses the singular use** of gonadotropin-releasing hormone (GnRH) agonists and antagonists. It does **not address the combined** use of luteinizing hormone-releasing hormone (LHRH) agonists AND anti-androgens, for which there is no corresponding medical document.

NOTE 3: This is not an all-inclusive listing of all GnRH preparations. Refer to the U.S. Food and Drug Administration (FDA) for all labeled indications of those GnRH preparations not listed in this policy.

ALERT: All self-injectable medications are administered under the pharmacy benefit.

Gonadotropin-releasing hormone **may be considered medically necessary** for the indications listed in the table below.

Drug Name		**Medically Necessary Indications**
Generic	**Brand**	
Cetrorelix acetate	Cetrotide®	• Inhibition of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian stimulation.
Ganirelix acetate	Ganirelix	• Inhibition of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian hyperstimulation
Goserelin acetate implant	Zoladex® (3.6 mg)	• Management of endometriosis, including pain relief and reduction of endometriotic lesions for the duration of therapy in women ages 18 years and older for up to 6 months; • Use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding; • Dysfunctional uterine bleeding.
Histrelin acetate	Supprelin LA®	• Treatment of children with central precocious puberty (CPP) with an early onset of secondary sexual characteristics (earlier than 8 years of age in females and 9 years of age in males).

Leuprolide acetate	Lupron Depot® (3.75 mg)	Endometriosis • Management of endometriosis, including pain relief and reduction of endometriotic lesions; • In combination with a norethindrone acetate for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms not to exceed 12 months. Uterine Leiomyomata (Fibroids) • Concomitantly with iron therapy is indicated for the preoperative hematologic improvement of women with anemia caused by fibroids for whom three months of hormonal suppression is deemed necessary.
	Lupron Depot® (11.25 mg)	Endometriosis • Management of endometriosis, including pain relief and reduction of endometriotic lesions; • In combination with a norethindrone acetate for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms not to exceed 12 months. Uterine Leiomyomata (Fibroids) • Concomitant use with iron therapy for preoperative hematologic improvement of women with anemia caused by fibroids for whom three months of hormonal suppression is deemed necessary.
	Lupron Depot PED®	• Treatment of pediatric patients with central precocious puberty (CPP).
	Fensolvi®	• Treatment of pediatric patients 2 years of age and older with central precocious puberty (CPP).
Nafarelin acetate	Synarel®	• Treatment of central precocious puberty (CPP) (gonadotropin-dependent precocious puberty) in children of both sexes; • Management of endometriosis, including pain relief and reduction of endometriotic lesions in women 18 years of age and older treated for 6 months.
Triptorelin	Triptodur®	• Treatment of pediatric patients 2 years and older with central precocious puberty.

Administration of GnRH analogs, hormones and antagonists **is considered experimental, investigational and/or unproven** for all other non-FDA approved indications for the GnRH products addressed in the table above.

Policy Guidelines

None.

Description

Acting on the pituitary gland in the brain, gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone-releasing hormone (LHRH), stimulates the function of the testes and ovaries.

Background
GnRH analogs are synthetic peptide drugs modeled after the human hypothalamic GnRH. Two types of analogs have been distinguished: GnRH agonists and GnRH antagonist. GnRH agonists drugs interact with GnRH receptors to elicit its biologic response, the release of pituitary gland hormones: follicle-stimulating hormones (FSH) and luteinizing hormone (LH). GnRH antagonist drugs competitively and reversibly binds to the GnRH receptors in the pituitary gland, blocking or suppressing the release of FSH and LH. In men, the reduction of LH subsequently leads to rapid suppression of testosterone release from the testes. In women, the reduction leads to suppression of estrogen release from the ovaries.

Repeated administration of these drugs may cause gonadal hormone dependent tissues or organs to reduce or cease activity, such as the normal prostate gland that is dependent on testosterone for growth and function. This effect is reversible on discontinuation of the drug therapy.

Regulatory Status
Although GnRH products may differ in specific labeled indications and dosing requirements, clinical evidence may not support differential effectiveness of one product over the other for U.S. Food and Drug Administration (FDA) approved clinical indications.

Cetrorelix acetate (Cetrotide®) is a synthetic injectable decapeptide analog of GnRH, a GnRH antagonist and originally FDA approved August 11, 2000. (1) It is used as a component of infertility regimens (recombinant FSH or human menopausal gonadotropin [hMG], Cetrorelix®, and human chorionic gonadotropin [hCG]) to inhibit premature LH surges in women undergoing controlled ovarian stimulation (COS).

Ganirelix acetate is a synthetic decapeptide analog of GnRH, like cetrorelix acetate, and a GnRH antagonist and originally FDA approved July 29, 1999. (2, 11) This drug is used for infertility treatment to inhibit LH surges. The brand Antagon® is no longer marketed in the U.S. and no longer appears on the FDA website; generic preparations may still be available.

Goserelin acetate (Zoladex®) is a GnRH analog, which is indicated in certain conditions requiring suppression of estrogen or testosterone secretion and originally FDA approved July 27, 1989.

(3) At this time, Zoladex® is available as a long acting, continuous releasing subcutaneous implant for a period of 28 days.

Histrelin acetate (Supprelin LA®) is a GnRH agonist that lowers the male hormone testosterone in blood. (4) Supprelin LA® is available as subcutaneous implants for continuous release of the drug. Supprelin LA® is utilized for treatment of children with central precious puberty. Supprelin LA® was originally FDA approved May 3, 2007. The brand Vantas® is not indicated for use in pediatric patients.

Leuprolide acetate (Lupron®, Lupron Depot®, Lupron Depot PED®, Fensolvi®) is a synthetic analog of naturally occurring GnRH or LHRH and an antagonist. (5-8) The analog possesses greater potency than the natural hormone. Because of its inhibitory effect on gonadotropin secretion and androgen or estrogen synthesis, leuprolide inhibits growth of hormone-dependent tumors. Leuprolide has reduced the size of the prostate gland and has inhibited prostatic tumor growth. There is also evidence to suggest that leuprolide inhibits the growth of estrogen-dependent mammary tumors mainly by inhibiting ovarian function and estrogen synthesis. Lupron® products are available as injectables.

Nafarelin acetate (Synarel®) is a metered nasal spray used in the palliative treatment of endometriosis and originally FDA approved April 12, 2006. (9) This drug like other GnRH analogs produces reversible hypo estrogenic state, which is thought to be principally responsible for the beneficial effects observed in endometriosis. A 6-month course of therapy can provide symptomatic relief and a reduction in endometrial lesions. Synarel® is also used for the treatment of central (via activation of the hypothalamic-pituitary-gonadal axis) precocious puberty (true precocious puberty GnRH-dependent precocious puberty, complete isosexual precocity) in children of both sexes and has been designated an orphan drug by the FDA for use in this condition. Precocious puberty is generally defined as the onset of sexual characteristics in girls or boys younger than 8 or 9 years of age respectively. The principle goals of therapy with GnRH analogs in this condition are to halt the premature development of secondary sexual characteristics and achieve a near normal adult height by slowing linear growth and skeletal maturation.

Triptorelin (Triptodur®) is an extended-release injectable suspension used for the treatment of pediatric patients 2 years and older with central precocious puberty. Triptodur® was FDA approved on June 29, 2017. (10)

NOTE 4: For oncologic indications for any of the above listed medications, see RX502.061 Oncology Medications.

Rationale

Cetrotide® (1)

Seven hundred thirty-two [732] patients were treated with Cetrotide (cetrorelix acetate for injection) in five (two Phase 2 dose-finding and three Phase 3) clinical trials. The clinical trial population consisted of Caucasians (95.5%) and Black, Asian, Arabian and others (4.5%). Women were between 19 and 40 years of age (mean: 32). The studies excluded subjects with polycystic ovary syndrome (PCOS), subjects with low or no ovarian reserve, and subjects with stage III-IV endometriosis.

Two dose regimens were investigated in these clinical trials, either a single dose per treatment cycle or multiple dosing. In the Phase 2 studies, a single dose of 3 mg was established as the minimal effective dose for the inhibition of premature luteinizing hormone (LH) surges with a protection period of at least 4 days. When Cetrotide is administered in a multidose regimen, 0.25 mg was established as the minimal effective dose. The extent and duration of LH-suppression is dose dependent.

In the Phase 3 program, efficacy of the single 3 mg dose regimen of Cetrotide and the multiple 0.25 mg dose regimen of Cetrotide was established separately in two adequate and well controlled clinical studies utilizing active comparators. A third non-comparative clinical study evaluated only the multiple 0.25 mg dose regimen of Cetrotide. The ovarian stimulation treatment with recombinant follicle stimulating hormone (FSH) or human menopausal gonadotropin (hMG) was initiated on day 2 or 3 of a normal menstrual cycle. The dose of gonadotropins was administered according to the individual patient's disposition and response.

In the single dose regimen study, Cetrotide 3 mg was administered on the day of controlled ovarian stimulation (COS) when adequate estradiol levels (400 pg/mL) were obtained, usually on day 7 (range day 5-12). If human chorionic gonadotropin (hCG) was not given within 4 days of the 3 mg dose of Cetrotide, then 0.25 mg of Cetrotide was administered daily beginning 96 hours after the 3 mg injection until and including the day of hCG administration.

In the two multiple dose regimen studies, Cetrotide 0.25 mg was started on day 5 or 6 of COS. Both gonadotropins and Cetrotide were continued daily (multiple dose regimen) until the injection of hCG.

Oocyte pick-up (OPU) followed by in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) as well as embryo transfer (ET) were subsequently performed. In addition to IVF and ICSI, one pregnancy was obtained after intrauterine insemination. In the five Phase 2 and Phase 3 clinical trials, 184 pregnancies have been reported out of a total of 732 patients (including 21 pregnancies following the replacement of frozen-thawed embryos).

In the 3 mg regimen, 9 patients received an additional dose of 0.25 mg of Cetrotide, and two other patients received two additional doses of 0.25 mg Cetrotide. The median number of days of Cetrotide® multiple dose treatment was 5 (range 1-15) in both studies.

Ganirelix Acetate (2, 11)

The efficacy of Ganirelix acetate injection was established in two adequate and well-controlled clinical studies which included women with normal endocrine and pelvic ultrasound parameters. The studies intended to exclude subjects with PCOS and subjects with low or no ovarian reserve. One cycle of study medication was administered to each randomized subject. For both studies, the administration of exogenous recombinant FSH (Follistim® [follitropin beta for injection]) 150 IU daily was initiated on the morning of Day 2 or 3 of a natural menstrual cycle. Ganirelix acetate injection was administered on the morning of Day 7 or 8 (Day 6 of recombinant FSH administration). The dose of recombinant FSH administered was adjusted according to individual responses starting on the day of initiation of Ganirelix acetate. Both recombinant FSH and Ganirelix acetate were continued daily until at least three follicles were 17 mm or greater in diameter at which time hCG [Pregnyl® (chorionic gonadotropin for injection, USP)] was administered. Following hCG administration, Ganirelix acetate and recombinant FSH administration were discontinued. Oocyte retrieval, followed by IVF or ICSI, was subsequently performed.

In a multicenter, double-blind, randomized, dose-finding study, the safety and efficacy of Ganirelix acetate injection were evaluated for the prevention of LH surges in women undergoing controlled ovarian hyperstimulation (COH) with recombinant FSH. Ganirelix acetate injection doses ranging from 62.5 mcg to 2,000 mcg and recombinant FSH were administered to 332 patients undergoing COH for IVF. Median serum LH on the day of hCG administration decreased with increasing doses of Ganirelix acetate. Median serum E2 (17β-estradiol) on the day of hCG administration was 1,475; 1,110; and 1,160 pg/mL for the 62.5 mcg, 125 mcg, and 250 mcg doses, respectively. Lower peak serum E2 levels of 823, 703, and 441 pg/mL were seen at higher doses of Ganirelix acetate 500 mcg, 1,000 mcg, and 2,000 mcg, respectively.

Transient LH rises alone were not deleterious to achieving pregnancy with Ganirelix acetate at doses of 125 mcg (3/6 subjects) and 250 mcg (1/1 subjects). In addition, none of the subjects with LH rises ≥ 10 mIU/mL had premature luteinization indicated by a serum progesterone above 2 ng/mL.

A multicenter, open-label, randomized study was conducted to assess the efficacy and safety of Ganirelix acetate injection in women undergoing COH. Follicular phase treatment with Ganirelix acetate 250 mcg was studied using a luteal phase GnRH agonist as a reference treatment. A total of 463 subjects were treated with Ganirelix acetate by subcutaneous injection once daily starting on Day 6 of recombinant FSH treatment. Recombinant FSH was maintained at 150 IU for the first 5 days of ovarian stimulation and was then adjusted by the investigator on the sixth day of gonadotropin use according to individual responses.

The midcycle LH surge initiates several physiologic actions including: ovulation, resumption of meiosis in the oocyte, and luteinization. In 463 subjects administered Ganirelix acetate injection 250 mcg, a premature LH surge prior to hCG administration, (LH rise ≥ 10 mIU/mL with a significant rise in serum progesterone > 2 ng/mL, or a significant decline in serum estradiol) occurred in less than 1% of subjects.

Zoladex® (3)

Endometriosis

In controlled clinical studies using the 3.6 mg formulation every 28 days for 6 months, Zoladex was shown to be as effective as danazol therapy in relieving clinical symptoms (dysmenorrhea, dyspareunia and pelvic pain) and signs (pelvic tenderness, pelvic induration) of endometriosis and decreasing the size of endometrial lesions as determined by laparoscopy. In one study comparing Zoladex with danazol (800 mg/day), 63% of Zoladex-treated patients and 42% of danazol-treated patients had a greater than or equal to 50% reduction in the extent of endometrial lesions. In the second study comparing Zoladex with danazol (600 mg/day), 62% of Zoladex-treated and 51% of danazol-treated patients had a greater than or equal to 50% reduction in the extent of endometrial lesions. The clinical significance of a decrease in endometriotic lesions is not known at this time; and in addition, laparoscopic staging of endometriosis does not necessarily correlate with severity of symptoms.

In these two studies, Zoladex led to amenorrhea in 92% and 80%, respectively, of all treated women within 8 weeks after initial administration. Menses usually resumed within 8 weeks following completion of therapy.

Within 4 weeks following initial administration, clinical symptoms were significantly reduced, and at the end of treatment were, on average, reduced by approximately 84%.

During the first two months of Zoladex use, some women experience vaginal bleeding of variable duration and intensity. In all likelihood, this bleeding represents estrogen withdrawal bleeding and is expected to stop spontaneously.

There is insufficient evidence to determine whether pregnancy rates are enhanced or adversely affected by the use of Zoladex.

Endometrial Thinning

Two trials were conducted with Zoladex prior to endometrial ablation for dysfunctional uterine bleeding.

Trial 0022, was a double-blind, prospective, randomized, parallel-group multicenter trial conducted in 358 premenopausal women with dysfunctional uterine bleeding. Eligible patients were randomized to receive either two depots of Zoladex 3.6 mg (n=180) or two placebo injections (n=178) administered four weeks apart. One hundred seventy-five patients in each group underwent endometrial ablation using either diathermy loop alone or in combination with rollerball approximately 2 weeks after the second injection. Endometrial thickness was assessed immediately before surgery using a transvaginal ultrasonic probe. The incidence of amenorrhea was compared between the Zoladex and placebo groups at 24 weeks after endometrial ablation.

The median endometrial thickness before surgery was significantly less in the Zoladex treatment group (1.50 mm) compared to the placebo group (3.55 mm). Six months after

surgery, 40% of patients (70/175) treated with Zoladex in Trial 0022 reported amenorrhea as compared with 26% who had received placebo injections (44/171), a difference that was statistically significant.

Trial 0003 was a single center, open-label, randomized trial in premenopausal women with dysfunctional uterine bleeding. The trial allowed for a comparison of 1 depot of Zoladex and 2 depots of Zoladex administered 4 weeks apart with ablation using Nd: YAG laser occurring 4 weeks after Zoladex administration. Forty patients were randomized into each of the Zoladex treatment groups.

The median endometrial thickness before surgery was significantly less in the group treated with two depots (0.5 mm) compared to the group treated with one depot (1 mm). No difference in the incidence of amenorrhea was found at 24 weeks (24% in both groups). Of the 74 patients that completed the trial, 53% reported hypomenorrhea and 20% reported normal menses six months after surgery.

Lupron Depot® 3.75 mg, Lupron Depot® 11.25 mg (5, 6)
The safety and efficacy of Lupron Depot 11.25 mg for the indicated populations has been established based on adequate and well-controlled studies in adults (See Table 1) of Lupron Depot 3.75 mg and on a single trial of Lupron Depot 11.25 mg.

Endometriosis
Lupron Depot 11.25 mg Monotherapy (6)
In controlled clinical studies, Lupron Depot 3.75 mg monthly for six months was shown to be comparable to danazol 800 mg/day in relieving the clinical sign/symptoms of endometriosis (pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and in reducing the size of endometrial implants as evidenced by laparoscopy.

The clinical significance of a decrease in endometriotic lesions is not known, and laparoscopic staging of endometriosis does not necessarily correlate with the severity of symptoms.

Lupron Depot 3.75 mg monthly induced amenorrhea in 74% and 98% of the women after the first and second month of treatment, respectively. Most of the remaining women reported episodes of only light bleeding or spotting. In the first, second and third post-treatment months, normal menstrual cycles resumed in 7%, 71% and 95% of women, respectively, excluding those who became pregnant.

In a pharmacokinetic/pharmacodynamic study of healthy female subjects (N=20) Lupron Depot 11.25 mg induced amenorrhea in 85% (N=17) of subjects during the initial month and 100% during the second month following the injection. All subjects remained amenorrheic through the remainder of the 12-week dosing interval. Episodes of light bleeding and spotting were reported by a majority of subjects during the first month after the injection and in a few subjects at later time-points. Menses resumed on average 12 weeks (range 2.9 to 20.4 weeks) following the end of the 12-week dosing interval.

Lupron Depot 11.25 mg produced similar pharmacodynamic effects in terms of hormonal and menstrual suppression to those achieved with monthly injections of Lupron Depot 3.75 mg during the controlled clinical trials for the management of endometriosis and the anemia caused by uterine fibroids.

A six-month pharmacokinetic/pharmacodynamic post-marketing study in 41 women that included both the Lupron Depot 3.75 mg dose (N=20) administered once monthly and the Lupron Depot 11.25 mg dose (N=21) administered once every three months did not reveal clinically significant differences in terms of efficacy in reducing painful symptoms of endometriosis or magnitude of the decrease in bone mineral density (BMD) associated with use of Lupron Depot 3.75 mg and Lupron Depot 11.25 mg. In both treatment groups, suppression of menses (defined as no new menses for at least 60 consecutive days) was achieved in 100% of the women who remained in the study for at least 60 days. Vertebral bone density measured by dual energy x-ray absorptiometry (DEXA) decreased compared with baseline by an average of 3.0% and 2.8% at six months for the two groups, respectively.

Lupron Depot with Norethindrone Acetate Add-Back Therapy (5)
The safety of co-administering Lupron Depot and norethindrone acetate was evaluated in two clinical studies with treatment duration of 12 months were conducted to evaluate the effect of co-administration of Lupron Depot 3.75 mg and norethindrone acetate on the loss of BMD associated with Lupron Depot 3.75 mg and on the efficacy of Lupron Depot in relieving symptoms of endometriosis. All women in these studies received calcium supplementation with 1000 mg elemental calcium. A total of 242 women were treated with monthly administration of Lupron Depot 3.75 mg (13 injections) and 191 of them were co-administered 5 mg norethindrone acetate taken daily. The population age range was 17-43 years old. The majority of women were Caucasian (87%).

One co-administration study was a controlled, randomized and double-blind study included 51 women treated monthly with Lupron Depot 3.75 mg alone and 55 women treated monthly with Lupron Depot 3.75 mg plus norethindrone acetate daily. Women in this trial were followed for up to 24 months after completing one year of treatment. The other study was an open-label single arm clinical study in 136 women of one year of treatment with Lupron Depot 3.75 mg monthly and daily norethindrone acetate 5 mg, with follow-up for up to 12 months after completing treatment (see Table 1).

The assessment of efficacy was based on the investigator's or the woman's monthly assessment of five signs or symptoms of endometriosis (dysmenorrhea, pelvic pain, deep dyspareunia, pelvic tenderness and pelvic induration).

Table 1 below provides detailed efficacy data regarding relief of symptoms of endometriosis based on the two studies of co-administration of Lupron Depot 3.75 mg monthly and norethindrone acetate 5 mg daily.

Table 1. Effect of Lupron Depot and Norethindrone Acetate on the Symptoms of Endometriosis and Mean Clinical Severity Score

			Percent of Women with Symptoms			Clinical Pain Severity Score		
			Baseline		Final	Baseline		Final
Variable	**Study**	**Group**	**N[3]**	**(%)[4]**	**(%)**	**N[3]**	**Value[5]**	**Change**
Dysmenorrhea	Controlled Study	LD[1,6]	51	(100)	(4)	50	3.2	-2.0
		LD/N[2]	55	(100)	(4)	54	3.1	-2.0
	Open Label Study	LD/N[7]	136	(99)	(9)	134	3.3	-2.1
Pelvic Pain	Controlled Study	LD[6]	51	(100)	(66)	50	2.9	-1.1
		LD/N	55	(96)	(56)	54	3.1	-1.1
	Open Label Study	LD/N[7]	136	(99)	(63)	134	3.2	-1.2
Deep Dyspareunia	Controlled Study	LD	42	(83)	(37)	25	2.4	-1.0
		LD/N	43	(84)	(45)	30	2.7	-0.8
	Open Label Study	LD/N	102	(91)	(53)	94	2.7	-1.0
Pelvic Tenderness	Controlled Study	LD[6]	51	(94)	(34)	50	2.5	-1.0
		LD/N	54	(91)	(34)	52	2.6	-0.9
	Open Label Study	LD/N[7]	136	(99)	(39)	134	2.9	-1.4
Pelvic Induration	Controlled Study	LD	51	(51)	(12)	50	1.9	-0.4
		LD/N	54	(46)	(17)	52	1.6	-0.4
	Open Label Study	LD/N[7]	136	(75)	(21)	134	2.2	-0.9

[1] LD = Lupron Depot 3.75 mg assessment.
[2] LD/N = Lupron Depot 3.75 mg plus norethindrone acetate 5 mg.
[3] Number of women that were included in the assessment.
[4] Percentage of women with the symptom/sign.
[5] Value description: 1= none; 2= mild; 3= moderate; 4= severe.
[6] 6-month study duration of treatment.
[7] 12-month study duration of treatment with 12 months of follow up.

Suppression of menses (menses was defined as three or more consecutive days of menstrual bleeding) was maintained throughout treatment in 84% and 73% of women receiving leuprolide acetate and norethindrone acetate, in the controlled study and open label study, respectively. The median time for menses resumption after treatment with leuprolide acetate and norethindrone acetate was 8 weeks.

Changes in Bone Density

The effect of Lupron Depot 3.75 mg and norethindrone acetate on BMD was evaluated by dual energy x-ray absorptiometry (DEXA) scan in the two clinical trials. For the open-label study, success in mitigating BMD loss was defined as the lower bound of the 95% confidence interval around the change from baseline at one year of treatment not to exceed -2.2%. The BMD data of the lumbar spine from these two studies are presented in Table 2.

Table 2. Mean Percent Change from Baseline in Bone Mineral Density of Lumbar Spine

	Lupron Depot 3.75 mg (LD only)		Lupron Depot 3.75 mg plus norethindrone acetate 5 mg daily (LD/N)			
	Controlled Study		Controlled Study		Open Label Study	
	N	Change Mean (95% CI)	N	Change Mean (95% CI)	N	Change Mean (95% CI)
Week 24[1]	41	-3.2% (-3.8, -2.6)	42	-0.3% (-0.8, 0.3)	115	-0.2% (-0.6, 0.2)
Week 53[2]	29	-6.3% (-7.1, -5.4)	32	-1.0% (-1.9, -0.1)	84	-1.1% (-1.6, -0.5)

CI: Confidence interval.

[1] Includes on-treatment measurements that fell within 2 to 252 days after the first day of treatment.

[2] Includes on-treatment measurements >252 days after the first day of treatment.

The change in BMD following discontinuation of treatment is shown in Table 3.

Table 3. Mean Percent Change from Baseline in BMD or Lumbar Spine in Post-Treatment Follow-Up Period [1]

Post Treatment Measurement	Controlled Study						Open Label Study		
	LD-Only			LD/N			LD/N		
	N	Mean % Change	95% CI (%)	N	Mean % Change	95% CI (%)	N	Mean % Change	95% CI (%)[2]
Month 8	19	-3.3	(-4.9, -1.8)	23	-0.9	(-2.1, 0.4)	89	-0.6	(-1.2, 0.0)
Month 12	16	-2.2	(-3.3, -1.1)	12	-0.7	(-2.1, 0.6)	65	0.1	(-0.6, 0.7)

BMD: Bone mineral density.

LD: Lupron Depot 3.75 mg.

LD/N: Lupron Depot 3.75 mg plus norethindrone acetate 5 mg daily.

[1] Patients with post treatment measurements.

[2] 95% CI (2-sided) of percent change in BMD values from baseline.

These clinical studies demonstrated that co-administration of leuprolide acetate and norethindrone acetate 5 mg daily is effective in significantly reducing the loss of BMD that occurs with both Lupron Depot 3.75 mg and 11.25 mg treatments, and in relieving symptoms of endometriosis.

Fibroids

Lupron Depot 3.75 mg monthly for a period of three to six months was studied in four controlled clinical trials.

In one of these clinical studies, enrollment was based on hematocrit ≤ 30% and/or hemoglobin ≤ 10.2 g/dL. Administration of Lupron Depot 3.75 mg monthly, concomitantly with iron, produced an increase of ≥ 6% hematocrit and ≥ 2 g/dL hemoglobin in 77% of women at three months of therapy. The mean change in hematocrit was 10.1% and the mean change in hemoglobin was 4.2 g/dL. Clinical response was judged to be a hematocrit of ≥ 36% and hemoglobin of ≥ 12 g/dL, thus allowing for autologous blood donation prior to surgery. At two

and three months, respectively, 71% and 75% of women met this criterion (Table 4). These data suggest however, that some women may benefit from iron alone or 1 to 2 months of Lupron Depot 3.75 mg.

Table 4. Percent of Women Achieving Hematocrit ≥ 36% and Hemoglobin ≥ 12 g/dL

Treatment Group	Week 4	Week 8	Week 12
Lupron Depot 3.75 mg with Iron (N=104)	40[1]	71[2]	75[1]
Iron Alone (N=98)	17	39	49

[1] p-value <0.01

[2] p-value <0.001

Excessive vaginal bleeding (menorrhagia or menometrorrhagia) decreased in 80% of women at three months. Episodes of spotting and menstrual-like bleeding were noted in 16% of women at final visit.

In this same study, a decrease in uterine volume and myoma volume of ≥25% was seen in 60% and 54% of women, respectively. The mean fibroid diameter was 6.3 cm at pretreatment and decreased to 5.6 cm at the end of treatment. Lupron Depot 3.75 mg was found to relieve symptoms of bloating, pelvic pain, and pressure.

In three other controlled clinical trials, enrollment was not based on hematologic status. Mean uterine volume decreased by 41% and myoma volume decreased by 37% at final visit as evidenced by ultrasound or MRI. The mean fibroid diameter was 5.6 cm at pretreatment and decreased to 4.7 cm at the end of treatment. These women also experienced a decrease in symptoms including excessive vaginal bleeding and pelvic discomfort. Ninety-five percent of these women became amenorrheic with 61%, 25%, and 4% experiencing amenorrhea during the first, second, and third treatment months, respectively.

In addition, post-treatment follow-up was carried out in one clinical trial for a small percentage of women on Lupron Depot 3.75 mg (N=46) among the 77% who demonstrated a ≥ 25% decrease in uterine volume while on therapy. Menses usually returned within two months of cessation of therapy. Mean time to return to pretreatment uterine size was 8.3 months. Regrowth did not appear to be related to pretreatment uterine volume.

Changes in Bone Density

In one of the studies for fibroids described above, when Lupron Depot 3.75 mg was administered for three months in uterine fibroid women, vertebral trabecular BMD as assessed by quantitative digital radiography (QDR) revealed a mean decrease of 2.7% compared with baseline. Six months after discontinuation of therapy, a trend toward recovery was observed.

Lupron Depot-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month administration (7)

In children with central precocious puberty (CPP), therapeutic doses of Lupron Depot-PED reduce stimulated and basal gonadotropins to prepubertal levels. Testosterone and estradiol are also reduced to prepubertal levels in males and females respectively. Reduction of

gonadotropins and sex steroids allow a return to age-appropriate physical and psychological growth and development. The following effects have been noted with the chronic administration of leuprolide: cessation of menses (in girls), normalization and stabilization of linear growth and bone age advancement, stabilization of clinical signs and symptoms of puberty.

Fifty-five CPP subjects (49 females and 6 males, naïve to previous GnRH treatment), were treated with Lupron Depot-PED 1-month formulations until age appropriate for entry into puberty (see treatment period data below) and a subset of 40 subjects were then followed post-treatment (see follow-up period data below).

Treatment Period Data

During the treatment period, Lupron Depot-PED suppressed gonadotropins and sex steroids to prepubertal levels. Suppression of peak stimulated luteinizing hormone concentrations to < 1.75 mIU/mL was achieved in 96% of subjects by month 1. Five subjects required increased doses of study drug to achieve or retain LH suppression. The mean ± standard deviation (SD) age at the start of treatment was 7 ± 2 years and the duration of treatment was 4 ± 2 years. Six months after the treatment period was finished, the mean peak stimulated LH was 20.6 ± SD 13.7 mIU/mL (n=30).

Suppression (defined as regression or no change) of the clinical/physical signs of puberty was achieved in most patients. In females, suppression of breast development ranged from 66.7 to 90.6% of subjects during the first 5 years of treatment. The mean stimulated estradiol was 15.1 pg/mL at baseline, decreased to the lower level of detection (5.0 pg/mL) by Week 4 and was maintained there during the first 5 years of treatment. In males, suppression of genitalia development ranged from 60% to 100% of subjects during the first 5 years of treatment. The mean stimulated testosterone was 347.7 ng/dL at baseline and was maintained at levels no greater than 25.3 ng/dL during the first 5 years of treatment.

A “flare effect” of transient bleeding or spotting during the first 4 weeks of treatment was observed in 19.4% (7/36) females who had not reached menarche at baseline. After the first 4 weeks and for the remainder of the treatment period, no subject reported menstrual-like bleeding, and only rare spotting was noted.

In many subjects, growth rate decreased on treatment, as did bone age: chronological age ratio. Through year 5, the mean growth rate ranged between 3.4 and 5.6 cm/yr. The mean ratio of bone age to chronological age decreased from 1.5 at baseline to 1.1 by end of treatment. The mean height standard deviation score changed from 1.6 at baseline to 0.7 at the end of the treatment phase.

Follow-up Period Data

Thirty-five females and 5 males participated in a post-treatment follow-up period to assess reproductive function (in females) and final height. At 6 months post-treatment, most subjects reverted to pubertal levels of LH (87.9%) and clinical signs of resumption of pubertal

progression were evident with increase in breast development in girls (66.7%) and increase in genitalia development in boys (80%).

Of the 40 patients evaluated in the follow-up, 33 were observed until they reached final or near-final adult height. These patients had a mean increase in final adult height compared to baseline predicted adult height. The mean final adult height standard deviation score was -0.2.

After stopping treatment, regular menses were reported for all female subjects who reached 12 years of age during follow-up; mean time to menses was approximately 1.5 years; mean age of onset of menstruation after stopping treatment was 12.9 years. Data to assess reproductive function was collected in a post-study survey of 20 girls who reached adulthood (ages 18-26): menstrual cycles were reported to be normal in 80% of women; 12 pregnancies were reported for a total of 7 of the 20 subjects, including multiple pregnancies for 4 subjects.

Lupron Depot-PED 11.25 mg or 30 mg for 3-month administration (7)
In a randomized, open-label clinical study of Lupron Depot-PED 3-Month formulations, 84 subjects (76 female, 8 male) between 1 and 11 years of age received the Lupron Depot-PED 11.25 mg or 30 mg for 3-month administration formulation. Each dose group had an equal number of treatment-naïve patients who had pubertal LH levels and patients previously treated with GnRHa therapies who had prepubertal LH levels at the time of study entry. The percentage of subjects with suppression of peak-stimulated LH to < 4.0 mIU/mL, as determined by assessments at months 2, 3 and 6 is 78.6% in the 11.25 mg dose and 95.2% in the 30 mg dose as shown in Table 5.

Table 5. Suppression of Peak-Stimulated LH from Month 2 Through Month 6

	Lupron Depot-PED 11.25 mg every 3 Months			**Lupron Depot-PED 30 mg every 3 Months**		
Parameter	**Naïve N=21**	**Prev Trt[a] N=21**	**Total N=42**	**Naïve N=21**	**Prev Trt[a] N=21**	**Total N=42**
Percent with Suppression	76.2	81.0	78.6	90.5	100	95.2
2-sided 95% CI	52.8, 91.8	58.1, 94.6	63.2, 89.7	69.6, 98.8	83.9, 100	83.8, 99.4

LH: luteinizing hormone.
CI: confidence interval.
[a] Previously treated with GnRHa for at least 6 months prior to enrollment in pivotal Study L-CP07-167.

For the Lupron Depot-PED 11.25 mg dose for 3-month administration, 93% (39/42) of subjects and for Lupron Depot-PED 30 mg dose for 3-month administration 100% (42/42) of subjects had sex steroid (estradiol or testosterone) suppressed to prepubertal levels at all visits. Clinical suppression of puberty in female patients was observed in 29 of 32 (90.6%) and 28 of 34 (82.4%) of patients in the 11.25 mg and 30 mg groups, respectively, at month 6. Clinical suppression of puberty in males was observed in 1 of 2 (50.0%) and 2 of 5 (40.0%) patients in the 11.25 mg and 30 mg groups, respectively, at month 6. In subjects with complete data for

bone age, 29 of 33 (87.9 %) in the 11.25 mg group and 30 of 40 in the 30 mg group (75.0%) had a decrease in the ratio of bone age to chronological age at month 6 compared to screening.

Fensolvi® (8)

The efficacy of Fensolvi was evaluated in an uncontrolled, open-label, single arm clinical trial in which 64 pediatric patients (62 females and 2 males, naïve to previous gonadotropin-releasing hormone (GnRH) agonist treatment) with CPP received at least one dose of Fensolvi at a dosing interval of 24 weeks and were observed for 12 months. The mean age was 7.5 years (range 4 to 9 years) at the start of treatment. In pediatric patients with CPP, Fensolvi reduced stimulated and basal gonadotropins to prepubertal levels. Suppression of peak stimulated luteinizing hormone (LH) concentrations to <4 IU/L was achieved in 87% of pediatric patients by month 6 and in 86% of patients by month 12. Suppression of estradiol or testosterone concentration to prepubertal levels at the 6-month assessment was achieved in 97% and 100% of patients, respectively. Suppression of estradiol or testosterone was maintained at the 12-month assessment with 98% (55/56 females) and 50% (1/2 males) maintaining suppression. Fensolvi arrested or reversed progression of clinical signs of puberty with reductions in growth velocity and bone age. Mean growth velocity decreased from 8.9 ± 13.1 cm/yr at 1 month to 6.9 ± 3.1 cm/yr at 6 months and to 6.4 ± 1.9 cm/yr at 12 months.

Table 6. Reproductive Hormone Levels in Pediatric Patients with CPP Treated with Fensolvi 45 mg Every 6 Months[a]

	% (n/N) of Patients Achieving Endpoints			
Endpoint[b]	**Month 3**	**Month 6**	**Month 9**	**Month 12**
LH levels <4 IU/L	85 (51/60)	87 (54/62)[c]	85 (50/59)	86 (50/58)
Estradiol levels<73.4 pmol/L (<20 pg/mL)	98 (56/57)	97 (58/60)	98 (56/57)	98 (55/56)
Testosterone levels <1 nmol/L (<28.4 ng/dL)	100 (2/2)	100 (2/2)	100 (2/2)	50 (1/2)
FSH levels <2.5 IU/L	62 (37/60)	66 (41/62)	44 (26/59)	55 (32/58)

CPP: central precocious puberty.
LH: luteinizing hormone.
FSH: follicle stimulating hormone.
[a] Intent-to-Treat population (N=62).
[b] Post GnRH agonist stimulation.
[c] Primary efficacy endpoint.

Eight female patients out of 62 did not meet the primary efficacy criteria for LH <4 IU/L at 6 months. In four of the eight patients, the LH level at 6 months was between 4.2 and 4.8 IU/L. The remaining four patients had LH levels >5 IU/L. However, post stimulation estradiol was suppressed to prepubertal levels (<20 pg/mL) in seven of the eight patients at month 6 and was maintained through month 12.

Supprelin LA® (4)

The efficacy of Supprelin LA in children with CPP has been evaluated in two single-arm, open label studies. Study 1 was conducted in 11 pretreated female patients, 3.7 to 11.0 years of age. Study 2 was conducted in 36 patients (33 females and 3 males), 4.5 to 11.6 years of age. Sixteen pretreated and 20 treatment-naïve patients were enrolled in Study 2. Baseline patient characteristics were typical of patients with CPP. Efficacy assessments were similar in both studies and included endpoints that measured the suppression of gonadotropins (luteinizing hormone and follicle stimulating hormone) and gonadal sex steroids (estrogen in girls and testosterone in boys, respectively) on treatment. Other assessments were clinical (evidence of stabilization or regression of signs of puberty) or gonadal steroid-dependent (bone age, linear growth). In Study 2, the primary measure of efficacy was LH suppression.

In Study 2, suppression of LH was induced in all treatment naïve subjects and maintained in all pretreated subjects at month 1 after implantation and continued through month 12 (suppression was defined as a peak LH < 4 mIU/mL following stimulation with the GnRH analog leuprolide acetate).

Secondary efficacy hormone assessments (FSH, estradiol and testosterone) and additional efficacy assessments (bone age advancement, linear growth, clinical progression of puberty) indicated stabilization of disease. Estradiol suppression was present in all 33 girls (100%) through month 9 and 97% at month 12. Testosterone suppression was maintained in the three pre-treated males participating in Study 2. The Supprelin LA effect on efficacy endpoints in the Study 1 was consistent with that observed in Study 2.

Synarel® (9)

Endometriosis

In controlled clinical studies, Synarel at doses of 400 and 800 µg/day for 6 months was shown to be comparable to danazol, 800 mg/day, in relieving the clinical symptoms of endometriosis (pelvic pain, dysmenorrhea, and dyspareunia) and in reducing the size of endometrial implants as determined by laparoscopy. The clinical significance of a decrease in endometriotic lesions is not known at this time and, in addition, laparoscopic staging of endometriosis does not necessarily correlate with severity of symptoms.

In a single controlled clinical trial, intranasal Synarel (nafarelin acetate) at a dose of 400 µg per day was shown to be clinically comparable to intramuscular leuprolide depot, 3.75 mg monthly, for the treatment of the symptoms (dysmenorrhea, dyspareunia and pelvic pain) associated with endometriosis.

Synarel 400 µg daily induced amenorrhea in approximately 65%, 80%, and 90% of the patients after 60, 90, and 120 days, respectively. In the first, second, and third post-treatment months, normal menstrual cycles resumed in 4%, 82%, and 100%, respectively, of those patients who did not become pregnant.

At the end of treatment, 60% of patients who received Synarel 400 µg/day were symptom free, 32% had mild symptoms, 7% had moderate symptoms, and 1% had severe symptoms. Of the

60% of patients who had complete relief of symptoms at the end of treatment, 17% had moderate symptoms 6 months after treatment was discontinued, 33% had mild symptoms, 50% remained symptom free, and no patient had severe symptoms.

During the first two months use of Synarel, some women experience vaginal bleeding of variable duration and intensity. In all likelihood, this bleeding represents estrogen withdrawal bleeding and is expected to stop spontaneously. If vaginal bleeding continues, the possibility of lack of compliance with the dosing regimen should be considered. If the patient is complying carefully with the regimen, an increase in dose to 400 µg twice a day should be considered.

There is no evidence that pregnancy rates are enhanced or adversely affected by the use of Synarel.

Central Precocious Puberty (CPP)

When used regularly in girls and boys with CPP at the recommended dose, Synarel suppresses LH and sex steroid hormone levels to prepubertal levels, affects a corresponding arrest of secondary sexual development, and slows linear growth and skeletal maturation. In some cases, initial estrogen withdrawal bleeding may occur, generally within 6 weeks after initiation of therapy. Thereafter, menstruation should cease.

In clinical studies the peak response of LH to GnRH stimulation was reduced from a pubertal response to a prepubertal response (< 15 mlU/mL) within one month of treatment.

Linear growth velocity, which is commonly pubertal in children with CPP, is reduced in most children within the first year of treatment to values of 5 to 6 cm/year or less. Children with CPP are frequently taller than their chronological age peers; height for chronological age approaches normal in most children during the second or third year of treatment with Synarel. Skeletal maturation rate (bone age velocity—change in bone age divided by change in chronological age) is usually abnormal (greater than 1) in children with CPP; in most children, bone age velocity approaches normal (1) during the first year of treatment. This results in a narrowing of the gap between bone age and chronological age, usually by the second or third year of treatment. The mean predicted adult height increases.

In clinical trials, breast development was arrested or regressed in 82% of girls, and genital development was arrested or regressed in 100% of boys. Because pubic hair growth is largely controlled by adrenal androgens, which are unaffected by nafarelin, pubic hair development was arrested or regressed only in 54% of girls and boys.

Reversal of the suppressive effects of Synarel has been demonstrated to occur in all children with CPP for whom one-year post-treatment follow-up is available (n=69). This demonstration consisted of the appearance or return of menses, the return of pubertal gonadotropin and gonadal sex steroid levels, and/or the advancement of secondary sexual development. Semen analysis was normal in the two ejaculated specimens obtained thus far from boys who have

been taken off therapy to resume puberty. Fertility has not been documented by pregnancies and the effect of long-term use of the drug on fertility is not known.

Triptodur (10)
In a single-arm open-label study, 44 children 2 to 9 years of age with central precocious puberty (CPP), 39 females and 5 males, all naïve to previous GnRH agonist treatment, were administered Triptodur 22.5 mg at a dosing interval of 24 weeks. Subjects were evaluated over two dosing intervals for a total of 12 months.

Triptodur 22.5 mg suppressed pituitary release of LH and FSH and, consequently, gonadal secretion of estradiol in girls and testosterone in boys (Table 7). At all time-points evaluated, ≥93% of children achieved LH suppression to prepubertal levels (i.e., serum LH ≤5 IU/L 30 minutes after GnRH agonist stimulation), ≥79% of girls achieved prepubertal levels of estradiol (i.e., <20 pg/mL), and ≥80% of boys achieved prepubertal levels of testosterone (i.e., <30 ng/dL). Triptodur arrested or reversed progression of clinical signs of puberty with 95% of children showing no increase in the bone age/chronological age ratio, and 89% showing stabilization of sexual maturation at Month 12.

Table 7. Efficacy of Triptodur 22.5 mg Administered Every 6 Months to Children with CPP[a]

Endpoint	% (n/N) of Children Achieving Endpoint					
	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12
% with prepubertal LH (GnRH-stim LH ≤5 IU/L)	95% (42/44)	95% (42/44)	95% (42/44)	93%[b] (41/44)	95% (42/44)	98% (43/44)
% girls with prepubertal estradiol (<20 pg/mL)	87% (34/39)	89% (34/38)	92% (36/39)	79% (31/39)	82% (32/39)	79% (31/39)
% boys with prepubertal testosterone (<30 ng/dL)	80% (4/5)	80% (4/5)	100% (5/5)	100% (5/5)	80% (4/5)	80% (4/5)
% with no increase in BA/CA[c] ratio vs. baseline	-	-	-	64% (28/44)	-	95% (42/44)
% achieving stabilization of sexual maturation	-	-	-	91% (40/44)	-	89% (39/44)
% girls with regression of uterine length	-	-	-	69% (27/39)	-	77% (30/39)
% boys with no progression in testis volumes	-	-	-	100% (5/5)	-	100% (5/5)

CPP: central precocious puberty; LH: luteinizing hormone.
[a] Intent-to-Treat population
[b] Primary efficacy endpoint.
[c] Bone Age/Chronological Age

Following the second Triptodur injection, 22 children (all girls) were assessed for evidence of an acute-on-chronic phenomenon (i.e., increase in basal LH >5 IU/L or serum estradiol level >20 pg/mL 48 hours after the second triptorelin injection). Of these, one girl who achieved

prepubertal hormone levels prior to the second injection showed biochemical evidence of acute-on-chronic phenomenon.

Summary of Evidence
The U.S. Food and Drug Administration (FDA) approves drugs for specific indications that are included in the drug's labeling. When a drug is used for an indication other than those specifically included in the labeling, it is referred to as an off-label, unlabeled use, or grant supported orphan drug use with marketing approval. When coverage is allowed for gonadotropin-releasing hormone (GnRH) therapies, it is done based solely on the FDA-approved label indications.

Due to the cost of manufacturing and diminished market demand, several preparations have been discontinued and are no longer marketed for use in the U.S. Discontinued preparations have been removed from the medically necessary indications of this medical policy. Some preparations may still be available in generic form and available for utilization.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1620, J1675, J1950, J1951, J3316, J9202, J9217, J9218, J9219, J9226, S0132, S9560

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Labels:

1. FDA – Product Labeling. Food and Drug Administration (FDA). Cetrotide® Highlights of prescribing information (6/2024). Initial FDA-Approval – 2000. Available at: <https://www.accessdata.fda.gov> (accessed June 4, 2025).
2. FDA – Product Labeling. Food and Drug Administration (FDA). Ganirelix Acetate Highlights of prescribing information (9/2024). Initial FDA-Approval – 1999. Available at: <https://www.accessdata.fda.gov> (accessed June 4, 2025).
3. FDA – Product Labeling. Food and Drug Administration (FDA). Zoladex® Implant 3.6 mg Highlights of prescribing information (3/2023). Initial FDA-Approval – 1989. Available at: <https://www.accessdata.fda.gov> (accessed June 4, 2025).

4. FDA – Product Labeling. Food and Drug Administration (FDA). Supprelin LA® Highlights of prescribing information (4/2022). Initial FDA-Approval – 2007. Available at: <https://www.accessdata.fda.gov> (accessed June 4, 2025).
5. FDA – Product Labeling. Food and Drug Administration (FDA). Lupron Depot 3.75 mg® Highlights of prescribing information (1/2023). Initial FDA-Approval – 1985. Available at: <https://www.accessdata.fda.gov> (accessed June 4, 2025).
6. FDA – Product Labeling. Food and Drug Administration (FDA). Lupron Depot 11.25 mg® Highlights of prescribing information (3/2020). Initial FDA-Approval – 1985. Available at: <https://www.accessdata.fda.gov> (accessed June 4, 2025).
7. FDA – Product Labeling. Food and Drug Administration (FDA). Lupron Depot-Ped® Highlights of prescribing information (5/2025). Initial FDA-Approval – 1985. Available at: <https://www.accessdata.fda.gov> (accessed June 4, 2025).
8. FDA – Product Labeling. Food and Drug Administration (FDA). Fensolvi® Highlights of prescribing information (10/2024). Initial FDA-Approval – 1985. Available at: <https://www.accessdata.fda.gov> (accessed June 4, 2025).
9. FDA – Product Labeling. Food and Drug Administration (FDA). Synarel® Nasal Solution Highlights of prescribing information (1/2023). Initial FDA-Approval – 2006. Available at: <https://www.accessdata.fda.gov> (accessed February 22, 2023).
10. FDA – Product Labeling. Food and Drug Administration (FDA). Triptodur® Extended-Release Highlights of prescribing information (12/2022). Initial FDA-Approval – 2017. Available at: <https://www.accessdata.fda.gov> (accessed June 4, 2025).

Other:

11. Merative™ Micromedex® DRUGDEX® (electronic version). Ganirelix Acetate. Merative, Ann Arbor, Michigan, USA. Available at: <https://www.micromedexsolutions.com> (accessed June 4, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
08/15/2025	Document updated with literature review. The following changes were made to Coverage: 1) Modified conditional criteria language for ganirelix acetate

	and Lupron Depot® 3.75 mg; and 2) Added “non-FDA approved” to experimental, investigational and/or unproven statement. No new references added; others updated.
02/01/2025	Reviewed. No changes.
06/01/2023	Document updated with literature review. Coverage unchanged. Reference 3 added; some updated and others removed.
10/01/2022	Reviewed. No changes.
12/15/2021	Document updated with literature review. The following changes were made to Coverage: 1) Added “In combination with a norethindrone acetate for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms not to exceed 12 months” added to Lupron Depot® (3.75mg); and 2) Replaced “children” with “of pediatric patients” in criteria for Lupron Depot PED. References revised and updated.
11/15/2020	Document updated with literature review. The following change was made to Coverage: Added Fensolvi® may be considered medically necessary for the FDA approved indication of treatment of pediatric patients 2 years of age and older with central precocious puberty (CPP). Rationale revised. References revised and updated.
04/01/2020	Document updated with literature review. The following changes were made to Coverage: 1) Removed Firmagon and Vantas as now part of RX502.061 Oncology Medications; 2) Removed oncology indications from Goserelin Acetate (Zoladex), Histrelin Acetate (Supprelin LA), Leuprolide Acetate (Eligard and Lupron), and Triptorelin Pamoate (Trelstar and Triptodur); 3) Removed oncology indications from the list of not medically necessary indications. References revised; some references removed.
04/15/2019	Document updated with literature review. The following indications were added to coverage: 1) Treatment of prostate cancer with Supprelin LA®; 2) Treatment of central precocious puberty with Vantas®; and 3) Treatment of gender dysphoria with Trelstar® and Triptodur®. The following preparations have changed in coverage: 1) Plenaxis™ was moved from NOTE 3 to NOTE 2, as it is no longer available in the United States; 2) Viadur® was added to NOTE 2, as it is no longer available in the United States; and 3) Antagon® was added to NOTE 3, as it may no longer be available for sale, but generic forms may still be in use in the United States. Cancer staging information for prostate, breast, and ovarian cancer was added to description. References 1-8, 10, 18, 19 were added; none removed.
01/01/2018	Document updated with literature review. The following was changed for Leuprolide Acetate (Eligard®, Lupron® and Viadur®), under oncology uses – breast cancer patients, by removing “who are not on concurrent aromatase inhibitor therapy for.” The following was added “Triptorelin Pamoate (Triptodur®)” as a treatment of central precocious puberty for children 2-years and older.

10/15/2016	Document updated with literature review. The following was changed for Firmagon® (Degarelix Acetate): considered medically necessary "for advanced prostate cancer treatment, including metastasis."
07/01/2015	Document updated with literature review. The following was added to the coverage section: 1) For in vitro fertilization, clarification to control ovarian stimulation/induction and/or final maturation of human embryos; 2) For Zoladex®, dysfunctional uterine bleeding may be considered medically necessary; 3) For Eligard®, Lupron®, and Viadur®, premenstrual syndrome may be considered medically necessary; and 4) For uterine leiomyomas in premenopausal women, clarification to improve preoperative anemia. The following indications were added to experimental, investigational and/or unproven listing; cryopreservation of oocytes, spermatozoa, and/or human embryos (including ovarian or testicular tissue) before or during chemotherapy; endometrial cancer; irritable bowel syndrome, obesity, polycystic ovarian disease, premature ovarian failure; and testicular cancer.
07/01/2012	Document updated with literature review. Coverage completely revised, with new indications, and all covered indications categorized as first-line therapy or second-line therapy in a table. Entire policy was completely revised. Document title changed from "Gonadotropin-Releasing Hormone (GnRH) Analogs, Hormones, Antagonists and Receptor Blockers."
11/6/2009	Codes Added
03/01/2009	Codes Revised/Added/Deleted
07/15/2008	Coverage Revised
04/15/2008	Revised/Updated Entire Document
07/15/2007	Coverage Revised
11/15/2006	Revised/Updated Entire Document
01/01/2006	Coverage Revised
07/01/2005	Codes Revised/Added/Deleted
03/29/2005	Coverage Revised
10/01/2004	Revised/Updated Entire Document
06/01/2001	Codes Revised/Added/Deleted
09/01/1996	Revised/Updated Entire Document
05/01/1996	Document number change
07/01/1995	Revised/Updated Entire Document
10/01/1994	Revised/Updated Entire Document
07/01/1993	Revised/Updated Entire Document
07/01/1992	Revised/Updated Entire Document
04/01/1992	Revised/Updated Entire Document
05/01/1990	New Medical Document