Therapeutic Class Overview
GnRH modulators

INTRODUCTION

Central Precocious Puberty (CPP)

- Puberty is a period of physical, hormonal, and psychological transition from childhood to adulthood, with accelerated linear growth and achievement of reproductive function *(Britto et al 2016)*. Pubertal timing is influenced by complex interactions of genetic, nutritional, environmental, and socioeconomic factors *(Macedo et al 2014).*
  - While there has been extensive discussion with regard to the definition of puberty, most pediatricians give an age limit of 8 years in girls and 9 to 9.5 years in boys for the lower limit of normal pubertal development *(Carel et al 2004)*.
- CPP is characterized by the early onset of pubertal manifestations in girls and boys *(Carel et al 2004)*.
  - CPP is caused by the disruption of the hypothalamic-pituitary-gonadal axis, which results in the early activation of pulsatile gonadotropin-releasing hormone (GnRH) secretion *(Carel and Léger 2008).*
  - These manifestations consist primarily of breast development in girls and testicular enlargement in boys *(Carel and Léger 2008)*.
- GnRH agonists are the treatment of choice for CPP. Chronic administration of potent GnRH agonists causes down-regulation of pituitary GnRH receptors, suppression of gonadotropin (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) secretion and finally suppression of the release of gonadal sex hormones *(Fuqua 2013, Klein et al 2016).*
  - There are several GnRH agonists available in varying doses and formulations. Depot formulations are generally preferred due to improved compliance *(Guaraldi et al 2016).* GnRH agonists that are Food and Drug Administration (FDA)-approved for the treatment of CPP include:
    - Lupron Depot-Ped (leuprolide), available as monthly or every 3 month intramuscular (IM) injections.
    - Synarel (nafarelin) intranasal spray, a short-acting spray that requires multiple inhalations daily.
    - Supprelin LA (histrelin), available as a 1-year subcutaneous (SC) implant device.
    - Triptodur (triptorelin), administered as a single IM injection every 24 weeks. Of note, Trelstar (triptorelin pamoate) IM injection was the first FDA-approved triptorelin formulation; it was used off-label to treat CPP until Triptodur was made available in 2017 *(Klein et al 2016)*.
  - The optimal time to discontinue a GnRH agonist has not been established, but retrospective analyses suggest that discontinuation around the age of 11 years is associated with optimal height outcomes *(Carel and Léger 2008).*

Endometriosis

- Endometriosis is a chronic, estrogen-dependent disorder characterized by deposits of endometrial tissue outside the endometrial cavity, such as the liver, diaphragm, umbilicus, and pleural cavity *(Brown and Farquhar 2015, Giudice 2010, Schenken 2018).*
  - Endometriosis affects 6% to 10% of women of reproductive age; it is present in approximately 38% of women with infertility and in up to 87% of women with chronic pelvic pain (*Armstrong 2010).*
  - The clinical presentation of endometriosis is highly variable and ranges from debilitating non-menstrual pelvic pain (NMPP) to infertility to no symptoms. Patients can present with dysmenorrhea, abdominal or pelvic pain, dyspareunia, and infertility *(Schrager et al 2013).*
- Although several pharmacological options are available for the treatment of endometriosis, none provide a cure, long-term relief of symptoms, or resolution of infertility.
  - GnRH agonists, such as Zoladex 3.6 mg (goserelin), Lupaneta Pack (leuprolide acetate/norethindrone), Lupron Depot 3.75 mg or Lupron Depot 11.25 mg 3-month injection (leuprolide), and Synarel (nafarelin) are recommended as second-line pharmacologic therapy after non-steroidal anti-inflammatory drugs (NSAIDS) and oral contraceptives *(American College of Obstetricians and Gynecologists [ACOG] 2010, Armstrong 2010, American Society for Reproductive Medicine [ASRM] 2014).*
    - GnRH agonists are generally not recommended as a long-term therapy, due to the potential for dose and duration-dependent bone loss *(ACOG 2010).*
  - Orilissa (elagolix), the first and only available oral GnRH antagonist, was FDA-approved in July 2018 for the management of moderate to severe pain associated with endometriosis.

- Elagolix exerts its effect by rapidly suppressing the pituitary ovarian hormones and produces a dose-dependent suppression of ovarian estrogen production that varies from partial to full suppression.
- Similar to GnRH agonists, elagolix is indicated for short-term use, ie, 6 months for patients taking 200 mg orally twice daily (for coexisting dyspareunia) and 24 months for patients taking 150 mg orally daily.
- Other GnRH antagonists, such as Cetrotide (cetrorelix), Firmagon (degarelix), and ganirelix are only available as an injectable formulation; however, these agents are not FDA-approved for the treatment of endometriosis.

Uterine fibroids

- Uterine fibroids, also known as uterine leiomyomas or myomas, are monoclonal tumors that arise from the uterine smooth-muscle tissue *(Sohn et al 2018).*
  - It is estimated that 60% of women of reproductive age are affected, and 80% of women develop the disease during their lifetime.
  - Heavy or prolonged menstrual bleeding, abnormal uterine bleeding, resultant anemia, pelvic pain, infertility, and/or recurrent pregnancy loss are generally associated with uterine fibroids.
  - The majority of women with uterine fibroids either remain asymptomatic or develop symptoms gradually over time. When patients are symptomatic, the number, size, and/or location of fibroids are critical determinants of its clinical manifestations.
- Although curative treatment of uterine fibroids relies on surgical therapies, medical treatments are considered first-line to preserve fertility and avoid or delay surgery. Lupron Depot 3.75 mg is the only GnRH agonist that has been FDA-approved for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata *(Sohn et al 2018).*
  - Lupron Depot 3.75 mg is administered concomitantly with iron therapy. The clinician may wish to consider a 1-month trial period on iron alone inasmuch as some of the patients will respond to iron alone. Lupron may be added if the response to iron alone is considered inadequate.

Infertility

- Infertility is typically defined as the inability to achieve pregnancy after 1 year of unprotected sexual intercourse *(Anwar and Anwar 2016).*
  - Infertility is common with a prevalence estimated at 9 to 18% *(Hanson et al 2017).*
  - Patients who are struggling to conceive report feelings of depression, anxiety, isolation, and loss of control *(Rooney and Domar 2018).*
  - An estimated 50% of infertility cases among heterosexual couples are attributable to female factors, 20% to male factors, and 30% to combined female and male factors or unknown factors (*Centers for Disease Control [CDC] 2018*, *Fauser 2018, Shreffler et al 2017*).
    - The most common causes of female infertility include ovulatory disorders (most commonly due to polycystic ovary syndrome [PCOS]), endometriosis, pelvic adhesions, tubal blockage, other tubal abnormalities, and hyperprolactinemia.
    - The most common causes of male infertility are low concentrations, poor motility, and abnormal morphology of sperm.
- Pharmacologic agents used in anovulatory women to induce or control ovulation include clomiphene (the most widely used fertility treatment), letrozole (off-label indication), gonadotropins (FSH products and human chorionic gonadotropin [hCG] products), and GnRH antagonists (cetrorelix and ganirelix). Other pharmacological agents used include metformin (in PCOS patients) and dopamine agonists (for hyperprolactinemic anovulation) *(Seli and Arici 2018).*
  - GnRH antagonists, such as cetrorelix and ganirelix, are used in conjunction with assisted reproductive technology (ART), which is defined as any fertility treatment in which either eggs or embryos are handled. The 2 most common ART procedures utilized in the U.S. are in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) *(CDC 2018).*
- Of note, all cancer indications for GnRH agonists are outside of the scope of this review.
- Medispan Class: Gonadotropin Releasing Hormone Agonists; Gonadotropin Releasing Hormone Antagonist

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cetrotide (cetrorelix) 0.25 mg injection	-
ganirelix 250 mcg injection	✔

Drug	Generic Availability
Lupaneta Pack (leuprolide acetate 3.75 mg depot suspension; norethindrone acetate 5 mg tablets and leuprolide acetate 11.25 mg depot suspension; norethindrone acetate 5 mg tablets)	-
Lupron Depot-Ped (leuprolide acetate for depot suspension) 7.5 mg, 11.25 mg, 15 mg (monthly) & 11.25 mg, 30 mg (3-month)	-
Lupron Depot (leuprolide acetate for depot suspension) 3.75 mg (monthly), 11.25 mg (3-month)	-
Orilissa (elagolix) 150 mg, 200 mg tablets	-
Supprelin LA (histrelin) 50 mg implant	-
Synarel (nafarelin) nasal spray	-
Triptodur (triptorelin) 22.5 mg extended-release suspension	-
Zoladex (goserelin) 3.6 mg implant	-

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Cetrotide (cetrorelix)	ganirelix	Lupaneta Pack (leuprolide/ norethindrone)	Lupron (leuprolide) Depot	Lupron Depot-Ped (leuprolide)	Orilissa (elagolix)	Supprelin LA (histrelin)	Synarel (nafarelin) intranasal spray	Triptodur (triptorelin)	Zoladex (goserelin) implant
Treatment of children with CPP					✔		✔	✔	✔	
Management of endometriosis, including pain relief and reduction of endometriotic lesions				✔				✔		✔
Use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding										✔
Initial management of the painful symptoms of endometriosis			✔	✔ †						
Management of recurrence of endometriosis symptoms			✔	✔ †						
Preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata				✔ ‡						
Management of moderate to severe pain associated with endometriosis						✔				
Inhibition of premature LH surges in women undergoing controlled ovarian stimulation*	✔	✔								

Abbreviations: CPP = central precocious puberty; LH = luteinizing hormone

*The word “stimulation” is used in the cetrorelix indication, while the word “hyperstimulation” is used in the ganirelix indication.

† In combination with norethindrone acetate 5 mg tablet taken once daily

‡ Concomitantly with iron therapy

(*Prescribing information: Cetrotide 2018, ganirelix 2018, Lupaneta Pack 2015, Lupron Depot-Ped 2017, Lupron Depot 2018, Orilissa 2018, Supprelin LA 2017, Synarel 2017, Triptodur 2018, Zoladex 2016*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

CPP

- The choice of GnRH agonist formulation depends on patient and clinician preference. These preparations have not been directly compared in randomized trials, but appear to be similarly effective in suppressing the pituitary-gonadal axis (*Harrington and Palmert 2017)*.
  - In a multicenter trial with histrelin implant for the treatment of CPP, peak LH and estradiol or testosterone were effectively suppressed, and no significant adverse events (AEs) were noted. Positive long-term safety and efficacy data were reported in 2 studies (a 2- and a 6-year study) that evaluated long-term hormonal suppression in CPP patients post histrelin implant insertion. More specifically, peak LH and FSH levels remained suppressed in both the 2- and the 6-year trial *(Harrington and Palmert 2017, Rahhal et al 2009, Silverman et al 2015*).
  - A randomized controlled trial (RCT) with 54 patients compared the 1-month (7.5 mg) and 3-month (11.25 mg and 22.5 mg) leuprolide formulations for the treatment of CPP. There were more patients with inadequate pubertal suppression in the 11.25 mg 3-month leuprolide depot group (as measured by mean stimulated LH levels > 4 IU/L) compared to the 7.5 mg monthly and 22.5 mg 3-month groups. Mean LH and FSH levels in the 22.5 mg 3-month dose group were not different from the monthly depot injections. No differences in estradiol levels, growth velocity, or bone age progression were observed between the dosing groups *(Fuld et al 2011).*
  - In a phase 3, randomized, open-label (OL) study (N = 84), leuprolide 11.25 mg 3-month depot was compared to leuprolide 30 mg 3-month depot in children with CPP. There were 9 treatment failures (peak stimulated LH > 4 IU/L) in the 11.25 mg group and 2 in the 30 mg group. Basal sex steroid suppression, growth rates, pubertal progression, bone age advancement, and AEs were similar between both doses *(Lee et al 2012).*
  - Clinical trials with nafarelin demonstrated a reduction in the peak response of LH to GnRH stimulation from a pubertal response to a pre-pubertal response within 1 month of treatment. Additionally, breast development was arrested or regressed in 82% of girls, while genital development was arrested or regressed in 100% of boys *(Synarel Product Information 2017)*.
  - The efficacy of triptorelin 6-month injection was evaluated in an OL, single-arm clinical trial in females and males with CPP, ages 2 to 9 (N = 44). At 12 months, 97.7% of patients achieved pre-pubertal LH levels. Mean stimulated FSH and mean basal FSH levels were also lower at 12 months, compared to baseline. Additionally, the Tanner stage (a scale of physical development) was stable or reduced (manifested by a reduction in physical development) in 88.6% of patients *(Klein et al 2016)*.

Endometriosis

- A Cochrane Review meta-analysis of 41 trials (N = 4935) in patients with endometriosis compared the safety and effectiveness of GnRH agonists to no treatment, placebo, danazol, intrauterine progestins, or other GnRH agonists (*Brown et al 2010*).
  - GnRH agonists were more effective than no treatment or placebo.
  - There was no statistically significant difference between GnRH agonists and danazol for dysmenorrhea associated with endometriosis.
  - There was a benefit in overall resolution for GnRH agonists compared with danazol.
  - There was no statistically significant difference in overall pain between GnRH agonists and levonorgestrel.
  - More AEs were reported in the GnRH agonist group.
  - No route of administration for GnRH agonists appeared to be superior to another.
- A RCT (N = 315) compared the efficacy of goserelin (3.6 mg every 28 days) to danazol 400 mg orally twice daily in females with endometriosis. Goserelin was found to be similar in efficacy and safety as compared to danazol. Both treatments significantly reduced mean subjective signs and symptoms scores during and after treatment *(Rock et al 1993).*
- A meta-analysis of 13 RCTs (N = 945) evaluated the effectiveness of GnRH agonists for endometriosis, with and without add-back therapy. Add-back therapy refers to the addition of hormone replacement therapy to GnRH agonists, in order to avoid AEs that are caused by GnRH agonist-induced hormone suppression. The evidence suggested that add-back therapy was more effective for symptomatic relief than GnRH agonists alone, both immediately after

treatment and at 6 months. Add-back therapy increased estrogen levels, but did not reduce the efficacy of GnRH agonists for treating dysmenorrhea and dyspareunia *(Wu et al 2014)*.

- The FDA approval of elagolix was based on the results of the Elaris Endometriosis trials, EM-I and EM-II, which were 2 phase 3, 6-month, double-blind (DB), placebo-controlled (PC), RCTs in women 18 to 49 years of age with moderate to severe endometriosis. Three treatment groups, elagolix 150 mg orally daily (n = 475), elagolix 200 mg orally twice daily (n = 477), and placebo (n = 734) were evaluated for efficacy and safety. (*Orilissa Dossier 2018, Taylor et al 2017*).
  - Patients were considered responders if they experienced a reduction of ≥ -0.81 from baseline score in dysmenorrhea pain and a reduction of ≥ -0.36 from baseline score in NMPP, and no increase in rescue analgesic use. At months 3 and 6, a significantly greater proportion of women in both elagolix dose groups met the clinical response criteria for the co-primary endpoints of dysmenorrhea and NMPP ($p < 0.001$).
  - The most common AEs were hot flushes, headache, and nausea. Bone mineral density (BMD) loss was significantly greater than placebo in the 150 mg daily and 200 mg twice daily groups at 6 months. Liver and kidney function parameters/analytes exhibited sporadic statistically significant changes throughout treatment but none of the differences between the elagolix doses and placebo were considered clinically significant. Additionally, there was 1 suicide reported in the EM-II trial, which was related to overdose with multiple non-trial medications.
  - Patients who completed EM-I or EM-II continued on to 1 of the 2 phase 3 extension trials, EM-III or EM-IV. The duration of treatment was 6 months (with continuation of the same elagolix dose from the 6-month EM-I/EM-II trials, for a total of 12 months of treatment), followed by a 12 month observation period *(Surrey et al 2018)*.
    - The data from EM-III and EM-IV demonstrated that the response rates for dysmenorrhea and NMPP were maintained in women who continued treatment with elagolix. A decrease of 5 to 8% in lumbar spine BMD after 12 months of continuous treatment occurred in 2 to 3% of the 150 mg daily group and in 26 to 30% of the 200 mg twice daily group. The percentage of women with > 8% decrease in BMD in the lumbar spine, total hip, or femoral neck was 2 to 8% in the 150 mg daily group and 21% in the 200 mg twice daily group.

Uterine fibroids

- PEARL II was a DB, non-inferiority trial that included 307 patients randomly assigned to 5 or 10 mg of ulipristal vs leuprolide acetate depot, for 3 months of treatment. Uterine bleeding was controlled in 90% of patients receiving 5 mg of ulipristal acetate, in 98% of those receiving 10 mg of ulipristal acetate, and in 89% of those receiving leuprolide acetate, for differences (as compared with leuprolide acetate) of 1.2% (95% confidence interval [CI], -9.3 to 11.8) for 5 mg of ulipristal acetate and 8.8% (95% CI, 0.4 to 18.3) for 10 mg of ulipristal acetate. Median times to amenorrhea were 7 days for patients receiving 5 mg of ulipristal acetate, 5 days for those receiving 10 mg of ulipristal acetate, and 21 days for those receiving leuprolide acetate. Moderate-to-severe hot flashes were reported for 11% of patients receiving 5 mg of ulipristal acetate, for 10% of those receiving 10 mg of ulipristal acetate, and for 40% of those receiving leuprolide acetate ($p < 0.001$ for each dose of ulipristal acetate vs leuprolide acetate) *(Donnez et al 2012)*.

Infertility

- A meta-analysis of 73 RCTs (N = 12,212) compared the efficacy and safety of GnRH antagonists (cetrorelix or ganirelix) to long-course GnRH agonist regimens in patients using these agents for controlled ovarian hyperstimulation in ART (*Al Inany et al 2016*).
  - There was no evidence of a difference in live birth rate between GnRH antagonist and long-course GnRH agonist regimens in 2303 patients (odds ratio [OR] = 1.02; 95% CI, 0.85 to 1.23; 12 RCTs; $I^2 = 27\%$).
  - GnRH antagonists were associated with a lower incidence of any grade of ovarian hyperstimulation syndrome (OHSS) compared to GnRH agonists in 7944 patients (OR = 0.61; 95% CI, 0.51 to 0.72; 36 RCTs; $I^2 = 31\%$).
  - There was no difference in miscarriage rate per woman between the GnRH antagonist group and GnRH agonist group as evaluated in 7082 patients (OR = 1.03; 95% CI, 0.82 to 1.29; 34 RCTs; $I^2 = 0\%$).

CLINICAL GUIDELINES

CPP

- American Academy of Pediatrics (AAP): Evaluation and referral of children with signs of early puberty *(Kaplowitz and Bloch 2016)*
  - Treatment with GnRH agonists such as leuprolide can be administered via injection at monthly or 3-month intervals or with annual insertion of SC histrelin implant.
  - If suppression of menses is the primary concern (rather than preservation of linear growth potential), then medroxyprogesterone depot IM injection every 3 months can be considered.

- Therapy should be continued until the physician determines that continued pubertal suppression is no longer beneficial to the child.

Endometriosis

- ACOG: Updates Guideline on Diagnosis and Treatment of Endometriosis (*ACOG 2010, Armstrong 2010)*
  - Progestins, danazol, extended-cycle combined oral contraceptives, NSAIDs, and GnRH agonists can be used for the initial treatment of pain in women with suspected endometriosis.
    - However, recurrence rates are high after the medication is discontinued. Empiric therapy with another suppressive medication is an option. For example, empiric therapy with a 3-month course of a GnRH agonist is appropriate if the initial treatment with an oral contraceptive or NSAID is unsuccessful.
  - In women with a history of endometriosis who wish to preserve their fertility, NSAIDs or combined oral contraceptives can be used to treat recurrent pain.
    - Oral or depot medroxyprogesterone acetate is also an effective treatment option.
    - If none of the above therapies is successful, then progestins, GnRH agonists, and androgens may be used.
    - The use of Mirena (levonorgestrel-releasing intrauterine system) reduces pelvic pain associated with endometriosis, but AEs are common.
  - If treatment with a GnRH agonist is successful, the use of an add-back regimen can reduce or eliminate bone mineral loss and provide symptomatic relief without reduction in pain relief.
    - Add-back regimens have been used in women undergoing long-term therapy; they may include progestins alone, low dose progestins, progestins plus bisphosphonates, or estrogens.
- ASRM: Treatment of pelvic pain associated with endometriosis: A committee opinion *(ASRM 2014)*
  - Endometriosis should be viewed as a chronic disease that requires a lifelong management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures.
  - Definitive diagnosis via laparoscopic surgery is recommended, with the option of treating visible endometriosis at that time.
  - Pharmacologic therapies such as NSAIDs, combined hormonal contraceptives, progestins, danazol, and GnRH agonists are recommended for the treatment of endometriosis.
    - Surgical treatment with removal of the uterus and ovaries (total hysterectomy and bilateral salpingo-oophorectomy) is recommended in women with disabling symptoms who have completed childbearing and have failed to respond to multiple alternative regimens.

Uterine fibroids

- Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program: Management of Uterine Fibroids *(AHRQ 2017)*
  - GnRH agonists, mifepristone, ulipristal, and uterine artery embolism reduce fibroid size, and improve symptoms and quality of life. Myomectomy and hysterectomy also improve quality of life.
    - Moderate-strength evidence suggests that GnRH agonists (with and without add-back therapy) reduce the size of fibroids, the overall size of the uterus, and bleeding symptoms.
    - Low-strength evidence suggests that fibroid-related quality of life improves with GnRH agonists (with and without add-back therapy).
  - For women in their 30s, the chance of needing retreatment for fibroids within the next 2 years was 6 to 7% after medical treatment or myomectomy and 44% after urinary artery embolization (UAE). For older women, the chance was 9 to 19% after medical treatment or UAE and 0% after myomectomy.
- ACOG: Alternatives to hysterectomy in the management of leiomyomas *(ACOG 2008)*
  - GnRH agonists have been shown to improve hematologic parameters, shorten hospital stay, and decrease blood loss, operating time, and postoperative pain when given for 2 to 3 months preoperatively. Benefits of preoperative GnRH agonist administration should be weighed against their cost and side effects for individual patients.
  - Abdominal myomectomy is a safe and effective alternative to hysterectomy for the treatment of women with symptomatic leiomyomas.
  - Hormone therapy may cause some modest increase in uterine leiomyoma size but does not appear to have an impact on clinical symptoms. Therefore, this treatment option should not be withheld from women who desire or need such therapy.

Infertility

- The 2018 ASRM guidelines for PCOS and a 2016 World Health Organization (WHO)-funded PCOS guidelines make the following recommendations *(Balen et al 2016, Teede et al 2018):*
  - Although off-label, letrozole is recommended as first-line therapy for ovulation induction in women with PCOS and anovulatory infertility.
  - Clomiphene is also considered a first-line treatment option in women with PCOS and anovulatory infertility. Per the ASRM guidelines, clomiphene could be used in preference to metformin, when treating an obese patient (BMI ≥ 30 kg/m^2). Both guidelines recommend the use of clomiphene in combination with metformin for PCOS patients with clomiphene resistance.
  - Gonadotropins can be used as second-line pharmacological agents in women with PCOS and anovulatory infertility who have failed oral ovulation induction therapy (clomiphene and/or metformin). No significant differences in efficacy between preparations of gonadotropin agents have been noted.
  - A GnRH antagonist protocol is preferred in women with PCOS undergoing an IVF ± ICSI cycle over a GnRH agonist long protocol. The preferred protocol is known to reduce the duration of stimulation, total gonadotropin dose, and incidence of OHSS.

SAFETY SUMMARY

Contraindications

- Pregnancy
- Cetrotide carries the additional contraindication of severe renal impairment.
- Elagolix carries additional contraindications for known osteoporosis, severe hepatic impairment (Child-Pugh C), and concomitant use with strong OATP1B1 inhibitors (eg, cyclosporine and gemfibrozil).
- Lupaneta Pack carries additional contraindications, including undiagnosed uterine bleeding, breast-feeding, known/suspected/history of breast or other hormone-sensitive cancers, thrombotic/thromboembolic disorders, and liver tumors/liver disease.
- Lupron Depot carries additional contraindications, including undiagnosed abnormal uterine bleeding and breast-feeding.
- Nafarelin carries an additional contraindication for undiagnosed vaginal bleeding.

Warnings and Precautions

- An initial rise in gonadotropin and sex steroid levels may be seen during the first 2 to 4 weeks of therapy, due to the initial stimulatory effect of the drug (leuprolide, histrelin, triptorelin).
- Psychiatric events have been reported in patients taking GnRH agonists. Symptoms include crying, irritability, anger, and aggression (elagolix, histrelin, leuprolide, nafarelin, triptorelin). Suicidal ideation is an additional warning with elagolix.
- Convulsions have been observed in patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, or concomitant medications that may be associated with convulsions. Convulsions have also been reported in patients without the conditions mentioned above (leuprolide, histrelin, nafarelin, triptorelin).
- A reduction in BMD may be observed with most of the GnRH agonists/antagonists.
- Ovarian cysts have been reported during the first 2 months of therapy with Synarel and in post-marketing experience with Zoladex. Many, but not all, occurred in women with polycystic ovarian disease. These cystic enlargements may resolve after 4 to 6 weeks of therapy, but in some cases may require discontinuation of drug and/or surgical intervention.

Key Adverse Effects

- The common AEs within this medication class (excluding histrelin) include hot flushes/sweats, headache, depression/emotional lability, acne, decreased libido, insomnia, and weight gain.
- Injection site pain was one of the most commonly reported AEs for leuprolide. Implant site reaction, including discomfort, bruising, soreness, pain, tingling, itching, implant area protrusion or swelling, was reported in 51% of patients in clinical trials with histrelin.
- Infections such as bronchitis, gastroenteritis, influenza, nasopharyngitis, otitis externa, pharyngitis, sinusitis, and upper respiratory tract infection were observed with triptorelin.

- In clinical trials, OHSS has been reported in 2.4% of patients treated with ganirelix and in 3.5% of patients treated with cetrorelix.

Drug Interactions

- Concomitant use of elagolix with a strong OATP1B1 inhibitor (eg. cyclosporine and gemfibrozil) is contraindicated.
- Concomitant use of elagolix with strong cytochrome P450 (CYP) 3A inhibitors should be limited to ≤ 1 month for the 200 mg twice daily dose and ≤ 6 months for the 150 mg daily dose. The co-administration of elagolix with inducers of CYP3A may decrease elagolix plasma concentrations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cetrotide (cetrorelix)	0.25 mg injection	SC	3 mg one time dose or 0.25 mg once daily	Dose should be adjusted based on individual response.
ganirelix	250 mcg injection	SC	Once daily	Dose should be adjusted based on individual response.
Lupaneta Pack (leuprolide/ norethindrone)	3.75 mg leuprolide syringe/5 mg norethindrone tablets 11.25 mg leuprolide syringe/5 mg norethindrone tablets	IM	Endometriosis: Leuprolide 3.75 mg monthly or 11.25 mg once every 3 months for up to 6 months and norethindrone once daily for up to 6 months. Retreatment should be considered for up to another 6 months if endometriosis symptoms recur	Initial treatment course is limited to 6 months and use is not recommended longer than a total of 12 months due to concerns about adverse impact on BMD.
Lupron Depot (leuprolide acetate depot) 3.75 & 11.25 mg	Injection	IM	Endometriosis: 3.75 mg once monthly or 11.25 mg once every 3 months, alone or in combination with norethindrone acetate Uterine leiomyomata: 3.75 mg once monthly or one 11.25 mg injection with concomitant iron therapy; 11.25 mg is indicated only for women for whom 3 months of hormonal suppression is deemed necessary	Duration of therapy for endometriosis is 6 months; duration of therapy for uterine leiomyomata is up to 3 months.
Lupron Depot-Ped (leuprolide acetate depot) 7.5 mg, 11.25 mg, 15 mg (monthly) & 11.25, 30 mg (3-month)	Powder for injection	IM	CPP: Once monthly (7.5 mg, 11.25 mg, or 15 mg), or leuprolide 11.25 mg or 30 mg once every 3 months	The dose of Lupron Depot-Ped should be individualized for each patient. The dose should be increased to the next available dose if adequate hormonal and clinical suppression is not achieved

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				with the fixed dosing starting dose.
Orilissa (elagolix)	Tablets	Oral	Once daily for the 150 mg dose (duration = 24 months); twice daily for the 200 mg dose in patients with co-existing dyspareunia (duration = 6 months)	A lower dose and duration of therapy is required for patients with moderate hepatic impairment (Child-Pugh Class B); elagolix is contraindicated in patients with severe hepatic impairment (Child-Pugh C).
Supprelin LA (histrelin)	Implant	SC	CPP: Once every 12 months	Implant injected in the inner aspect of the upper arm.
Synarel (nafarelin)	Nasal spray	Intranasal	CPP: Twice daily (up to 3 times daily when a dose increase is required) Endometriosis: Twice daily	Sneezing during or immediately after treatment should be avoided, as this may impair drug absorption. For the endometriosis indication, treatment should be started between days 2 and 4 of the menstrual cycle.
Triptodur (triptorelin)	Injection	IM	CPP: Once every 24 weeks	Response (LH levels or serum concentration of sex steroid levels) should be monitored beginning 1 to 2 months post therapy initiation and during therapy as necessary to confirm maintenance of efficacy.
Zoladex (goserelin)	3.6 mg implant	SC	Endometriosis: Once every 28 days for a total of 6 months Endometrial thinning: Once every 28 days for a total of 1 to 2 months	No adjustment necessary in renal or hepatic impairment. For the endometriosis indication, data are limited to patients ≥ 18 years of age treated for 6 months. Retreatment is not recommended.

Abbreviations: BMD = bone mineral density; CPP = central precocious puberty; IM = intramuscular; LH = luteinizing hormone; SC = subcutaneous

See the current prescribing information for full details

CONCLUSION

- CPP is characterized by the early onset of pubertal manifestations in girls and boys.
  - GnRH agonists are the treatment of choice for CPP. Chronic administration of potent GnRH agonists causes down-regulation of pituitary GnRH receptors, suppression of gonadotropin (LH and FSH) secretion and finally suppression of the release of gonadal sex hormones.
  - There are several FDA-approved GnRH agonists available in the form of implants, depot injections, and nasal spray. Depot formulations are generally preferred due to improved compliance. These GnRH agonists have not been directly compared in randomized trials, but appear to be similarly effective in suppressing the pituitary-gonadal axis.

- According to the AAP 2016 guidelines on the evaluation and referral of children with signs of early puberty, treatment with GnRH agonists such as leuprolide can be administered via injection at monthly or 3-month intervals or with annual insertion of SC histrelin implant. Therapy should be continued until the physician determines that continued pubertal suppression is no longer beneficial to the child.

- Endometriosis is a common gynecological condition characterized by deposits of endometrial tissue outside the endometrial cavity, such as the liver, diaphragm, umbilicus, and pleural cavity.
  - A Cochrane Review meta-analysis of 41 trials (N = 4935) in patients with endometriosis found no statistically significant difference between GnRH agonists and danazol for dysmenorrhea associated with endometriosis. However, a benefit in overall resolution for GnRH agonists compared with danazol was observed. Additionally, there was no statistically significant difference in overall pain between GnRH agonists and levonorgestrel. No route of administration for GnRH appeared to be superior to another.
  - The safety and efficacy of Orilissa (elagolix), a recently approved oral GnRH antagonist, were demonstrated in 2 placebo-controlled studies in 1686 premenopausal women with moderate to severe endometriosis pain. In both studies, a higher proportion of women treated with elagolix were responders vs placebo for dysmenorrhea and NMPP in a dose-dependent manner at month 3 ($p \leq 0.001$ for all comparisons except non-menstrual pelvic pain with elagolix 150 mg once daily in study 2, $p \leq 0.01$).
  - ACOG's 2010 endometriosis guidelines recommend progestins, danazol, extended-cycle combined oral contraceptives, NSAIDs, and GnRH agonists for the initial treatment of pain in women with suspected endometriosis. GnRH agonists can be used empirically in case of recurrence of endometriosis.
  - The 2014 ASRM guidelines recommend a definitive diagnosis via laparoscopic surgery, with the option of treating visible endometriosis at that time. Pharmacologic therapies such as NSAIDs, combined hormonal contraceptives, progestins, danazol, and GnRH agonists are recommended for the treatment of endometriosis.
- Although curative treatment of uterine fibroids relies on surgical therapies, medical treatments are considered first-line to preserve fertility and avoid or delay surgery. Lupron Depot 3.75 mg is the only GnRH agonist that has been FDA-approved for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata.
  - AHRQ's 2017 guidelines for the management of uterine fibroids recommend GnRH agonists to reduce fibroid size and improve symptoms (moderate-strength evidence). Fibroid-related quality of life may also improve with GnRH agonists (low-strength evidence).
- Infertility is a common condition that can have a substantially negative emotional, physical, and financial impact on a couple. GnRH antagonists, such as cetrorelix and ganirelix, may be reserved for second-line treatment to prevent premature LH surges, allowing for controlled ovarian stimulation during ART procedures.
  - The 2018 ASRM guidelines for PCOS and 2016 WHO-funded PCOS guidelines recommend letrozole (off-label) or clomiphene for first-line therapy in women with PCOS who have anovulatory infertility. Gonadotropins are recommended as an option in anovulatory women with PCOS who have failed clomiphene (± metformin).

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