Therapeutic Class Overview

Gonadotropin-releasing hormone (GnRH) agonists/ luteinizing hormone-releasing hormone (LHRH) agonists

INTRODUCTION

- 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)*.
- Central precocious puberty (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)*.
- 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 *(Brown and Farquhar 2015).*
  - Endometriosis commonly manifests as chronic pain and infertility *(Armstrong 2011).*
  - It 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 2011).*
- 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 are generally considered safe and are well-tolerated *(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.
      - Nafarelin is also indicated for the management of endometriosis.
      - Supprelin LA (histrelin), available as a 1-year subcutaneous (SC) implant device.
    - Triptodur (triptorelin), administered as a single IM injection every 24 weeks.
      - Trelstar (triptorelin pamoate) IM injection, which was the first FDA-approved triptorelin formulation, is indicated for the palliative treatment of advanced prostate cancer. Prior to the FDA-approval of Triptodur, Trelstar monthly and every 3 month injections were used off-label to treat CPP *(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).*
- Zoladex (goserelin) 3.6 mg implant is a GnRH agonist that is indicated for the management of endometriosis and as an endometrial thinning agent prior to endometrial ablation.
  - Goserelin 3.6 mg implant carries additional indications for the management and palliative treatment of prostate cancer and the palliative treatment of breast cancer.
  - The goserelin implant is also available in a 10.8 mg dose, which is only indicated for the management and palliative treatment of prostate cancer.
- Lupron Depot 3.75 mg monthly and 11.25 mg every 3 month IM injections are indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Lupron Depot monthly with norethindrone acetate 5 mg daily is also indicated for initial management of endometriosis and for management of recurrence of symptoms.
- Lupron Depot 3.75 mg concomitantly with iron therapy is indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata. 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.

- Experience with Lupron Depot in females has been limited to women 18 years of age and older.
- Of note, all cancer indications for GnRH agonists are outside of the scope of this review.
- Medispan Class: Gonadotropin Releasing Hormone Agonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Lupaneta Pack (leuprolide acetate 3.75 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)	-
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 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Lupaneta Pack (leuprolide/ norethindrone)	Lupron (leuprolide) Depot	Lupron Depot-Ped (leuprolide)	Supprelin LA (histrelin)	Synarel (nafarelin) intranasal spray	Triptodur (triptorelin)	Zoladex (goserelin) 3.6 mg 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		✔					

(*Prescribing information: Lupaneta Pack 2015, Lupron Depot-Ped 2017, Lupron Depot 3.75 mg 2013, Lupron Depot 11.25 mg 2013, Supprelin LA 2017, Synarel 2017, Triptodur 2017, Zoladex [3.6 mg] 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 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 open-label, 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.
- An 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).*

CLINICAL GUIDELINES

CPP

- American Academy of Pediatrics: 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

- American College of Obstetrics and Gynecology (ACOG) Updates: Guideline on Diagnosis and Treatment of Endometriosis (*Armstrong 2010)*
  - Progestins, danazol, extended-cycle combined oral contraceptives, nonsteroidal anti-inflammatory drugs (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 are 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.
    - 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.

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 for 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.

SAFETY SUMMARY

Contraindications

- Pregnancy
- Nafarelin carries an additional contraindication for undiagnosed vaginal bleeding.
- 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.

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 including crying, irritability, anger, and aggression. (leuprolide, histrelin, nafarelin, triptorelin)
- Convulsions have been observed in patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system (CNS) anomalies or tumors, or concomitant medications that may be associated with convulsions. (leuprolide, histrelin, nafarelin, triptorelin)
- Loss of bone mineral density can occur with Lupaneta Pack, so its use is not recommended for more than two 6-month treatment courses.
- Endometrial cysts have been reported during the first 2 months of therapy. 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 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.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Lupaneta Pack (leuprolide/ norethindrone)	11.25 mg leuprolide syringe/5 mg norethindrone tablets	IM	Endometriosis: Leuprolide every 3 months for up to 6 months and norethindrone 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 bone mineral density Bone mineral density should be assessed prior to retreatment
Lupron Depot (leuprolide acetate depot) 3.75 & 11.25 mg	Injection	IM	Endometriosis: 3.75 mg monthly or 11.25 mg every 3 months, alone or in combination with norethindrone acetate Uterine leiomyomata: 3.75 mg 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	Endometriosis: The choice of leuprolide depot alone or with norethindrone acetate therapy for initial management of the signs and symptoms of endometriosis should be made by the health care provider in consultation with the patient, and should take into consideration the risks and benefits of the addition of norethindrone acetate to leuprolide depot alone. The recommended duration of treatment is 6 months. Uterine leiomyomata: The recommended duration of

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				therapy 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: Monthly	
Supprelin LA (histrelin)	Implant	SC	CPP: 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: Every 24 weeks	
Zoladex (goserelin)	3.6 mg implant	SC	Endometriosis: Every 28 days for a total of 6 months Endometrial thinning: 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.

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 American Academy of Pediatrics 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.

- ACOG's 2010 endometriosis guidelines recommend progestins, danazol, extended-cycle combined oral contraceptives, nonsteroidal anti-inflammatory drugs (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.
- AHRQ's 2017 guidelines for the management of uterine fibroids recommend GnRH agonists to reduce fibroid size and improve symptoms and quality of life (moderate-strength evidence). Fibroid-related quality of life may also improve with GnRH agonists (low strength-evidence).

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