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Coverage Policy Number IP0333

Gonadotropin-Releasing Hormone (GnRH) Antagonists for Infertility Use

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Treatment of Gender Dysphoria
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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for the following Gonadotropin-Releasing Hormones (GnRH) Antagonists for Infertility Use:

- Cetrorelix acetate 0.25 mg injection (generic for Cetrotide)
- Cetrotide® Injection (cetrorelix injection)
- Fyremadel® (ganirelix acetate injection)
- Ganirelix acetate (generic for Ganirelix)

Injectable fertility medications are specifically excluded under most benefit plans. Please refer to the applicable benefit plan document to determine benefit availability and the terms and conditions of coverage.
The use of injectable fertility medications for the treatment of gender dysphoria is addressed in a separate coverage policy. Please refer to the related coverage policy link above (Treatment of Gender Dysphoria).

Medical Necessity Criteria

Gonadotropin-Releasing Hormones (GnRH) Antagonists (Cetrorelix acetate, Cetrotide, Fyremadel, ganirelix acetate) for Infertility Use are considered medically necessary when the following are met:

1. **Infertility.** Individual meets the following criteria:
   A. Inhibition of premature luteinizing hormone (LH) surges in a woman undergoing controlled ovarian stimulation (COS) in conjunction with assisted reproductive procedures
   B. Preferred product criteria is met for the products listed in the below table

Individual and Family Plans:

Product	Criteria
Cetrotide injection (cetrorelix acetate 0.25 mg injection)	The patient has tried the bioequivalent generic product **cetrorelix acetate 0.25 mg injection,** AND cannot take due to a formulation difference in the inactive ingredient(s) e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which would result, per the prescriber, in a significant allergy or serious adverse reaction.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Gonadotropin-Releasing Hormones (GnRH) Antagonists (Cetrorelix acetate, Cetrotide, Fyremadel, ganirelix acetate) for Infertility Use is considered medically necessary for continued use when the above medical necessity criteria are met.

Authorization Duration

Initial approval duration: up to 12 months.
Reauthorization approval duration: up to 12 months.

Conditions Not Covered

Gonadotropin-Releasing Hormones (GnRH) Antagonists (Cetrorelix acetate, Cetrotide, Fyremadel, ganirelix acetate) are considered experimental, investigational or unproven for **ANY** other infertility use.

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J3490†	Unclassified drugs

HCPCS Codes	Description
S0132	Injection, ganirelix acetate, 250 mcg

†Note: May be considered for coverage when used to report Cetrotide®

Background

OVERVIEW

Cetrotide and Ganirelix are synthetic decapeptides with gonadotropin-releasing hormone (GnRH) antagonist activity.[1,2,16,17] These agents are utilized for assisted reproductive technologies (ART),[1-7, 16, 17] although other uses besides infertility have been noted.[8] GnRH antagonists have emerged as an alternative to GnRH agonists (e.g., leuprolide injection) in preventing premature luteinizing hormone (LH) surges.[3,5] In comparison with GnRH agonists, the pharmacological mechanism by which GnRH antagonists suppress the release of gonadotropins is completely different. The agonists act through downregulation of receptors and desensitization of the gonadotrophic cells. Alternatively, the antagonists bind competitively to the receptors, thereby preventing endogenous GnRH from exerting its stimulatory effects on the pituitary cells. Competitive blockade of the receptors leads to an immediate arrest of gonadotrophin secretion. The mechanism of action is dependent on the equilibrium between endogenous GnRH and the applied antagonists. The antagonist effect is highly dose-dependent compared with the agonists. Utilizing GnRH antagonists for ovulatory induction in assisted conception will result in a dramatic reduction in the duration of GnRH analog treatment and reduce the amount of gonadotropin necessary for stimulation. Other potential benefits for GnRH antagonist therapy include a lower risk for developing severe ovarian hyperstimulation syndrome (OHSS), fewer treatment days, and avoiding estrogen deprivation symptoms (e.g., hot flushes, sleep disturbances, headache).[3] When used for *in vitro* fertilization (IVF), current data suggest that pregnancy and live birth rates are comparable for GnRH agonists and antagonists.[9]

Table 1. Characteristics of the GnRH Antagonists.[1,2]

Category	Ganirelix, Fyremadel (ganirelix acetate for injection)	Cetrotide® (cetrorelix acetate for injection)
Indications	Indicated for the inhibition of premature LH surges in women undergoing controlled ovarian hyperstimulation.	Indicated for the inhibition of premature LH surges in women undergoing controlled ovarian stimulation.
Dosing and administration	After initiating FSH therapy on Day 2 or 3 of the cycle, Ganirelix 250 mcg may be administered SC QD during the mid to late portion of the follicular phase. Treatment should be continued daily until the day of hCG administration.	Ovarian stimulation therapy with gonadotropins (FSH, hMG) is started on cycle Day 2 or 3. Cetrotide may be administered SC QD (0.25 mg dose) during the early- to mid-follicular phase. Cetrotide 0.25 mg is administered on either stimulation day 5 (morning or evening) or day 6 (morning) and continued daily until the day of hCG administration.
Contra-indications	Known hypersensitivity to Ganirelix acetate or to any of its components; hypersensitivity to GnRH or any other GnRH analog; and known or suspected pregnancy.	Hypersensitivity to Cetrotide, extrinsic peptide hormones or mannitol; known hypersensitivity to GnRH or any other GnRH analogs; known or suspected pregnancy and lactation; and severe renal impairment.
Precautions	Cases of hypersensitivity reactions, including anaphylactoid reactions, have been reported, as early as with the first dose, during post-marketing surveillance.	Cases of hypersensitivity, including anaphylactoid reactions with the first dose, have been noted. Treatment is not advised in women with severe allergic conditions.
Laboratory	A neutrophil count ≥ 8.3 (x 10^9/L) was noted in 11.9% (up to 16.8 x 10^9/L) of all patients treated within the adequate and well-controlled clinical trials. In addition, downward shifts in hematocrit and total bilirubin within the Ganirelix acetate injection group were observed. The clinical significance of these findings was not determined.	After the exclusion of preexisting conditions, liver enzyme elevations were found in 1% to 2% of patients receiving Cetrotide during controlled ovarian stimulation. The elevations range up to three times the upper limit of normal. The clinical significance of these findings was not determined. During stimulation with hMG, Cetrotide had no

		notable effects on hormone levels aside from inhibition of LH surges.
Pregnancy Category	X	X
Supplied	Ganirelix acetate injection is supplied as disposable, sterile, prefilled 1 mL glass syringes containing 250 mcg/0.5 mL of Ganirelix acetate.	Cetrotide is available in a carton of one packaged tray. Each tray contains: one glass vial of Cetrotide (0.26 to 0.27 mg cetrorelix acetate [corresponding to 0.25 mg cetrorelix]), one pre-filled glass syringe with 1 mL of Sterile Water for Injection, one 20 gauge needle, and one 27 gauge needle.
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light.	Store refrigerated at 2 ºC to 8ºC (36 ºF to 46ºF). Store the packaged tray in the outer carton to protect from light.

GnRH – Gonadotropin-releasing hormone; LH – Luteinizing hormone; FSH – Follicle stimulating hormone; SC – Subcutaneously; QD – Once-daily; hCG – Human chorionic gonadotropin; hMG – Human menopausal gonadotropin.

Guidelines

The American Society of Reproductive Medicine (ASRM) Practice Committee guideline (2016) on the prevention and treatment of moderate and severe ovarian hyperstimulation syndrome (OHSS) notes that stimulation protocols utilizing GnRH antagonists for ovulation suppression are associated with a lower incidence of OHSS compared with protocols that use a GnRH agonist.[15] The mechanism is thought to be related to a reduction in circulating estradiol levels seen with GnRH antagonist suppression. OHSS is an uncommon but serious complication associated with controlled ovarian stimulation during ART. Moderate to severe OHSS occurs in approximately 1% to 5% of cycles. Signs and symptoms include ovarian enlargement, ascites, hemoconcentration, hypercoagulability, and electrolyte imbalances. Severe OHSS can lead to serious complications, including pleural effusion, acute renal insufficiency, and venous thromboembolism. The guideline also notes that there is insufficient evidence that clomiphene independently reduces OHSS risk.

The ASRM Practice Committee notes that use of GnRH antagonists may allow more flexibility than other protocols for ovarian stimulation in female patients who want to preserve fertility prior to gonadotoxic therapy.[13] The Committee adds that the risk of OHSS may delay cancer therapy in these patients and strategies to reduce this risk include the use of GnRH antagonist protocols with GnRH agonists to trigger the final maturation of oocytes.

References

1. Ganirelix [prescribing information]. Parsippany, NJ: Ferring Pharmaceuticals Inc.; March 2019.
2. Cetrotide® [prescribing information]. Rockland, MA: EMD Serono; May 2018.
3. Al-Inany HG, About-Setta AM, Aboulghar M. Gonadotropin-releasing hormone antagonists for assisted conception. *Cochrane Database Syst Rev*. 2006 July 19;3:CD001750.
4. Wilcox J, Potter D, Moore M, et al. Prospective, randomized trial comparing cetrorelix acetate and ganirelix acetate in a programmed, flexible protocol for premature luteinizing hormone surge prevention in assisted reproductive technologies. *Fertil Steril*. 2005;84:108-117.
5. Griesinger G, Felberbaum FE, Schultze-Mosgau A, Diedrick K. Gonadotropin-releasing hormone antagonists for assisted reproductive techniques. Are there clinical differences between agents. *Drugs*. 2004;64(6);563-575.
6. Shapiro DB, Mithcell-Leef D. GnRH antagonists in *in vitro* fertilization: where we are now. *Minerva Ginecol*. 2003;55:373-388.
7. Devroey P, Fauser BCJM, Diedrich K, on behalf of the Evian Annual Reproduction (EVAR) Workshop Group 2008. Approaches to improve the diagnosis and management of infertility. *Hum Reprod Update*. 2009;15(4):391-408.
8. Anon: Thomson MICROMEDEX® DrugKnowledge® System (electronic version). Thomson MICROMEDEX, Greenwood Village, Colorado, USA. http://www.micromedexsolutions.com/home/dispatch. Accessed on September 2, 2020.
9. Devroey P, Aboulghar M, Garcia-Velasco J, et al. Improving the patient's experience of IVF/ICSI: a proposal for an ovarian stimulation protocol with GnRH antagonist co-treatment. *Hum Reprod*. 2009;24(4):764-774.

10. Check JH, Brasile D, Choe JK, et al. The effect of cetrorelix vs. ganirelix on pregnancy outcome using minimal gonadotropin stimulation in women with elevated day 3 serum follicle stimulating hormone levels. *Clin Exp Obstet Gynecol.* 2009;36(3):148-149.
11. Copperman AB, Benadiva C. Optimal usage of the GnRH antagonists: a review of the literature. *Reprod Biol Endocrinol.* 2013;11:20.
12. Graziano A, Caserta D, Piva I, et al. The addition of GnRH antagonists in intrauterine insemination cycles: a pilot study. *Eur Rev Med Pharmacol Sci.* 2013;17:1604-1610.
13. The Practice Committee for the American Society of Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. *Fertil Steril.* 2013;100:1214-1223.
14. Al-Inany HG, Youssef MA, Ayeleke RO, et al. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology (review). *Cochrane Database Syst Rev.* 2016, Issue 4. Art. No.: CD001750.
15. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. Practice Committee of the American Society for Reproductive Medicine. Available at: .https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/practice-guidelines/for-non-members/prevention_and_treatment_of_moderate_to_severe_ohss.pdf. Accessed on September 2, 2020.
16. Fyremadel® (ganirelix acetate subcutaneous injection) [prescribing information]. Parsippany, NJ: Ferring Pharmaceuticals Inc.; January 2022.
17. Cetrorelix acetate for injection [prescribing information]. Gurnee, IL: Akorn Operating Company LLC; October 2021.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes	12/15/2024

The policy effective date is in force until updated or retired