



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject Infertility Injectables

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Hyperlink to Related Coverage Policies

Infertility Services

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), 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 supercedes** 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. 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. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

Note: 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 dosage, frequency, site of administration, and duration of therapy are reasonable clinically appropriate, and supported by evidence-based literature.

If coverage is available for injectable fertility medications, then CIGNA covers as medically necessary according to the following table:

Drug Name	Usage
Cetrotide	Inhibition of premature luteinizing hormone (LH) surges in a woman undergoing controlled ovarian stimulation (COS) in conjunction with assisted reproductive procedures.
Follitropin Therapy	Use in combination with hCG (human Chorionic Gonadotropin) therapy for EITHER of the following: <ul style="list-style-type: none"> • ovulation stimulation in females for EITHER of the following: <ul style="list-style-type: none"> ➢ as part of Assisted Reproductive Technology (ART) program ➢ oligoovulatory or anovulatory infertile woman in whom the

Drug Name	Usage
	<p>cause of infertility is functional and not due to primary ovarian failure</p> <ul style="list-style-type: none"> • spermatogenesis stimulation in a male for primary or secondary hypogonadotropic hypogonadism not due to primary testicular failure <p>PLEASE NOTE: Follistim® AQ is a preferred brand follitropin therapy product.</p> <p>Non-preferred brand follitropin therapy (Bravelle® and Gonal-F®) will only be covered when there is failure, contraindication, or intolerance to Follistim® AQ.</p>
Ganirelix	<p>Inhibition of premature luteinizing hormone (LH) surges in a woman undergoing controlled ovarian stimulation (COS) in conjunction with assisted reproductive procedures.</p>
Human Chorionic Gonadotropin Therapy	<p>Use when ANY of the following criteria are met:</p> <ul style="list-style-type: none"> • in combination with ovulation stimulation therapy in females for ANY of the following: <ul style="list-style-type: none"> ➢ as part of an Assisted Reproductive Technology (ART) program ➢ anovulatory infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure ➢ treatment of corpus luteum dysfunction • in males for ANY of the following: <ul style="list-style-type: none"> ➢ alone or in combination with menotropins or clomiphene therapy for spermatogenesis stimulation as a result of primary or secondary hypogonadotropic hypogonadism ➢ diagnosis or treatment of cryptorchidism ➢ diagnosis of hypogonadism ➢ management of hypogonadotropic hypogonadism <p>Human Chorionic Gonadotropin Therapy includes Novarel® and Pregnyl®</p>
Luveris	<p>When BOTH of the following criteria are met:</p> <ul style="list-style-type: none"> • use in combination with human follicle-stimulating hormone (follitropin alfa, Gonal-f®) for the stimulation of follicular development in an infertile hypogonadotropic hypogonadal woman • in a woman with a profound luteinizing hormone (LH) deficiency defined as LH < 1.2 international units/L.
Menotropin Therapy	<p>Use in combination with hCG (human Chorionic Gonadotropin) therapy for EITHER of the following:</p> <ul style="list-style-type: none"> • ovulation stimulation in a woman for EITHER of the following: <ul style="list-style-type: none"> ➢ as part of Assisted Reproductive Technology (ART) program ➢ oligoovulatory or anovulatory infertile woman in whom the cause of infertility is functional and not due to primary ovarian failure • spermatogenesis stimulation in a male for primary or secondary

Drug Name	Usage
	hypogonadotropic hypogonadism not due to primary testicular failure Menotropin Therapy includes Menopur® and Repronex®
Ovidrel	Use in combination with ovulation stimulation therapy in a woman when EITHER of the following criteria is met: <ul style="list-style-type: none"> • as part of Assisted Reproductive Technology (ART) program • anovulatory infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure

FDA Approved Indications / FDA Recommended Dosing / Drug Availability

Drug Name	Approved Indication	Recommended Dosing	Drug Availability
Cetrotide	Cetrotide (cetorelix acetate for injection) is indicated for the inhibition of premature LH surges in women undergoing controlled ovarian stimulation.	Ovarian stimulation therapy with gonadotropins (FSH, hMG) is started on cycle Day 2 or 3. The dose of gonadotropins should be adjusted according to individual response. Cetrotide (cetorelix acetate for injection) may be administered subcutaneously either once daily (0.25 mg dose) or once (3 mg dose) during the early- to mid-follicular phase. In the single dose regimen, 3 mg of Cetrotide is administered when the serum estradiol level is indicative of an appropriate stimulation response, usually on stimulation day 7 (range day 5-9). If hCG has not been administered within four days after injection of Cetrotide 3 mg, Cetrotide 0.25 mg should be administered once daily until the day of hCG administration. In the multiple dose regimen, 0.25 mg of Cetrotide is administered on either stimulation day 5 (morning or evening) or day 6 (morning) and continued daily until the day of hCG administration. When assessment by ultrasound shows a sufficient number of follicles of adequate size, hCG is administered to induce ovulation and final maturation of the oocytes. No	Cetrotide (cetorelix acetate for injection) 0.25 mg is available in a carton of one packaged tray - each packaged tray contains: one glass vial containing 0.26 - 0.27 mg cetorelix acetate (corresponding to 0.25 mg cetorelix). Cetrotide (cetorelix acetate for injection) 3 mg is available in a carton of one packaged tray - each packaged tray contains: one glass vial containing 3.12 - 3.24 mg cetorelix acetate (corresponding to 3 mg cetorelix).

Drug Name	Approved Indication	Recommended Dosing	Drug Availability
		hCG should be administered if the ovaries show an excessive response to the treatment with gonadotropins to reduce the chance of developing ovarian hyperstimulation syndrome (OHSS).	
Follitropin Therapy	<p>Follistim AQ Follistim AQ (follitropin beta injection) is indicated for the development of multiple follicles in ovulatory individuals participating in an Assisted Reproductive Technology (ART) program. Follistim AQ is also indicated for the induction of ovulation and pregnancy in anovulatory infertile individuals in whom the cause of infertility is functional and not due to primary ovarian failure.</p> <p>Bravelle Bravelle is indicated for ovulation induction in individuals who have previously received pituitary suppression.</p> <p>Gonal-f Gonal-f (follitropin alfa injection) is indicated for the induction of ovulation and pregnancy in the oligo-anovulatory infertile individual in whom the cause of infertility is functional and not due to primary ovarian failure. Gonal-f is also indicated for the development of multiple follicles in the ovulatory individual participating in an ART program.</p>	Please refer to specific recommended dosing information for each agent per FDA label. Initial doses vary based on indication, although to minimize side effects, the lowest effective dose should be administered for each agent. Individuals treated for ovulation induction generally require longer treatment and lower doses, while individuals undergoing assisted reproductive technology programs generally receive higher doses for approximately 10 days. Individuals treated with follitropins require extensive monitoring.	<p>Three types of follitropins for injection are currently available in the United States. Purified urofollitropin is available as Bravelle, recombinant follitropin beta is marketed in the United States as Follistim AQ, and as Puregon in Europe, and recombinant follitropin alfa is marketed as Gonal-F.</p> <p>Follistim AQ Two-vial package containing 1-10mL lyophilized multiple dose vial containing: 10,000 USP Units chorionic gonadotropin per vial.</p> <p>Bravelle Single dose vial containing 82.5 IU of FSH, to deliver 75 IU FSH after reconstitution.</p> <p>Gonal-f Each Gonal-f RFF Pen is filled with 415 IU, 568 IU, or 1026 IU follitropin alfa to deliver a minimum total of 300 IU in 0.5 mL, 450 IU in 0.75 mL,</p>

Drug Name	Approved Indication	Recommended Dosing	Drug Availability
			<p>or 900 IU in 1.5 mL, respectively. Each Pen is supplied in a carton containing 29G x 1/2 inch disposable needles to be used for administration.</p> <p>Gonal-f RFF (follitropin alfa for injection) is supplied in a sterile, lyophilized form in single-dose vials containing 82 IU with diluent in a pre-filled syringe. Following reconstitution with the diluent as described, upon administration each vial will deliver a dose of 75 IU.</p> <p>Gonal-f (follitropin alfa for injection) is supplied in a sterile, lyophilized form in multiple dose vials filled with 600 IU or 1200 IU in order to deliver 450 IU and 1050 IU FSH, respectively, after reconstitution with diluent.</p>
Ganirelix	Ganirelix Acetate Injection is indicated for the inhibition of premature LH surges in women undergoing controlled ovarian hyperstimulation.	After initiating FSH therapy on Day 2 or 3 of the cycle, Ganirelix Acetate Injection 250 µg may be administered subcutaneously once daily during the mid to late portion of the follicular phase. By taking advantage of endogenous pituitary FSH secretion, the requirement for exogenously administered FSH may be reduced. Treatment with Ganirelix Acetate should be continued daily until the day of hCG administration. When a sufficient number of follicles of adequate size are present, as assessed by ultrasound, final maturation of follicles is	Disposable, sterile, prefilled 1 mL glass syringes containing 250 µg/0.5 mL of Ganirelix Acetate.

Drug Name	Approved Indication	Recommended Dosing	Drug Availability
		<p>induced by administering hCG. The administration of hCG should be withheld in cases where the ovaries are abnormally enlarged on the last day of FSH therapy to reduce the chance of developing OHSS (Ovarian Hyperstimulation Syndrome).</p>	
<p>Human Chorionic Gonadotropin Therapy</p>	<p>Novarel and Pregnyl</p> <ul style="list-style-type: none"> • Prepubertal cryptorchidism not due to anatomic obstruction. In general, HCG is thought to induce testicular descent in situations when descent would have occurred at puberty. HCG thus may help to predict whether or not orchiopexy will be needed in the future. Although, in some cases, descent following HCG administration is permanent, in most cases the response is temporary. Therapy is usually instituted between the ages of 4 and 9 • Selected cases of hypogonadotropic hypogonadism (hypogonadism secondary to a pituitary deficiency) in males • Induction of ovulation and pregnancy in the anovulatory, infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure, and who has been appropriately pretreated with human menotropins 	<p>The dosage regimen employed in any particular case with either Novarel or Pregnyl will depend upon the indication for use, the age and weight of the individual, and the physician's preference.</p>	<p>Novarel Chorionic Gonadotropin for Injection, USP, is available as individually packaged vials containing 10,000 USP Units per vial.</p> <p>Pregnyl Two-vial package containing 1-10mL lyophilized multiple dose vial containing: 10,000 USP Units chorionic gonadotropin per vial.</p>
<p>Luveris</p>	<p>Luveris (lutropin alfa for injection), concomitantly administered with Gonal-f (follitropin alfa for injection), is indicated for stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency (LH < 1.2 IU/L). A definitive effect on pregnancy in this population has not been demonstrated. The safety and effectiveness of concomitant administration of Luveris with any other preparation of recombinant human FSH or urinary human FSH is unknown.</p>	<p>It is recommended that 75 IU Luveris be concomitantly administered subcutaneously with 75 IU to 150 IU Gonal-f as two separate injections in the initial treatment cycle. Luveris and Gonal-f should be administered daily until adequate follicular development is indicated by ovary ultrasonography and serum estradiol. Treatment duration should not normally exceed 14 days unless signs of imminent follicular development are present. To complete follicular development and effect ovulation in the absence of an</p>	<p>Luveris (lutropin alfa for injection) is supplied in a sterile, lyophilized single dose vial containing 82.5 IU Luveris to deliver 75 IU Luveris, after reconstitution with the diluent.</p>

Drug Name	Approved Indication	Recommended Dosing	Drug Availability
		<p>endogenous LH surge, human chorionic gonadotropin (hCG) should be given one day after the last dose of Luveris and Gonal-f. Treatment with hCG should be withheld if the ovaries are abnormally enlarged or if excessive estradiol production has occurred. If the ovaries are abnormally enlarged or abdominal pain occurs, treatment with Luveris and Gonal-f should be discontinued and hCG should not be administered, and the patient should be advised not to have intercourse; this may reduce the chances of developing Ovarian Hyperstimulation Syndrome and, should spontaneous ovulation occur, reduce the chances of multiple gestation.</p>	
<p>Menotropin Therapy</p>	<p>Menopur Menopur administered subcutaneously is indicated for the development of multiple follicles and pregnancy in the ovulatory patients participating in an ART program.</p> <p>Repronex Repronex, in conjunction with hCG, is indicated for multiple follicular development (controlled ovarian stimulation) and ovulation induction in patients who have previously received pituitary suppression.</p>	<p>Menotropins must be administered parenterally. Because absorption is greater with subcutaneous (SC) use than intramuscular (IM) use, the two routes are not bioequivalent. The distribution and metabolism of menotropins have not been studied. About 10% of the dose is excreted unchanged in the urine. Pharmacokinetics have not been studied in special populations.</p> <p>Menopur The recommended initial dose of Menopur for patients who have received a GnRH agonist for pituitary suppression is 225 IU. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every two days and should not exceed 150 IU per adjustment. The maximum daily dose of</p>	<p>Menopur Menopur is available by prescription in 5 mL vials containing 75 IU FSH and 75 IU LH activity with accompanying diluent.</p> <p>Repronex Repronex is available by prescription in 5 mL vials containing 75 IU FSH and 75 IU LH activity with accompanying diluent.</p>

Drug Name	Approved Indication	Recommended Dosing	Drug Availability
		<p>Menopur given should not exceed 450 IU and dosing beyond 20 days is not recommended. Once adequate follicular development is evident, hCG should be administered to induce final follicular maturation in preparation for oocyte retrieval.</p> <p>Repronex The dose of Repronex to stimulate development of ovarian follicles must be individualized for each patient. The lowest dose consistent with achieving good results based on clinical experience and reported clinical data should be used. The recommended initial dose of Repronex for patients who have received GnRH agonist or antagonist pituitary suppression is 225 IU. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of Repronex given should not exceed 450 IU and dosing beyond 12 days is not recommended.</p>	
Ovidrel	<p>Ovidrel preFilled syringe (choriogonadotropin alfa injection) is indicated for the induction of final follicular maturation and early luteinization in infertile women who have undergone pituitary desensitization and who have been appropriately pretreated with follicle stimulating hormones as part of an Assisted Reproductive Technology (ART) program such as in vitro fertilization and embryo transfer. Ovidrel PreFilled Syringe is also indicated for the induction of ovulation (OI) and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian</p>	<p>Ovidrel is for subcutaneous use only. For infertile women undergoing Assisted Reproductive Technologies (ART), Ovidrel® PreFilled Syringe 250 µg should be administered one day following the last dose of the follicle stimulating agent. Ovidrel® PreFilled Syringe should not be administered until adequate follicular development is indicated by serum estradiol and vaginal ultrasonography. Administration should be withheld in situations where</p>	<p>OvidrelR PreFilled Syringe (choriogonadotropin alfa injection) is supplied in a sterile, liquid single dose pre-filled 1 mL syringe. Each OvidrelR PreFilled Syringe is filled with 0.515 mL containing 257.5 µg of chorio-gonadotropin alfa, 28.1 mg mannitol, 505 µg 85%</p>

Drug Name	Approved Indication	Recommended Dosing	Drug Availability
	failure.	there is an excessive ovarian response, as evidenced by clinically significant ovarian enlargement or excessive estradiol production.	O-phosphoric acid, 103 µg L-methionine, 51.5 µg Poloxamer 188, Sodium Hydroxide (for pH adjustment), and Water for Injection to deliver 250 µg of chorio-gonadotropin alfa in 0.5 mL. The following package combination is available: • 1 pre-filled syringe containing 250 µg OvidrelR PreFilled Syringe NDC 44087-1150-1
			Luveris (lutropin alfa for injection) is supplied in a sterile, lyophilized single dose vial containing 82.5 IU Luveris to deliver 75 IU Luveris, after reconstitution with the diluent. The following package combination is available: 1 vial Luveris 75 IU and 1 vial 1 mL Sterile Water for Injection.

General Background

Cetrotide

Pharmacology

Cetorelix is a gonadotropin-releasing hormone (GnRH) antagonist indicated for the prevention of premature luteinizing hormone (LH) surges in subfertile women undergoing controlled ovarian stimulation (COS) in conjunction with assisted reproductive procedures. Cetorelix is a synthetic decapeptide GnRH antagonist which competitively blocks GnRH receptors. Cetorelix competes with endogenous GnRH for receptor binding sites on gonadotropic cells of the pituitary. Binding of cetorelix to the receptor suppresses the release of the gonadotropins LH and follicle stimulating hormone (FSH), key regulatory hormones that govern ovarian growth and follicular development. The effects of cetorelix on gonadotropins are reversible. The time to maximum peak concentration for cetorelix is one hour, and it features a dose-dependent half-life of 5–63 hours. Its main route of excretion is through the bile, and it has no active metabolites.

Clinical Efficacy

Six randomized, controlled, parallel trials and two meta-analyses have demonstrated cetorelix to be effective in the prevention of premature LH surges. Cetorelix had fewer days of stimulation (cetorelix: 7–10.6; GnRH agonists: 10–12.2), reduced the amount of HMG or FSH used, and avoided the initial flare of LH that is observed

with GnRH agonist therapy. The overall clinical pregnancy rates were similar between cetrorelix (20–31.9%) and GnRH agonists (22–34.3%).

Adverse Reactions

Cetrorelix is safe and well-tolerated. Adverse events are mostly associated with localized site irritations following injection. Nausea and headache have also been reported. Cetrorelix is not associated with gonadotropin flares common to GnRH agonist treatment. The most severe complication of cetrorelix is ovarian hyperstimulation syndrome (OHSS), which occurred in 0.9–3.5% of patients receiving cetrorelix and in 3.8–11.1% of patients receiving GnRH agonists in the clinical trials. A meta-analysis established a lower incidence of OHSS with cetrorelix-treated patients compared to ganirelix.

No formal drug interaction studies have been conducted with cetrorelix. Cetrorelix use is contraindicated in women who: are allergic to cetrorelix acetate, mannitol or exogenous peptide hormones (medicines similar to cetrorelix); are allergic to GnRH or any other GnRH analogs; have kidney disease; are pregnant or think they are pregnant; or are breast-feeding.

Cetrorelix safely and effectively inhibits LH surges in women undergoing COS. It is associated with less use of adjunctive stimulation medications and fewer treatment days per cycle compared to GnRH agonists. While clinical pregnancy rates are similar with cetrorelix compared to GnRH agonists, a consistently lower trend in pregnancy rates with cetrorelix occurs. Cetrorelix offers the advantage of not causing troublesome gonadotropin flares or vasomotor symptoms associated with suppressed estradiol concentrations. The incidence of reported adverse events is few, and there is significantly less risk of OHSS development compared to other GnRH analogs.

Follitropin Therapy

Pharmacology

Follitropins are useful in anovulatory and oligovulatory patients, patients with unexplained infertility, and patients undergoing ART programs (i.e., in vitro fertilization [IVF] or intracytoplasmic sperm injection). These agents are typically used together with gonadotropin-releasing hormone (GnRH) agonists to suppress the pituitary gland and prevent premature ovulation. Follitropins are labeled for use in combination with human chorionic gonadotropin (hCG) to induce ovulation in anovulatory females without primary ovarian failure, stimulate follicular development in ovulatory females undergoing IFV, and stimulate spermatogenesis in males with hypogonadotropic hypogonadism.

Urofollitropin (uFSH) is purified follicle-stimulating hormone (FSH) obtained from the urine of postmenopausal women and biologically standardized for FSH activity. Recombinant follitropin (rFSH) alfa and recombinant follitropin beta are produced by modified Chinese Hamster Ovary (CHO) cells and are biologically standardized for FSH activity. These preparations contain no luteinizing hormone (LH) activity. To induce ovulation after follicular maturation, hCG must be administered to provide the necessary LH activity. FSH is also the primary hormone responsible for spermatogenesis, and follitropins in combination with hCG can help male patients achieve normal spermatogenesis.

The absorption rates of urofollitropin or follitropin alfa administered subcutaneously (SC) or intramuscularly (IM) do not differ significantly. However, the manufacturers recommend that these agents be administered as a subcutaneous injection except for urofollitropin use in anovulatory infertile patients, which may be administered SC or IM. Follitropin beta may be administered as either a subcutaneous or intramuscular injection except for the cartridge and pen device, which must be administered SC. There is very little significant data available that describes the metabolism and elimination of the follitropins or their use in special populations.

Clinical Efficacy

Follitropins and menotropins have been compared in both in-vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) patients and polycystic ovary syndrome (PCOS) patients. Menotropins are another type of gonadotropin used to stimulate ovulation. In IVF/ICSI patients, pregnancy rates per cycle tend to be slightly higher with follitropins than menotropins. The treatment effect is greatest when GnRH agonists are not used. However, there is no efficacy difference when GnRH agonists are used. In PCOS patients, the two agents produce equivalent pregnancy rates, although the risk of OHSS is lower with follitropins. Comparative trials assessing the efficacy of the recombinant follitropins demonstrate that there is no difference in the degree of stimulation, number of oocytes retrieved, or clinical pregnancy or delivery rates between the two agents. One

study showed that urofollitropin and follitropin beta had comparable efficacy in controlled ovarian hyperstimulation in women undergoing IVF.

Adverse Reactions/Contraindications

Ovarian hyperstimulation syndrome (OHSS) is a rare but serious side effect that may occur following follitropin administration. Other severe and rare side effects include pulmonary complications, thromboembolic events, hemoperitoneum, and adnexal torsion. Other potential reactions include dizziness, dry skin, rash, hair loss, headache, breast tenderness, injection site reactions, tachycardia, flu-like symptoms, weight gain, acne, nausea, vomiting, diarrhea, abdominal cramps, bloating, ovarian cysts, and abdominal pain. In men, the most common adverse effects associated with follitropin therapy include gynecomastia, acne, breast pain, fatigue, and injection site pain. Drug interaction studies are lacking.

Follitropins are contraindicated in women who exhibit a high FSH level indicating primary ovarian failure; uncontrolled thyroid or adrenal dysfunction; an organic intracranial lesion such as pituitary tumor; sex hormone dependent tumors of the reproductive tract and accessory organs; causes of infertility other than anovulation unless they are candidates for IVF; abnormal uterine bleeding of undetermined origin; ovarian cysts or enlargement not due to polycystic ovary syndrome; prior hypersensitivity to purified urofollitropins or recombinant FSH preparations; or pregnancy. Follitropins are contraindicated in men who exhibit: normal pituitary function, primary testicular failure, and infertility disorders other than hypogonadotropic hypogonadism.

Ganirelix

Pharmacology

Ganirelix is a gonadotropin-releasing hormone (GnRH) antagonist indicated for the prevention of premature luteinizing hormone (LH) surges in subfertile women undergoing controlled ovarian stimulation (COS) in conjunction with assisted reproductive procedures. Ganirelix is a synthetic decapeptide GnRH antagonist which competitively blocks GnRH receptors. Ganirelix competes with endogenous GnRH for receptor binding sites on gonadotropic cells of the pituitary. Binding of ganirelix to the receptor suppresses the release of the gonadotropins LH and follicle stimulating hormone (FSH), key regulatory hormones that govern ovarian growth and follicular development. The effects of ganirelix on gonadotropins are reversible. When administered subcutaneously, peak concentrations are reached within one hour, with an absolute bioavailability of 91.1%. The mean terminal half-life ranges from 13–16 hours. Ganirelix is hepatically metabolized to two primary metabolites, with elimination occurring primarily through the bile and, to a lesser extent, through the urine.

Clinical Efficacy

The efficacy of ganirelix in the treatment of COS was established in nine published trials. Ganirelix 0.25 mg/day was demonstrated to prevent LH surges and have the best clinical outcomes. Ganirelix shortened the median treatment duration by 18–21 days, reduced the amount of FSH used, and avoided the initial flare of LH that is observed with GnRH agonist therapy. A trend toward decreased pregnancy rates was seen with ganirelix compared to GnRH agonist therapy. Ongoing pregnancy rates were 20–31% for ganirelix patients and 26–36% for patients receiving GnRH agonist therapy.

Adverse Reactions

Ganirelix is well-tolerated. The most frequent adverse events include headache, abdominal pain, nausea, vaginal bleeding, and local injection site reactions. The most severe complication of ganirelix is ovarian hyperstimulation syndrome (OHSS), which occurred in approximately 2% of patients in clinical trials with ganirelix. The majority of women had mild-to-moderate forms, and only 1–2% of cases were considered severe. The incidence of OHSS is similar between ganirelix and GnRH agonists.

No formal drug interaction studies have been conducted with ganirelix. Ganirelix use is contraindicated in women who: are allergic to ganirelix acetate or any of its components; are allergic to GnRH or any other GnRH analogs; or are pregnant or think they are pregnant.

Ganirelix safely and effectively inhibits LH surges in women undergoing COS. The advantage of ganirelix over GnRH agonists is a flexible therapy with a shorter treatment option. A small but consistent trend in decreased pregnancy rates occurs with GnRH antagonists compared with GnRH agonists.

Human Chorionic Gonadotropin Therapy

Pharmacology

Human Chorionic Gonadotropin (hCG) is a gonad-stimulating polypeptide hormone secreted by the placenta that is obtained from the urine of pregnant women. The action of hCG is virtually identical to that of pituitary LH (luteinizing hormone) although hCG appears to have a small degree of FSH (follicle-stimulating hormone) activity as well. It stimulates production of gonadal steroid hormones by stimulating the interstitial cells (Leydig cells) of the testis to produce androgens and the corpus luteum of the ovary to produce progesterone. Androgen stimulation in the male leads to the development of secondary sex characteristics and may stimulate testicular descent when no anatomical impediment to descent is present. This descent is usually reversible when hCG is discontinued. During the normal menstrual cycle, LH participates with FSH in the development and maturation of the normal ovarian follicle, and the mid-cycle LH surge triggers ovulation; hCG can substitute for LH in this function.

Due to its polypeptide nature, chorionic gonadotropin is destroyed in the gastrointestinal tract, and therefore must be administered parenterally. Human Chorionic Gonadotropin must be administered intramuscularly. Following intramuscular administration, approximately 10–12% of the dose of hCG is excreted in urine within 24 hours, but detectable amounts may continue to be excreted in urine for up to 3–4 days.

Adverse Reactions/Contraindications

Principal serious adverse reactions with human Chorionic Gonadotropin include ovarian hyperstimulation, enlargement of preexisting ovarian cysts or rupture of ovarian cysts with resultant hemoperitoneum, multiple births, and arterial thromboembolism. Other adverse effects of hCG include headache, irritability, restlessness, depression, fatigue or tiredness, edema, gynecomastia, aggressive behavior, and pain at the injection site. Precocious puberty may occur in prepubertal males receiving hCG. Drug interaction studies are lacking.

Human Chorionic Gonadotropin is contraindicated in patients who exhibit: precocious puberty, prostatic carcinoma or other androgen-dependent neoplasm, or prior allergic reaction to hCG. Since androgens may cause fluid retention, hCG should be used with caution in patients with cardiac or renal disease, epilepsy, migraine, or asthma.

Luveris

Pharmacology

Lutropin alfa is recombinant human luteinizing hormone (rhLH) indicated for the stimulation of follicular development in infertile hypogonadotropic hypogonadal women with a profound luteinizing hormone (LH) deficiency defined as LH < 1.2 international units/L. Lutropin alfa is given concomitantly with recombinant human follicle-stimulating hormone (follitropin alfa, Gonal-f[®]). Lutropin alfa is classified as a gonadotropin, but is the first gonadotropin to contain only rhLH.

In the ovaries during the follicular phase, LH binds rapidly and reversibly to theca cell receptors and stimulates androgens, which act as substrates for the granulosa cell aromatase enzyme to produce estradiol. While follicle-stimulating hormone (FSH) alone can produce follicular growth, LH is needed for steroid biosynthesis and adequate follicular function and maturation. When given subcutaneously or intramuscularly, lutropin alfa follows a one-compartment pharmacokinetic model and has a terminal half-life of about 18 hours. The steady-state volume of distribution is near 10 liters, and the mean residence time is six hours, indicating a low risk of drug accumulation during daily use. Following subcutaneous administration, lutropin alfa is eliminated with a total body clearance of 2–3 L/h with less than 5% of the drug being excreted unchanged renally.

Clinical Efficacy

Six clinical trials have studied lutropin alfa in women classified as being infertile due to hypogonadotropic hypogonadism. Of the six clinical trials, three were placebo-controlled trials, two were observational studies, and one was a pilot study to determine if there is a ceiling effect of LH. Three studies are available as abstracts only. All study participants were premenopausal adult women of normal body mass index, thyroid function, and serum prolactin and testosterone levels. Another factor common to study participants was the presence of LH deficiency.

The primary endpoint in most of the trials is follicular development, defined as:

- at least one follicle with a diameter \geq 17 or 18 mm
- a preovulatory serum estradiol (E2) peak level (\geq 400 to 587 pmol/L)

- a mid-luteal serum progesterone (P4) peak level (≥ 25 to 32 nmol/L)

To complete follicular development and induce ovulation in the absence of an endogenous LH surge, a single dose of human chorionic gonadotropin (hCG) 5,000–10,000 international units is administered after the treatment period. If ovarian hyperstimulation or excessive estradiol production occurred, hCG was not given.

The European Recombinant Human LH Study Group conducted a randomized, dose-finding study in 38 women throughout Europe. All women received rhFSH 150 international units plus either 0, 25, 75, or 225 international units daily of lutropin alfa subcutaneously for up to 14 days, with the possibility of repeating for two additional cycles. This study was one of a few pivotal studies Serono, Inc. used to obtain U.S. Food and Drug Administration (FDA) approval. As a result, the FDA carefully analyzed the statistics and concluded their own results. The sponsor analysis revealed that 11% in the no therapy group, 25% in the 25 international units group, 64% in the 75 international units group, and 70% in the 225 international units group achieved follicular development ($p=0.0044$). The FDA analysis revealed 11%, 25%, 45%, and 40%, respectively ($p=0.157$) and concluded there was no difference between the groups. There were five people at risk for ovarian hyperstimulation syndrome (OHSS), and they did not receive hCG. The study authors included these people at risk for OHSS as successes, but the FDA considered these subjects failures; hence, the differences between the two analyses. There was no difference between the groups in terms of adverse events. Overall, the authors concluded that 75 international units daily is the minimum effective dose of lutropin alfa to obtain follicular development.

Overall, the primary endpoint of follicular development was met in 38–64% of patients in the placebo trials and 51.6–86.8% of patients in the observational trials. Most women who will respond to lutropin alfa will respond to 75 international units, while a small minority of them may need higher doses. When clinical pregnancy was assessed as a secondary outcome in the observational studies, up to 30% of the completed cycles resulted in pregnancy.

Adverse Reactions

The clinical trials reported an adverse event rate similar to that experienced with recombinant human FSH alone. Most adverse drug reactions were mild to moderate and self-limiting. There is a 6% risk of developing OHSS, but it does not appear that lutropin alfa causes OHSS at a greater rate than other gonadotropins.

No formal drug interaction studies have been conducted with lutropin alfa. Lutropin alfa is contraindicated in women who exhibit any of the following: prior hypersensitivity to human LH preparations or one of their excipients; primary ovarian failure; uncontrolled thyroid or adrenal dysfunction; uncontrolled organic intracranial lesion, such as a pituitary tumor; abnormal uterine bleeding of undetermined origin; ovarian cyst or enlargement of undetermined origin; sex hormone-dependent tumors of the reproductive tract and accessory organs; or pregnancy.

Menotropin Therapy

Pharmacology

Menotropins are useful in anovulatory and oligoovulatory patients, patients with unexplained infertility, and patients undergoing assisted reproductive technology programs (i.e., in vitro fertilization [IVF] or intracytoplasmic sperm injection). These agents are typically used together with gonadotropin-releasing hormone (GnRH) agonists to suppress the pituitary gland and prevent premature ovulation. Menotropins are used in combination with human chorionic gonadotropin (hCG) to induce ovulation in anovulatory females without primary ovarian failure, stimulate follicular development in ovulatory females undergoing IFV, and stimulate spermatogenesis in males with hypogonadotropic hypogonadism.

Menotropins are a purified gonadotropin preparation obtained from the urine of postmenopausal women. Menotropins are biologically standardized for hormonal activity, providing one international unit (IU) of follicle-stimulating hormone (FSH) activity for each one IU of luteinizing hormone (LH) activity. Menotropins provide the pharmacologic activity of both FSH and LH. In women without primary ovarian failure, the FSH effects are dominant, stimulating growth and maturation of ovarian follicles. Additional LH must be given, as hCG, to induce ovulation after follicular maturation. In men with pituitary hypofunction, menotropins exert primarily LH effects and induce spermatogenesis.

Clinical Efficacy

Menotropins and follitropins have been compared in both in-vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) patients and polycystic ovary syndrome (PCOS) patients. Follitropins are another type of gonadotropin used to stimulate ovulation. In IVF/ICSI patients, pregnancy rates per cycle tend to be slightly higher with follitropins than menotropins. The treatment effect is greatest when GnRH agonists are not used. However, there is no efficacy difference when GnRH agonists are used. In PCOS patients, the two agents produce equivalent pregnancy rates, although the risk of ovarian hyperstimulation syndrome (OHSS) is lower with follitropins. Comparative trials between the two available brands of menotropins are lacking.

Adverse Reactions/Contraindications

The most common side effects in women are uncomplicated ovarian enlargement, nonspecific ovarian disease, vaginal hemorrhage, abdominal pain or cramping, enlarged abdomen, headache, and nausea. Severe adverse reactions may occur and include pulmonary complications, thromboembolic events, OHSS, hemoperitoneum, and torsion of the ovaries, uterine ligaments, or uterine tubes. Injection site reactions are more common with SC than IM administration. Drug interaction studies have not been conducted.

Menotropins are contraindicated in women who exhibit: a high FSH level indicating primary ovarian failure; uncontrolled thyroid or adrenal dysfunction; an organic intracranial lesion such as pituitary tumor; sex hormone-dependent tumors of the reproductive tract and accessory organs; causes of infertility other than anovulation unless they are candidates for IVF; abnormal uterine bleeding of undetermined origin; ovarian cysts or enlargement not due to polycystic ovary syndrome; prior hypersensitivity to menotropins; or pregnancy.

Ovidrel

Pharmacology

Choriogonadotropin alfa is a recombinant DNA-derived form of human chorionic gonadotropin (hCG), which is a gonad-stimulating polypeptide hormone secreted by the placenta. The action of hCG is virtually identical to that of pituitary LH (luteinizing hormone), although hCG appears to have a small degree of FSH (follicle-stimulating hormone) activity as well. It stimulates production of gonadal steroid hormones by stimulating the interstitial cells (Leydig cells) of the testis to produce androgens and the corpus luteum of the ovary to produce progesterone. Androgen stimulation in the male leads to the development of secondary sex characteristics and may stimulate testicular descent when no anatomical impediment to descent is present. This descent is usually reversible when hCG is discontinued. During the normal menstrual cycle, LH participates with FSH in the development and maturation of the normal ovarian follicle, and the mid-cycle LH surge triggers ovulation; hCG can substitute for LH in this function.

Due to its polypeptide nature, chorionic gonadotropin is destroyed in the gastrointestinal tract and, therefore, must be administered parenterally. Choriogonadotropin alfa must be administered subcutaneously. One-tenth of the dose of choriogonadotropin alfa is excreted in the urine.

Adverse Reactions/Contraindications

Principal serious adverse reactions with choriogonadotropin alfa include ovarian hyperstimulation; enlargement of preexisting ovarian cysts or rupture of ovarian cysts with resultant hemoperitoneum; multiple births; and arterial thromboembolism. Other adverse effects of choriogonadotropin alfa include injection site disorders (i.e., pain, bruising), abdominal pain, nausea, and vomiting. Drug interaction studies are lacking.

Choriogonadotropin alfa is contraindicated in women who exhibit: primary ovarian failure; uncontrolled thyroid or adrenal dysfunction; an uncontrolled organic intracranial lesion such as pituitary tumor; sex hormone dependent tumors of the reproductive tract and accessory organs; abnormal uterine bleeding of undetermined origin; ovarian cyst or enlargement of undetermined origin; prior hypersensitivity to hCG preparations or one of their excipients; or pregnancy.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

If benefit coverage is available for injectable fertility medications under the Pharmacy Benefit plan, the following may be considered for coverage:

HCPCS Codes	Description
J0725	Injection, chorionic gonadatropin, per 1,000 USP units
J3355	Injection, Urofollitropin, 75 IU
J3490 [†]	Unclassified drugs
J3590 ^{††}	Unclassified biologics
S0122	Injection, Menotropins , 75 IU
S0126	Injection, Follitropin alpha, 75 IU
S0128	Injection, Follitropin beta 75 IU
S0132	Injection, ganirelix acetate, 250 mcg

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

††Note: May be considered for coverage when used to report Luveris.

ICD-9-CM Diagnosis Codes	Description
256.8	Other ovarian dysfunction
257.2	Other testicular hypofunction
606.0-606.9	Infertility, male
628.0-628.9	Infertility, female
752.51	Undescended testis

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	1/15/2008	7002	Choriogonadotropin Alfa (Ovidrel®)
Great-West Healthcare	1/2007	P05.103.1	Infertility
CIGNA HealthCare	1/15/2008	5019	Lutropin Alfa (Luveris®)
Great-West Healthcare	1/2007	P05.103.1	Infertility

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