



CIGNA PHARMACY COVERAGE POLICY

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

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Subject Follitropin Therapy

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Hyperlink to Related Coverage Positions Infertility Services

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant'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 participant'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 participant'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 group 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 ©2010 CIGNA

Coverage Policy

Follistim[®] AQ is a preferred brand follitropin therapy product.

Non-preferred brand follitropin therapy (Bravelle[®] and Gonal-F[®]) will only be covered when there is failure, contraindication, or intolerance to Follistim[®] AQ.

Note: Injectable fertility medications are specifically excluded under most CIGNA pharmacy benefit plans. Please refer to the applicable benefit plan document to determine benefit availability and the terms and conditions of coverage.

If coverage is available for injectable fertility medications, then:

CIGNA covers follitropin therapy as medically necessary when used in combination with hCG (human Chorionic Gonadotropin) therapy for either of the following:

- ovulation stimulation in females for either of the following:
 - as part of Assisted Reproductive Technology (ART) program
 - oligoovulatory or anovulatory infertile individuals in whom the cause of infertility is functional and not due to primary ovarian failure
- spermatogenesis stimulation in males for primary or secondary hypogonadotropic hypogonadism not due to primary testicular failure

FDA Approved Indications

Follistim AQ

Follistim AQ (follitropin beta injection) is indicated for the development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program. Follistim AQ is also indicated for the induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure.

Bravelle

Bravelle is indicated for ovulation induction in patients who have previously received pituitary suppression.

Gonal-f

Gonal-f (follitropin alfa injection) is indicated for the induction of ovulation and pregnancy in the oligo-anovulatory infertile patient 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 patient participating in an ART program.

FDA Recommended Dosing

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. Patients treated for ovulation induction generally require longer treatment and lower doses, while patients undergoing assisted reproductive technology programs generally receive higher doses for approximately 10 days. Patients treated with follitropins require extensive monitoring.

Drug Availability

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.

Follistim AQ

Two-vial package containing 1-10mL lyophilized multiple dose vial containing: 10,000 USP Units chorionic gonadotropin per vial.

Bravelle

Single dose vial containing 82.5 IU of FSH, to deliver 75 IU FSH after reconstitution.

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, 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.

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.

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.

General Background

Pharmacology

Follitropins are useful in anovulatory and oligoovulatory 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 IVF, 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.

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
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J3355	Injection, Urofollitropin, 75 IU
S0126	Injection, Follitropin alpha, 75 IU
S0128	Injection, Follitropin beta 75 IU

ICD-9-CM Diagnosis Codes	Description
256.8	Other ovarian dysfunction
257.2	Other testicular hypofunction
628.0	Female infertility associated with anovulation

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