LifeWise
Health Plan of Washington

PHARMACY / MEDICAL POLICY – 5.01.610

Pharmacologic Treatment in Assisted Reproduction

Effective Date:	**Jan 3, 2025***	RELATED MEDICAL POLICIES:
Last Revised:	Sept. 10, 2024	4.02.503 Infertility and Reproductive Services
Replaces:	N/A	
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Introduction

Assisted reproduction supports problems with the reproductive system that affects the ability to conceive. Different types of reproductive problems affect men and women, but the end result is the inability to conceive or complete a pregnancy. There are many reasons for infertility and drug options vary depending on the cause of infertility and type of infertility treatment required. Even though drug treatment exists, it does not mean it is covered; the member's contract determines this. This policy describes when drugs used in assisted reproduction may be considered medically necessary if covered by the member's contract.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Chorionic Gonadotropins	
Brand Chorionic Gonadotropin, IM **Managed under Pharmacy and Medical benefit**	**Brand Chorionic Gonadotropin may be considered medically necessary for use in assisted reproduction when the following criteria are met:** • The individual has tried and failed or had intolerance to use of Novarel (chorionic gonadotropin) or Ovidrel (choriogonadotropin alfa) **Note:** This policy does not apply to the use of chorionic gonadotropin for the treatment of non-assisted reproduction related conditions including but not limited to prepubertal cryptorchidism and hypogonadotropic hypogonadism.
Pregnyl (chorionic gonadotropin), IM **Managed under Pharmacy and Medical benefit**	**Pregnyl (chorionic gonadotropin) may be considered medically necessary for use in assisted reproduction when the following criteria are met:** • The individual has tried and failed or had intolerance to use of Novarel (chorionic gonadotropin) or Ovidrel (choriogonadotropin alfa) **Note:** This policy does not apply to the use of chorionic gonadotropin for the treatment of non-assisted reproduction related conditions including but not limited to prepubertal cryptorchidism and hypogonadotropic hypogonadism.
Follitropins	
Follistim AQ (follitropin beta), SC **Managed under Pharmacy and Medical benefit**	**Follistim AQ (follitropin beta) may be considered medically necessary for use in assisted reproduction when the following criteria are met:** • The individual has tried and failed or had intolerance to use of Gonal-f (follitropin alfa) or Gonal-f RFF (follitropin alfa) **Note:** This policy does not apply to the use of Follistim AQ (follitropin beta) for the treatment of non-assisted reproduction related conditions.
Gonadotropin Releasing Hormone (GnRH) Antagonists	
Brand Ganirelix, SC **Managed under Pharmacy and Medical benefit**	**Brand Ganirelix may be considered medically necessary for use in assisted reproduction when the following criteria are met:** • The individual has tried and failed or had intolerance to the following: ○ Generic cetrorelix or Cetrotide (cetrorelix)

Drug	Medical Necessity
	AND ○ Generic ganirelix or Fyremadel (ganirelix) **Note:** This policy does not apply to the use of brand Ganirelix for the treatment of non-assisted reproduction related conditions.
Generic ganirelix, SC **Fyremadel (ganirelix), SC** **Managed under Pharmacy and Medical benefit**	**Generic ganirelix and Fyremadel (ganirelix) may be considered medically necessary for use in assisted reproduction when the following criteria are met:** • The individual has tried and failed or had intolerance to use of generic cetrorelix or brand Cetrotide (cetrorelix) **Note:** This policy does not apply to the use of generic ganirelix or Fyremadel (ganirelix) for the treatment of non-assisted reproduction related conditions.

Drug	Not Medically Necessary
As listed	**All other uses of the drugs listed for assisted reproduction are considered not medically necessary.** **Note:** This policy does not apply to the use of drugs listed for the treatment of non-assisted reproduction related conditions.

Length of Approval	
Approval	**Criteria**
Initial authorization	**All drugs listed in policy may be approved up to 12 months.**
Re-authorization criteria	**Future re-authorization of all drugs listed in policy may be approved up to 12 months as long as the drug-specific coverage criteria are met.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis and medication history

Coding

Code	Description
HCPCS	
J0725	Injection, chorionic gonadotropin, per 1,000 USP units
S0128	Injection, follitropin beta, 75 IU
S0132	Injection, ganirelix acetate, 250 mcg (Ganirelix, Fyremadel)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Note: Many benefit plans exclude assisted reproduction. Please refer to the applicable benefit plan to determine benefit availability and the terms, conditions, and limitations of coverage.

Benefit Application

Pharmacy / Medical Benefit

Brand Chorionic Gonadotropin, brand Ganirelix, Follistim AQ (follitropin beta), Fyremadel (ganirelix), generic ganirelix, and Pregnyl (chorionic gonadotropin) are managed through both the pharmacy and medical benefit.

Evidence Review

Background

Infertility is defined as the inability to conceive after ≥1 year of unprotected intercourse. A total of 6.7% of women ages 15-44 years in the US are infertile and 12.1% have impaired fecundity,

defined as difficulty getting pregnant or carrying a pregnancy to term. Assisted reproduction services have been used by 7.3 million US women or 12% of women ages 15-44 years.

Infertility has a number of different causes including combined factors (40%), male factors (26%-30%), unexplained causes (28%), ovulatory dysfunction (21%-25%), tubal factors (14%-20%), and other factors (cervical, peritoneal or uterine factors or abnormalities) (10%-13%).

- Ovulation disorders can be caused by polycystic ovary syndrome (PCOS), diminished ovarian reserve, functional hypothalamic amenorrhea, improper functioning of the hypothalamus and pituitary glands, premature ovarian insufficiency, and menopause. Of these, the most common is PCOS which accounts for 80% of infertility due to anovulation. Individuals with PCOS have normal or low follicle stimulating hormone (FSH) and mildly increased luteinizing hormone (LH).
- Fallopian tube obstruction or tubal occlusion can be caused by a history of pelvic infection, ruptured appendicitis, history of gonorrhea or chlamydia, endometriosis, or a history of abdominal surgery.
- Abnormal uterine contour or other anatomic abnormalities such as fibroids can also cause infertility.
- Other factors which decrease fertility include increasing age, smoking, excessive alcohol use, extreme weight gain or loss, and excessive stress. Functional hypothalamic amenorrhea (FHA) is defined as chronic anovulation without identifiable cause associated with stress, weight loss, and/or excessive exercise. Hypogonadotropic amenorrhea (HA) involves low or absent gonadotropin releasing hormone (GnRH) secretion due to FHA, congenital or iatrogenic causes, or pituitary adenomas.

Standards of Practice

The following outlines the steps in the process of ovulation induction.

- Initial ovulation induction typically occurs with oral agents such as clomiphene or letrozole.
- Clomiphene resistance or failure to ovulate on clomiphene occurs in approximately 20% of women. Of those who ovulate on clomiphene, 50% do not become pregnant within 6 months and are considered clomiphene failures. In both groups of individuals, second-line treatment may include gonadotropins or laparoscopic ovarian diathermy. During treatment, follicle growth is regularly monitored via serial transvaginal ultrasounds every 1-3 days and serum estradiol is assessed daily.

- If individuals are treated with gonadotropins, these drugs are administered for 7-12 days at the beginning of a cycle. Initially, low dose treatment is recommended (37.5-75 IU/d) to decrease risk of multiple pregnancy. This dose may be increased based on response to therapy. Combination FSH and LH products are recommended for individuals with hypogonadotropic amenorrhea such as human menopausal gonadotropin or low-dose human menopausal gonadotropin. In individuals with PCOS, only FSH is required. Of note, LH doesn't appear harmful and combination products such as human menopausal gonadotropin are often given in PCOS.
- In both hypogonadotropic amenorrhea and PCOS, human chorionic gonadotropin (hCG; 5,000-10,000 units purified hCG or 250 mcg recombinant) is administered after development of a mature follicle to stimulate ovum release. In PCOS, a GnRH agonist (leuprolide 500 mcg SC or triptorelin 200 mcg SC) with progesterone supplementation during the luteal phase is an alternative to hCG if a GnRH agonist was not given earlier to prevent LH surge. Additionally, progesterone supplementation with low-dose hCG every 3-4 days are recommended in individuals with hypogonadotropic amenorrhea to support normal luteal functions.

The American Society of Reproductive Medicine, European Society of Endocrinology and the Pediatric Endocrinology Society published guidelines on the diagnosis and treatment of FHA in 2018. The guidelines recommend first correcting any energy imbalance by increasing calorie consumption, improving nutrition, or decreasing exercise. If individuals wish to conceive, GnRH is recommended first line; however, this is not available in the U.S. Gonadotropin therapy is recommended second-line for ovulation induction.

The following outlines a general overview of the ART process:

- Protocols for *in vitro* fertilization (IVF) typically involve suppression of gonadotropin release to prevent premature LH surges. This allows greater retrieval of oocytes and higher pregnancy rates. Both GnRH agonists and antagonists are used for this purpose in IVF protocols.
- Follicle growth is stimulated via gonadotropins as described above.
- This is followed by hCG or GnRH agonists that trigger the final maturation of oocytes in preparation for retrieval and fertilization. GnRH agonists can only be used for this purpose if GnRH antagonists at standard doses were used to suppress gonadotropin release and prevent premature LH surges.
- Eggs are collected typically using transvaginal ultrasound as a guide.

- Fertilization occurs either via IVF or intracytoplasmic sperm injection. This is followed by laboratory procedures for embryo culture.
- Embryos are placed in the uterus followed by luteal phase support such as progesterone, estrogen, or hCG.

Summary of Evidence

Meaningful Differences in Efficacy in Clinical Trials

Specialty fertility drugs are used in the process of ovulation induction as well as in the setting of assisted reproductive technology such as IVF or intracytoplasmic sperm injection. A total of four guidelines and six meta-analyses pertaining to the efficacy of specialty fertility drugs were identified. In the setting of infertility due to PCOS, the American Society of Reproductive Medicine and the World Health Organization guidelines recommend gonadotropins as second-line treatment for ovulation induction following non-specialty first-line agents such as clomiphene and letrozole. Both guidelines recommend IVF as third-line treatment in this setting.

All guidelines and meta-analyses found no difference or insufficient evidence of a difference in the primary efficacy measures of live birth rate or pregnancy between gonadotropins in the setting of ovulation induction and IVF. Specifically, no difference was found between urinary or recombinant FSH or between FSH products and hMG. The World Health Organization guidelines recommend that the choice of gonadotropin is based on cost of therapy as no difference in effectiveness has been identified. A total of two meta-analyses assessed GnRH antagonist and agonist protocols in IVF both found no differences in the live birth rate. Finally, a single meta-analysis compared GnRH agonists and hCG for oocyte triggering found no difference in the live birth rate.

Differences in Safety Profiles

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening complication of fertility drugs and consists of an increase in vascular permeability resulting in a rapid accumulation of fluid in the peritoneal cavity, thorax, and pericardium. The American Society of Reproductive Medicine and World Health Organization guidelines as well as three meta-analyses found decreased risk of OHSS with GnRH antagonists compared to GnRH agonists. Therefore, both guidelines recommend the use of GnRH antagonists protocols in IVF.

Additionally, a meta-analysis found the risk of OHSS was decreased with GnRH agonists compared to hCG in the setting oocyte triggering.

The risk of cancer following fertility treatment has been assessed in a guideline and meta-analysis, both limited by low-quality study data. The American Society of Reproductive Medicine guideline found a small increase in absolute risk of borderline ovarian tumors following fertility treatment; however, there was insufficient evidence of increased risk with any particular fertility drug. There was no evidence of increased cancer risk with any other cancer type. The meta-analysis found inconclusive evidence of endometrial cancer risk with gonadotropins; no other specialty drugs were evaluated. Lastly, a meta-analysis found no increased risk of cardiovascular (CV) outcome with exposure to fertility drugs.

2021 Update

Reviewed prescribing information for all drugs listed in policy and market availability for products. No new evidence was identified that would change coverage criteria. Changed policy title from Pharmacologic Treatment of Infertility to Pharmacologic Treatment in Assisted Reproduction to further align with the member benefit booklet and contract language. Updated policy criteria for all drugs from "treatment of infertility" to "use in assisted reproduction" to sync with policy title change.

2022 Update

Reviewed prescribing information for all drugs listed in policy. No new evidence was identified that would change coverage criteria.

2023 Update

Reviewed prescribing information for all drugs listed in policy. Bravelle (urofollitropin) was removed from the policy as it has been discontinued.

2024 Update

Reviewed prescribing information for all drugs listed in policy. No new evidence was identified that would change coverage criteria.

References

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History

Date	Comments
07/01/20	New policy, approved June 25, 2020, effective October 2, 2020, following 90-day provider notification. Add to Prescription Drug section. Bravelle (urofollitropin), brand Chorionic Gonadotropin, Follistim AQ, and Pregnyl (chorionic gonadotropin) may be considered medically necessary for the treatment of infertility when criteria are met. Coverage criteria for Bravelle (urofollitropin), brand Chorionic Gonadotropin, Follistim AQ, and Pregnyl (chorionic gonadotropin) becomes effective for dates of service on or after October 2, 2020.
02/01/21	Interim Review, approved January 21, 2021. Added Follistim AQ (follitropin beta) to require coverage review under the Medical Benefit. Added HCPC code S0128 for Follistim.
01/01/22	Annual Review, approved December 2, 2021. Changed policy title from Pharmacologic Treatment of Infertility to Pharmacologic Treatment in Assisted Reproduction. Updated policy criteria for all drugs from “treatment of infertility” to “use in assisted reproduction”.
01/01/23	Annual Review, approved December 23, 2022. No changes to policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization.
12/01/23	Annual Review, approved November 20, 2023. Bravelle (urofollitropin) was removed from the policy as it has been discontinued. Removed HCPCS code J3355 as Bravelle (urofollitropin) has been discontinued.
09/01/24	Annual Review, approved August 26, 2024. No changes to policy statements.

Date	Comments
10/01/24	Interim Review, approved September 10, 2024. The following policy changes are effective January 3, 2025, following a 90-day provider notification. Added coverage criteria for brand Ganirelix, generic ganirelix, and Fyremadel (ganirelix). Added S0132 to support criteria changes.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.