

# Pharmacy Policy Bulletin

## Fertility – Select Healthcare Reform Plans

**Number:** J-0951

**Category:** Prior Authorization

**Line(s) of Business:**

- Commercial
- Healthcare Reform
- Medicare

**Benefit(s):**

**Prior Authorization (1., 2., or 3.)**

- 1.** Fertility Agent Oral = Yes w/ Prior Authorization (clomiphene citrate Serophene)
- 2.** Fertility Agent Oral (Vaginal) = Yes w/ Prior Authorization (Crinone, Endometrin, First-Progesterone VGSf)
- 3.** Fertility Agent Injectable = Yes w/ Prior Authorization (Follistim AQ, Gonal-F, Gonal RFF, Gonal RFF Redi-Ject, Menopur, Ovidrel, Pregnyl (chorionic gonadotropin), Novarel (chorionic gonadotropin), Cetrotide, Ganirelix acetate)

**Region(s):**

- All
- Delaware
- New York
- Pennsylvania
- West Virginia

**Additional Restriction(s):**

Does not apply to Pennsylvania Healthcare Reform *Individual* members (see J-472).

**Drugs Products**

Clomiphene

- clomiphene citrate
- Serophene (clomiphene citrate)

Gonadotropins

- *Follicle Stimulating Hormone (FSH)*
  - Follistim AQ (follitropin beta solution for injection)
  - Gonal-F, RFF, RFF Redi-Ject (follitropin alfa solution for injection)
- *Menotropins*
  - Menopur (menotropins for injection)
- *Human Chorionic Gonadotropin (HCG)*
  - Ovidrel (choriogonadotropin alfa (hamster) solution for injection)
  - Pregnyl (chorionic gonadotropin for injection, USP)
  - Novarel (chorionic gonadotropin for injection, USP)

Gonadotropin releasing hormone antagonists (GnRAs)

- Cetrotide (cetorelix)
- Ganirelix acetate injection

Hormones

- Crinone (progesterone gel)
- Endometrin (progesterone vaginal insert)
- First-Progesterone VGS (progesterone vaginal suppository)

**FDA-Approved Indications:**

<b>Product</b>	<b>FDA-Approved Indications</b>
Cetrotide (cetorelix)	<ul style="list-style-type: none"><li>• Assisted reproductive technology</li><li>• Ovulation induction</li></ul>
clomiphene citrate	<ul style="list-style-type: none"><li>• Ovulation induction</li></ul>

Crinone (progesterone)	<ul style="list-style-type: none"> <li>• Assisted reproductive technology</li> <li>• Secondary physiologic amenorrhea</li> </ul>
Endometrin (progesterone)	<ul style="list-style-type: none"> <li>• Assisted reproductive technology</li> </ul>
Follistim AQ (follitropin beta)	<ul style="list-style-type: none"> <li>• Assisted reproductive technology</li> <li>• Male hypogonadotropic hypogonadism, not associated with testicular failure</li> <li>• Ovulation induction</li> </ul>
Ganirelix acetate	<ul style="list-style-type: none"> <li>• Assisted reproductive technology</li> </ul>
Gonal-F (follitropin alfa)	<ul style="list-style-type: none"> <li>• Assisted reproductive technology</li> <li>• Male hypogonadotropic hypogonadism, not associated with testicular failure</li> <li>• Ovulation induction</li> </ul>
Menopur (menotropins)	<ul style="list-style-type: none"> <li>• Assisted reproductive technology</li> </ul>
Novarel (chorionic gonadotropin)	<ul style="list-style-type: none"> <li>• Assisted reproductive technology</li> <li>• Male cryptorchidism</li> <li>• Male hypogonadotropic hypogonadism</li> <li>• Ovulation induction</li> </ul>
Ovidrel (chorionic gonadotropin)	<ul style="list-style-type: none"> <li>• Assisted reproductive technology</li> <li>• Ovulation induction</li> </ul>
Pregnyl (chorionic gonadotropin)	<ul style="list-style-type: none"> <li>• Assisted reproductive technology</li> <li>• Male cryptorchidism</li> <li>• Male hypogonadotropic hypogonadism</li> <li>• Ovulation induction</li> </ul>
Serophene (clomiphene citrate)	<ul style="list-style-type: none"> <li>• Ovulation induction</li> </ul>

**Background:**

Infertility is the medically documented, diminished ability to conceive or induce conception. Infertility is defined as inability to conceive after 12 months of regular unprotected intercourse (or 6 months for women over the age of 35). The cause of infertility can be a female factor, a male factor, or a combination of both.

Assisted Reproductive Technology (ART) encompasses all of the following techniques (not an all-inclusive list):

- Artificial Insemination (AI)
- In Vitro Fertilization (IVF)
- Gamete Intrafallopian Transfer (GIFT)
- Zygote Intrafallopian Transfer (ZIFT)
- Tubal Embryo Transfer (TET)
- Frozen Embryo Transfer (FET)
- Peritoneal Ovum Sperm Transfer

ART refers to the technology used to help achieve pregnancy (retrieval/transfer). This can include medications to support early pregnancy.

ART services are generally excluded from standard medical-surgical contracts and are not eligible for reimbursement. However, all medical, surgical and diagnostic services performed to diagnose and treat infertility are generally covered, unless the individual member's contract contains an exclusion pertaining to the diagnosis and treatment of infertility.

According to the American Society for Reproductive Medicine's (ASRM) Evidence-based treatments for couples with unexplained infertility treatment guidelines, for most couples with unexplained infertility, the best initial therapy is a course (typically 3 or 4 cycles of ovarian stimulation (with oral medications) and intrauterine insemination (OS-IUI) followed by in vitro fertilization for those unsuccessful with OS-IUI treatments. If a particular fertility treatment is going to be successful, it should be effective within 3 cycles. One cycle means one ovulation cycle, which would be about one month.

When used in the Approval Criteria section, the terms "male" and "female" refer to biological sex, not gender. A male patient possesses a male reproductive system, and a female patient possesses a female reproductive system.

For the purposes of this policy, "intersex" patients may have male and female reproductive organs and may qualify for coverage under either sex.

Clomiphene

- Clomiphene is a selective estrogen receptor modulator that competes with circulating estrogens for estrogen-binding sites, thus blocking the normal negative feedback of endogenous estrogens. This action permits normal release of gonadotropin releasing hormone causing stimulation of follicle stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH stimulate the ovaries to develop follicles with some oocytes developing into mature follicles.

#### Gonadotropins

- Follicle stimulating hormone (FSH) mimics endogenous FSH which is required for normal growth and maturation of follicles and production of gonadal steroids. To mimic the endogenous luteinizing surge, human chorionic gonadotropin is administered with products containing only FSH.
- Luteinizing hormone (LH) stimulates the androgen secretion during the ovarian follicular phase. Androgens serve as a substrate for an aromatase enzyme which ultimately results in production of estradiol. Estradiol supports FSH induced follicular development. LH is responsible for final maturation and subsequent ovulation of the egg, aids in the development of the uterine lining to facilitate implantation, and maintaining pregnancy during the early stages.
- Menotropins are purified products containing human FSH and LH which mimic the action of endogenous gonadotropins that regulate ovarian and testicular function. FSH activity is much higher compared to LH activity in menotropins.
- Human chorionic gonadotropins (HCGs) stimulate the production of gonadal steroid hormones by stimulating the interstitial cells of the testis to produce androgens and the corpus luteum of the ovary to produce progesterone.
- The primary physiological effect of gonadotropins is to promote gametogenesis and/or gonadal steroid production. Receptors for gonadotropins are expressed in the ovary on a variety of cells as well as in the testes. In the male, gonadotropins stimulate the de novo synthesis of testosterone and play a role in spermatogenesis. In females, the gonadotropins produce estrogen, promote growth of the developing follicles, induce ovulation and stimulate progesterone synthesis.

#### Progesterones

- Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain a pregnancy.
- First-Progesterone VGS is compounded kit with established safety that has been on the market since 2005. It is not FDA-approved but is used off-label in multiple infertility conditions.
- Endometrin has a limitation of use that efficacy in women 35 years of age and older has not been clearly established.

## Approval Criteria

### I. Approval Criteria

#### A. clomiphene citrate or Serophene

When a benefit, coverage of clomiphene citrate or Serophene may be approved when all of the following criteria are met **(1., 2., and 3.):**

1. The member is female.
2. The member has a diagnosis of infertility.
3. The member will not be using the product with assisted reproductive technology (ART).

#### B. Follistim AQ or Gonal-F

When a benefit, coverage of Follistim AQ or Gonal-F may be approved if all of the following criteria are met **(1. and 2.):**

1. The member meets one (1) of the following criteria **(a. or b.):**
  - a. The member is female and meets all of the following criteria **(i. and ii.):**
    - i. The member has a diagnosis of infertility.
    - ii. If the member is using the product as part of an ART treatment program, the member has the associated ART/IVF medical benefit.
  - b. The member is male and meets all of the following criteria **(i. and ii.):**
    - i. The member has a diagnosis of primary or secondary hypogonadotropic hypogonadism.
    - ii. Infertility is not caused by primary testicular failure.
2. If the request is for Gonal-F the member has experienced therapeutic failure, contraindication, or intolerance to plan-preferred Follistim AQ.

#### C. Ganirelix acetate, Menopur, or Endometrin

When a benefit, coverage of Ganirelix acetate, Menopur, or Endometrin may be approved when all of the following criteria are met **(1., 2., 3., and 4.):**

1. The member is female.
2. The member has a diagnosis of infertility.

3. The member is using the product as part of an ART treatment program.
4. The member has the associated ART/IVF medical benefit.

**D. Cetrotide or Ovidrel**

When a benefit, coverage of Cetrotide or Ovidrel may be approved when all of the following criteria are met **(1., 2., and 3.)**:

1. The member is female.
2. The member has a diagnosis of infertility.
3. If the member is using the product with ART, the member has the associated ART/IVF benefit.

**E. Novarel (chorionic gonadotropin) or Pregnyl (chorionic gonadotropin)**

When a benefit, coverage of Novarel (chorionic gonadotropin) or Pregnyl (chorionic gonadotropin) may be approved when one (1) of the following criteria is met **(1. or 2.)**:

1. The member is female and meets all of the following criteria **(a. and b.)**:
  - a. The member has a diagnosis of infertility.
  - b. If the member is using the product as part of an ART treatment program, the member has the associated ART/IVF benefit.
2. The member is male and meets one of the following criteria **(a. or b.)**:
  - a. The member is an adult and meets all of the following criteria **(i. and ii.)**:
    - i. The member has a diagnosis of hypogonadotropic hypogonadism.
    - ii. Hypogonadotropic hypogonadism is secondary to pituitary deficiency.
  - b. The member is prepubescent and meets all of the following criteria **(i. and ii.)**:
    - i. The member has a diagnosis of cryptorchidism.
    - ii. Cryptorchidism is not caused by anatomical obstruction.

**F. Crinone**

When a benefit, coverage of Crinone may be approved when one (1) of the following criteria is met **(1. or 2.)**:

1. The member is female and meets all of the following criteria **(a., b., and c.)**:
  - a. The member has a diagnosis of infertility.
  - b. The member is using Crinone as part of an ART treatment program.
  - c. The member has the associated ART/IVF benefit.
2. The member is female and has a diagnosis of secondary amenorrhea.

#### **G. First-Progesterone VGS**

When a benefit, coverage of First-Progesterone VGS may be approved when the following criterion is met **(1.)**:

1. The member is female and is using the product for one (1) of the following **(a., b., or c.)**:
  - a. The treatment of infertility or the prevention of early pregnancy failure (e.g. miscarriage) in women with corpus luteum insufficiency.
  - b. To supplement progesterone in women with infertility and corpus luteum insufficiency as part of an ART treatment program.
  - c. Prophylaxis for preterm delivery.
- II. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

#### **Limitations of Coverage**

- I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.
- II. For HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

#### **Authorization Duration**

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**Select HCR Plans:**

**I. Male or Female Infertility (including hyogonadotropic hypogonadism)**

**A.** If approved, up to a 6 month authorization may be granted.

- 1.** Total cumulative authorizations for treatment of infertility not to exceed 24 months of duration.

**II. Secondary amenorrhea**

**A.** If approved, up to a 1 month authorization may be granted.

**III. Cryptorchidism**

**A.** If approved, up to a 6 week authorization may be granted.

**Automatic Approval Criteria**

None

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**References:**

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