envolve Pharmacy Solutions

# Clinical Policy: Infertility and Fertility Preservation

Reference Number: ERX.SPA.283
Effective Date: 12.01.18
Last Review Date: 11.21
Line of Business: Commercial, Medicaid

Revision Log

**See Important Reminder at the end of this policy for important regulatory and legal information.**

**Description**
Gonadotropins requiring prior authorization are: menotropins (Menopur®); follitropin alfa, recombinant (Gonal-f® multi-dose, Gonal-f® RFF, Gonal-f® RFF Redi-ject); follitropin beta, recombinant (Follistim® AQ); urofollitropin (Bravelle®); choriogonadotropin alfa (Ovidrel®); and human chorionic gonadotropin (hCG; generic, Novarel®, Pregnyl®).

Gonadotropin-releasing hormone (GnRH) antagonists requiring prior authorization are: ganirelix acetate and cetrorelix (Cetrotide®).

**FDA Approved Indication(s)**

| Drugs | | | Indications, Female | | Indications, Male | |
|---|---|---|---|---|---|---|
| **Drug Name** | **Brand Name** | **Drug Class** | **OI** | **ART** | **HH** | **Prepubertal Cryptorchidism** |
| Menotropin | Menopur | Gonadotropin (hMG - FSH and LH) | x | x | | |
| Follitropin alfa, recombinant | Gonal-f | Gonadotropin (FSH) | x | x | x | |
| Follitropin alfa, recombinant | Gonal-f RFF | Gonadotropin (FHS) | x | x | | |
| Follitropin alfa, recombinant | Gonal-f RFF Redi-ject | Gonadotropin (FSH) | x | x | | |
| Follitropin beta, recombinant | Follistim-AQ | Gonadotropin (FSH) | x | x | x | |
| Urofollitropin | Bravelle | Gonadotropin (FSH) | x | x | | |
| Ganirelix acetate | N/A | GnRH antagonist | x | x | | |
| Cetrorelix | Cetrotide | GnRH antagonist | x | x | | |
| Choriogonadotropin alfa | Ovidrel | Gonadotropin (hCG) | x | x | | |
| Human chorionic gonadotropin | Novarel | Gonadotropin (hCG) | x | x | x | x |
| Human chorionic gonadotropin | Pregnyl | Gonadotropin (hCG) | x | x | x | x |

*Abbreviations: ART: assisted reproductive technology; GnRH: gonadotropin-releasing hormone; HH: hypogonadotropic hypogonadism; hCG: human chorionic gonadotropin (produced by the placenta after implantation; hMG: human menopausal gonadotropin (combination of LH and FSH); OI: ovulation induction*

- Menopur is indicated for:
  - Development of multiple follicles and pregnancy in ovulatory women as part of an assisted reproductive technology (ART) cycle.

- Gonal-f is indicated for:
  - Induction of ovulation and pregnancy in the anovulatory infertile patient in whom the cause of infertility is functional and not due to primary ovarian failure (known as primary ovarian insufficiency; POI).
  - Development of multiple follicles in the ovulatory patient participating in an ART program.

  - Induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism (HH) in whom the cause of infertility is not due to primary testicular failure (i.e. primary hypogonadism).

- Gonal-F RFF and Gonal-f RFF Redi-ject are indicated for:
  - Induction of ovulation and pregnancy in oligo-anovulatory women in whom the cause of infertility is functional and not due to POI.
  - Development of multiple follicles in ovulatory women as part of an ART cycle/program.

- Follistim AQ is indicated for:
  - Induction of ovulation and pregnancy in anovulatory infertile women in whom the cause of infertility is functional and not due to POI.
  - Pregnancy in normal ovulatory women undergoing controlled ovarian stimulation as part of an in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycle [ART cycle].
  - Induction of spermatogenesis in men with primary and secondary HH in whom the cause of infertility is not due to primary testicular failure.

- Bravelle is indicated for:
  - Induction of ovulation in women who have previously received pituitary suppression.
  - Development of multiple follicles as part of an ART cycle in ovulatory women who have previously received pituitary suppression.

- Ganirelix is indicated for:
  - Inhibition of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian hyperstimulation (COH).

- Cetrotide is indicated for:
  - The inhibition of premature LH surges in women undergoing COH.

- Ovidrel is indicated for:
  - 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 (FSH) as part of an ART program such as IVF and embryo transfer.
  - Induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to POI.

- Novarel and Pregnyl are indicated for:
  - Prepubertal cryptorchidism not due to anatomic obstruction.
  - Selected cases of HH 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 POI, and who has been appropriately pretreated with human menotropins.

**Policy/Criteria**
*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

*Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.*

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Menopur, Gonal-f, Gonal-f RFF, Gonal f RFF Redi-ject, Follistim-AQ, Bravelle, ganirelex acetate, Cetrotide, Ovidrel, Novarel, and Pregnyl are **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Infertility, Female** (must meet all)**:**

1. Diagnosis of infertility;
2. Age ≥ 18 years;
3. Prescribed by or in consultation with a reproductive endocrinologist;
4. The requested drug(s) is for one of the following (a or b):
   a. OI, and all of the following (i and ii):
      i. Member has been diagnosed with an ovulatory disorder;
      ii. If the ovulatory disorder is secondary to hyperprolactinemia, failure of dopamine agonist treatment, unless contraindicated or clinically significant adverse effects are experienced (*see Appendix B*);
   b. ART, and both of the following (i and ii):
      i. If infertility is secondary to an ovulatory disorder, member has failed OI or is not a candidate for OI (e.g., member has been diagnosed with tubal blockage, uterine cavity abnormality, diminished ovarian reserve; member's partner has been diagnosed with severe male factor infertility).
      ii. If unexplained infertility, failure of at least 3 cycles of clomiphene citrate or letrozole (*see Appendix B*) combined with intrauterine insemination, unless contraindicated or clinically significant adverse effects are experienced;
5. Member does not have POI.

**Approval duration: 30 days or up to specified trial duration if available**

**B. Fertility Preservation, Female** (must meet all)**:**

1. Request is for fertility preservation (embryo or oocyte cryopreservation) secondary to planned gonadotoxic therapy or gonadectomy;
2. Member meets one of the following (a or b):
   a. Age ≥ 18 years and (i and ii):
      i. Member has received fertility preservation counseling (documented);
      ii. Member has executed an informed consent;
   b. Of reproductive age (peri/postpubertal - off-label use) and member meets both of the following (i and ii):
      i. All consent/assent signees have received fertility preservation counseling (documented);
      ii. Parent(s)/guardian(s) and member have executed informed consents and assents respectively;
3. Prescribed by or in consultation with a reproductive endocrinologist;
4. Member does not have POI.

**Approval duration: 30 days or up to specified trial duration if available**

**C. Infertility, Male** (must meet all)**:**

1. Request is for Gonal-f, Follistim-AQ, Novarel, or Pregnyl;
2. Diagnosis of infertility due to HH;
3. Prescribed by or in consultation with a reproductive endocrinologist or urologist;
4. Age ≥ 18 years;
5. Product(s) are requested in one of the following ways (a or b):
   a. Novarel or Pregnyl as single-agent therapy to increase testosterone to the normal range (400 to 800 ng/dL);
   b. Gonal-f or Follistim-AQ in combination with either Novarel or Pregnyl to induce spermatogenesis once serum testosterone is within the normal range;
6. Testosterone therapy is not prescribed concomitantly;
7. Member does not have primary testicular failure.

**Approval duration: 6 months**

**D. Prepubertal Cryptorchidism (Undescended Testes)** (must meet all)**:**

1. Request is for Novarel or Pregnyl;

2. Diagnosis of prepubertal cryptorchidism;
3. Prescribed by or in consultation with a pediatric specialist in one of the following areas: endocrinology, urology, genetics, surgery;
4. Age ≤ 9 years;
5. One of the following (a or b):
   a. Member is not a candidate for corrective surgery;
   b. hCG will be used in coordination with surgery.

**Approval duration: 3 months**

**E. Other diagnoses/indications**

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**II. Continued Therapy**

**A. Infertility and Fertility Preservation, Female** (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. Request is for an OI or ART cycle currently underway.

**Approval duration: 30 days or up to specified trial duration if available**
*(For additional reproductive attempts please refer to the initial criteria.)*

**B. Infertility, Male** (must meet all)**:**

1. Request is for Gonal-f, Follistim-AQ, Novarel, or Pregnyl;
2. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
3. Member is responding positively to therapy;
4. If request is for Novarel or Pregnyl (a or b):
   a. Pregnancy has not yet been achieved;
   b. Pregnancy has been achieved, and another pregnancy is being considered;
5. If request is for Gonal-f or Follistim-AQ (a or b):
   a. Prescribed in combination with Novarel or Pregnyl;
   b. Current reproductive attempt has not yet achieved pregnancy *(if pregnancy has been achieved, refer to initial criteria for subsequent Gonal-F or Follistim-AQ requests).*

**Approval duration: 6 months**

**C. Prepubertal Cryptorchidism (Undescended Testes)** (must meet all)**:**

1. Request is for Novarel or Pregnyl;
2. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
3. Member is responding positively to therapy.

**Approval duration: 3 months**
*(Treatment for this indication should not exceed a total of 3 months.)*

**D. Other diagnoses/indications** (must meet 1 or 2)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   **Approval duration: Duration of request or 6 months (whichever is less)**; or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**III. Diagnoses/Indications for which coverage is NOT authorized:**

**A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents;

**B.** Treatment of obesity.

## IV. Appendices/General Information

*Appendix A: Abbreviation/Acronym Key*

ART: assisted reproductive technology
ASCO: American Society of Clinical Oncology
AYA: adolescent and young adult
COH: controlled ovarian hyperstimulation
FDA: Food and Drug Administration
FSH: follicle-stimulating hormone
hCG: human chorionic gonadotropin
HH: hypogonadotropic hypogonadism
hMG: human menopausal gonadotropin
ICSI: intracytoplasmic sperm injection
IVF: in vitro fertilization
LH: luteinizing hormone
NCCN: National Comprehensive Cancer Network
POI: primary ovarian insufficiency, primary ovarian failure

*Appendix B: Therapeutic Alternatives*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| cabergoline | **Hyperprolactinemia (labeled):**<br>Initial: 0.25 mg PO twice weekly; may increase by 0.25 mg twice weekly (no more often than every 4 weeks) up to a maximum or 1 mg twice weekly according to the patient's serum prolactin level. | 1 mg twice weekly |
| bromocriptine (Parlodel®) | **Hyperprolactinemia (labeled):**<br>Initial: 1.25 to 2.5 mg PO daily; may be increased by 2.5 mg daily as tolerated every 2 to 7 days until optimal response (range: 2.5 to 15 mg/day). | 15 mg/day |
| clomiphene citrate | **Treatment of ovulatory dysfunction in women desiring pregnancy (labeled):**<br>Initial: 50 mg PO once daily for 5 days. Begin on or about the fifth day of cycle if progestin-induced bleeding is scheduled or spontaneous uterine bleeding occurs prior to therapy. Therapy may be initiated at any time in patients with no recent uterine bleeding.<br>Subsequent doses may be increased to 100 mg once daily for 5 days only if ovulation does not occur at the initial dose. If needed, the 5-day cycle may be repeated as early as 30 days after the previous one. Exclude the presence of pregnancy. The lowest effective dose should be used.<br>Maximum dose: 100 mg once daily for 5 days for up to 6 cycles. | 150 mg/day per expert review<br><br>Durations: 5 to 7 days per expert review |
| letrozole (Femara) | **Infertility - ovulation stimulation in anovulatory females (off-label):**<br>Initial: 2.5 mg PO once daily for 5 days, starting on day 3, 4, or 5 following menses or progestin induced bleed; may increase to 5 mg/day for 5 days in subsequent cycles if ovulation does not occur. | 7.5 mg/day<br><br>Durations: 5 to 7 days per expert review |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s): pregnancy; for additional contraindications, please refer to the product package inserts.
- Boxed warning(s): none reported

*Appendix D: General Information*

- Female Infertility

  - OI refers to pharmacological treatment of anovulation with fertility medications to induce ovulation. OI is used in conjunction with intercourse or intrauterine insemination.
  - ART procedures include but are not limited to 1) in vitro fertilization (IVF), 2) intracytoplasmic sperm injection (ICSI), and 3) assisted reproductive hatching. IVF is the most common type of ART. An IVF interval generally is two weeks in length and includes 1) ovarian stimulation with fertility medications to induce development of multiple ovarian follicles/oocytes (i.e., COH), 2) aspiration and fertilization of oocyte(s) in the laboratory setting ("in vitro"), and then 3) transfer of the embryo(s) into the uterine cavity.
- Male Infertility
  - Male infertility secondary to HH is amendable to treatment with fertility drugs. Once reproductive attempts are complete, transition to testosterone replacement therapy is an option if needed for long-term treatment.
- Prepubertal Males: cryptorchidism
  - Corrective surgery for cryptorchidism (orchidopexy) is considered first-line therapy. Surgery and/or gonadotropin therapy typically would be completed by 24 months of age to avoid potential negative fertility and cancer risk sequelae.
- Fertility Medications
  - Fertility medications are used together in coordinated individualized regimens. The regimens in Section V: Dosage and Administration are presented as general guidelines drawn from FDA labels and expert input. Care should be taken not to interrupt a reproductive attempt currently underway.
- Fertility Preservation
  - For females, ART may be preferable to OI in cases of fertility preservation (embyro or oocyte cryopreservation) secondary to planned gonadotoxic therapy or gonadectomy.
    **Gonadotoxic therapies or gonadectomy may be undertaken as treatment for cancer as well as benign autoimmune or hematologic conditions such as systemic lupus erythematosus, multiple sclerosis, autoimmune thrombocytopenia, rheumatoid arthritis, Wegener's granulomatosis and Behçet's disease.*
  - For males, various fertility preservation strategies are available but do not typically involve the medications central to the present policy.*
    **See Practice Committee of the American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril, 2019;112:1022-33, for more information in this regard.*
  - The American Society of Clinical Oncology (ASCO, 2018), American Society for Reproductive Medicine (ASRM, 2018/2019), Society for Assisted Reproductive Technology (SART)/ASRM (2007), and National Comprehensive Cancer Network (NCCN, 2020) provide guidance for fertility preservation prior to gonadotoxic medical treatment for patients of reproductive age as well as prepubertal patients. Selected ASCO recommendations are listed below:
    - Adult women
      - Recommendation 3.1. Embryo cryopreservation is an established fertility preservation method, and it has routinely been used for storing surplus embryos after in vitro fertilization.
      - Recommendation 3.2. Cryopreservation of unfertilized oocytes is an option, and may be especially well suited to women who do not have a male partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing.
      - Recommendation 3.5 (updated). There is conflicting evidence to recommend GnRH agonists and other means of ovarian suppression for fertility preservation. The Panel recognizes that, when proven fertility preservation methods such as oocyte, embryo, or ovarian tissue cryopreservation are not feasible, and in the setting of young women with breast cancer, GnRH agonists may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. However, GnRH agonists should not be used in place of proven fertility preservation methods.
      - Recommendation 3.6 (updated). Ovarian tissue cryopreservation for the purpose of future transplantation does not require ovarian stimulation and can be performed immediately. In addition, it does not require sexual maturity and hence may be the only method available in children. Finally, this method may also restore global

ovarian function. However, it should be noted further investigation is needed to confirm whether it is safe in patients with leukemias.

- Adult men
  - Recommendation 2.1. Sperm cryopreservation is effective, and health care providers should discuss sperm banking with postpubertal males receiving cancer treatment.
  - Recommendation 2.2. Hormonal gonadoprotection: Hormonal therapy in men is not successful in preserving fertility. It is not recommended.
  - Recommendation 2.3. Other methods, such as testicular tissue cryopreservation and reimplantation or grafting of human testicular tissue, should be performed only as part of clinical trials or approved experimental protocols.
- Special Considerations: Children:
  - Recommendation 5.1. Suggest established methods of fertility preservation (eg, semen or oocyte cryopreservation) for postpubertal children, with patient assent and parent or guardian consent. For prepubertal children, the only fertility preservation options are ovarian and testicular cryopreservation, which are investigational.

## V. Dosage and Administration

| Drug Name | Dosing Regimen | Maximum Dose |
|---|---|---|
| *Infertility, Female* | | |
| ***Follicle stimulating agents*** | | |
| Menopur (menotropins) | Up to 450 IU SC per day | • Doses are individualized.<br>• Duration typically would not exceed one month per reproductive attempt; there may be exceptions. |
| Bravelle (urofollitropin) | Up to 450 IU IM or SC per day | |
| Gonal-f, Gonal-f RFF, Gonal-f RFF Redi-ject (follitropin alpha, recombinant) | Up to 450 SC IU per day | |
| Follistim-AQ (follitropin beta, recombinant) | Up to 500 IU SC per day | |
| ***Pituitary suppression agents*** | | |
| Ganirelix acetate | 250 mcg SC per day | • Doses and durations as noted above. |
| Cetrotide (cetrorelix) | 0.25 mg SC per day | |
| ***Ovulatory "trigger" agents*** | | |
| Ovidrel (choriogonadotropin alfa; recombinant hCG) | 250 mcg SC once | • Doses are individualized.<br>• An agent from this category is typically given once per reproductive attempt. |
| hCG (Novarel, Pregnyl; urinary hCG) | 5,000 to 10,000 USP units IM once | |
| *Infertility, Male: Due to hypogonadotropic hypogonadism* | | |
| Novarel, Pregnyl (hCG) | Dosing may range from 500 to 4,000 USP Units IM on BIW/TIW schedules for up to 12 months to achieve/maintain normal testosterone levels. | Regimens and maximum doses/durations vary; single agent hCG therapy followed by follitropin/hCG combination therapy may extend up to 24 months or at times longer. |
| Gonal-f (follitropin alfa, recombinant) | 150 to 300 IU SC TIW up to 18 months in combination with hCG at the dose required to maintain normal testosterone levels. | |
| Follistim-AQ (follitropin beta, recombinant) | 150 to 225 IU SC on BIW/TIW schedules up to 12 months in combination with hCG at the dose required to maintain normal testosterone levels. | |

| Drug Name | Dosing Regimen | Maximum Dose |
|---|---|---|
| *Prepubertal Cryptorchidism* | | |
| Novarel, Pregnyl (hCG) | Dosing may range from 500 to 5,000 IM USP Units with varying schedules (e.g., every 2nd/3rd day, TIW) with prn repeat courses up to 3 months. | Regimens and maximum doses vary. Maximum duration: 3 months. |

## VI. Product Availability

| Drug Name | Availability |
|---|---|
| Menopur | Injection: 75 U FSH and 75 U LH/vial |
| Bravelle | Injection: 75 U FSH/vial |
| Gonal-F multi dose vial | Injection: 450 U/vial; 1,050 U/vial |
| Gonal-F RFF single dose vial | Injection: 75 U/vial |
| Gonal-F RFF Redi-ject | Prefilled auto-injection device: 300 U/0.5 mL, 450 U/0.75 mL, 900 U/1.5 mL |
| Follistim-AQ | Injection cartridge: 150 U, 300 U, 600 U, 900 U |
| Ganirelix acetate | Prefilled syringe: 250 mcg/0.5 mL |
| Cetrotide | Injection: 0.25 mg/vial |
| Ovidrel | Prefilled syringe: 250 mcg/0.5 mL |
| Novarel | Injection: 5,000 U/vial, 10,000 U/vial |
| Pregnyl | Injection: 10,000 U/vial |
| Chorionic gonadotropin (hCG) | Injection: 10,000 U/vial |

## VII. References

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| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Policy created. | 08.21.18 | 11.18 |
| 4Q 2019 annual review: no significant changes; references reviewed and updated. | 09.03.19 | 11.19 |
| 4Q 2020 annual review: step therapies added to OI and ART; 150 unit cartridge added to Follistim-AQ; exclusion added for use of policy drugs as treatment for obesity; general information appendix and references reviewed and updated. | 09.01.20 | 11.20 |
| 4Q 2021 annual review: no significant changes; references reviewed and updated. | 07.21.21 | 11.21 |

**Important Reminder**
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.