Clinical Policy: Infertility and Fertility Preservation

Reference Number: CP.PHAR.131
Effective Date: 11.16.16
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Line of Business: Commercial, HIM*, HIM-Medical Benefit, Medicaid

Coding Implications
Revision Log

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

Description

- Gonadotropins requiring prior authorization:
  - 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®); human chorionic gonadotropin (hCG; generic, Novarel®*, Pregnyl®).
- Gonadotropin-releasing hormone (GnRH) antagonists requiring prior authorization:
  - Ganirelex acetate; Cetrorelix (Cetrotide®).

**For Health Insurance Marketplace (HIM),* if request is through pharmacy benefit, Gonal-f multi-dose and Novarel is non-formulary and cannot be approved using these criteria; refer to the formulary exception policy, HIM.PA.103.*

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		
Ganirelex 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. *[Includes OI and ART.]*

- 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.

It is the policy of health plans affiliated with Centene Corporation® 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 and Fertility Preservation, Female (must meet all)**:**

1. One of the following diagnoses (a or b):
   a. Infertility and age ≥ 18 years;
   b. Fertility preservation (embryo or oocyte cryopreservation) secondary to planned gonadotoxic therapy or gonadectomy, and (i or ii):
      i. Age ≥ 18 years and member meets both of the following (a and b):
         a) Member has received counseling (documented);
         b) Member has executed an informed consent;
      ii. Of reproductive age (peri/postpubertal; off-label use) and member meets both of the following (a and b):
         a) All consent/assent signees have received counseling (documented);
         b) Parent(s)/guardian(s) and member have executed informed consents and assents respectively;
2. Prescribed by or in consultation with a reproductive endocrinologist;
3. Product(s) are requested for (a or b):
   a. OI;
   b. ART and (i or ii):
      i. OI has failed;
      ii. Member is not a candidate for OI (examples follow):
         a) Undertaking fertility preservation (embryo or oocyte cryopreservation) secondary to planned gonadotoxic therapy or gonadectomy;
         b) Tubal blockage;
         c) Uterine cavity abnormality;
         d) Severe male factor infertility;
         e) Diminished ovarian reserve;
4. Member does not have POI.

Approval duration:

Medicaid/Commercial - 30 days or up to specified trial duration if available
HIM - 30 days or up to specified trial duration if available (*refer to HIM.PA.103 for Gonal-f multi-dose and Novarel)*

B. 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:
Medicaid/Commercial – 6 months
HIM – 6 months (*refer to HIM.PA.103 for Gonal-f multi-dose and Novarel)*

C. 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:
Medicaid/Commercial – 3 months
HIM – 3 months (*refer to HIM.PA.103 for Novarel)*

D. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

II. Continued Therapy

A. Infertility and Fertility Preservation, Female (must meet all)**:**
1. Currently receiving medication via Centene benefit 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:

Medicaid/Commercial - 30 days or up to specified trial duration if available
HIM - 30 days or up to specified trial duration if available (*refer to HIM.PA.103 for Gonal-f multi-dose and Novarel)*
(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 Centene benefit 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 and b):
   a. Will be used 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:
Medicaid/Commercial – 6 months
HIM – 6 months (*refer to HIM.PA.103 for Gonal-f multi-dose and Novarel)*

C. Prepubertal Cryptorchidism (undescended testes) (must meet all)**:**
1. Request is for Novarel or Pregnyl;
2. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
3. Member is responding positively to therapy.

Approval duration:
Medicaid/Commercial – 3 months
HIM – 3 months (*refer to HIM.PA.103 for Novarel)*
(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 Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

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 policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid and HIM-Medical Benefit or evidence of coverage documents.

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 Comprehenswive Cancer Network
POI: primary ovarian insufficiency, primary ovarian failure

Appendix B: Therapeutic Alternatives

Not applicable.

Appendix C: Contraindications/Boxed Warnings

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

Appendix D: General Information

- Female Infertility and Fertility Preservation
  - ART includes OI; however, OI as notated in the policy criteria refers to non-ART assisted reproduction encompassing fertility medications and intercourse or intrauterine insemination.
  - ART includes 1) in vitro fertilization (IVF; most common), 2) intracytoplasmic sperm injection (ICSI), and 3) assisted reproductive hatching. An IVF interval is generally two weeks in length and includes 1) ovarian stimulation by fertility medications, 2) aspiration and fertilization of oocyte(s) in the laboratory ("in vitro"), then 3) transfer of the embryo(s) into the uterine cavity. ART may be preferable to OI in cases of fertility preservation (embyro or oocyte cryopreservation) secondary to planned gonadotoxic therapy or gonadectomy*, tubal blockage or uterine cavity abnormality, severe male factor infertility, or diminished ovarian reserve.
    - *Gonadotoxic therapies or gonadectomy may be undertaken as treatment for cancer as well as treatment for benign conditions, including autoimmune and hematologic conditions such as systemic lupus erythematosus, multiple sclerosis, autoimmune thrombocytopenia, rheumatoid arthritis, Wegener's granulomatosis and Behçet's disease.
  - The American Society of Clinical Oncology (ASCO; 2013) and Society for Assisted Reproductive Technology/American Society for Reproductive Medicine (2007) provide guidelines, including around informed consent, that may help inform requests for fertility preservation prior to gonadotoxic medical treatment for females of reproductive age. ASCO recommendations in this regard are listed below (see article for complete list of recommendations). The ASCO recommendations align with the

National Comprehensive Cancer Network (NCCN) recommendations as presented in Adolescent and Young Adult (AYA) Oncology (Version 1.2020):

- Adult females:
  - Present both embryo and oocyte cryopreservation as established fertility preservation methods.
  - Inform patients that there is insufficient evidence regarding the effectiveness of ovarian suppression (GnRH analogs) as a fertility preservation method, and these agents should not be relied on to preserve fertility.
- Adult males:
  - Present sperm cryopreservation (sperm banking) as the only established fertility preservation method.
  - Do not recommend hormonal therapy in men; it is not successful in preserving fertility.
- Female and male children:
  - Use established methods of fertility preservation (semen cryopreservation and oocyte cyropreservation) for postpubertal minor children, with patient assent, if appropriate, and parent or guardian consent.

- Male Infertility
  - Once reproductive attempts are complete, transition to testosterone replacement therapy is an option if needed for long-term treatment.
  - See above section for fertility preservation in males.
- Prepubertal 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 drugs are used together in coordinated, individualized regimens. The regimens in *Table V* are presented as general guidelines drawn from FDA labels and expert input. Care should be taken not to interrupt a reproductive attempt currently underway.
  - Drugs not listed in the policy that may have roles in female infertility or fertility preservation include GnRH agonists, aromatase inhibitors (e.g., letrozole), dopamine agonists, tamoxifen and clomiphene citrate.
  - mGH has been used off-label for male HH-associated infertility to induce spermatogenesis.

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. • Duration typically would not exceed one month per
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	

Drug Name	Dosing Regimen	Maximum Dose
Follistim-AQ (follitropin beta, recombinant)	Up to 500 IU SC per day	reproductive attempt; there may be exceptions.
Pituitary suppression agents		
Ganirelex 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. • 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.	
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: 300 U, 600 U, 900 U

Drug Name	Availability
Ganirelex 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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Infertility, Female

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Fertility Preservation

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Infertility, Male - Hypogonadotropic Hypogonadism

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Prepubertal Cryptorchidism

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Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
S0122	Injection, menotropins, 75 iu
S0126	Injection, follitropin alfa, 75 iu
S0128	Injection, follitropin beta, 75 iu
J3355	Injection, urofollitropin, 75 iu
S0132	Injection, ganirelix acetate, 250 mcg
J0725	Injection, chorionic gonadotropin, per 1,000 usp units

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2018 annual review: policy adapted from previously approved CP.CPA.26 and HIM.PA.148 policies; HIM-Medical Benefit and Medicaid lines of business added; two additional products added - Gonal-f and Gonal-f RFF Redi-ject; criteria updated and organized around three criteria sets for female infertility (includes fertility preservation), male fertility, and prepubertal cryptorchidism; policy name changed from Infertility Therapy to Infertility and Fertility Preservation; references reviewed and updated.	08.21.18	11.18
4Q 2019 annual review: HIM-MB added; HIM pharmacy nonformulary status added for two products; references reviewed and updated.	09.03.19	11.19

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the non-formulary policy; HIM.PA.103.