

UnitedHealthcare Pharmacy
Clinical Pharmacy Programs

Program Number	2021 P 2149-6
Program	Prior Authorization/Medical Necessity Supported By Fertility Solutions
Medication	Follistim [®] AQ (follitropin beta), Gonal-f [™] (follitropin alfa), Gonal-f [™] RFF (follitropin alfa) *, Menopur [®] (menotropins)*†
P&T Approval Date	7/2018, 11/2018, 5/2019, 8/2019, 8/2020, 9/2021
Effective Date	12/1/2021; Oxford only: N/A

1. Background:

The body produces two types of gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), both of which play a role in fertility and human reproduction. After they are produced by the pituitary gland, gonadotropins trigger production of other sex hormones which then promote production of egg and sperm. Gonadotropins are used in the treatment of infertility, a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse or therapeutic donor insemination.

Gonal-f and Gonal-f RFF (follitropin alfa) are indicated for the induction of ovulation and pregnancy in oligo-anovulatory infertile women in whom the cause of infertility is functional and not due to primary ovarian failure. Gonal-f and Gonal-f RFF are also indicated for the development of multiple follicles in ovulatory women participating in an Assisted Reproductive Technology (ART) program. Gonal-f is indicated for the induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism in whom the cause of infertility is not due to primary testicular failure.⁵

Follistim AQ (follitropin beta) is indicated for induction of ovulation and pregnancy in anovulatory infertile women in whom the cause of infertility is functional and not due to primary ovarian failure. It is also indicated for pregnancy in normal ovulatory women undergoing controlled ovarian stimulation as part of an in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycle. In males, Follistim AQ is indicated for 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.⁶

Menopur (menotropins) is indicated for the development of multiple follicles and pregnancy in ovulatory women participating in an assisted reproductive technology (ART) program.⁷ hMG is used for the treatment of ovulation induction in women with ovulatory dysfunction including polycystic ovary syndrome (PCOS) who failed on clomiphene as well for ovulation induction in the setting of hypogonadotropic hypogonadism. hMG is also used for induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism in whom the cause of infertility is not due to primary testicular failure.⁵⁻¹³

The clinically appropriate dosing for hMG agents when used in an ART cycle without an FSH product is 450 IU/day or less for not more than 14 days of treatment. When used as part of a mixed stimulation protocol (hMG + FSH) or when used alone for ovulation induction or controlled ovarian stimulation the clinically appropriate maximum dosing for hMG agents is 225 IU/day and 150 IU/day, respectively. Exceeding this daily dose and duration of treatment has not been proven to be efficacious in terms of pregnancy outcome.^{9,13} The clinically appropriate dosing for FSH agents is 450 IU/day or less when used for an ART cycle, or 225 IU/day and 150 IU/day or less when used for ovulation induction or controlled

ovarian stimulation, respectively, for not more than 14 days of treatment. Exceeding this daily dose and duration of treatment has not been proven to be efficacious in terms of pregnancy outcome.^{10,14}

This is an optional program that is put in place for clients or businesses that have elected to provide coverage for gonadotropins, managed through the Optum Fertility Solutions program

2. Coverage Criteria^a:

A. Coverage Criteria for Ovarian Stimulation & Ovarian Induction

1. **Follistim AQ, Gonal-f, Gonal-f RFF, or Menopur** will be approved based on all of the following criteria:

a. Prognosis for conception must be $\geq 5\%$

-AND-

b. Adequate ovarian reserve as indicated but not limited to at least **one** the following markers (one or more of the following within the previous 6 months):

- (1) FSH level < 15 mIU/ml if > 35 years of age
- (2) FSH level < 20 mIU/ml if ≤ 35 years of age
- (3) AMH level > 0.3 ng/ml
- (4) Antral follicle count > 6

-AND-

c. Evidence of adequate ovarian response to stimulation if there has been previously monitored, medicated-stimulated infertility treatment within the previous 6 months. Examples of adequate ovarian response are:

- (1) One follicle ≥ 15 mm diameter for IUI
- (2) Minimum of 1 follicle ≥ 15 mm diameter for ART

-AND-

d. If the request is for Gonal-f/Gonal-f RFF, the following criterion:

- (1) History of failure, contraindication, or intolerance to Follistim AQ

-AND-

e. **Follistim AQ, Gonal-f, Gonal-f RFF, or Menopur** will be utilized for one of the following indications (See additional coverage criteria for each indication):

- (1) Controlled Ovulation Induction (see Section B)
- (2) Ovarian Stimulation (see Section C)

B. Ovulation Induction

1. **Follistim AQ, Gonal-f, or Gonal-f RFF, or Menopur** will be approved based on **all** of the following criteria*† :

a. Patient meets the coverage criteria in section A.

-AND-

b. Failure to ovulate with either Clomid (clomiphene citrate) or Femara (letrozole)

-AND-

c. **One** of the following exists:

- (1) Anovulation
- (2) Oligo-ovulation
- (3) **Both** of the following:
 - (a) Amenorrhea
 - (b) Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated

-AND-

d. **One** of the following:

- (1) For assisted reproductive technologies (ART)^b, dose does not exceed 450 IU/day, for no more than 14 days per cycle
- (2) For ovulation induction, dose does not exceed 225 IU/day, for no more than 14 days per cycle.

-AND-

e. The use of **Follistim AQ, Gonal-f, Gonal-f RFF, or Menopur** applies to **NONE** of the following situations:

- (1) Use of gonadotropins beyond the 6th gonadotropin induced ovulatory cycle.
- (2) When there are ≥ 4 follicles which are ≥ 15 mm in diameter from a previously gonadotropin-induced ovulation, despite a dosage adjustment (e.g., doses of gonadotropin down to 37.5 IU per day).
- (3) When used alone for individuals with unexplained infertility.
- (4) When there is a failure to respond to ovulation induction (e.g., doses of gonadotropins up to 225 IU per day and no follicles ≥ 15 mm in diameter).
- (5) In lieu of clomiphene or letrozole to correct a thin endometrial lining.²⁸⁻³⁰
- (6) An estradiol level < 100 pg/ml/follicle ≥ 15 mm in diameter.
- (7) Doses that exceed 450 IU/day for ART or 225 IU/day for ovulation induction, respectively.
- (8) Duration of therapy that exceeds 14 days per cycle.

Authorization will be issued for 3 months.[§]

C. Controlled Ovarian Stimulation

1. **Follistim AQ, Gonal-f, or Gonal-f RFF, or Menopur** will be approved based on **all** of the following criteria*† :

a. Patient meets the coverage criteria in section A.

-AND-

b. Used alone or in conjunction with intrauterine insemination (IUI)

-AND-

c. **One** of the following:

- (1) Treatment in individuals with diminished ovarian reserve that have not responded to clomiphene or letrozole
- (2) Initial treatment for individuals with diminished ovarian reserve
- (3) In the setting of unilateral proximal tubal disease in conjunction with IUI when there is no evidence of tubal compromise on the patent side when at least 2 cycles of oral agents (clomiphene or letrozole) have failed to yield a dominant follicle on the side with a patent fallopian tube

-AND-

d. **One** of the following:

- (1) For assisted reproductive technologies (ART)^b, total gonadotropin dose does not exceed 450 IU/day, for no more than 14 days per cycle
- (2) For controlled ovulation stimulation, dose does not exceed 150 IU/day, for no more than 14 days per cycle.

-AND-

e. The use of **Follistim AQ, Gonal-f, Gonal-f RFF, or Menopur** applies to **NONE** of the following situations:

- (1) Treatment in individuals with unexplained infertility, endometriosis, bilateral tubal factor infertility, recurrent pregnancy loss, male factor infertility
- (2) In lieu of clomiphene or letrozole to correct a thin endometrial lining
- (3) When there is a failure to respond to ovarian stimulation, (e.g., doses of gonadotropins up to 150 IU per day and no follicles ≥ 15 mm in diameter)
- (4) An estradiol level <100 pg/ml/follicle ≥ 15 mm in diameter
- (5) When there are ≥ 4 follicles which are ≥ 15 mm in diameter from a previously gonadotropin-induced ovulation, despite a dosage adjustment.
- (6) Following ART cycles that fail to result in conception due to poor ovarian response or poor quality oocytes or embryos.
- (7) Doses that exceed 450 IU/day for ART or 150 IU/day for controlled ovulation

- stimulation, respectively
- (8) Duration of therapy that exceeds 14 days per cycle.
 - (9) Beyond 4 cycles for individuals age <38, 2 cycles for individuals age 38-39, and 1 cycle for individuals age 40 and older in the setting ovarian stimulation for diminished ovarian reserve.
 - (10) In the setting of very poor/futile prognosis, defined as a FSH level ≥ 15 mIU/ml if ≥ 40 years of age or FSH level ≥ 20 mIU/ml if < 40 years of age.

Authorization will be issued for 3 months.[§]

D. Male Hypogonadotropic Hypogonadism

1. Follistim AQ, Gonal-f, or Gonal-f RFF, or Menopur will be approved based on **all** of the following criteria*† :

a. **One** of the following:

(1) Diagnosis of male primary hypogonadotropic hypogonadism

-OR-

(2) Diagnosis of male secondary hypogonadotropic hypogonadism

-AND-

b. For induction of spermatogenesis

-AND-

c. Infertility is not due to primary testicular failure

-AND-

d. If the request is for Gonal-f or Gonal-f RFF, the following criterion:

(1) History of failure, contraindication, or intolerance to Follistim AQ

Authorization will be issued for 3 months.[§]

^a State mandates may apply. Any federal regulatory requirements and the member specific benefit plan coverage may also impact coverage criteria. Other policies and utilization management programs may apply.

^b ART includes all fertility treatments in which both eggs and embryos are handled, including in vitro fertilization.³⁷

3. Additional Clinical Programs:

- Notwithstanding Coverage Criteria, UnitedHealthcare may approve initial and re-authorization based solely on previous claim/medication history, diagnosis codes (ICD-10) and/or claim logic. Use of automated approval and re-approval processes varies by program and/or therapeutic class.
- Supply limits may be in place.

*Infertility is typically excluded from coverage for UnitedHealthcare. Please refer to member's specific benefits for coverage determination.

‡ Optum Fertility Solutions review only: Please refer to the Clinical Policy on Human Menopausal Gonadotropin (hMG) Used in the Treatment of Infertility for state-specific requirements that may apply.

§ Optum Fertility Solutions review only: Authorizations will be reviewed according to the [Fertility Solutions Medical Necessity Clinical Guideline - Infertility](#).

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Program	Prior Authorization/Medical Necessity (For Optum Fertility Solutions) - Follistim AQ (follitropin beta), Gonal-f (follitropin alfa), Gonal-f RFF (follitropin alfa)
Change Control	
7/2018	New program
11/2018	Corrected maximum dosing for ovulation induction to 225 IU/day and controlled ovarian stimulation to 150 IU/day. Added definition of ART. Moved Follistim AQ criteria in to general requirements sections.
5/2019	Annual review. Revised coverage rationale for ovulation induction and controlled ovarian stimulation. Updated references.
8/2019	Revised coverage rationale to change step therapy criteria. Require trial of Follistim AQ before Gonal F.
8/2020	Annual review with no changes to coverage criteria.
9/2021	Annual review. Updated coverage rationale for ovulation induction and controlled ovarian stimulation.