

FOLLICLE STIMULATING HORMONE (FSH) GONADOTROPINS

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Related Policy

- [Acquired Rare Disease Drug Therapy Exception Process](#)
- [Infertility Diagnosis and Treatment](#)

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

CONDITIONS OF COVERAGE

Applicable Lines of Business/ Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General benefits package (medical) ² Pharmacy ²
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes ¹
Precertification with Medical Director Review Required	No
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	All
Special Considerations	¹ Precertification through Optum is required for all FSH agents. ² Members should refer to their benefit plan document or certificate of coverage for details regarding benefit coverage for each eligible plan and product.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some Certificates of Coverage and some Oxford Health Plan pharmacy riders contain an explicit exclusion for infertility treatments, including infertility drugs. The member-specific benefit document must be used to adjudicate infertility benefits.

Some states mandate benefit coverage for infertility treatments, including infertility drugs. These mandates may vary from state to state. Oxford Health Plans follows these mandates, where applicable.

Some Certificates of Coverage allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the policy titled [Acquired Rare Disease Drug Therapy Exception Process](#).

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Oxford has engaged Optum to perform reviews of requests for pre-certification (Oxford continues to be responsible for decisions to limit or deny coverage and for appeals). All authorization/pre-certification requests are handled by Optum. To pre-certify a procedure related to the treatment of infertility, please call Optum at 877-512-9340.

This policy addresses the following gonadotropins:

- Bravelle (urofollitropin)
- Gonal-f/Gonal-f RFF (follitropin alfa)
- Follistim AQ (follitropin beta)

All follicle stimulating hormone (FSH) gonadotropins currently available on the U.S. market are considered to be therapeutically equivalent.

The clinically appropriate dosing for FSH agents is 450 IU per day or less for an assisted reproductive technology (ART) cycle when administered alone. The total dose of gonadotropin should not exceed 450 IU per day when used in any mixed stimulation protocol of FSH and human menopausal gonadotropin (hMG) (e.g., FSH 300 IU/day with hMG 150 IU/day), 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.

The clinically appropriate dosing for FSH agents is 150 IU/day or less when used for ovulation induction, or controlled ovarian stimulation, 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.

The following information pertains to medical necessity review:

General Requirements (applicable to all medical necessity requests): ^{8,9,20,36}

For initial and continuation of therapy, ALL of the following must be met for consideration of treatment:

- Prognosis for conception must be $\geq 5\%$; and
- 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):
 - FSH level < 15 mIU/ml if > 35 years of age; or

- FSH level < 20 mIU/ml if ≤ 35 years of age; or
- AMH level > 0.3 ng/ml; or
- Antral follicle count > 6;
- and
- 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:
 - One follicle ≥ 15 mm diameter for IUI
 - Minimum of 1 follicle ≥ 15 mm diameter for ART

Preferred Product: Gonal-f and Gonal-f RFF* are the preferred FSH agents

Infertility treatment with Follistim AQ or Bravelle is medically necessary for the indications specified in this policy when ONE of the following criteria are met:

- History of failure, contraindication, or intolerance to Gonal-f or Gonal-f RFF; or
- **Both** of the following:
 - Patient is currently on Follistim AQ or Bravelle therapy; and
 - One of the following:
 - Patient has not received a manufacturer supplied sample at no cost from a prescriber office or a 30 day free trial from a pharmacy as a means to establish as a current user of Follistim AQ or Bravelle; or
 - Both of the following:
 - Patient has received a manufacturer supplied sample at no cost from a prescriber office or a 30 day free trial from a pharmacy as a means to establish as a current user of Follistim AQ or Bravelle; and
 - History of failure, contraindication, or intolerance to Gonal-f or Gonal-f RFF.

Diagnosis-Specific Requirements³⁶

The information below indicates additional requirements for those indications having specific medical necessity criteria in the list of proven indications.

FSH gonadotropins are proven and medically necessary for:

Ovulation Induction

Gonadotropins are proven and medically necessary for the treatment of ovulatory dysfunction when ONE of the following criteria are met:

- Anovulation; or
- Oligo-ovulation; or
- **All** of the following:
 - Amenorrhea; and
 - Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated; and
 - Failure to ovulate with either Clomid (clomiphene citrate) or Femara (letrozole); and
- **One** of the following:
 - For assisted reproductive technologies (ART), dose does not exceed 450 IU/day, for no more than 14 days per cycle; or
 - For ovulation induction, dose does not exceed 150 IU/day, for no more than 14 days per cycle.

Gonadotropins are unproven and not medically necessary for the treatment of ovulatory dysfunction in the following situations:

- Beyond the 6th gonadotropin induced ovulatory cycle.
- 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).
- When used alone for individuals with unexplained infertility.
- When there is a failure to respond to ovulation stimulation, (e.g., doses of gonadotropins up to 225 IU per day and no follicles ≥ 15 mm in diameter).
- In lieu of clomiphene or letrozole to correct a thin endometrial lining.³¹⁻³³
- An estradiol level <100 pg/ml/follicle ≥15 mm in diameter.
- Doses that exceed 450 IU/day for ART or 150 IU/day for ovulation induction, respectively.
- Duration of therapy that exceeds 14 days per cycle.

Controlled Ovarian Stimulation

Gonadotropins are proven and medically necessary for the treatment of controlled ovarian stimulation when ALL of the following criteria are met:

- Used alone or in conjunction with intrauterine insemination; and
- **One** of the following:

- Treatment in individuals with diminished ovarian reserve that have not responded to clomiphene or letrozole; or
 - Initial treatment for individuals with diminished ovarian reserve; or
 - Initial treatment for individuals ≥ 40 years of age; or
 - In the setting of unilateral tubal disease 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
- **One** of the following:
 - For assisted reproductive technologies (ART), dose does not exceed 450 IU/day, for no more than 14 days per cycle; or
 - For controlled ovulation stimulation, dose does not exceed 150 IU/day, for no more than 14 days per cycle.

Gonadotropins are unproven and not medically necessary for the treatment of controlled ovarian stimulation in the following situations:³⁶

- Treatment in individuals with unexplained infertility, endometriosis, bilateral tubal factor infertility, recurrent pregnancy loss or male factor infertility.^{19,20}
- In lieu of clomiphene or letrozole to correct a thin endometrial lining.³¹⁻³⁴
- When there is a failure to respond to ovarian stimulation, (e.g., doses of gonadotropins up to 225 IU per day and no follicles ≥ 15 mm in diameter).
- An estradiol level <100 pg/ml/follicle ≥ 15 mm in diameter).
- When there are ≥ 4 follicles which are ≥ 15 mm in diameter from a previously gonadotropin-induced ovulation, despite a dosage adjustment.
- Following ART cycles that fail to result in conception due to poor ovarian response or poor quality oocytes or embryos.
- Doses that exceed 450 IU/day for ART or 150 IU/day for controlled ovulation stimulation, respectively.
- Duration of therapy that exceeds 14 days per cycle.
- 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.
- 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.

Hypogonadotropic Hypogonadism

Gonadotropins are proven and medically necessary for the treatment of hypogonadotropic hypogonadism when ALL of the following criteria are met:

- **One** of the following:
 - Diagnosis of primary hypogonadotropic hypogonadism; or
 - Diagnosis of secondary hypogonadotropic hypogonadism;
 and
- For the induction of spermatogenesis; and
- Infertility is not due to primary testicular failure.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Follitropin alfa (Gonal-f®), follitropin beta (Follistim® AQ), and urofollitropin (Bravelle®) are all follicular stimulating hormone products. All three products are indicated for ovulation induction and follicular development in women as part of assisted reproductive technology (ART). Follitropin alfa and follitropin beta are also indicated for induction of spermatogenesis in males with primary and secondary hypogonadotropic hypogonadism in whom the cause of infertility is not due to primary testicular failure.⁵⁻⁷

FSH agents are 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.

The American Society for Reproductive Medicine (ASRM) defines infertility as a disease,* defined by the failure to achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or therapeutic donor insemination. Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months for women over age 35 years. It affects about 10% to 15% of couples.^{2,21}

In addition to age, other factors that influence fertility include lifestyle (smoking, alcohol, caffeine, drugs, and body mass index) and the timing and frequency of intercourse. Normal sperm can survive at least 3 days, but an oocyte can be fertilized for only 12 to 24 hours.

The major causes of infertility include tubal and peritoneal pathology (30% - 40%), ovulatory dysfunction (15%), and male factor (30% - 40%). Uterine and cervical factors are uncommon. Patients without an identifiable cause are classified as unexplained infertility (10%).

Follicle stimulating hormone (FSH) is needed in women for the growth and development of follicles in the ovaries. Follicles are small round sacs that contain the egg cells. In women, the level of FSH is critical for the onset and duration of follicular development, and consequently for the timing and number of follicles reaching maturity.

FSH therapy is used for the development of eggs in women who have problems with ovulation and who are undergoing ovulation induction treatment. Some women will also be using this medicine for the development of more eggs when participating in an assisted reproductive technology (ART) program, such as in vitro fertilization.

*ASRM cites a definition of the term "disease" provided by Dorland's Illustrated Medical Dictionary, 31st edition, 2007:535: "any deviation from or interruption of the normal structure or function of any part, organ, or system of the body as manifested by characteristic symptoms and signs; the etiology, pathology, and prognosis may be known or unknown."

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

HCPCS Code	Description
J3355	Injection, urofollitropin, 75 IU
S0126	Injection, follitropin alfa, 75 IU
S0128	Injection, follitropin beta, 75 IU
S4042	Management of ovulation induction (interpretation of diagnostic tests and studies, nonface-to-face medical management of the patient), per cycle

ICD-10 Diagnosis Code	Description
E28.39	Other primary ovarian failure
E28.8	Other ovarian dysfunction
E29.1	Testicular hypofunction
N91.0	Primary amenorrhea
N91.1	Secondary amenorrhea
N91.2	Amenorrhea, unspecified
N97.0	Female infertility associated with anovulation

CLINICAL EVIDENCE

Proven/Medically Necessary

Pooled data from two multi-center, open-label, randomized, comparative, active-controlled parallel-group trials compared the efficacy and safety of highly purified human-derived follicle-stimulating hormone (urofollitropin (Bravelle®), n=120) and recombinant follitropin beta (Follistim®, n=118) in infertile, premenopausal women undergoing in vitro fertilization. Eligible patients underwent pituitary down-regulation with 0.5mg/day leuprolide acetate subcutaneously (SC) 7 days before the anticipated onset of the next menses and continued for ≤ 20 days or until their serum estrogen was ≤ 45 pg/mL and endometrial thickness was ≤ 7mm on transvaginal ultrasound. Patients successfully achieving down-regulation requirements were then randomized to receive 225IU of Bravelle® or Follistim®, once daily SC, for 5 days. After the initial 5 days of treatment, investigators assessed ovarian response. If necessary, per protocol, the dose of gonadotropin was increased in increments of 75 to 150 IU/day on alternate days, to a maximum of 450 IU/day. The duration of controlled ovarian stimulation was not to exceed 12 days. Patients were eligible to receive hCG if there were at least three follicles with a diameter of ≥ 16mm and an appropriate serum estrogen level. A single dose of hCG (10,000 IU of Novarel®) was administered intramuscularly 1 day after the final dose of gonadotropin to 94.2% of the Bravelle® and 97.5% of the Follistim® group and underwent oocyte retrieval. There were no clinically or significantly meaningful differences between the intent-to-treat analysis and the primary efficacy responders analyses. Efficacy data were from the analyses conducted on patients who received hCG. There

were no significant differences among treatment groups in mean number of oocytes retrieved per cycle, fertilized, or transferred, peak serum E2 levels, patients with ET, continuing pregnancies, or live births. There were no significant differences among the treatment groups in the number, nature, of adverse events ($p=0.680$), severe adverse events ($p=0.307$), or serious adverse events ($p=0.161$). The authors concluded that Bravelle[®] and Follistim[®] had comparable safety and efficacy in controlled ovarian hyperstimulation in women undergoing IVF-ET.^{22, 23}

In a multi-center, open-label, randomized, parallel-group trial, Lenton et al. evaluated the efficacy and safety of recombinant follicle stimulating hormone (rFSH, follitropin alfa) with highly purified urinary human FSH (uFSH, urofollitropin HP). 155 patients were enrolled in the trial and underwent pituitary desensitization with either intranasal or subcutaneous buserelin from day 21 of their cycle for a minimum of 10 days prior to receiving gonadotropin, and were randomized into two comparable groups to receive either 150 IU of subcutaneous rFSH ($n=80$) or uFSH ($n=75$) for 6 days. Of the 155 patients receiving at least 1 dose of FSH, 137 (88.4%) also received hCG; 68 (85%) rFSH and 69 (92%) uFSH. Those not receiving hCG was due to inadequate stimulation. After 6 days of stimulation, the mean number of follicles >10 mm were similar between the two groups (rFSH: 2.2 ± 2.8 , uFSH: 2.0 ± 3.2). On the day of hCG administration, the mean number of follicles >10 mm were also not significantly different between the two groups (rFSH 12.5 ± 6.0 ; uFSH 13.1 ± 6.1). The number of oocytes retrieved per patient was 10.2 ± 6.0 for rFSH patients compared with 10.8 ± 6.1 in the uFSH group (not significant). There were no significant differences in the primary or secondary efficacy endpoints however trended more in favor of rFSH vs. uFSH: clinical pregnancies (44.3% rFSH vs. 41.4% uFSH), live births (33.8% rFSH vs. 26.7% uFSH), and miscarriage rate (0.0 rFSH vs. 16.7%). Ovarian hyperstimulation syndrome occurred in 8.6% and 7.9% of rFSH and uFSH patients, respectively. The authors concluded the protocol used was effective in inducing multiple follicular development and high numbers of oocytes retrieved for both medications.²⁴

Technology Assessments

A 2011 Cochrane review was published which compared the effectiveness of recombinant FSH (rFSH) with the three main types of urinary gonadotropins (hMG, purified FSH, and highly purified FSH) for ovarian stimulation in women undergoing IVF and ICSI treatment cycles.²⁵ With the analysis of 42 trials with a total of 9,606 couples, the authors concluded that:

- Comparing rFSH to all other gonadotropins combined, irrespective of down-regulation protocol used, did not result in any evidence of a statistically significant difference in live birth rate (28 trials, 7,339 couples, odds ratio (OR) 0.97, 95% CI 0.87 to 1.08).
 - Suggests that for a group with a 25% live birth rate using urinary gonadotropins, the rate would be between 22.5% and 26.5% using rFSH.
- Comparing rFSH to all other gonadotropins combined, there was no evidence of a difference in the OHSS rate (32 trials, 7,740 couples, OR 1.18, 95% CI 0.86 to 1.61).
 - Suggests that for a group with a 2% risk of OHSS using urinary gonadotropins, the risk would be between 1.7% and 3.2% with rFSH.
- When considering different urinary gonadotropins separately, there were significantly fewer live births after rFSH than hMG (11 trials, $N=3,197$, OR 0.84, 95% CI 0.72 to 0.99).
 - Suggests that for a live birth rate of 25% using hMG, use of rFSH instead would be expected to result in a rate between 19% and 25%.
- No evidence of a difference in live births when rFSH was compared with purified FSH (5 trials, $N=1,430$, OR 1.26, 95% CI 0.96 to 1.64) or compared to highly purified FSH (13 trials, $N=2,712$, OR 1.03, 95% IC 0.86 to 1.22).
- All available gonadotropins are equally effective and safe. The choice of product will depend on the availability, convenience, and associated costs.

Hypogonadotropic Hypogonadism

Combined analysis of four similarly designed, phase III, open-label, non-comparative trials compared the efficacy and safety of recombinant human FSH (rFSH) and human chorionic gonadotropin (hCG) treatment for male hypogonadotropic hypogonadism (HH) in different populations and sought to identify characteristics predictive of spermatogenesis. The four trials enrolled 100 men aged between 16 and 55 years with complete idiopathic or acquired HH who were azoospermic at study entry. In all studies, patients underwent a pretreatment phase with hCG to normalize serum testosterone (T) concentration. Patients then received a starting dose of 1,000 IU three times weekly or 2,000 IU twice weekly, which was adjusted according to response, for a minimum of 3 months and a maximum of 6 months. At the end of this phase, men were required to produce a semen sample to verify azoospermia. After the pretreatment phase, men with serum T levels within normal range and were still azoospermic were eligible to enter the treatment phase with rFSH. During the treatment phase, hCG was continued at the same dosing and schedule previously and was combined with 150 IU rFSH administered three times weekly for up to 18 months. Assessments were conducted every 3 months where the rFSH dose was adjusted according to changes in spermatozoa count until the maximum dose was reached (225 IU or 300 IU, three times weekly). The baseline and demographic characteristics in each study were broadly similar. One study, performed in Japan, were a majority of Japanese in origin, while the other three were majority of Caucasian. A total of 81 patients completed the pretreatment phase, 77 had idiopathic HH and four had acquired disease. Fifteen of 19 men were excluded during the pretreatment phase and

were considered to be ineligible. The primary efficacy endpoint of a spermatozoa concentration of $\geq 1.5 \times 10^6/\text{mL}$ was achieved in 56 (69%) of 81 men, in a median time of 9 months in three studies and 12 months in the other. The secondary efficacy endpoints, spermatogenesis, defined as a sperm concentration $>0 \times 10^6/\text{mL}$, occurred in 68 (84%) of 81 men. The median time ranged from 6 to 9 months. All studies demonstrated significantly increased testis volume from pre-to post-treatment. Of the 100 men enrolled, 51 were seeking fertility. A total of 16 pregnancies occurred in 14 partners (27%), which led to 11 healthy babies. A total of 27 patients required the dose of rFSH to be increased above 150 IU three times weekly, of which 23 patients resulted in spermatogenesis. Eighteen patients reached the primary efficacy endpoint. Seven patients among the 71 patients who completed 189 months of treatment remained azoospermic throughout the treatment period. All of these patients had idiopathic HH or Kallmann's syndrome. The combination of rFSH and hCG was well tolerated with few men discontinuing treatment due to adverse events. The authors concluded that combination therapy with rFSH and hCG is effective in the restoration of fertility in the majority of men with hypogonadotropic hypogonadism.

Technology Assessments

A 2013 Cochrane review was published to determine the effect of systemic follicle-stimulating hormone (FSH) on live birth and pregnancy rates when administered to men with idiopathic male factor subfertility.²⁹ Six randomized controlled trials with 456 participants were included in the analysis. The authors concluded that there was encouraging preliminary data from these studies suggest a beneficial effect on live birth and pregnancy of gonadotropin treatment for men with idiopathic male subfertility, but the numbers of trials and participants are small; therefore evidence is insufficient to permit final conclusions.

Professional Societies

In 2012, the European Association of Urology published guidelines for male infertility.³⁰ These guidelines included the treatment recommendations for hypogonadotropic hypogonadism. The guidelines state that hypogonadotropic hypogonadism can be treated medically. The standard treatment is hCG, with the later addition of hMG or recombinant FSH, depending on initial testicular volume. In some cases of idiopathic hypogonadotropic hypogonadism, spontaneous reversibility of reproductive function has been observed.

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
07/01/2018	<ul style="list-style-type: none"> Updated supporting information to reflect the most current references; no change to coverage rationale or lists of applicable codes Archived previous policy version PHARMACY 289.3 T2