Follicle Stimulating Hormone (FSH) Gonadotropins

Policy Number: PHARMACY 289.9 T2
Effective Date: September 1, 2020

Coverage Rationale

Oxford has engaged Optum to perform reviews of requests for prior authorization of infertility related services (assisted reproductive technologies). Oxford continues to be responsible for decisions to limit or deny coverage and for appeals. All prior authorization requests are handled by Optum. To obtain prior authorization for a procedure related to the treatment of infertility, call Optum at 877-512-9340.

This policy addresses the following gonadotropins:
- 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 the medical necessity review:

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

For initial and continuation of therapy with FSH agents, all of the following must be met for consideration of treatment:
Prognosis for conception must be ≥ 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

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

**Diagnosis-Specific Requirements**

Infertility treatment with Follistim AQ is medically necessary for the indications for FSH gonadotropins specified in this policy.

Infertility treatment with Gonal-f and Gonal-f RFF is medically necessary for the indications for FSH gonadotropins specified in this policy when there is a history of failure, contraindication, or intolerance to Follistim AQ.

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 all of the following criteria are met:

- Failure to ovulate with both Clomid (clomiphene citrate) and Femara (letrozole)*; and

- One of the following:
  - Anovulation; or
  - Oligo-ovulation; or
  - Both of the following:
    - Amenorrhea; and
    - Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated

- One of the following:
  - For assisted reproductive technologies (ART), dose does not exceed 450 IU/day, for no more than 14 days per cycle;
  - For ovulation induction, dose does not exceed 225 IU/day, for no more than 14 days per cycle.

* PCOS, anovulatory or oligo-ovulatory patients who fail to ovulate with clomiphene after dosage adjustment up to 150 mg per day should attempt ovulation induction with letrozole before proceeding to gonadotropins. Patients diagnosed with hypothalamic amenorrhea (failure to withdraw to progesterone) who demonstrate hypoestrogenemia may move directly to gonadotropins.

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 lining31-33
An estradiol level < 100 pg/ml/follicle ≥ 15 mm in diameter
Doses that exceed 450 IU/day for ART or 225 IU/day for ovulation induction, respectively
Duration of therapy that exceeds 14 days per cycle; a longer than 14-day stimulation may be considered in the setting of hypothalamic amenorrhea

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 (IUI); 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
  - Treatment for individuals ≥ 40 years of age in conjunction with ART; or
  - 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
- 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 infertility19,20
- In lieu of clomiphene or letrozole to correct a thin endometrial lining31-34
- 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)
- 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, individuals >40 years of age without ART
- In the setting of very poor/futile prognosis, defined as an 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.

Prior Authorization Requirements

Prior authorization is required through Optum in all sites of service.
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.

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<td>Injection, follitropin alfa, 75 IU</td>
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<tr>
<td>S0128</td>
<td>Injection, follitropin beta, 75 IU</td>
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<tr>
<td>S4042</td>
<td>Management of ovulation induction (interpretation of diagnostic tests and studies, nonface-to-face medical management of the patient), per cycle</td>
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<tr>
<th>Diagnosis Code</th>
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<td>E28.8</td>
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Benefit Considerations

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 plan 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 plan 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 Administrative Policy titled: Acquired Rare Disease Drug Therapy Exception Process.

Clinical Evidence

Proven

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 225 IU 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 ≥ 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, urofolliropin 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 2019 Cochrane review was published comparing the effectiveness and safety of gonadotropins as a second-line treatment for ovulation induction in women with clomiphene citrate-resistant polycystic ovary syndrome (PCOS), and women who do not ovulate or conceive after clomiphene citrate.37 The review included 15 trials with 2387 women. Ten trials compared rFSH with urinary-derived gonadotropins (three compared rFSH with human menopausal gonadotropin, and seven compared rFSH with FSH-HP), four trials compared FSH-P with HMG. There were no trials that compared FSH-HP with FSH-P. One trial compared FSH with continued clomiphene citrate. The authors concluded that there may be little or no difference in live birth, incidence of multiple pregnancy, clinical pregnancy rate, or miscarriage rate between urinary-derived gonadotropins and recombinant follicle stimulating hormone in women with polycystic ovary syndrome. For human menopausal gonadotropin or highly purified human menopausal gonadotropin versus urinary follicle stimulating hormone it is uncertain whether one or the other improves or lowers live birth, incidence of multiple pregnancy, clinical pregnancy rate, or miscarriage rate. It is uncertain whether any of the interventions reduce the incidence of ovarian hyperstimulation syndrome. It is suggested to weigh costs and convenience in the decision to use one or the other gonadotropin. In women with clomiphene citrate failure, gonadotropins resulted in more live births than continued clomiphene citrate without increasing multiple pregnancies.

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% CI 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 ≥ 1.5 x 10^6/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 x 10^6/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**

**European Association of Urology**

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.
Follitropin alfa (Gonal-F®), and follitropin beta (Follistim® AQ) are follicular stimulating hormone products. These 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.\textsuperscript{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.\textsuperscript{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, 31\textsuperscript{st} 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.”

References


