



Horizon BCBSNJ
Medical Necessity Guideline

Section Drugs
Policy Number
Effective Date 6/25/04
Review Date 7/22/05, 7/25/08, 5/12/09

Subject:

DRUG CLASS Follitropin-Fertility Agent

BRAND NAME (generic) Gonal-F (follitropin alfa)

Bravelle (urofollitropin)

Follistim (follitropin beta)

IMPORTANT NOTE:

*The purpose of this policy is to provide general information applicable to the administration of outpatient prescription drug benefits that Horizon Blue Cross Blue Shield of New Jersey and Horizon Healthcare of New Jersey, Inc. (collectively "Horizon BCBSNJ") insures or administers. **Outpatient prescription drugs are not covered under all Horizon benefit plans.** If the member's contract benefits differ from the pharmacy guideline, the contract prevails. Although a service, supply drug or procedure may be medically necessary, it may be subject to limitations and/or exclusions under a member's benefit plan. If a service, supply drug or procedure is not covered and the member proceeds to obtain the service, supply drug or procedure, the member may be responsible for the cost. Decisions regarding treatment and treatment plans are the responsibility of the physician. This policy is not intended to direct the course of clinical care a physician provides to a member, and it does not replace a physician's or pharmacist's independent professional clinical judgment or duty to exercise special knowledge and skill in the treatment of Horizon BCBSNJ members. Horizon BCBSNJ is not responsible for, does not provide, and does not hold itself out as a provider of medical care. The physician remains responsible for the quality and type of health care services provided to a Horizon BCBSNJ member.*

Horizon BCBSNJ pharmacy guidelines do not constitute medical advice, authorization, certification, approval, explanation of benefits, offer of coverage, contract or guarantee of payment.

FDA-APPROVED INDICATIONS

Gonal-F:

For Females:

Gonal-F is indicated for the induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure. Gonal-F is also indicated for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology (ART) program.

Selection of Patients:

- Before treatment with Gonal-F is instituted, a thorough gynecologic and endocrinologic evaluation must be performed. This should include assessment of pelvic anatomy. Patients with tubal obstruction should receive Gonal-F only if enrolled in an in vitro fertilization program.
- Primary ovarian failure should be excluded by the determination of gonadotropin levels.
- Appropriate evaluation should be performed to exclude pregnancy.
- Evaluation of partner's fertility potential should be included in the evaluation.
- Patients in later reproductive life have a greater predisposition to endometrial carcinoma as well as a higher incidence of anovulatory disorders. A thorough diagnostic evaluation should always be performed in patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities before starting Gonal-F.

For Males:

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.

Selection of Patients:

- Before treatment with Gonal-F is instituted for azoospermia, a thorough medical and endocrinologic evaluation must be performed.
- Hypogonadotropic hypogonadism should be confirmed and primary testicular failure should be excluded by the determination of gonadotropin levels.
- Prior to Gonal-F therapy for azoospermia in patients with hypogonadotropic hypogonadism, serum testosterone levels should be normalized.

Bravelle:

Bravelle, in conjunction with hCG, is indicated for ovulation induction in patients who have previously received pituitary suppression.

Bravelle, in conjunction with hCG, is indicated for *multiple* follicular development (controlled ovarian stimulation) during ART cycles in patients who have previously received pituitary suppression.

Selection of Patients:

- Before treatment with Bravelle is instituted, a thorough gynecologic and endocrinologic evaluation must be performed. Except for those patients enrolled in an *in vitro* fertilization program, this should include a hysterosalpingography to rule out uterine and tubal pathology) and documentation of anovulation by means of basal body temperature, serial vaginal smears, examination of cervical mucus, determination of serum or urine progesterone, urinary pregnanediol and endometrial biopsy. Patients with tubal pathology should receive Bravelle only if enrolled in an *in vitro* fertilization program.
- Primary ovarian failure should be excluded by determination of gonadotropin levels.
- Careful examination should be made to rule out the presence of an early pregnancy.
- Patients in late reproductive life have a greater predilection to endometrial carcinoma as well as a higher incidence of anovulatory disorders. Cervical dilation and curettage should always be done for diagnosis before starting Bravelle therapy in such patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities.
- Evaluation of the partner's fertility potential should be included in the workup.

Follistim:

Follistim is indicated for the development of multiple follicles in ovulatory female patients participating in an Assisted Reproductive Technology (ART) program. Follistim is also indicated for induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure.

Selection of Patients:

- A thorough gynecologic and endocrinologic evaluation of the patient must be performed. The evaluation should include a hysterosalpingogram (to rule out uterine pathology) an documentation of anovulation by means of reviewing a patient's history, performing a physical examination, determining serum hormonal levels as indicated, and optionally performing an endometrial biopsy. Patients with tubal pathology should receive Follistim only if enrolled in an ART program.
- Primary ovarian failure should be excluded by the determination of circulating gonadotropin levels.
- Careful examination should be made to rule out early pregnancy.
- Evaluation of the partner's fertility potential should be included in the workup.

Medical Necessity Guideline:

1. The following questionnaire may be used to determine medical necessity of Gonal-F, Follistim and Bravelle prescriptions.

CRITERIA FOR REVIEW

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|---|-----|----|
| 1. Does the patient have the diagnosis of infertility?
[If the answer to this question is no, no further questions required] | Yes | No |
|---|-----|----|

2. Is the patient male? [If the answer to this question is yes, may skip to question 10]	Yes	No
3. Will the patient be undergoing intrauterine insemination (IUI)? [If the answer is no, then skip to question 5.]	Yes	No
4. Is the patient < 45 years of age? [If the answer is no, then please forward request to Horizon Pharmacy Service pharmacy_services@horizonblue.com . When Horizon approves please proceed to question 9.] [If the answer is yes, then skip to question 8.]	Yes	No
5. Is or will the patient be undergoing follicle stimulation as part of an Assisted Reproductive Technology (ART) program (i.e., in vitro fertilization -IVF, gamete intrafallopian transfer -GIFT, tubal embryo transfer-TET, zygote intrafallopian transfer -ZIFT)? [If the answer is yes, then please forward request to Horizon Pharmacy Service pharmacy_services@horizonblue.com . When Horizon approves please proceed to question 8.]	Yes	No
6. Is or will the patient be undergoing treatment for induction of ovulation? [If the answer to this question is no, then no further questions required.]	Yes	No
7. Has the patient failed an adequate trial with clomiphene citrate therapy? (an adequate trial would be 3 complete monthly cycles, for example, 50 mg daily for 5 days per month for 3 monthly cycles)	Yes	No
8. Has pregnancy been excluded as confirmed by a negative urine or serum pregnancy test?	Yes	No
9. Does the patient have any of the following contraindications to follitropin therapy? - High levels of FSH indicating primary ovarian failure - Uncontrolled thyroid or adrenal dysfunction - An organic intracranial lesion such as a pituitary or hypothalamic tumor - Tumor of the ovary, breast or uterus - The presence of any cause of infertility other than either anovulation or unexplained infertility, unless they are candidates for in vitro fertilization - Abnormal uterine bleeding of undetermined origin - Clinically significant ovarian cysts or enlargement not due to polycystic ovary syndrome - Primary ovarian failure [If patient is going through IUI or ART procedure, skip to question 14.] [If patient is going through ovulation induction, skip to question 13.]	Yes	No
10. Is the prescription for Gonal-f? [If the answer to this question is no, no further questions required]	Yes	No
11. Does the patient have a diagnosis of hypogonadotropic hypogonadism?	Yes	No
12. Does the patient have any of the following contraindications to follitropin therapy? - High levels of FSH indicating primary gonadal failure - Uncontrolled thyroid or adrenal dysfunction - Sex hormone dependent tumors of the reproductive tract and accessory organs - An organic intracranial lesion such as a pituitary tumor - primary testicular failure	Yes	No
13. Was the partner of the patient found to be fertile?	Yes	No
14. Will the patient require more than the dispensing limit of 4500 International Units every 30 days?	Yes	No

Guidelines for Approval

Duration of Approval – 3 months, Approval sets 1, 2, 3, and 4

Set 1 – IUI < 45y/o		Set 2 – Ovulation Induction	
Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)
1	2	1	2
3	9	6	3
4	14	7	5
8		8	9
		13	14
SET 3 IUI and >=45 y/o		SET 4 ART Procedure IVF, GIFT, TET, or ZIFT	
Yes to question(s)	NEEDS APPROVAL FROM HORIZON	Yes to question(s)	NEEDS APPROVAL FROM HORIZON
1	2	1	2
3	4	5	3
8	9	8	9
	14		14
Duration of Approval, Approval set 5 12 months – For Gonadotropin only			
Set 5 – Hypogonadotropic Hypogonadism			
Yes to question(s)	No to question(s)	No to question(s)	
1		12	
2		14	
10			
11			
13			

Horizon BCBSNJ Pharmacy Guideline Development Process: This Horizon BCBSNJ Pharmacy Guideline (the “Pharmacy Guideline”) has been developed by Horizon BCBSNJ’s Pharmacy Drug Policy Subcommittee, Clinical Issues Subcommittee, and Quality Improvement Committee which include practicing physicians and pharmacists. This guideline is consistent with generally accepted standards of medical and pharmacy practice, and reflects Horizon BCBSNJ’s view of the subject health care services, supplies drugs or procedures, and in what circumstances they are deemed to be medically necessary or experimental/ investigational in nature. This Pharmacy Guideline also considers whether and to what degree the subject health care services, supplies or procedures are clinically appropriate, in terms of type, frequency, extent, site and duration and if they are considered effective for the illnesses, injuries or diseases discussed. Where relevant, this Pharmacy Guideline considers whether the subject prescription drugs are being requested primarily for the convenience of the covered person or the health care provider. It may also consider whether the prescription drugs are more costly than alternative prescription drugs that are at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the relevant illness, injury or disease. In reaching its conclusion regarding what it considers to be the generally accepted standards of medical and pharmacy practice, Horizon BCBSNJ reviews and considers the following: all credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, physician and health care provider specialty society recommendations, the views of physicians and health care providers practicing in relevant clinical areas (including, but not limited to, the prevailing opinion within the appropriate specialty), the findings and directives of the Food and Drug Administration and any other relevant factor as determined by applicable State and Federal laws and regulations.

BLACK BOX WARNINGS

None

RATIONALE

The intent of the criteria is to ensure that patients follow selection elements noted in labeling. Since the products are used interchangeably in the treatment of female infertility, all will be considered for the treatment of ovulation induction in anovulatory infertile females in whom the cause is functional and not due to primary ovarian failure and for use in conjunction with ART procedures. For male infertility uses, only Gonadotropin will be approved. Because follitropin therapy can harm a fetus, pregnancy must be ruled out before their use. Unless the patient is undergoing an Assisted Reproductive Technology (ART) procedure, the partner must have their fertility evaluated and be found fertile. Follitropin therapy is contraindicated in female patients with a high circulating FSH level indicating primary ovarian failure; an uncontrolled thyroid and adrenal dysfunction; an organic intracranial lesion such as a pituitary or hypothalamic tumor; a tumor of the

ovary, breast, or uterus; the presence of any cause of infertility other than either anovulation or unexplained infertility, unless they are candidates for in vitro fertilization; abnormal uterine bleeding of undetermined origin; or clinically significant ovarian cysts or enlargement not due to polycystic ovary syndrome. Follitropin therapy is contraindicated in male patients with high levels of FSH indicating primary gonadal failure; uncontrolled thyroid or adrenal dysfunction; sex hormone dependent tumors of the reproductive tract and accessory organs; or an organic intracranial lesion such as a pituitary tumor.

Horizon BCBSNJ has requested that all requests for patients undergoing an ART procedure – either a non-IUI procedure, or IUI and ≥ 45 years of age be sent to Horizon BCBSNJ services to verify whether the patient has coverage for this indication. If the patient qualifies for coverage, Horizon BCBSNJ will contact CVS Caremark to proceed with the clinical questions in the criteria. If the patient does not qualify for coverage, Horizon BCBSNJ will send a denial letter to the physician and inform CVS Caremark of this decision. Horizon BCBSNJ has requested a question addressing the dosage limit of 4500 International Units every 30 days.

ADDITIONAL INFORMATION

Dosage and Administration

Follistim:

Assisted Reproductive Technologies:

A starting dose of 150 to 225 IU of Follistim is recommended for at least the first four days of treatment. After this, the dose may be adjusted for the individual patient based upon the ovarian response. In clinical studies with patients who are responding, it was shown that daily maintenance dosages that range from 75 to 300 IU for six to twelve days are sufficient, although longer treatment may be necessary. However, in patients that were low or poor responders, maintenance doses of 375 to 600 IU were administered according to individual response. This latter category comprised approximately 10% of the women evaluated during clinical studies. The maximum, individualized, daily dose of Follistim that has been used in clinical studies is 600 IU. When a sufficient number of follicles of adequate size are present, the final maturation of the follicles is induced by administering hCG at a dose of 5000 to 10,000 IU. Oocyte (egg) retrieval is performed 34 to 36 hours later. The administration of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of Follistim therapy. This will reduce the change of developing OHSS.

Ovulation Induction:

There are a variety of treatment protocols available for ovulation induction. In studies using Follistim, a stepwise gradually increasing dosing scheme was used. The starting dose was 75 IU of Follistim for up to 14 days. The dose was then increased by 37.5 IU of Follistim at weekly intervals until follicular growth and/or serum estradiol levels indicated an adequate response. The maximum, individualized, daily dose of Follistim that has been safely used for ovulation induction patients during clinical trials was 300 IU. The patient should be treated until ultrasonic visualizations and/or serum estradiol determinations indicate pre-ovulatory conditions equivalent to or greater than those of the normal individual followed by hCG 5000 to 10,000 IU. If the ovaries are abnormally enlarged on the last day of Follistim therapy, hCG must be withheld during this course of treatment. This will reduce the chances of developing OHSS.

During treatment with Follistim and during a two-week post-treatment period, patients should be examined at least every other day for signs of excessive ovarian stimulation. It is recommended that Follistim administration be stopped if the ovaries become abnormally enlarged or abdominal pain occurs. Most OHSS occurs after treatment has been discontinued and reaches its maximum at about seven to ten days post-ovulation.

For ovulation induction, the couple should be encouraged to have intercourse daily, beginning on the day prior to administration of hCG and until ovulation becomes apparent from the indices employed for the determination of progesterational activity. Care should be taken to insure insemination. In light of the foregoing indices and parameters mentioned, unless a physician is willing to devote considerable time to these patients and be familiar with and conduct these necessary laboratory studies, he/she should not use Follistim.

Gonal-F:

Infertile Patients with Oligo-Anovulation:

The dose of Gonal-F to stimulate development of the follicle must be individualized for each patient.

The lowest dose consistent with the expectation of good results should be used. Over the course of treatment, doses of Gonal-F may range up to 300 IU per day depending on the individual patient response. Gonal -F should be administered until adequate follicular development is indicated by serum estradiol and vaginal ultrasonography. A response is generally evident after 5 to 7 days. Subsequent monitoring intervals should be based on individual patient response.

It is recommended that the initial dose of the first cycle be 75 IU of Gonal-F per day. An incremental adjustment in dose of up to 37.5 IU may be considered after 14 days. Further dose increases of the same magnitude could be made if

necessary every seven days. Treatment duration should not exceed 35 days unless an E2 (estradiol) rise indicates imminent follicular development. To complete follicular development and effect ovulation in the absence of an endogenous LH surge, hCG 5000 to 10,000 IU should be given 1 day after the last dose of Gonal-F. Human chorionic gonadotropin (hCG) should be withheld if the serum estradiol is greater than 2000 pg/mL. If the ovaries are abnormally enlarged or abdominal pain occurs, Gonal-F treatment should be discontinued, hCG should not be administered, and the patient should be advised not to have intercourse; this will reduce the chance of development of Ovarian Hyperstimulation Syndrome (OHSS) and, should spontaneous ovulation occur, reduce the chance of multiple gestation. A follow-up visit should be conducted in the luteal phase.

The initial dose administered in the subsequent cycles should be individualized for each patient based on her response in the preceding cycle. Doses larger than 300 IU of FSH per day are not routinely recommended. As in the initial cycle, 5000 to 10,000 U of hCG must be given 1 day after the last dose of Gonal-F to complete follicular development and induce ovulation. The precautions described above should be followed to minimize the chance of development of Ovarian Hyperstimulation Syndrome.

The couple should be encouraged to have intercourse daily, beginning on the day prior to the administration of hCG until ovulation becomes apparent from the indices employed for the determination of progestational activity. Care should be taken to ensure insemination. In light of the indices and parameters mentioned, unless a physician is willing to devote considerable time to these patients and be familiar with and conduct the necessary laboratory studies, he/she should not use Gonal-F.

Assisted Reproductive Technologies:

As in the treatment of patients with polycystic ovary syndrome, the dose of Gonal-F to stimulate development of the follicle must be individualized for each patient. For Assisted Reproductive Technologies, therapy with Gonal-F should be initiated in the early follicular phase (cycle day 2 or 3) at a dose of 150 IU per day, until sufficient follicular development is attained. In most cases, therapy should not exceed 10 days.

In patients undergoing Assisted Reproductive Technologies, whose endogenous gonadotropin levels are suppressed, Gonal-F should be initiated at a dose of 225 IU per day. Treatment should be continued until adequate follicular development is indicated as determined by ultrasound in combination with measurement of serum estradiol levels. Adjustments in dose may be considered after five days based on the patient's response. Subsequently, dosages should be adjusted no more frequently than every 3 to 5 days and by no more than 75 to 150 IU additionally at each adjustment. Doses greater than 450 IU per day are not recommended. Once adequate follicular development is evident, hCG (5000 to 10,000 IU) should be administered to induce final follicular maturation in preparation for oocyte retrieval. The administration of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of therapy. This should reduce the chance of developing OHSS.

Male Patients with Hypogonadotropic Hypogonadism:

The dose of Gonal-F to induce spermatogenesis must be individualized for each patient.

Gonal-F must be given in conjunction with hCG. Prior to concomitant therapy with Gonal-F and hCG, pretreatment with hCG alone (1000 to 2250 IU two to three times per week) is required. Treatment should continue for a period sufficient to achieve serum testosterone levels within the normal range. Such pre-treatment may require 3 to 6 months and the dose of hCG may need to be increased to achieve normal testosterone levels.

After normal testosterone levels are reached, the recommended dose of Gonal-F is 150 IU administered subcutaneously three times per week and the recommended dose of hCG is 1000 IU, or the dose required to maintain normal testosterone levels, three times per week. The lowest dose of Gonal-F, which induces spermatogenesis, should be utilized. If azoospermia persists, the dose of Gonal-F may be increased to a maximum dose of 300 IU three times per week. Gonal-F may need to be administered for up to 18 months to achieve adequate spermatogenesis.

Use all products immediately after reconstitution. Discard any unused product.

Bravelle:

Infertile patients with oligo-anovulation:

The dose of Bravelle to stimulate development of ovarian follicles must be individualized for each patient. The lowest dose consistent with achieving good results based on clinical experience and reported clinical data should be used.

The recommended initial dose of Bravelle for patients who have received GnRH agonist or antagonist pituitary suppression is 150IU daily for the first 5 days of treatment. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of Bravelle should not exceed 450 IU and in most cases dosing beyond 12 days is not recommended.

If patient response to Bravelle is appropriate, hCG (5000 to 10,000 USP units) should be given one day following the last dose of Bravelle. The hCG should be withheld if the serum estradiol is greater than 2000 pg/ml, if the ovaries are abnormally enlarged, or if abdominal pain occurs, and the patient should be advised to refrain from intercourse. These precautions may reduce the risk of Ovarian Hyperstimulation Syndrome and multiple gestations. Patients should be followed closely for at least two weeks after hCG administration. If there is inadequate follicle development or ovulation without subsequent pregnancy, the course of treatment with Bravelle may be repeated. The couple should be encouraged to have intercourse daily, beginning on the day prior to the administration of hCG until ovulation become apparent from the indices employed for the determination of progestational activity. In the light of the foregoing indices and parameters mentioned, unless the physician is willing to devote considerable time to these patients and be familiar with and conduct the necessary laboratory studies, he/she should not use Bravelle.

CONTRAINDICATIONS/WARNINGS

Contraindications:

Women:

- A high FSH level indicating primary ovarian failure
- Uncontrolled thyroid and adrenal dysfunction
- An organic intracranial lesion, such as a pituitary tumor
- The presence of any cause of infertility other than anovulation, unless they are candidates for in vitro fertilization
- Abnormal bleeding of undetermined origin
- Ovarian cysts or enlargement not due to polycystic ovarian syndrome
- Prior hypersensitivity to follitropins
- Pregnancy Category X, therefore follitropins are contraindicated in women who are pregnant and may cause fetal harm when administered to pregnant women.

Men:

- Prior sensitivity to follitropins or the excipients
- High levels of FSH indicating primary gonadal failure
- Uncontrolled thyroid or adrenal dysfunction
- Sex hormone dependent tumors of the reproductive tract and accessory organs
- An organic intracranial lesion such as a pituitary tumor

Warnings:

Ovarian Hyperstimulation Syndrome (OHSS) is a medical event distinct from uncomplicated ovarian enlargement. OHSS may progress rapidly to become a serious medical event. It is characterized by an apparent dramatic increase in vascular permeability that can result in a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain.

Serious pulmonary conditions (i.e., atelectasis, acute respiratory distress syndrome) have been reported. In addition, thromboembolic events both in association with, and separate from the Ovarian Hyperstimulation Syndrome, have been reported following follitropin therapy. Intravascular thrombosis and embolism, which may originate in venous or arterial vessels, can result in reduced blood flow to critical organs or the extremities. Sequelae of such events have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of a limb. In rare cases, pulmonary complications and/or thromboembolic events have resulted in death.

Multiple births have been associated with follitropin treatment. Both patient and partner should be advised of the potential risk of multiple births before starting treatment.

REFERENCES

1. Gonal-F Product Information. Serono Laboratories, Inc. March 2001.
2. Follistim Product Information. Organon Inc. December 1998.
3. Fertinex Product Information. Serono Laboratories, Inc. March 1999
4. Bravelle Product Information. Ferring Pharmaceuticals, Inc. December 2002.
5. Facts and Comparisons. www.efactsweb.com. 2001.
6. USPDI. Thomson MICROMEDEX. 2007.

7. MICROMEDEX Thompson Healthcare. MICROMEDEX Inc. Greenwood Village, CO. March 2007.

Pharmacy Guidelines can be highly technical and are designed for use by the Horizon BCBSNJ professional staff in making coverage determinations. Members referring to this policy should discuss it with their treating physician or pharmacist, and should refer to their specific benefit plan for the terms, conditions, limitations and exclusions of their coverage.

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