Infertility Step Therapy/Quantity Limit Criteria

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonal-F®, RFF</td>
<td>follitropin alpha</td>
<td>injection</td>
</tr>
</tbody>
</table>

FDA APPROVED INDICATIONS4,5
The following information is taken from individual drug prescribing information and is provided here as background information only. Not all FDA-approved indications may be considered medically necessary. All criteria are found in the section “Step Therapy/Quantity Limit PA Criteria for Approval”

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

Gonal-f® is also indicated for spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism in whom the cause of infertility is not due to primary testicular failure.

CONTRAINDICATIONS
Gonal-f® RFF Pen (follitropin alfa injection) is contraindicated in women who exhibit:

- 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.
- Abnormal uterine bleeding of undetermined origin.
- Ovarian cyst or enlargement of undetermined origin, not due to polycystic ovary.
- Pregnancy.

CLINICAL RATIONALE

About one third of infertility is due to problems with ovulation. During normal ovulation, pulsatile release of gonadotropin releasing hormone (GnRH) from the hypothalamus initiates a normal menstrual cycle. GnRH stimulates pituitary release of the endogenous gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH), which act on the ovary to stimulate oocyte growth. A rapid increase in LH concentrations midcycle (about day 14), the "LH surge", triggers ovulation. Conception usually occurs 24-36 hours after ovulation. 15

Induction of ovulation is now generally accomplished in 2 steps: FSH/LH or clomiphene (which stimulates pituitary release of FSH and LH) are used for follicular stimulation, and human chorionic gonadotropin (hCG), which is normally produced by the placenta, is used to simulate the LH surge and induce final follicular maturation and ovulation. 15
In women with anatomically normal reproductive tracts, controlled ovarian hyperstimulation (COH) can increase fertility by 15-25%. Administration of oral clomiphene or injectable gonadotropins (FSH alone or combined with LH) stimulates production of oocytes. Ultrasound and serum estradiol determinations during the cycle monitor follicular response. When 2 or 3 follicles reach an average diameter of 18-20 mm, either ovulation is induced by injection of hCG or the oocytes are harvested by transvaginal ultrasound-guided aspiration, depending on whether COH is to be followed by intrauterine insemination (IUI) or in vitro fertilization (IVF). IUI is used alone mostly in single women with a sperm donor, but also in couples with cervical factor infertility, decreased sperm count, or mild abnormalities in sperm motility and morphology. In unexplained infertility or documented ovarian failure, IUI is often combined with COH. One or two inseminations are usually performed between 36-40 hours after injection of hCG. 15

In women with ovulatory failure or those who have unexplained infertility with normal estradiol and gonadotropin levels, clomiphene is considered a reasonable first approach to ovulation induction. It may be combined with IUI to increase the likelihood of conception, particularly in couples with oligospermia. If 3 or 4 cycles of clomiphene fail to result in a pregnancy, or the woman is of advanced fertility age, injectable FSH/LH may be tried for ovulation induction. When this approach also fails, assisted reproductive technologies (ART) can be tried. ART is used from the beginning in women with tubal factor infertility. 15

**Estrogen Antagonists- Clomiphene**

Clomiphene is thought to act by binding to estrogen-receptor containing tissues (including the hypothalamus) and triggering release of GnRH, which in turn stimulates pituitary release of FSH and LH. After treatment with clomiphene, 80% of anovulatory patients will ovulate and about 30-40% will become pregnant. Most pregnancies (75%) occur in 3-6 treatment cycles. Adverse effects of clomiphene include hot flashes, gastrointestinal disturbances, breast discomfort, reversible visual changes, headache and abnormal uterine bleeding. Ovarian hyperstimulation syndrome (OHSS) can occur rarely, but is more common with use of injectable FSH and LH. 15

Impediments to achieving pregnancy must be excluded or adequately treated before beginning clomiphene therapy. Patients most likely to achieve success with clomiphene include patients with polycystic ovary syndrome, amenorrhea-galactorrhea syndrome, psychogenic amenorrhea, post-oral-contraceptive amenorrhea, and certain cases of secondary amenorrhea of undetermined etiology. Properly timed coitus in relationship to ovulation is important. A basal body temperature graph or other appropriate tests may help the patient and her physician determine if ovulation occurred. Once ovulation has been established, each course of clomiphene should be started on or about the 5th day of the cycle. Long-term cyclic therapy is not recommended beyond a total of about six cycles (including three ovulatory cycles). Clomiphene is indicated only in patients with demonstrated ovulatory dysfunction who meet certain conditions and criteria which are outlined in prescribing information. 1,2

**Gonadotropins**

FSH and LH

Injectable FSH and LH are used in patients who have failed to ovulate with clomiphene and in those who are not candidates for clomiphene because of hypothalamic anovulation. They are also used when large numbers of oocytes are needed, as in ART procedures. Preparations available in the US differ in their mixture of FSH/LH and in their source. Repronex contains equal amounts of FSH and LH isolated from the urine of postmenopausal women. Bravelle also contains human menopausal gonadotropins, but is primarily FSH. Follitropin alfa (Gonal-f) and follitropin beta (Follistim) are recombinant FSH products. Lutropin alfa (Luveris) is a recombinant LH preparation. Mixed human gonadotropins and those containing primarily or only FSH are associated with similar pregnancy rates. 15
The most serious adverse effect of FSH/LH preparations is OHSS, which occurs late in the menstrual cycle or during early pregnancy. Increased ovary size first leads to abdominal pain, and later to nausea, vomiting and, occasionally, diarrhea. In its most severe form, OHSS can cause ascites, vascular, renal and respiratory problems, with fatalities reported rarely. Injection site reactions can also occur. 15

Human Chorionic Gonadotropin (hCG)
Structurally similar to LF, hCG is used to induce final follicular maturation and ovulation by simulating the LH surge. The recombinant form of hCG (Ovidrel) has been shown to be as effective as urinary hCG and may cause fewer injection site reactions. 15

Before starting treatment with gonadotropins, a thorough gynecologic and endocrinologic evaluation must be performed. Please see gonadotropin prescribing information for required evaluation procedures and patient selection criteria.

**Gonadotropin Releasing Hormone (GnRH) Antagonists**
Following SC injection, GnRH antagonists cause a rapid decrease in hypothalamic secretion of FSH and LH and are useful to prevent premature ovulation. Some regimens using GnRH antagonists have been associated with slightly lower pregnancy rates than those using GnRH agonists, but also a lower incidence of OHSS. 15

Adverse effects of GnRH antagonists include nausea, headache, injection site reactions, and possibly OHSS. Hypersensitivity reactions have occurred rarely with cetrorelix. 15

**References**
8. Menopur prescribing information. Ferring Pharmaceuticals, Inc.
Infertility Step Therapy/Quantity Limit

OBJECTIVE
The intent of the step therapy criteria for the Gonal F agents is to accommodate for use of non-preferred agents when the preferred agent—Follistim AQ cannot be used due to allergy, intolerance, contraindication, or treatment failure. The step therapy edit will be applied to patients initiating therapy with Gonal-F. Patients who are currently being treated with Gonal-F will be allowed to continue therapy if found in the patient’s claims history or medication history.

The intent of the Gonal F, RFF Quantity Limit (QL) program is to encourage appropriate prescribing quantities as recommended by FDA-approved product labeling.

TARGET DRUGS – STEP THERAPY
Gonal F®, RFF (follitropin alpha)

QUANTITY LIMIT TARGET DRUGS - RECOMMENDED LIMITS

<table>
<thead>
<tr>
<th>Agent*</th>
<th>Dosage Form</th>
<th>Strength/ Formulation</th>
<th>Dispensing Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonal F</td>
<td>injection</td>
<td>450 units/vial</td>
<td>10 vials/Rx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1050 units/vial</td>
<td>5 vials/Rx</td>
</tr>
<tr>
<td>Gonal F RFF</td>
<td>injection</td>
<td>75 units/vial</td>
<td>60 vials/Rx:No</td>
</tr>
<tr>
<td>Gonal F RFF pen</td>
<td>injection</td>
<td>300 units/cartridge</td>
<td>15 cartrtridges/Rx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>450 units/cartridge</td>
<td>10 cartrtridges/Rx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>900 units/cartridge</td>
<td>5 cartridges/Rx</td>
</tr>
</tbody>
</table>

*Quantity limit allows single agent per month

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Gonal F, RFF will be approved when BOTH of the following is met:

1. ONE of the following:
   a. The patient is currently receiving the requested brand agent OR
   b. The patient’s medication history includes use of Follistim AQ OR
   c. The patient has a contraindication, allergy, or intolerance, to the Follistim AQ AND
2. The patient is not receiving concomitant Follistim AQ or Bravelle AND
3. ONE of the following:
   a. The quantity requested is within the set quantity limit OR
   b. The quantity requested is above the quantity limit and the prescriber has submitted documentation to support therapy with a higher dose or higher quantity for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 12 months
Infertility Step Therapy/Quantity Limit

ELECTRONIC EDIT

STEP THERAPY
For the Infertility step therapy edit, the 30-day search period was chosen to capture the most recent or current therapy for one preferred agent.

SUMMARY OF INFERTILITY AGENTS STEP THERAPY

<table>
<thead>
<tr>
<th>Targeted Agent(s)</th>
<th>Gonal F, Gonal F RFF (multisource code: M, N, O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is auto-grandfathering implemented? (with look-back time frame)</td>
<td>Yes (30 days)</td>
</tr>
<tr>
<td>Prerequisite Agent(s)</td>
<td>Follistim AQ (multisource code: M, N, O)</td>
</tr>
<tr>
<td>Number of prerequisites required</td>
<td>1</td>
</tr>
<tr>
<td>Prerequisite look-back time frame</td>
<td>90 days</td>
</tr>
<tr>
<td>Age-related edit?</td>
<td>NA</td>
</tr>
<tr>
<td>Additional comments</td>
<td>dynamic PA message: Use 10012 if urgent, if not fax 8774808130</td>
</tr>
</tbody>
</table>

a - The system searches for a claim with a days supply that begins or ends in the past 30 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 60 days prior to the new claim.

Dynamic PA edit is in place to allow dispensing pharmacists to override the PA if member requires therapy within 48 hours. The override will allow coverage of target medication without submitting a PA request. The Dynamic PA will not override any quantity limits.

DETAILS OF INFERTILITY AGENTS STEP THERAPY

<table>
<thead>
<tr>
<th>Targeted Agents</th>
<th>GPIs (multisource codes)</th>
<th>Prerequisite Agents</th>
<th>GPIs (multisource codes)</th>
<th>Look-back Time frames</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonal F, Gonal F RFF (multisource code: M, N, or O)</td>
<td>3006203005**** (M, N, or O)</td>
<td>ANY ONE of: Follistim AQ</td>
<td>3006203010**** (M, N, or O)</td>
<td>90 days</td>
</tr>
</tbody>
</table>

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

QUANTITY LIMIT
The quantity limit edit for Gonal F, RFF (GPIs in table above, all multi-source codes) allows for approval for patients prescribed quantities at or below the program limits; for Gonal F, RFF, step therapy requirements must be met also.

PRIOR AUTHORIZATION CRITERIA QUESTION SET
Initial and Renewal Evaluation

1. Is the patient currently receiving therapy with the requested agent? If yes, continue to 4. If no, continue to 2.

2. Has the patient previously tried and failed Follistim AQ? If yes, continue to 4. If no, continue to 3.
3. Does the patient have an allergy, contraindication, or intolerance to Follistim AQ? 
   If yes, continue to 4. If no, deny.

4. Is the patient taking this medication in combination with another FSH (i.e., Bravelle, Follistim AQ) 
   If yes, continue to 5. If no, continue to 6

5. Will the FSH (i.e., Bravelle, Follistim AQ) be discontinued upon initiation of Gonal F? 
   If yes, continue to 6. If no, deny

6. Is the quantity requested within the set limit? 
   If yes, approve for 12 months. If no, continue to 7

7. Has the prescriber submitted documentation in support of therapy with a higher dose for the 
   intended diagnosis? 
   If yes, pharmacist must review and may approve for 12 months based on review of information 
   provided. If no, deny.