**INSTRUCTIONS FOR USE**

The following Coverage Policy applies to health benefit plans administered by Cigna companies. Coverage Policies are intended to provide guidance in interpreting certain standard Cigna benefit plans. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of Cigna. Copyright ©2017 Cigna

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**Coverage Policy**

Note: Injectable fertility medications are specifically excluded under most benefit plans. Please refer to the applicable benefit plan document to determine benefit availability and the terms and conditions of coverage.

When coverage is available and medically necessary (refer to the table below), the dosage, frequency, duration of therapy and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Infertility Injectables.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Criteria for Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follitropin Therapy</strong></td>
<td><strong>PLEASE NOTE: Follistim® AQ is a preferred brand follitropin therapy product.</strong></td>
</tr>
<tr>
<td><strong>Bravelle</strong> (urofollitropin)</td>
<td>Use in combination with hCG (human chorionic gonadotropin) therapy meeting BOTH of the following:</td>
</tr>
<tr>
<td></td>
<td>• EITHER of the following:</td>
</tr>
<tr>
<td></td>
<td>o Ovulation stimulation in females for EITHER of the following:</td>
</tr>
<tr>
<td></td>
<td>▪ As part of an Assisted Reproductive Technology (ART) program</td>
</tr>
<tr>
<td></td>
<td>▪ Oligoovulatory or anovulatory infertile women in whom the cause of infertility is functional and not due to primary ovarian failure</td>
</tr>
<tr>
<td></td>
<td>o Spermatogenesis stimulation in a male for primary or secondary hypogonadotropic hypogonadism not due to primary testicular failure</td>
</tr>
<tr>
<td></td>
<td>• Documented cycle failure with Follistim® AQ</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Criteria for Use</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------</td>
</tr>
</tbody>
</table>
| **Follistim AQ**<br>(follitropin beta) | Use in combination with hCG (human chorionic gonadotropin) therapy for EITHER of the following:  
  - Ovulation stimulation in females for EITHER of the following:  
    - As part of an Assisted Reproductive Technology (ART) program  
    - Oligoovulatory or anovulatory infertile women in whom the cause of infertility is functional and not due to primary ovarian failure  
  - Spermatogenesis stimulation in a male for primary or secondary hypogonadotropic hypogonadism not due to primary testicular failure |
| **Gonal-f**<br>(follitropin alfa) | Use in combination with hCG (human chorionic gonadotropin) therapy meeting BOTH of the following:  
  - EITHER of the following:  
    - Ovulation stimulation in females for EITHER of the following:  
      - As part of an Assisted Reproductive Technology (ART) program  
      - Oligoovulatory or anovulatory infertile women in whom the cause of infertility is functional and not due to primary ovarian failure  
    - Spermatogenesis stimulation in a male for primary or secondary hypogonadotropic hypogonadism not due to primary testicular failure  
  - Documented cycle failure with Follistim AQ |
| **Gonadotropin Releasing Hormone Agonist**<br>Leuprolide acetate*, Lupron Depot®* | Use in documented infertility for EITHER of the following:  
  - Use in combination with urofollitropin or menotropins in a woman with premature LH surge to suppress luteinizing hormone (LH) production  
  - To prevent severe ovarian hyperstimulation syndrome (OHSS) associated with in vitro fertilization |
| **Gonadotropin Releasing Hormone Antagonists**<br>Cetrotide®<br>(cetrorelix acetate) | Inhibition of premature luteinizing hormone (LH) surges in a woman undergoing controlled ovarian stimulation (COS) in conjunction with assisted reproductive procedures |
| **Ganirelix acetate** |  |
| **Human Chorionic Gonadotropins (hCG)**<br>Chorionic Gonadotropin, Novarel®, Pregnyl®<br>(chorionic gonadotropin) | Use when EITHER of the following are met:  
  - In combination with ovulation stimulation therapy in females for ANY of the following:  
    - As part of an Assisted Reproductive Technology (ART) program  
    - Anovulatory infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure  
    - Treatment of corpus luteum dysfunction  
  - In males for the following:  
    - Alone or in combination with follicitrops or menotropins for spermatogenesis stimulation as a result of documented primary or secondary hypogonadotropic hypogonadism |
| **Ovidrel**<br>(choriogonadotropin alfa injection) | Use in combination with ovulation stimulation therapy in a woman when EITHER of the following criteria is met:  
  - As part of an Assisted Reproductive Technology (ART) program  
  - Anovulatory infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure |
<p>| <strong>Menotropin Therapy</strong>&lt;br&gt;Menopur®&lt;br&gt;(menotropins for | Use in combination with hCG (human chorionic gonadotropin) therapy for EITHER for the following: |</p>
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Criteria for Use</th>
</tr>
</thead>
</table>
| injection | • Ovulation stimulation in a woman for EITHER of the following:  
  o As part of an Assisted Reproductive Technology (ART) program  
  o Oligoovulatory or anovulatory infertile woman in whom the cause of infertility is functional and not due to primary ovarian failure  
  • Spermatogenesis stimulation in a male for primary or secondary hypogonadotropic hypogonadism not due to primary testicular failure |

* The use of leuprolide acetate, Lupron Depot® for other indications are addressed in separate coverage policies (Oncology Medications, Pharmacy Prior Authorization). Please refer to the related coverage policy links above.  

Cigna does not cover the use of Infertility Injectables for any other indication because it is considered experimental, investigational or unproven.  

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

### FDA Approved Indications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>FDA Approved Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follitropins</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Bravelle (urofollitropin) | **Induction of Ovulation in Women who have Previously Received Pituitary Suppression**  
Prior to initiation of treatment with Bravelle:  
• Perform a complete gynecologic and endocrinologic evaluation  
• Exclude a diagnosis of primary ovarian failure  
• Exclude the possibility of pregnancy  
• Demonstrate tubal patency  
• Evaluate the fertility status of the male partner  

**Development of Multiple Follicles as Part of an Assisted Reproductive Technology (ART) Cycle in Ovulatory Women Who Have Previously Received Pituitary Suppression**  
Prior to initiation of treatment with Bravelle:  
• Perform a complete gynecologic and endocrinologic evaluation, and diagnose the cause of infertility  
• Exclude the possibility of pregnancy  
• Evaluate the fertility status of the male partner  
• Exclude women with primary ovarian failure |
| Follistim AQ (follitropin beta) | **Follistim AQ (follitropin beta injection) Cartridge is indicated:**  
**In Women for:**  
**Induction of Ovulation and Pregnancy in Anovulatory Infertile Women in Whom the Cause of Infertility is Functional and Not Due to Primary Ovarian Failure**  
Prior to initiation of treatment with Follistim AQ Cartridge:  
• Women should have a complete gynecologic and endocrinologic evaluation.  
• Primary ovarian failure should be excluded.  
• The possibility of pregnancy should be excluded.  
• Tubal patency should be demonstrated.  
• The fertility status of the male partner should be evaluated.  

**Pregnancy in Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) Cycle**  
Prior to initiation of treatment with Follistim AQ Cartridge:  
• Women should have a complete gynecologic and endocrinologic evaluation and diagnosis of cause of infertility.  
• The possibility of pregnancy should be excluded.  
• The fertility status of the male partner should be evaluated. |
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>FDA Approved Indication</th>
</tr>
</thead>
</table>
| **In Men for:**
**Induction of Spermatogenesis in Men with Primary and Secondary Hypogonadotropic Hypogonadism (HH) in Whom the Cause of Infertility is Not Due to Primary Testicular Failure**
Prior to initiation of treatment with Follistim AQ Cartridge:
- Men should have a complete medical and endocrinologic evaluation.
- Hypogonadotropic hypogonadism should be confirmed and primary testicular failure should be excluded.
- Serum testosterone levels should be normalized with human chorionic gonadotropin (hCG) treatment.
- The fertility status of the female partner should be evaluated.

| **Gonal-f**
(follitropin alfa) | **Women**
Gonal-f (follitropin alfa for injection) is indicated for the induction of ovulation and pregnancy in the anovulatory infertile patient 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**
1. Before treatment with Gonal-f is instituted, a thorough gynecologic and endocrinologic evaluation must be performed. This should include an assessment of pelvic anatomy. Patients with tubal obstruction should receive Gonal-f only if enrolled in an in vitro fertilization program.
2. Primary ovarian failure should be excluded by the determination of gonadotropin levels.
3. Appropriate evaluation should be performed to exclude pregnancy.
4. 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 therapy.
5. Evaluation of the partner’s fertility potential should be included in the initial evaluation.

**Men**
Gonal-f (follitropin alfa for injection) 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**
1. Before treatment with Gonal-f is instituted for azoospermia, a thorough medical and endocrinologic evaluation must be performed.
2. Hypogonadotropic hypogonadism should be confirmed, and primary testicular failure should be excluded by the determination of gonadotropin levels.
3. Prior to Gonal-f therapy for azoospermia in patients with hypogonadotropic hypogonadism, serum testosterone levels should be normalized.

| **Gonal-f RFF.**
**Gonal-f RFF Pen**
(follitropin alfa) | **Gonal-f RFF (follitropin alfa for 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.**

**Selection of Patients**
1. Before treatment with Gonal-f RFF is instituted, a thorough gynecologic and
endocrinologic evaluation must be performed. This should include an
assessment of pelvic anatomy. Patients with tubal obstruction should receive
Gonal-f RFF only if enrolled in an \textit{in vitro} fertilization program.

2. Primary ovarian failure should be excluded by the determination of
gonadotropin levels.

3. Appropriate evaluation should be performed to exclude pregnancy.

4. 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 RFF therapy.

5. Evaluation of the partner's fertility potential should be included in the initial
evaluation.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>FDA Approved Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonal-f RFF Redi-ject (follitropin alfa)</td>
<td>\textbf{Induction of Ovulation and Pregnancy in Oligo-Anovulatory Women in whom the Cause of Infertility is Functional and Not Due to Primary Ovarian Failure}</td>
</tr>
<tr>
<td></td>
<td>Prior to initiation of treatment with Gonal-f RFF Redi-ject:</td>
</tr>
<tr>
<td></td>
<td>\begin{itemize}</td>
</tr>
<tr>
<td></td>
<td>\item Perform a complete gynecologic and endocrinologic evaluation</td>
</tr>
<tr>
<td></td>
<td>\item Exclude primary ovarian failure</td>
</tr>
<tr>
<td></td>
<td>\item Exclude the possibility of pregnancy</td>
</tr>
<tr>
<td></td>
<td>\item Demonstrate tubal patency</td>
</tr>
<tr>
<td></td>
<td>\item Evaluate the fertility status of the male partner</td>
</tr>
<tr>
<td></td>
<td>\end{itemize}</td>
</tr>
<tr>
<td></td>
<td>\textbf{Development of Multiple Follicles in Ovulatory Women as Part of an Assisted Reproductive Technology (ART) Cycle}</td>
</tr>
<tr>
<td></td>
<td>Prior to initiation of treatment with Gonal-f RFF Redi-ject:</td>
</tr>
<tr>
<td></td>
<td>\begin{itemize}</td>
</tr>
<tr>
<td></td>
<td>\item Perform a complete gynecologic and endocrinologic evaluation, and diagnose the cause of infertility</td>
</tr>
<tr>
<td></td>
<td>\item Exclude the possibility of pregnancy</td>
</tr>
<tr>
<td></td>
<td>\item Evaluate the fertility status of the male partner</td>
</tr>
<tr>
<td></td>
<td>\end{itemize}</td>
</tr>
</tbody>
</table>

Gonadotropin Releasing Hormone Agonist

<table>
<thead>
<tr>
<th>Leuproline acetate, Lupron Depot</th>
<th>Not FDA approved for infertility \begin{itemize} \item Advanced prostatic cancer \item Central precocious puberty \end{itemize}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lupron Depot 7.5 mg for 1-month administration, 22.5 mg for 3-month administration, 30 mg for 4-month administration, and 45 mg for 6-month administration (leuproline acetate) are indicated in the palliative treatment of advanced prostatic cancer.</td>
</tr>
<tr>
<td></td>
<td>Lupron Depot 3.75 mg (for 1 month administration) and Lupron Depot-3 Month 11.25 mg are indicated for endometriosis and uterine leiomyomata (fibroids).</td>
</tr>
</tbody>
</table>

Gonadotropin Releasing Hormone Antagonists

<table>
<thead>
<tr>
<th>Cetrotide (cetrorelix acetate)</th>
<th>Cetrotide (cetrorelix acetate for injection) is indicated for the inhibition of premature LH surges in women undergoing controlled ovarian stimulation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganirelix acetate</td>
<td>Ganirelix Acetate Injection is indicated for the inhibition of premature LH surges in women undergoing controlled ovarian hyperstimulation.</td>
</tr>
</tbody>
</table>

Human Chorionic Gonadotropins (hCG)

<table>
<thead>
<tr>
<th>Chorionic Gonadotropin, Novarel, Pregnyl (chorionic gonadotropin)</th>
<th>HCG HAS NOT BEEN DEMONSTRATED TO BE EFFECTIVE ADJUNCTIVE THERAPY IN THE TREATMENT OF OBESITY. THERE IS NO SUBSTANTIAL EVIDENCE THAT IT INCREASES WEIGHT LOSS BEYOND THAT RESULTING FROM CALORIC RESTRICTION, THAT IT CAUSES A MORE ATTRACTIVE OR &quot;NORMAL&quot; DISTRIBUTION OF FAT, OR THAT IT DECREASES THE HUNGER AND DISCOMFORT ASSOCIATED WITH CALORIE-RESTRICTED DIETS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Name</td>
<td>FDA Approved Indication</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1. Prepubertal cryptorchidism not due to anatomical obstruction. In general, HCG is thought to induce testicular descent in situations when descent would have occurred at puberty. HCG thus may help predict whether or not orchiopexy will be needed in the future. Although, in some cases, descent following HCG administration is permanent, in most cases, the response is temporary. Therapy is usually instituted between the ages 4 and 9.</td>
<td></td>
</tr>
<tr>
<td>2. Selected cases of hypogonadotropic hypogonadism (hypogonadism secondary to a pituitary deficiency) in males.</td>
<td></td>
</tr>
<tr>
<td>3. Induction of ovulation and pregnancy in the anovulatory, infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure, and who has been appropriately pretreated with human menotropins.</td>
<td></td>
</tr>
<tr>
<td>Ovidrel (choriogonadotropin alfa injection)</td>
<td>Ovidrel PreFilled Syringe (choriogonadotropin alfa injection) is indicated for the induction of final follicular maturation and early luteinization in infertile women who have undergone pituitary desensitization and who have been appropriately pretreated with follicle stimulating hormones as part of an Assisted Reproductive Technology (ART) program such as in vitro fertilization and embryo transfer. Ovidrel PreFilled Syringe is also indicated for the induction of ovulation (OI) and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure.</td>
</tr>
<tr>
<td>Selection of Patients</td>
<td></td>
</tr>
<tr>
<td>1. Before treatment with gonadotropins is instituted, a thorough gynecologic and endocrinologic evaluation must be performed. This should include an assessment of pelvic anatomy. Patients with tubal obstruction should receive Ovidrel PreFilled Syringe only if enrolled in an in vitro fertilization program.</td>
<td></td>
</tr>
<tr>
<td>2. Primary ovarian failure should be excluded by the determination of gonadotropin levels.</td>
<td></td>
</tr>
<tr>
<td>3. Appropriate evaluation should be performed to exclude pregnancy.</td>
<td></td>
</tr>
<tr>
<td>4. 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 FSH and Ovidrel PreFilled Syringe therapy.</td>
<td></td>
</tr>
<tr>
<td>5. Evaluation of the partner's fertility potential should be included in the initial evaluation.</td>
<td></td>
</tr>
<tr>
<td>Menotropins</td>
<td></td>
</tr>
<tr>
<td>Menopur (menotropins for injection)</td>
<td>Development of Multiple Follicles and Pregnancy in Ovulatory Women as Part of an Assisted Reproductive Technology (ART) Cycle</td>
</tr>
<tr>
<td>Prior to initiation of treatment with Menopur:</td>
<td></td>
</tr>
<tr>
<td>• Perform a complete gynecologic and endocrinologic evaluation, and diagnose the cause of infertility</td>
<td></td>
</tr>
<tr>
<td>• Exclude the possibility of pregnancy</td>
<td></td>
</tr>
<tr>
<td>• Evaluate the fertility status of the male partner</td>
<td></td>
</tr>
<tr>
<td>• Exclude a diagnosis of primary ovarian failure</td>
<td></td>
</tr>
<tr>
<td>FDA Recommended Dosing</td>
<td></td>
</tr>
<tr>
<td>Drug Name</td>
<td>FDA Recommended Dosing</td>
</tr>
<tr>
<td>Follitropins</td>
<td></td>
</tr>
<tr>
<td>Bravelle (urofollitropin)</td>
<td>General Dosing Information</td>
</tr>
<tr>
<td>• Administer Bravelle subcutaneously in the abdomen or intramuscularly as described in Instructions for Use.</td>
<td></td>
</tr>
<tr>
<td>• A healthcare provider should administer Bravelle intramuscularly.</td>
<td></td>
</tr>
<tr>
<td>Recommended Dosing for Induction of Ovulation</td>
<td>The dosing scheme is stepwise and is individualized for each woman.</td>
</tr>
</tbody>
</table>

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For women who have received GnRH agonist or antagonist pituitary suppression, a starting dose of 150 International Units per day of Bravelle is administered subcutaneously or intramuscularly for 5 days in the first cycle of treatment. In subsequent cycles of treatment, the starting dose (and dosage adjustments) of Bravelle should be determined based on the history of the ovarian response to Bravelle.

The following should be considered when planning the woman’s individualized dose of Bravelle:
- Appropriate Bravelle dose adjustment(s), based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results), should be used to prevent multiple follicular growth and cycle cancellation.
- Do not make adjustments in dose more frequently than once every 2 days and do not exceed more than 75 to 150 International Units per adjustment.
- Use the lowest dose of Bravelle that will achieve desired results.
- The maximum, individualized, daily dose of Bravelle is 450 International Units per day.
- In general, do not exceed 12 days of treatment.
- When pre-ovulatory conditions are reached, administer human chorionic gonadotropin (hCG) to induce final oocyte maturation and ovulation.
- Withhold hCG in cases where the ovarian monitoring on the last day of Bravelle treatment suggests an increased risk of ovarian hyperstimulation syndrome (OHSS).
- Encourage the woman and her partner to have intercourse daily, beginning on the day prior to the administration of hCG and until ovulation becomes apparent. Discourage intercourse when the risk for OHSS is increased.

Recommended Dosing for Assisted Reproduction Technology (ART)
The recommended dosing scheme for patients undergoing IVF follows a stepwise approach and is individualized for each woman. The recommended initial dose of Bravelle for women who have received a GnRH agonist for pituitary suppression is 225 International Units. Bravelle may be administered together with Menopur (menotropins for injection, USP), and the total initial dose when the products are combined should not exceed 225 International Units (150 International Units of Bravelle and 75 International Units of Menopur or 75 International Units of Bravelle and 150 International Units of Menopur).
- Beginning on cycle day 2 or 3, a starting dose of 225 International Units of Bravelle is administered subcutaneously daily until sufficient follicular development, as determined by ultrasound in combination with measurement of serum estradiol levels, is attained. In most cases, therapy should not exceed 12 days.
- Adjust the dose after 5 days based on the woman’s ovarian response, as determined by ultrasound evaluation of follicular growth and serum estradiol levels.
- Do not make additional dosage adjustments more frequently than every 2 days or by more than 75 - 150 International Units at each adjustment.
- Continue treatment until adequate follicular development is evident, and then administer hCG.
- Withhold the administration of hCG in cases where the ovarian monitoring suggests an increased risk of OHSS on the last day of Bravelle therapy.
- Do not administer daily doses of Bravelle or Bravelle in combination with Menopur that exceed 450 International Units.

**Follistim AQ**
(follitropin beta)

**General Dosing Information**
- Follistim AQ Cartridge with the pen injector device delivers on average an 18% higher amount of follitropin beta when compared to reconstituted Follistim delivered with a conventional syringe and needle. When administering Follistim AQ Cartridge, a lower starting dose and lower dose adjustments (as compared to reconstituted Follistim) should be considered. For that purpose the following Dose Conversion Table is provided:
**Drug Name** | **FDA Recommended Dosing**
---|---

### Table 1: Follistim AQ Cartridge Administered Subcutaneously With the Follistim Pen Dose Conversion Table*

<table>
<thead>
<tr>
<th>Lyophilized recombinant FSH dosing with ampules or vials, using conventional syringe</th>
<th>Follistim AQ Cartridge dosing with the Follistim Pen</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 IU</td>
<td>50 IU</td>
</tr>
<tr>
<td>150 IU</td>
<td>125 IU</td>
</tr>
<tr>
<td>225 IU</td>
<td>175 IU</td>
</tr>
<tr>
<td>300 IU</td>
<td>250 IU</td>
</tr>
<tr>
<td>375 IU</td>
<td>300 IU</td>
</tr>
<tr>
<td>450 IU</td>
<td>375 IU</td>
</tr>
</tbody>
</table>

* Each value represents an 18% difference rounded to the nearest 25 IU increment.

**Recommended Dosing in Anovulatory Women Undergoing Ovulation Induction**

The dosing scheme is stepwise and is individualized for each woman.

- A starting daily dose of 50 international units of Follistim AQ Cartridge is administered subcutaneously daily for at least the first 7 days.
- Subsequent dosage adjustments are made at weekly intervals based upon ovarian response. If an increase in dose is indicated by the ovarian response, the increase should be made by 25 or 50 international units of Follistim AQ Cartridge at weekly intervals until follicular growth and/or serum estradiol levels indicate an adequate ovarian response.
- The following should be considered when planning the woman's individualized dose:
  - Appropriate Follistim AQ Cartridge dose adjustment(s) should be used to prevent multiple follicular growth and cycle cancellation.
  - The maximum, individualized, daily dose of Follistim AQ Cartridge is 250 international units.
- Treatment should continue until ultrasonic visualizations and/or serum estradiol determinations approximate the pre-ovulatory conditions seen in normal individuals.
- When pre-ovulatory conditions are reached, 5,000 to 10,000 international units of hCG are used to induce final oocyte maturation and ovulation. The administration of hCG must be withheld in cases where the ovarian monitoring suggests an increased risk of OHSS on the last day of Follistim AQ Cartridge therapy.
- The woman and her partner should be encouraged to have intercourse daily, beginning on the day prior to the administration of hCG and until ovulation becomes apparent.
- During treatment with Follistim AQ Cartridge and during a two-week post-treatment period, the woman should be assessed at least every other day for signs of excessive ovarian stimulation. It is recommended that Follistim AQ Cartridge administration be stopped if the ovarian monitoring suggests an increased risk of OHSS or abdominal pain occurs. Most OHSS occurs after treatment has been discontinued and reaches its maximum at about seven to ten days post-ovulation.

**Recommended Dosing in Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) Cycle**

The dosing scheme follows a stepwise approach and is individualized for each woman.

- A starting dose of 200 international units (actual cartridge doses) of Follistim AQ Cartridge is administered subcutaneously daily for at least the first 7 days of treatment.
- Subsequent to the first 7 days of treatment, the dose can be adjusted down or up based upon the woman's ovarian response as determined by ultrasound evaluation.
of follicular growth and serum estradiol levels. Dosage reduction in high responders can be considered from the 6th day of treatment onward according to individual response.

The following should be considered when planning the woman's individualized dose:

- For most normal responding women, the daily starting dose can be continued until pre-ovulatory conditions are achieved (seven to twelve days).
- For low or poor responding women, the daily dose should be increased according to the ovarian response. The maximum, individualized, daily dose of Follistim AQ Cartridge is 500 international units.
- For high responding women [those at particular risk of abnormal ovarian enlargement and/or ovarian hyperstimulation syndrome (OHSS)], decrease or temporarily stop the daily dose, or discontinue the cycle according to individual response.
- When a sufficient number of follicles of adequate size are present, dosing of Follistim AQ Cartridge is stopped and final maturation of the oocytes is induced by administering hCG at a dose of 5,000 to 10,000 international units. The administration of hCG should be withheld in cases where the ovarian monitoring suggests an increased risk of OHSS on the last day of Follistim AQ Cartridge therapy.
- Oocyte (egg) retrieval should be performed 34 to 36 hours following the administration of hCG.

**Recommended Dosing for Induction of Spermatogenesis in Men**

- Pretreatment with hCG is required prior to concomitant therapy with Follistim AQ Cartridge and hCG. An initial dosage of 1,500 international units of hCG should be administered at twice weekly intervals to normalize serum testosterone levels. If serum testosterone levels have not normalized after 8 weeks of hCG treatment, the hCG dose can be increased to 3,000 international units twice weekly.
- After normal serum testosterone levels have been reached, Follistim AQ Cartridge should be administered by subcutaneous injection concomitantly with hCG treatment. Follistim is given at a dosage of 450 international units per week, as either 225 international units twice weekly or 150 international units three times per week, in combination with the same hCG dose used to normalize testosterone levels. Based on delivery of a higher dose of follitropin beta with the Follistim AQ Cartridge and pen injector, a lower dose of Follistim AQ Cartridge may be considered.

The concomitant therapy should be continued for at least 3 to 4 months before any improvement in spermatogenesis can be expected. If a man has not responded after this period, the combination therapy may be continued. Treatment response has been noted at up to 12 months.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>FDA Recommended Dosing</th>
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</thead>
</table>
| **Gonal-f (follitropin alfa)** | Infertile Patients with oligo-anovulation  
The dose of Gonal-f (follitropin alfa for injection) 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, ADMINISTERED SUBCUTANEOUSLY. 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 rise indicates imminent follicular development. To complete follicular development and effect ovulation in the absence of an endogenous LH surge, chorionic gonadotropin, hCG, (5,000 USP units) should be given 1 day after the last dose of Gonal-f. Chorionic gonadotropin should be withheld if the serum estradiol is greater than 2,000 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 may reduce the chance of development of the Ovarian Hyperstimulation Syndrome 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, 5,000 USP units 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 the 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, it should become obvious that, 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 oligo-anovulatory infertility, 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 ten days.

In patients undergoing ART, 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 to dose may be considered after five days based on the patient's response; subsequently dosage should be adjusted no more frequently than every 3-5 days and by no more than 75-150 IU additionally at each adjustment. Doses greater than 450 IU per day are not recommended. Once adequate follicular development is evident, hCG (5,000 to 10,000 USP units) 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 (follitropin alfa for injection) 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 (1,000 to 2,250 USP units 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 pretreatment may require 3 to 6 months and the dose of hCG may need to be increased to achieve normal serum testosterone levels. After normal serum testosterone levels are reached, the recommended dose of Gonal-f is 150 IU.
Gonal-f RFF, Gonal-f RFF Pen (follitropin alfa)

**Infertile Patients with oligo-anovulation**

The dose of Gonal-f RFF (follitropin alfa for injection) 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 RFF may range up to 300 IU per day depending on the individual patient response. Gonal-f RFF 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 RFF per day, ADMINISTERED SUBCUTANEOUSLY. 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 rise indicates imminent follicular development. To complete follicular development and effect ovulation in the absence of an endogenous LH surge, chorionic gonadotropin, hCG, should be given after the last dose of Gonal-f RFF. Chorionic gonadotropin should be withheld if the serum estradiol is greater than 2,000 pg/mL. If the ovaries are abnormally enlarged or abdominal pain occurs, Gonal-f RFF treatment should be discontinued, hCG should not be administered, and the patient should be advised not to have intercourse; this may reduce the chance of development of the Ovarian Hyperstimulation Syndrome 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, hCG must be given after the last dose of Gonal-f RFF to complete follicular development and induce ovulation. The precautions described above should be followed to minimize the chance of development of the 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, it should become obvious that, 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 RFF.

**Assisted Reproductive Technologies**

As in the treatment of patients with oligo-anovulatory infertility, the dose of Gonal-f RFF to stimulate development of the follicle must be individualized for each patient. For Assisted Reproductive Technologies, therapy with Gonal-f RFF 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 ten days. In patients undergoing ART under 35 years old, whose endogenous gonadotropin levels are suppressed, Gonal-f RFF should be initiated at a dose of 150 IU per day. In patients 35 years old and older whose endogenous gonadotropin levels are suppressed, Gonal-f RFF should be initiated at a dose of 225 IU per day. Treatment...
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>FDA Recommended Dosing</th>
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<tbody>
<tr>
<td>Gonal-f RFF Redi-ject (follitropin alfa)</td>
<td>should be continued until adequate follicular development is indicated as determined by ultrasound in combination with measurement of serum estradiol levels. Adjustments to dose may be considered after five days based on the patient's response; subsequently dosage should be adjusted no more frequently than every 3-5 days and by no more than 75-150 IU additionally at each adjustment. Doses greater than 450 IU per day are not recommended. Once adequate follicular development is evident, hCG 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.</td>
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</table>

### General Dosing Information
- Gonal-f RFF Redi-ject is a pre-filled disposable auto-injection device intended for multiple dose use.
- Gonal-f RFF Redi-ject can be set in 12.5 International Units increments.
- Administer Gonal-f RFF Redi-ject subcutaneously in the abdomen as described in Instructions for Use.
- Do not attempt to mix any other medications inside of the device with Gonal-f RFF Redi-ject.

### Recommended Dosing for Ovulation Induction
The dosing scheme is stepwise and is individualized for each woman. Starting doses less than 37.5 International Units have not been studied in clinical trials and are not recommended.
- A starting daily dose of 75 International Units of Gonal-f RFF Redi-ject is administered subcutaneously daily for 14 days in the first cycle of use. In subsequent cycles of treatment, the starting dose (and dosage adjustments) of Gonal-f RFF Redi-ject should be determined based on the history of the ovarian response to Gonal-f RFF Redi-ject.
- The following should be considered when planning the woman's individualized dose:
  - Appropriate Gonal-f RFF Redi-ject dose adjustment(s) should be used to prevent multiple follicular growth and cycle cancellation.
  - The maximum, individualized, daily dose of Gonal-f RFF Redi-ject is 300 International Units per day.
  - In general, do not exceed 35 days of treatment.
- If indicated by the ovarian response after the initial 14 days, make an incremental adjustment in dose, up to 37.5 International Units.
- If indicated by the ovarian response, make additional incremental adjustments in dose, up to 37.5 International Units, every 7 days.
- Treatment should continue until follicular growth and/or serum estradiol levels indicate an adequate ovarian response.
- When pre-ovulatory conditions are reached, administer human chorionic gonadotropin (hCG) to induce final oocyte maturation and ovulation. Withhold hCG in cases where the ovarian monitoring suggests an increased risk of ovarian hyperstimulation syndrome (OHSS) on the last day of Gonal-f RFF Redi-ject therapy.
- Encourage the woman and her partner to have intercourse daily, beginning on the day prior to the administration of hCG and until ovulation becomes apparent. Discourage intercourse when the risk for OHSS is increased.

### Recommended Dosing for Assisted Reproductive Technology
The dosing scheme follows a stepwise approach and is individualized for each woman.
- Beginning on cycle day 2 or 3, a starting dose of 150 International Units of Gonal-f RFF Redi-ject is administered subcutaneously daily until sufficient follicular development, as determined by ultrasound in combination with measurement of serum estradiol levels, is attained. In most cases, therapy should not exceed 10
In women under 35 years of age whose endogenous gonadotropin levels are suppressed, initiate Gonal-f RFF Redi-ject administration at a dose of 150 International Units per day.

In women 35 years of age and older whose endogenous gonadotropin levels are suppressed, initiate Gonal-f RFF Redi-ject administration at a dose of 225 International Units per day.

- Adjust the dose after 5 days based on the woman's ovarian response, as determined by ultrasound evaluation of follicular growth and serum estradiol levels.
- Do not make additional dosage adjustments more frequently than every 3-5 days or by more than 75-150 International Units at each adjustment.
- Continue treatment until adequate follicular development is evident, and then administer hCG.
  The administration of hCG should be withheld in cases where the ovarian monitoring suggests an increased risk of OHSS on the last day of Gonal-f RFF Redi-ject therapy.
- Doses greater than 450 International Units per day are not recommended.

### Gonadotropin Releasing Hormone Agonist

**Leuprolide acetate, Lupron Depot**

Not FDA approved for infertility

### Gonadotropin Releasing Hormone Antagonists

**Cetrotide**

(cetrorelix acetate)

Ovarian stimulation therapy with gonadotropins (FSH, hMG) is started on cycle Day 2 or 3. The dose of gonadotropins should be adjusted according to individual response.

Cetrotide (cetrorelix acetate for injection) 0.25 mg may be administered subcutaneously once daily during the early- to mid-follicular phase. In the single dose regimen, 3 mg of

Cetrotide 0.25 mg is administered on either stimulation day 5 (morning or evening) or day 6 (morning) and continued daily until the day of hCG administration. When assessment by ultrasound shows a sufficient number of follicles of adequate size, hCG is administered to induce ovulation and final maturation of the oocytes. No hCG should be administered if the ovaries show an excessive response to the treatment with gonadotropins to reduce the chance of developing ovarian hyperstimulation syndrome (OHSS).

**Ganirelix acetate**

After initiating FSH therapy on Day 2 or 3 of the cycle, Ganirelix Acetate Injection 250 mcg may be administered subcutaneously once daily during the mid to late portion of the follicular phase. By taking advantage of endogenous pituitary FSH secretion, the requirement for exogenously administered FSH may be reduced. Treatment with Ganirelix Acetate should be continued daily until the day of hCG administration. When a sufficient number of follicles of adequate size are present, as assessed by ultrasound, final maturation of follicles is induced by administering hCG. The administration of hCG should be withheld in cases where the ovaries are abnormally enlarged on the last day of FSH therapy to reduce the chance of developing OHSS (Ovarian Hyperstimulation Syndrome).

### Human Chorionic Gonadotropins (hCG)

**Chorionic Gonadotropin, Novarel, Pregnyl**

(chorionic gonadotropin)

For intramuscular use only. The dosage regimen employed in any particular case will depend upon the indication for the use, the age and weight of the patient, and the physician's preference. The following regimens have been advocated by various authorities:

*Prepubertal cryptorchidism not due to anatomical obstruction. Therapy is usually instituted in children between the ages of 4 and 9.*

1. 4000 USP units 3 times weekly for 3 weeks.
2. 5000 USP units every second day for 4 injections.
### Drug Name

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>FDA Recommended Dosing</th>
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<tbody>
<tr>
<td><strong>3.</strong> 15 injections for 500 to 1000 USP units over a period of 6 weeks.</td>
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<tr>
<td><strong>4.</strong> 500 USP units 3 times weekly for 4 to 6 weeks. If this course of treatment is not successful, another series is begun 1 month later, giving 1000 USP units per injection.</td>
<td></td>
</tr>
<tr>
<td><strong>Selected cases of hypogonadotropic hypogonadism in males.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>1.</strong> 500 to 1000 USP units 3 times a week for 3 weeks, followed by the same dose twice a week for 3 weeks.</td>
<td></td>
</tr>
<tr>
<td><strong>2.</strong> 4000 USP units 3 times weekly for 6 to 9 months, following which the dosage may be reduced to 2000 USP units 3 times weekly for an additional 3 months.</td>
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<tr>
<td><strong>Induction of ovulation and pregnancy in the anovulatory, infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure and who has been appropriately pretreated with human menotropins.</strong> (See prescribing information for menotropins for dosage and administration for that drug product.)</td>
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</tr>
<tr>
<td><strong>5000 to 10,000 USP units 1 day following the last dose of menotropins. (A dosage of 10,000 USP units is recommended in the labeling for menotropins.)</strong></td>
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</table>

### Ovidrel

(choriogonadotropin alfa injection)

**For Subcutaneous Use Only**

**Infertile Women Undergoing Assisted Reproductive Technologies (ART)**

Ovidrel PreFilled Syringe 250 µg should be administered one day following the last dose of the follicle stimulating agent. Ovidrel PreFilled Syringe should not be administered until adequate follicular development is indicated by serum estradiol and vaginal ultrasonography. Administration should be withheld in situations where there is an excessive ovarian response, as evidenced by clinically significant ovarian enlargement or excessive estradiol production.

**Infertile Women Undergoing Ovulation Induction (OI)**

Ovidrel PreFilled Syringe should not be administered until adequate follicular development is indicated by serum estradiol and vaginal ultrasonography.

Ovidrel PreFilled Syringe 250 µg should be administered one day following the last dose of the follicle stimulating agent.

Ovidrel PreFilled Syringe administration should be withheld in situations where there is an excessive ovarian response, as evidenced by multiple follicular development, clinically significant ovarian enlargement or excessive estradiol production.

### Menotropins

**Menopur**

(menotropins for injection)

**General Dosing Information**

- Administer Menopur subcutaneously in the abdomen as described in Instructions for Use.
- Menopur may be administered together with Bravelle (urofollitropin for injection, purified).

**Recommended Dosing for Assisted Reproductive Technology**

The recommended dosing scheme for patients undergoing IVF follows a stepwise approach and is individualized for each woman. The recommended initial dose of Menopur for women who have received a GnRH agonist for pituitary suppression is 225 International Units. Menopur may be administered together with Bravelle (urofollitropin for injection, purified) and the total initial dose when the products are combined should not exceed 225 International Units (150 International Units of Menopur and 75 International Units of Bravelle or 75 International Units of Menopur and 150 International Units of Bravelle).

- Beginning on cycle day 2 or 3, a starting dose of 225 International Units of Menopur is administered subcutaneously daily. Adjust the dose after 5 days based on the woman's ovarian response, as determined by ultrasound.
- Do not make additional dosage adjustments more frequently than every 2 days or by more than 150 International Units at each adjustment.
- Continue treatment until adequate follicular development is evident, and then administer hCG. Withhold the administration of hCG in cases where the ovarian monitoring suggests an increased risk of OHSS on the last day of Menopur therapy.
- Do not administer daily doses of Menopur or Menopur in combination with Bravelle that exceed 450 International Units.
- Therapy should not exceed 20 days.

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### Drug Availability

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follitropins</strong></td>
<td></td>
</tr>
<tr>
<td>Bravelle (urofollitropin)</td>
<td>Available as a lyophilized powder for injection containing 82.5 International Units (IU) of FSH, to deliver 75 IU FSH after reconstituting</td>
</tr>
<tr>
<td>Follistim AQ (follitropin beta)</td>
<td>Available in cartridges containing 175 IU per 0.210 mL, 350 IU per 0.420 mL, 650 IU per 0.780 mL, and 975 IU per 1.170 mL.</td>
</tr>
<tr>
<td>Gonal-f (follitropin alfa)</td>
<td>Supplied in a sterile, lyophilized form in multiple dose vials filled with 600 IU or 1200 IU in order to deliver 450 IU and 1050 IU FSH, respectively, after reconstitution with diluent.</td>
</tr>
<tr>
<td><strong>Gonal-f RFF, Gonal-f RFF Pen, Gonal-f RFF Redi-ject (follitropin alfa)</strong></td>
<td><strong>RFF = revised female formulation</strong></td>
</tr>
<tr>
<td><strong>Gonal-f RFF</strong>: Supplied in a sterile, lyophilized form in single-dose vials containing 82 IU with diluent (Sterile Water for Injection, USP) in a pre-filled syringe. Following reconstitution with the diluent as described, upon administration each vial will deliver a dose of 75 IU.</td>
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<tr>
<td><strong>Gonal-f RFF Pen</strong>: Available as a disposable, prefilled multiple-dose delivery system. Each Gonal-f RFF Pen is filled with 415 IU, 568 IU, or 1026 IU follitropin alfa to deliver a minimum total of 300 IU in 0.5 mL, 450 IU in 0.75 mL, or 900 IU in 1.5 mL, respectively.</td>
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</tr>
<tr>
<td><strong>Gonal-f RFF Redi-ject</strong>: Available as 300 International Units (IU) per 0.5 mL, 450 IU per 0.75 mL, and 900 IU per 1.5 mL in prefilled, multiple dose disposable delivery systems.</td>
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</tr>
<tr>
<td><strong>Gonadotropin Releasing Hormone Agonist</strong></td>
<td></td>
</tr>
<tr>
<td>Leuprolide acetate, Lupron Depot®</td>
<td>Leuprolide acetate injection is available from various manufacturers in a multi-dose vial of 14 mg/2.8 mL (concentration of 1 mg/0.2 mL).</td>
</tr>
</tbody>
</table>
| Lupron Depot (indicated for prostate cancer) is available as follows:  
  - 7.5 mg for 1-month administration  
  - 22.5 mg for 3-month administration  
  - 30 mg for 4-month administration  
  - 45 mg for 6-month administration  |
| Lupron Depot (indicated for endometriosis and uterine leiomyomata) is available as follows:  
  - 3.75 mg for 1-month administration  
  - 11.25 mg for 3-month administration  |
<p>| <strong>Gonadotropin Releasing Hormone Antagonists</strong> |                                                                                                                                                   |
| Cetrotide (cetrorelix acetate) | Available in a carton of one packaged tray containing one vial (which contains 0.26 - 0.27 mg cetrorelix acetate, corresponding to 0.25 mg cetrorelix), one pre-filled syringe with 1 mL of Sterile Water for Injection, one 20 gauge needle, one 27 gauge needle, and two alcohol swabs. |</p>
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Availability</th>
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</thead>
<tbody>
<tr>
<td>Ganirelix acetate</td>
<td>Available as a disposable, ready for use, prefilled syringe containing 250 mcg/0.5 mL aqueous solution of Ganirelix Acetate. Each syringe is affixed with a 27 gauge x ½-inch needle closed by a needle shield of natural rubber latex.</td>
</tr>
<tr>
<td><strong>Human Chorionic Gonadotropins (hCG)</strong></td>
<td></td>
</tr>
<tr>
<td>Chorionic Gonadotropin</td>
<td>Available as 10,000 USP Units in a 10 mL multiple dose vial.</td>
</tr>
<tr>
<td>Novarel (chorionic gonadotropin)</td>
<td>Available as individually packaged vials containing 10,000 USP Units per vial.</td>
</tr>
<tr>
<td>Pregnyl (chorionic gonadotropin)</td>
<td>Available as a 10 mL lyophilized multiple dose vial containing: 10,000 USP units chorionic gonadotropin per vial.</td>
</tr>
<tr>
<td>Ovidrel (choriogonadotropin alfa injection)</td>
<td>Available as a pre-filled syringe containing 250 μg choriogonadotropin alfa in 0.5 mL.</td>
</tr>
<tr>
<td><strong>Menotropins</strong></td>
<td></td>
</tr>
<tr>
<td>Menopur (menotropins for injection)</td>
<td>Available as a lyophilized powder for injection containing 75 International Units FSH and 75 International units of LH activity, supplied as lyophilized powder or pellet in sterile vials with diluent vials and Q-Cap® vial adapters.</td>
</tr>
</tbody>
</table>

**General Background**

**Guidelines**

- **American Association of Clinical Endocrinologists (AACE)**
  A diagnosis of hypogonadotropic hypogonadism is characterized by a low level of testosterone and low levels of follicle stimulating hormone (FSH) and lutenizing hormone (LH). For the induction of spermatogenesis, AACE recommends that individuals with hypogonadotropic hypogonadism receive treatment with human chorionic gonadotropin (hCG) with or without human menopausal gonadotropin (or FSH) or gonadotropin-releasing hormone (GnRH). Individuals with hyogonadotropic hypogonadism of prepubertal onset generally require therapy hCG in combination with human menopausal gonadotropin (or FSH). hCG therapy alone may be used in men with partial gonadotropin deficiency or in those who were previously stimulated peripubertally or maintain production of sperm with hCG. (Petak, 2002)

- **American Society for Reproductive Medicine (ASRM)**
  The ASRM recommends before gonadotropins are prescribed in an anovulatory woman a comprehensive evaluation of the individual be conducted, including analysis of semen. In women who have hypogonadic amenorrhea or polycystic ovary syndrome, ovulation may be induced using gonadotropins, but not as first line therapy. Gonadotropin naïve individuals should be started with a low dose and the dose should be individualized for future cycles based on previous response. Prudent treatment with gonadotropins and patient monitoring are recommended to decrease the chance of multiple pregnancy, but cautions the risk cannot be completely eliminated. The organization recognizes the greater quality and better outcomes associated with the currently available gonadotropin formulations and states that there are no proven differences in regards to safety, efficacy or purity between any of the available marketed gonadotropin products. (ASRM, 2008)

- **European Association of Urology (EAU)**
  The EAU Guidelines on Male Hypogonadism state that in cases of secondary hypogonadism and only where fertility is a concern, hCG treatment is appropriate, particular in individuals with low gonadotropin levels. (Dohle, 2016) Per the Guidelines on Male Infertility, for cases of acquired hypogonadal hypogonadism, which can be a result of various drugs (e.g., hormones), spermatogenesis can be stimulated by the use of concurrent hCG with FSH or human menopausal gonadotropins (HMGs). In individuals whose hypogonadal hypogonadism is hypothalamic in origin, pulse dosing of a gonadotropin releasing hormone (GnRH) is considered an alternative to hCG. Individuals who were hypogonadic prior to puberty may take as long as two years of GnRH treatment to produce sperm. (Jungwirth, 2016)

**Follitropins**

**Pharmacology**
Follitropins are useful in anovulatory and oligoovulatory patients, patients with unexplained infertility, and patients undergoing ART programs (i.e., in vitro fertilization [IVF] or intracytoplasmic sperm injection). These agents are typically used together with gonadotropin-releasing hormone (GnRH) agonists to suppress the pituitary gland and prevent premature ovulation. Follitropins are labeled for use in combination with human chorionic gonadotropin (hCG) to induce ovulation in anovulatory females without primary ovarian failure, stimulate follicular development in ovulatory females undergoing IFV, and stimulate spermatogenesis in males with hypogonadotropic hypogonadism.

Urofollitropin (uFSH) is purified follicle-stimulating hormone (FSH) obtained from the urine of postmenopausal women and biologically standardized for FSH activity. Recombinant follitropin (rFSH) alfa and recombinant follitropin beta are produced by modified Chinese Hamster Ovary (CHO) cells and are biologically standardized for FSH activity. These preparations contain no luteinizing hormone (LH) activity. To induce ovulation after follicular maturation, hCG must be administered to provide the necessary LH activity. FSH is also the primary hormone responsible for spermatogenesis, and follitropins in combination with hCG can help male patients achieve normal spermatogenesis.

Clinical Efficacy
Follitropins and menotropins have been compared in both in-vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) patients and polycystic ovary syndrome (PCOS) patients. Menotropins are another type of gonadotropin used to stimulate ovulation. In IVF/ICSI patients, pregnancy rates per cycle tend to be slightly higher with follitropins than menotropins. The treatment effect is greatest when GnRH agonists are not used, however, there is no efficacy difference when GnRH agonists are used. In PCOS patients, the two agents produce equivalent pregnancy rates, although the risk of OHSS is lower with follitropins. Comparative trials assessing the efficacy of the recombinant follitropins demonstrate that there is no difference in the degree of stimulation, number of oocytes retrieved, or clinical pregnancy or delivery rates between the two agents. (Harlin, 2000) One study showed that urofollitropin and follitropin beta had comparable efficacy in controlled ovarian hyperstimulation in women undergoing IVF.

A systematic review of 42 trials, encompassing over 9000 couples, evaluated the performance of recombinant gonadotrophin (rFHS) to three forms of urinary gonadotropins (i.e. HMG, FSH-P, FSH-HP) on ovarian stimulation in females participating in IVF or ICSI treatment cycles. The data revealed no statistically significant difference in live birth rate, regardless of the down-regulation protocol used. In addition, the data did not reveal differences in the OHSS rate. The authors expressed doubt that additional evaluations of these compounds will uncover significant differences in efficacy or safety and that the choice of gonadotropin should be based on convenience, drug availability, and financial considerations. (van Wely, 2011)

Gonadotropin Releasing Hormone (GnRH) Agonist (Leuprolide)
Pharmacology
Leuprolide is a synthetic analog of endogenous gonadotropin-releasing hormone (GnRH), or gonadorelin. GnRH regulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH) synthesis and secretion by the anterior pituitary gland. In response to GnRH, FSH and LH synthesis initially increase, causing a transient increase in circulating levels of sex hormones. With continued administration for more than one to three weeks, the pituitary gland down-regulates and desensitizes GnRH receptors, reducing FSH and LH secretion. Although the physiologic effects are complicated, the end result of continuous GnRH use is chemical castration, or markedly reduced estrogen levels in females and testosterone levels in males. In men, testosterone increases transiently during the first week after the initial dose, then falls to castrate levels after two to four weeks of continued therapy. Similarly, in women, estradiol increases transiently and then falls to postmenopausal levels by three weeks after initiating continuous therapy. Consequently, physiologic functions and tissues that are dependent on gonadal steroids for their maintenance become quiescent. Normal pituitary and gonadal function typically returns within three months of discontinuing GnRH agonist therapy. Leuprolide is not active when administered orally. The average terminal elimination half-life of leuprolide is approximately three hours. Approximately 46% of leuprolide is protein bound. The drug is eliminated via a combination of hepatic metabolism and urinary excretion.

Clinical Efficacy - Infertility
Gonadotropin-releasing hormone (GnRH) antagonists have been used to avoid the luteinizing hormone (LH) surge that can occur during controlled ovarian hyperstimulation (COH). The agonists medications can precipitate hypo-estrogenic side-effects, flare-up or require a long down-regulation period, and these can be
avoided by use of the GnRH antagonists. Because the antagonists directly and quickly inhibit the release of gonadotropin, they may be used at any time during the follicular phase, and they are used in many protocols. Individuals treated with antagonists have fewer incidences of ovarian hyperstimulation syndrome (OHSS). The objective of a Systematic Cochrane review (Al- Inany, 2011) was analysis of the safety and effectiveness of GnRH antagonists compared to the standard long protocols of GnRH agonists for COH in Assisted Reproductive Technology (ART). In over 7000 individuals included in 45 randomized controlled trials (RCTs), in which examined the agonists to the long agonist regimens, there was no statistically significant difference in the rate of live births (9 RCTs) or ongoing pregnancy (28 RCTs). The analysis did reveal a statistically significant reduction in the incidence of OHSS (29 RCTs). The authors determined that use of antagonists compared with long GnRH protocols was linked to a significant decrease in OHSS and did not reveal differences in live-birth rates.

American Hospital Formulary Service (AHFS) recognizes off-label use of leuprolide to potentially stimulate reproductive function. (AHFS, 2017)

**Gonadotropin Releasing Hormone (GnRH) Antagonists**

**Pharmacology**
Cetrotide (cetrorelix acetate) and ganirelix acetate are synthetic decapeptide GnRH antagonists which competitively blocks GnRH receptors. Cetrorelix and ganirelix compete with endogenous GnRH for receptor binding sites on gonadotropic cells of the pituitary. Binding of cetroelix or ganirelix to the receptor suppresses the release of the gonadotropins LH and follicle stimulating hormone (FSH), which are key regulatory hormones that govern ovarian growth and follicular development. The effects of cetrorelix and ganirelix on gonadotropins are reversible.

**Clinical Efficacy**
- **Cetrotide (cetrorelix acetate)**
  Six randomized, controlled, parallel trials and two meta-analyses have demonstrated cetrorelix to be effective in the prevention of premature LH surges. Cetrorelix had fewer days of stimulation (cetrorelix: 7–10.6; GnRH agonists:10–12.2), reduced the amount of HMG or FSH used, and avoided the initial flare of LH that is observed with GnRH agonist therapy. The overall clinical pregnancy rates were similar between cetrorelix (20– 31.9%) and GnRH agonists (22–34.3%).

- **Ganirelix acetate**
  The efficacy of ganirelix in the treatment of COS was established in nine published trials. Ganirelix 0.25 mg/day was demonstrated to prevent LH surges and have the best clinical outcomes. Ganirelix shortened the median treatment duration by 18–21 days, reduced the amount of FSH used, and avoided the initial flare of LH that is observed with GnRH agonist therapy. A trend toward decreased pregnancy rates was seen with ganirelix compared to GnRH agonist therapy. Ongoing pregnancy rates were 20–31% for ganirelix patients and 26–36% for patients receiving GnRH agonist therapy.

**Human Chorionic Gonadotropin Therapy**

**Pharmacology**
- **Chorionic Gonadotropin, Novarel, Pregnyl (chorionic gonadotropin)**
  Human Chorionic Gonadotropin (hCG) is a gonad-stimulating polypeptide hormone secreted by the placenta that is obtained from the urine of pregnant women. The action of hCG is virtually identical to that of pituitary LH (luteinizing hormone) although hCG appears to have a small degree of FSH (follicle-stimulating hormone) activity as well. It stimulates production of gonadal steroid hormones by stimulating the interstitial cells (Leydig cells) of the testes to produce androgens and the corpus luteum of the ovary to produce progesterone. Androgen stimulation in the male leads to the development of secondary sex characteristics and may stimulate testicular descent when no anatomical impediment to descent is present. This descent is usually reversible when hCG is discontinued. During the normal menstrual cycle, LH participates with FSH in the development and maturation of the normal ovarian follicle, and the mid-cycle LH surge triggers ovulation; hCG can substitute for LH in this function.

- **Ovidrel (choriogonadotropin alfa injection)**
  Choriogonadotropin alfa is a recombinant DNA-derived form of human chorionic gonadotropin (hCG), which is a gonad-stimulating polypeptide hormone secreted by the placenta. The action of hCG is virtually identical to that
of pituitary LH (luteinizing hormone), although hCG appears to have a small degree of FSH (follicle-stimulating hormone) activity as well. It stimulates production of gonadal steroid hormones by stimulating the interstitial cells (Leydig cells) of the testes to produce androgens and the corpus luteum of the ovary to produce progesterone. Androgen stimulation in the male leads to the development of secondary sex characteristics and may stimulate testicular descent when no anatomical impediment to descent is present. This descent is usually reversible when hCG is discontinued. During the normal menstrual cycle, LH participates with FSH in the development and maturation of the normal ovarian follicle, and the mid-cycle LH surge triggers ovulation; hCG can substitute for LH in this function.

**Menotropins**

**Pharmacology**

Menotropins are useful in anovulatory and oligoovulatory patients, patients with unexplained infertility, and patients undergoing assisted reproductive technology programs (i.e., in vitro fertilization [IVF] or intracytoplasmic sperm injection). These agents are typically used together with gonadotropin-releasing hormone (GnRH) agonists to suppress the pituitary gland and prevent premature ovulation. Menotropins are used in combination with human chorionic gonadotropin (hCG) to induce ovulation in anovulatory females without primary ovarian failure, stimulate follicular development in ovulatory females undergoing IFV, and stimulate spermatogenesis in males with hypogonadotropic hypogonadism.

Menotropins are a purified gonadotropin preparation obtained from the urine of postmenopausal women. Menotropins are biologically standardized for hormonal activity, providing one international unit (IU) of follicle-stimulating hormone (FSH) activity for each one IU of luteinizing hormone (LH) activity. Menotropins provide the pharmacologic activity of both FSH and LH. In women without primary ovarian failure, the FSH effects are dominant, stimulating growth and maturation of ovarian follicles. Additional LH must be given, as hCG, to induce ovulation after follicular maturation. In men with pituitary hypofunction, menotropins exert primarily LH effects and induce spermatogenesis.

**Clinical Efficacy**

Menotropins and follitropins have been compared in both in-vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) patients and polycystic ovary syndrome (PCOS) patients. Follitropins are another type of gonadotropin used to stimulate ovulation. In IVF/ICSI patients, pregnancy rates per cycle tend to be slightly higher with follitropins than menotropins. The treatment effect is greatest when GnRH agonists are not used. However, there is no efficacy difference when GnRH agonists are used. In PCOS patients, the two agents produce equivalent pregnancy rates, although the risk of ovarian hyperstimulation syndrome (OHSS) is lower with follitropins.

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**Coding/Billing Information**

**Note:**
1. This list of codes may not be all-inclusive.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

If benefit coverage is available for injectable fertility medications under the Pharmacy Benefit plan, the following may be considered for coverage:

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0725</td>
<td>Injection, chorionic gonadotropin, per 1,000 USP units</td>
</tr>
<tr>
<td>J1950**</td>
<td>Injection, leuprolide acetate (for depot suspension), per 3.75 mg</td>
</tr>
<tr>
<td>J3355</td>
<td>Injection, urofollitropin, 75</td>
</tr>
<tr>
<td>J3490†</td>
<td>Unclassified drugs</td>
</tr>
<tr>
<td>J9217**</td>
<td>Leuprolide acetate [Lupron Depot] (for depot suspension), 7.5 mg</td>
</tr>
<tr>
<td>S0122</td>
<td>Injection, menotropins, 75 IU</td>
</tr>
<tr>
<td>S0126</td>
<td>Injection, follitropin alpha, 75 IU</td>
</tr>
<tr>
<td>S0128</td>
<td>Injection, follitropin beta 75 IU</td>
</tr>
<tr>
<td>S0132</td>
<td>Injection, ganirelix acetate, 250 mcg</td>
</tr>
</tbody>
</table>
**when covered by medical benefit, pre-certification is not required**

†Note: May be considered for coverage when used to report Cetrotide® and Ovidrel®.

References

5. APP Pharmaceuticals, LLC. Chorionic Gonadotropin For Injection, USP [product information]. Schaumburg, IL: APP Pharmaceuticals, LLC. February 2016.