FOLLICLE STIMULATING HORMONES (FSH) USED IN THE TREATMENT OF INFERTILITY

Policy Number: PHARMACY 144.16 T2
Effective Date: October 1, 2014

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The services described in Oxford policies are subject to the terms, conditions and limitations of the Member's contract or certificate. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage enrollees. Oxford reserves the right, in its sole discretion, to modify policies as necessary without prior written notice unless otherwise required by Oxford's administrative procedures or applicable state law. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

Certain policies may not be applicable to Self-Funded Members and certain insured products. Refer to the Member’s plan of benefits or Certificate of Coverage to determine whether coverage is provided or if there are any exclusions or benefit limitations applicable to any of these policies. If there is a difference between any policy and the Member’s plan of benefits or Certificate of Coverage, the plan of benefits or Certificate of Coverage will govern.

CONDITIONS OF COVERAGE

<table>
<thead>
<tr>
<th>Applicable Lines of Business/Products</th>
<th>This policy applies to Oxford Commercial plan membership.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit Type</td>
<td>General benefits package (medical)¹ Pharmacy¹</td>
</tr>
<tr>
<td>Referral Required</td>
<td>No</td>
</tr>
<tr>
<td>(Does not apply to non-gatekeeper products)</td>
<td></td>
</tr>
<tr>
<td>Authorization Required</td>
<td>Yes²</td>
</tr>
<tr>
<td>(Precertification always required for inpatient admission)</td>
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</tr>
<tr>
<td>Precertification with Medical Director Review Required</td>
<td>No³</td>
</tr>
<tr>
<td>Applicable Site(s) of Service</td>
<td>All</td>
</tr>
<tr>
<td>(If site of service is not listed, Medical Director review is)</td>
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</tr>
</tbody>
</table>

Related Policies:
- Diagnostic (Basic) Procedures for Infertility
- Infertility Procedures Requiring Notification and/or Precertification
- Treatment of Infertility
- Treatment of Infertility for Connecticut Groups
- Treatment of Infertility for New Jersey Large Groups
- Treatment of Infertility for New Jersey Small Groups
- Treatment of Infertility for New York Large and Small Groups
Special Considerations

1 Refer to Coverage Rationale for details regarding benefit coverage for each eligible plan and product.
2 Precertification through Oxford’s Medical Management Department is required for all FSH agents.
3 Review by a Medical Director or their designee is required for doses totalling more than 450 IU/day when used for an ART cycle or 150 IU/day when used for ovulation induction, or controlled ovarian stimulation and as specifically indicated in Coverage Rationale.

COVERAGE RATIONALE

Coverage for follicle stimulating hormone (FSH) therapy is subject to both benefit availability and clinical criteria.

It is important to note that in addition to the following benefit considerations, clinical criteria below must also be met.

Note: For Members with benefit coverage availability for FSH agents, those Members currently on a course of therapy will be allowed to remain on therapy.

- **Connecticut Plans and Products:** Coverage is provided under the general benefits package (i.e., medical).

- **New Jersey Group Plans:** Coverage is provided under a Member’s prescription drug rider, if available, subject to applicable cost share. For those Members without a prescription drug rider, coverage is provided under the general benefits package (i.e., medical), subject to one office visit copayment per 30 day supply.

- **New York Large Group Plans:** Coverage is provided under a Member’s prescription drug rider, subject to applicable cost share, when used in the setting of comprehensive level (mid-level) fertility enhancement techniques such as ovulation induction.

  Note: The advanced infertility services benefit must also be available when an FSH agent is used in the setting of an advanced reproductive technique (ART) such as in vitro fertilization (IVF) or gamete intrafallopian transfer (GIFT).

- **New York Small Group Plans:** Coverage is provided under a Member’s prescription drug rider, subject to applicable cost share, when used in the setting of comprehensive level (mid-level) fertility enhancement techniques such as ovulation induction.

  Note: Coverage for an FSH agent is excluded when used in the setting of an advanced reproductive technique (ART) such as in vitro fertilization (IVF) or gamete intrafallopian transfer (GIFT).

- Infertility drugs including FSH agents are excluded from coverage for the following plans and products:
  - New Jersey Individual
  - New York Individual
  - Healthy New York Individual and Group
• Self-funded groups are not required to adopt the guidelines outlined within this policy, but may elect the same or similar guidelines. Consult with individual group benefit administrators or benefit documentation to determine the availability and structure of coverage.

• Religious employers are permitted to exclude coverage for treatments that are contrary to their bona fide religious tenets. Refer to the Member's specific certificate of coverage, summary of benefits, and/or health benefit plan documentation for details.

For Members with benefit coverage availability for FSH agents, clinical criteria below must also be met.

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

The clinically appropriate dosing for FSH agents is 450 IU/day or less when used for an ART cycle, or 150 IU/day or less when used for ovulation induction, or controlled ovarian stimulation, for not more than 14 days of treatment. Exceeding this daily dose and duration of treatment has not been proven to be efficacious in terms of pregnancy outcome.

The clinical criteria applied to coverage of an FSH agent are determined primarily by active legislation of the state in which a Member's plan or product is underwritten.

• Connecticut Plans and Products: The Member must be under the care of a board certified reproductive endocrinologist (or urologist, for male patients) and have been unable to conceive/produce conception/sustain a successful pregnancy during a one-year period.

In addition to the above, the following criteria apply to selection of an FSH agent in the patient for whom the therapy is prescribed:

  o Gonal-f® (follitropin alfa):
    ▪ Female: When used 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 or when used for the development of multiple follicles in the ovulatory patient participating in an assisted reproductive technologies (ART) program.
    ▪ Male: When used 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.

  o Bravelle® (urofollitropin) or Follistim® (follitropin beta):
    Review by a Medical Director or their designee is required
    ▪ Female: History of contraindication or intolerance to treatment with Gonal-f® (as evidenced by clinical office notes documenting adverse reaction, e.g., Gonal-f® antigen specific allergic reaction) and/or history of failure of treatment with Gonal-f® (as evidenced by clinical office notes documenting three [3] cycles of at least 750 units administered per cycle).
    ▪ Male: History of contraindication or intolerance to treatment with Gonal-f® (as evidenced by clinical office notes documenting adverse reaction, e.g., Gonal-f® antigen specific allergic reaction) and/or history of failure of treatment with Gonal-f®.

• New Jersey Large Group Plans: The Member must be under the care of a board certified reproductive endocrinologist (or urologist, for male patients) and meet the following criteria for age and medical history (as per New Jersey state mandate):
Inability to conceive after 24 months of unprotected intercourse for females less than age 35, or
Inability to conceive after 12 months of unprotected intercourse for females greater than or equal to age 35, or
Inability to carry conceived pregnancy to live birth, or
Inability of male to impregnate a female partner, or
One of the partners is considered medically sterile.

In addition to the above, the following criteria apply to selection of an FSH agent in the patient for whom the therapy is prescribed:

- Female: An FSH agent may be approved when used 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 or when used for the development of multiple follicles in the ovulatory patient participating in an assisted reproductive technologies (ART) program.
- Male: An FSH agent may be approved when used 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.

**New Jersey Small Group Plans:** The Member must be under the care of a board certified reproductive endocrinologist (or urologist, for male patients) and have failed to achieve pregnancy after 12 months of unprotected coitus (sexual intercourse).

In addition to the above, the following criteria apply to selection of an FSH agent in the patient for whom the therapy is prescribed:

- Female: An FSH agent may be approved when used 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 or when used for the development of multiple follicles in the ovulatory patient participating in an assisted reproductive technologies (ART) program.
- Male: An FSH agent may be approved when used 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.

**New York Large and Small Group Plans:** The Member must be under the care of a board certified reproductive endocrinologist (or urologist, for male patients) and meet the following criteria for age and medical history (as per New York state mandate):

- Member has reached 21 years of age, and
- Member has not yet reached 45 years of age, and
- Member demonstrates at least one of the following qualifiers:
  - Failure to achieve pregnancy after 12 months or more of regular unprotected heterosexual intercourse; or
  - Female age 35 years or older and is unable to achieve pregnancy after 6 months of regular unprotected heterosexual intercourse; or
  - Female with documented FSH levels less than or equal to 19 mIU/ml on day 3 of the menstrual cycle; or
  - Female with a documented anatomic variant resulting in the inability to achieve pregnancy (e.g., severe pelvic inflammatory disease, endometriosis, or ectopic pregnancy requiring surgical removal of both fallopian tubes); or
  - Male with anatomical variants such as aspermia or varicocele resulting in an inability to reproduce.

In addition to the above, the following criteria apply to selection of an FSH agent in the patient for whom the therapy is prescribed:
• **Gonal-f® (follitropin alfa):**
  - **Female:** When used 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 or when used for the development of multiple follicles in the ovulatory patient participating in an assisted reproductive technologies (ART) program.
  - **Male:** when used 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.

• **Bravelle® (urofollitropin) or Follistim® (follitropin beta):**
  
  **Review by a Medical Director or their designee is required**
  
  - **Female:** History of contraindication or intolerance to treatment with Gonal-f® (as evidenced by clinical office notes documenting adverse reaction, e.g., Gonal-f® antigen specific allergic reaction) and/or history of failure of treatment with Gonal-f® (as evidenced by clinical office notes documenting three [3] cycles of at least 750 units administered per cycle).
  - **Male:** History of contraindication or intolerance to treatment with Gonal-f® (as evidenced by clinical office notes documenting adverse reaction, e.g., Gonal-f® antigen specific allergic reaction) and/or history of failure of treatment with Gonal-f®.

**Authorization Guidelines:**
The following timeframe and quantity guidelines will be applied to authorizations.

- **Initial Supply:** Oxford may authorize up to 3 fills (initial supply and 2 refills not to exceed the maximum daily dose/refill day [e.g. a refill may consist of 450 IU each day for 2 days for ART, or 150 IU each day for 2 days for ovulation induction or controlled ovarian stimulation] of a follicle stimulating hormone (FSH) agent per Member.
- **Subsequent Refill(s):** When requested 1 or more months after the first fill: may be authorized for an additional 3 fills subject to benefit considerations and clinical criteria noted above.

**BENEFIT CONSIDERATIONS**

Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances. Some states also mandate usage of other Compendium references. Where such mandates apply, they supersede language in the benefit document or in the notification criteria.

- For Oxford Members with coverage for infertility services, including prescription drugs, certain benefit limitations and/or maximums may apply. Refer to the Member’s specific certificate of coverage, summary of benefits, and/or health benefit plan documentation for details.
- Infertility drugs including follicle stimulating hormones (FSH) agents are excluded from coverage for the following plans and products:
  - New Jersey Individual
  - New York Individual
  - Healthy New York Individual and Group
- Self-funded groups are not required to adopt the guidelines outlined within this policy, but may elect the same or similar guidelines. Consult with individual group benefit administrators or benefit documentation to determine the availability and structure of coverage.
• Religious employers are permitted to exclude coverage for treatments that are contrary to their bona fide religious tenets. Refer to the Member's specific certificate of coverage, summary of benefits, and/or health benefit plan documentation for details.
• Members currently on a course of therapy will be allowed to remain on therapy.

**BACKGROUND**

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

Members currently on a course of therapy will be allowed to remain on therapy.

The American Society for Reproductive Medicine (ASRM) defines infertility as a disease*, defined by the failure to achieve a successful pregnancy after 12 months of more of regular unprotected intercourse. It affects about 10% to 15% of couples.

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

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

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

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

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

**APPLICABLE CODES**

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the Member’s plan of benefits or Certificate of Coverage. This list of codes may not be all inclusive.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>J3355</td>
<td>Injection, urofollitropin, 75 IU</td>
</tr>
<tr>
<td>S0126</td>
<td>Injection, follitropin alfa, 75 IU</td>
</tr>
<tr>
<td>S0128</td>
<td>Injection, follitropin beta, 75 IU</td>
</tr>
</tbody>
</table>
The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee.

9. N.Y. Insurance Law § 3216 (13), 3221 (6) and 4303 (1990, 2002).

POLICY HISTORY/REVISION INFORMATION

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
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<tbody>
<tr>
<td>10/01/2014</td>
<td>Revised conditions of coverage and coverage rationale:</td>
</tr>
<tr>
<td></td>
<td>o Updated criteria/authorization guidelines to indicate the clinically appropriate dosing for FSH agents is:</td>
</tr>
</tbody>
</table>

Follicle Stimulating Hormones (FSH) Used in the Treatment of Infertility: Clinical Policy (Effective 10/01/2014)
- 450 IU/day or less when used for an ART cycle; or
- 150 IU/day or less when used for ovulation induction or controlled ovarian stimulation
- Archived previous policy version PHARMACY 144.15 T2