Introduction

Infertility is a problem or problems with the reproductive system that affects the ability to conceive. Different types of reproductive problems affect men and women, but the end result is the inability to conceive or complete a pregnancy. There are many reasons for infertility and drug options vary depending on the cause of infertility and type of infertility treatment required. Even though drug treatment exists, it does not mean it is covered; the member’s contract determines this. This policy describes when infertility drugs may be considered medically necessary if covered by the member’s contract.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chorionic Gonadotropins</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Brand Chorionic Gonadotropin, IM</strong></td>
<td><strong>Brand Chorionic Gonadotropin may be considered medically necessary for the treatment of infertility when the following criteria are met:</strong></td>
</tr>
<tr>
<td>Managed under Pharmacy and Medical benefit</td>
<td>- The patient has tried and failed or had intolerance to use of Novarel® (chorionic gonadotropin) or Ovidrel® (choriogonadotropin alfa)</td>
</tr>
<tr>
<td></td>
<td><strong>Note:</strong> This policy does not apply to the use of chorionic gonadotropin for the treatment of non-infertility related conditions including but not limited to prepubertal cryptorchidism and hypogonadotropic hypogonadism.</td>
</tr>
<tr>
<td><strong>Pregnyl® (chorionic gonadotropin), IM</strong></td>
<td><strong>Pregnyl® (chorionic gonadotropin) may be considered medically necessary for the treatment of infertility when the following criteria are met:</strong></td>
</tr>
<tr>
<td>Managed under Pharmacy and Medical benefit</td>
<td>- The patient has tried and failed or had intolerance to use of Novarel® (chorionic gonadotropin) or Ovidrel® (choriogonadotropin alfa)</td>
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</tr>
<tr>
<td><strong>Follitropins</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Bravelle® (urofollitropin), IM and SC</strong></td>
<td><strong>Bravelle® (urofollitropin) may be considered medically necessary for the treatment of infertility when the following criteria are met:</strong></td>
</tr>
<tr>
<td>Managed under Pharmacy and Medical benefit</td>
<td>- The patient has tried and failed or had intolerance to use of Gonal-f® (follitropin alfa) or Gonal-f® RFF (follitropin alfa)</td>
</tr>
<tr>
<td></td>
<td><strong>Note:</strong> This policy does not apply to the use of Bravelle® (urofollitropin) for the treatment of non-infertility related conditions.</td>
</tr>
<tr>
<td><strong>Follistim® AQ (follitropin beta), SC</strong></td>
<td><strong>Follistim® AQ (follitropin beta) may be considered medically necessary for the treatment of infertility when the following criteria are met:</strong></td>
</tr>
<tr>
<td>Managed under Pharmacy benefit</td>
<td>- The patient has tried and failed or had intolerance to use of Gonal-f® (follitropin alfa) or Gonal-f® RFF (follitropin alfa)</td>
</tr>
</tbody>
</table>
Drug Medical Necessity

Note: This policy does not apply to the use of Follistim® AQ (follitropin beta) for the treatment of non-infertility related conditions.

Drug Not Medically Necessary

As listed

All other uses of the drugs listed for the treatment of infertility are considered not medically necessary.

Note: This policy does not apply to the use of drugs listed for the treatment of non-infertility related conditions.

Length of Approval

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial authorization</td>
<td>All drugs listed in policy may be approved up to 12 months.</td>
</tr>
<tr>
<td>Re-authorization criteria</td>
<td>Future re-authorization of all drugs listed in policy may be approved up to 12 months as long as the drug-specific coverage criteria are met.</td>
</tr>
</tbody>
</table>

Documentation Requirements

The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis and medication history

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0725</td>
<td>Injection, chorionic gonadotropin, per 1,000 USP units</td>
</tr>
<tr>
<td>J3355</td>
<td>Injection, urofollitropin, 75 IU</td>
</tr>
</tbody>
</table>

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).
**Related Information**

**Note:** Many benefit plans exclude infertility treatment. Please refer to the applicable benefit plan to determine benefit availability and the terms, conditions, and limitations of coverage.

**Benefit Application**

**Pharmacy Benefit**

Follistim® AQ is managed through the Pharmacy benefit.

**Pharmacy / Medical Benefit**

Bravelle® (urofollitropin), brand Chorionic Gonadotropin, and Pregnyl® (chorionic gonadotropin) are managed through both the Pharmacy and Medical benefit.

**Evidence Review**

**Background**

Infertility is defined as the inability to conceive after ≥1 year of unprotected intercourse. A total of 6.7% of women ages 15-44 years in the US are infertile and 12.1% have impaired fecundity, defined as difficulty getting pregnant or carrying a pregnancy to term. Infertility services have been used by 7.3 million US women or 12% of women ages 15-44 years.

Infertility has a number of different causes including combined factors (40%), male factors (26%-30%), unexplained causes (28%), ovulatory dysfunction (21%-25%), tubal factors (14%-20%), and other factors (cervical, peritoneal or uterine factors or abnormalities) (10%-13%).

- Ovulation disorders can be caused by polycystic ovary syndrome (PCOS), diminished ovarian reserve, functional hypothalamic amenorrhea, improper functioning of the hypothalamus
and pituitary glands, premature ovarian insufficiency, and menopause. Of these, the most common is PCOS which accounts for 80% of infertility due to anovulation. Patients with PCOS have normal or low follicle stimulating hormone (FSH) and mildly increased luteinizing hormone (LH).

- Fallopian tube obstruction or tubal occlusion can be caused by a history of pelvic infection, ruptured appendicitis, history of gonorrhea or chlamydia, endometriosis, or a history of abdominal surgery.

- Abnormal uterine contour or other anatomic abnormalities such as fibroids can also cause infertility.

- Other factors which decrease fertility include increasing age, smoking, excessive alcohol use, extreme weight gain or loss, and excessive stress. Functional hypothalamic amenorrhea (FHA) is defined as chronic anovulation without identifiable cause associated with stress, weight loss, and/or excessive exercise. Hypogonadotropic amenorrhea (HA) involves low or absent gonadotropin releasing hormone (GnRH) secretion due to FHA, congenital or iatrogenic causes, or pituitary adenomas.

**Standards of Practice**

The following outlines the steps in the process of ovulation induction.

- Initial ovulation induction typically occurs with oral agents such as clomiphene or letrozole.

- Clomiphene resistance or failure to ovulate on clomiphene occurs in approximately 20% of women. Of those who ovulate on clomiphene, 50% do not become pregnant within 6 months and are considered clomiphene failures. In both groups of patients, second-line treatment may include gonadotropins or laparoscopic ovarian diathermy. During treatment, follicle growth is regularly monitored via serial transvaginal ultrasounds every 1-3 days and serum estradiol is assessed daily.

- If patients are treated with gonadotropins, these drugs are administered for 7-12 days at the beginning of a cycle. Initially, low dose treatment is recommended (37.5-75 IU/d) to decrease risk of multiple pregnancy. This dose may be increased based on response to therapy. Combination FSH and LH products are recommended for patients with hypogonadotropic amenorrhea such as human menopausal gonadotropin or low-dose human menopausal gonadotropin. In patients with PCOS, only FSH is required. Of note, LH
doesn’t appear harmful and combination products such as human menopausal gonadotropin are often given in PCOS.

- In both hypogonadotropic amenorrhea and PCOS, human chorionic gonadotropin (hCG; 5,000-10,000 units purified hCG or 250 mcg recombinant) is administered after development of a mature follicle to stimulate ovum release. In PCOS, a GnRH agonist (leuprolide 500 mcg SC or triptorelin 200 mcg SC) with progesterone supplementation during the luteal phase is an alternative to hCG if a GnRH agonist was not given earlier to prevent LH surge. Additionally, progesterone supplementation with low-dose hCG every 3-4 days are recommended in patients with hypogonadotropic amenorrhea to support normal luteal functions.

The American Society of Reproductive Medicine, European Society of Endocrinology and the Pediatric Endocrinology Society published guidelines on the diagnosis and treatment of FHA in 2018. The guidelines recommend first correcting any energy imbalance by increasing calorie consumption, improving nutrition, or decreasing exercise. If patients wish to conceive, GnRH is recommended first line; however, this is not available in the US. Gonadotropin therapy is recommended second-line for ovulation induction.

The following outlines a general overview of the ART process:

- Protocols for in vitro fertilization (IVF) typically involve suppression of gonadotropin release to prevent premature LH surges. This allows greater retrieval of oocytes and higher pregnancy rates. Both GnRH agonists and antagonists are used for this purpose in IVF protocols.

- Follicle growth is stimulated via gonadotropins as described above.

- This is followed by hCG or GnRH agonists that trigger the final maturation of oocytes in preparation for retrieval and fertilization. GnRH agonists can only be used for this purpose if GnRH antagonists at standard doses were used to suppress gonadotropin release and prevent premature LH surges.

- Eggs are collected typically using transvaginal ultrasound as a guide.

- Fertilization occurs either via IVF or intracytoplasmic sperm injection. This is followed by laboratory procedures for embryo culture.

- Embryos are placed in the uterus followed by luteal phase support such as progesterone, estrogen, or hCG.
Summary of Evidence

Meaningful Differences in Efficacy in Clinical Trials

Specialty fertility drugs are used in the process of ovulation induction as well as in the setting of assisted reproductive technology such as IVF or intracytoplasmic sperm injection. A total of four guidelines and six meta-analyses pertaining to the efficacy of specialty fertility drugs were identified. In the setting of infertility due to PCOS, the American Society of Reproductive Medicine and the World Health Organization guidelines recommend gonadotropins as second-line treatment for ovulation induction following non-specialty first-line agents such as clomiphene and letrozole. Both guidelines recommend IVF as third-line treatment in this setting.

All guidelines and meta-analyses found no difference or insufficient evidence of a difference in the primary efficacy measures of live birth rate or pregnancy between gonadotropins in the setting of ovulation induction and IVF. Specifically, no difference was found between urinary or recombinant FSH or between FSH products and hMG. The World Health Organization guidelines recommend that the choice of gonadotropin is based on cost of therapy as no difference in effectiveness has been identified. A total of two meta-analyses assessed GnRH antagonist and agonist protocols in IVF both found no differences in the live birth rate. Finally, a single meta-analysis compared GnRH agonists and hCG for oocyte triggering found no difference in the live birth rate.

Differences in Safety Profiles

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening complication of fertility drugs and consists of an increase in vascular permeability resulting in a rapid accumulation of fluid in the peritoneal cavity, thorax, and pericardium. The American Society of Reproductive Medicine and World Health Organization guidelines as well as three meta-analyses found decreased risk of OHSS with GnRH antagonists compared to GnRH agonists. Therefore, both guidelines recommend the use of GnRH antagonists protocols in IVF. Additionally, a meta-analysis found the risk of OHSS was decreased with GnRH agonists compared to hCG in the setting oocyte triggering.

The risk of cancer following fertility treatment has been assessed in a guideline and meta-analysis, both limited by low-quality study data. The American Society of Reproductive Medicine guideline found a small increase in absolute risk of borderline ovarian tumors following fertility treatment; however, there was insufficient evidence of increased risk with any particular fertility drug. There was no evidence of increased cancer risk with any other cancer type. The meta-
analysis found inconclusive evidence of endometrial cancer risk with gonadotropins; no other specialty drugs were evaluated. Lastly, a meta-analysis found no increased risk of cardiovascular (CV) outcome with exposure to fertility drugs.

References


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**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/01/20</td>
<td>New policy, approved June 25, 2020, effective October 2, 2020, following 90-day provider notification. Add to Prescription Drug section. Bravelle (urofollitropin), brand Chorionic Gonadotropin, Follistim AQ, and Pregnyl (chorionic gonadotropin) may be considered medically necessary for the treatment of infertility when criteria are met. Coverage criteria for Bravelle (urofollitropin), brand Chorionic Gonadotropin, Follistim AQ, and Pregnyl (chorionic gonadotropin) becomes effective for dates of service on or after October 2, 2020.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2020 Premera All Rights Reserved. **Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
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Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-5797 (TDD)
Email AppealsDepartmentInquiries@Premera.com

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Amharic):
لا يجوز لهؤلاء المرضى أن يتقاضوا مبلغًا على مكانة غير متساوية. هذه الملاحظة تلبي معايير الشفافية. قد يكون هناك إجراءات إضافية في هذه الملاحظة، يمكنك طلب المساعدة من محامي يحمل شهادة في القانون ويتخصص في حقوق المرضى.

Premera Blue Cross يلتزم بالتشريعات الفيدرالية المتعلقة بالحقوق المدنية، ولا تستخدم العنصر القاسي في سياق الطلب أو_coverage. إذا كنت بحاجة إلى المساعدة في تفكيك هذه المعلومات أو الخطة، يمكنك الاتصال بanical

Arabic (Chinese):

中文 (Chinese):

本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動。以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Lakkooofa bilibilaa 800-722-1471 (TTY: 800-842-5357) ti bilibilaa.

Français (French):

Appelez le 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):


Italiano (Italian):

Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date che chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente.
Chiama 800-722-1471 (TTY: 800-842-5357).
Este Aviso contiene información importante. Es posible que haya fechas clave en este aviso. Se debe buscar y revisar la información con anticipación para poder hacer las acciones necesarias.

Español (Spanish):
Este Aviso contiene información importante. Es posible que haya fechas clave en este aviso. Se debe buscar y revisar la información con anticipación para poder hacer las acciones necesarias.

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German (Deutsch):
Dieser Hinweis enthält wichtige Informationen. Es ist möglich, dass Schlüsseldaten in diesem Hinweis enthalten sind. Sie sollten daher frühzeitig recherchiert und geprüft werden, um die notwendigen Maßnahmen rechtzeitig zu unternehmen.

Italiano (Italian):
Questa notifica contiene informazioni importanti. È possibile che ci siano date chiave in questo avviso. È importante controllare e analizzare attentamente l'informazione per poter adottare le opportune azioni in tempo.

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir dados importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357) ou prenda.

Română (Romanian):

Polski (Polish):

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir dados importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357) ou prenda.