Preferred Specialty Management
Infertility – Follitropins/Clomiphene

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NPF Coverage Policy

Drugs Affected
- Clomiphene Citrate tablets (generics)
- Bravelle® (urofollitropin, purified injection)
- Gonal-f®, Gonal-f® RFF, Gonal-f® RFF Redi-ject (follitropin alfa injection)
- Follistim® AQ (follitropin beta injection)

The Preferred Specialty Management (PSM) program requires the individual to meet Prior Authorization (PA)
criteria and requires the individual to try the Step 1 product, when clinically appropriate. Currently, utilization of the
collateral source materials including Coverage Policies and; 4) the specific facts of the particular
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.

Step 1: Clomiphene citrate

Step 2: Gonal-f, Gonal-f RFF, Gonal-f RFF Redi-ject
Step 3: Follistim AQ, Bravelle

Cigna covers Follitropins as medically necessary when the following criteria are met:

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| Gonal-F, Gonal-F RFF, Gonal-F RFF Redi-ject | 1. Approve if the individual meets the following criteria:  
  A. The individual meets one of the following criteria (i, ii, iii, iv, or v):  
  i. The individual has tried clomiphene tablets; OR  
  ii. The individual has tried Femara® (letrozole tablets, generics) for ovulatory dysfunction; OR  
  iii. The individual has previously received and/or is continuing infertility treatment with injectable agents (e.g., individual has tried injectable infertility agents in previous cycles and is re-starting new cycle of treatments); OR  
  iv. The individual has other causes of infertility other than due to ovulatory dysfunction; OR  
  v. Follitropins are used for the induction of spermatogenesis in individuals with primary or secondary hypogonadism. |
| Follistim AQ, Bravelle | 1. Approve if the individual has tried at least one of Gonal-F, Gonal-F RFF, or Gonal-F RFF Redi-ject. |

Conditions Not Covered

Any other exception is considered not medically necessary.

Background

Overview

This policy involves the use of clomiphene citrate tablets and the following injectable follitropin products: Gonal-f, Gonal-f RFF, Gonal-f RFF Redi-ject, Follistim AQ, and Bravelle.¹ ⁶

Clomiphene citrate tablet is indicated for the treatment of ovulatory dysfunction in women desiring pregnancy.¹ Individuals most likely to achieve success with clomiphene therapy include individuals with polycystic ovarian syndrome (PCOS), amenorrhea-galactorrhea syndrome, psychogenic amenorrhea, post-oral-contraceptive amenorrhea, and certain cases of secondary amenorrhea of undetermined etiology. The Gonal-f products and Follistim AQ are indicated for the induction of ovulation and pregnancy in the anovulatory infertile individual, in whom the cause of infertility is functional and not due to primary ovarian failure.² ⁵ Gonal-f products are also indicated for the development of multiple follicles in the ovulatory individuals participating in an Assisted Reproductive Technology (ART) program.² ⁴ Follistim AQ is also indicated in normal ovulatory women undergoing controlled ovarian stimulation as part of an in vitro fertilization (IVF) or intracytoplasmic sperm injection cycle (ICSI).⁵ Gonal-f (but not Gonal F RFF) and Follistim AQ are also 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.² ⁵ Bravelle is indicated for the induction of ovulation in women who have previously received pituitary suppression and for the development of multiple follicles as part of an ART cycle in ovulatory women who have previously received pituitary suppression.⁶ (Note: Bravelle is currently discontinued).

Femara® (letrozole tablets, generics) is an aromatase inhibitor that is indicated for the first and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer.⁸ It is also indicated for adjuvant treatment of early breast cancer in this population and for extended adjuvant treatment of early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy. There are data supporting the use of letrozole tablets for ovulation induction.⁶ In one double-blind, randomized controlled trial, letrozole improved pregnancy outcomes compared with clomiphene, in
individual with anovulatory PCOS. In a Cochrane meta-analysis of twenty-six trials, comparing letrozole with placebo, clomiphene, or laparoscopic ovarian drilling, there were higher pregnancy rates with letrozole. The Endocrine Society clinical practice guideline on the diagnosis and treatment of PCOS (2013) recommends clomiphene citrate or comparable estrogen modulators such as letrozole as the first-line treatment of anovulatory infertility in women with PCOS. A summary of evidence-based recommendations provided to the World Health Organization (WHO) for the development of global guidance on the management of anovulatory infertility in women with PCOS also recommends the use of letrozole as first-line therapy (when available and permissible) and as second-line therapy in clomiphene citrate resistance and/or failure.

The American Society of Reproductive Medicine (ASRM) published a practice committee opinion on clomiphene use in infertile women. Clomiphene is noted to be an effective first-line treatment for the majority of women with anovulatory infertility. Some causes of anovulatory infertility are PCOS, obesity, hypothalamic dysfunction related to eating disorders, extremes of weight loss, exercise or other stress, hyperprolactinemia, pituitary tumors, or thyroid disease in some cases. Clomiphene is ineffective in women with hypogonadotropic hypogonadism (hypothalamic amenorrhea) in which case the hypothalamic-pituitary-ovarian axis is severely dysfunctional. It is also ineffective in women with hypergonadotropic hypogonadism. Clomiphene is taken orally, typically for 5 days, starting on the 2nd to the 5th day after the onset of spontaneous or progestin-induced menses. The standard effective dose of clomiphene ranges from 50 mg/day to 250 mg/day. ASRM notes that doses > 100 mg/day are not FDA-approved and the higher doses are not associated with significant improvement in clinical pregnancy rates. If clomiphene is used to induce ovulation, pregnancy is most likely to occur in the first three to six cycles; therapy beyond six cycles is generally not recommended. For women who are resistant or refractory to standard clomiphene treatment, combined treatment regimens with metformin, glucocorticoids, or gonadotropins may be tried. Alternatives to clomiphene therapy in clomiphene citrate-resistant individuals include aromatase inhibitors (e.g., Femara® [letrozole tablets]), tamoxifen, insulin-sensitizing agents, ovarian drilling, gonadotropins, and in vitro fertilization.

Recent guidelines on the management of PCOS, funded by the Australian National Health and Medical Research Council of Australia (NHMRC) and supported by a partnership with the European Society of Human Reproduction and Embryology (ESHRE) and the ASRM, were released (2018). The guidelines note that letrozole should be considered the first-line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy, and live birth rates. Both metformin and clomiphene can be used alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and pregnancy rates. Clomiphene may be preferred over metformin for this use in women who are obese (body mass index ≥ 30 kg/m²). Gonadotropins can be used as second-line therapy for women with PCOS who have failed first line oral ovulation induction therapy and are anovulatory and infertile with no other infertility factors. Gonadotropins may be preferred over the combination therapy of clomiphene and metformin in individuals who are clomiphene-resistant.

References


**Last Revision Details**

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<th>No criteria changes</th>
<th>01/29/2020</th>
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<tbody>
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