

PREFERRED SPECIALTY MANAGEMENT POLICY

- POLICY:** Infertility – Follitropins, Clomiphene Preferred Specialty Management Policy
- Clomiphene Citrate tablets (generics – multiple manufacturers)
 - Bravelle® (urofollitropin, purified injection – Ferring Pharmaceuticals) [currently unavailable]
 - Gonal-f®, Gonal-f® RFF, Gonal-f® RFF Redi-ject (follitropin alfa injection – Serono)
 - Follistim® AQ (follitropin beta injection – Organon)

REVIEW DATE: 02/03/2021

OVERVIEW

The Gonal-f products, Follistim AQ, and Bravelle are gonadotropins (follicle stimulating hormones [FSH]).¹⁻⁶ [Note: Bravelle is currently unavailable]. The Gonal-f products and Follistim AQ are 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. The Gonal-f products are also indicated for the development of multiple follicles in ovulatory patients participating in an assisted reproductive technology (ART) program.¹⁻³ Follistim AQ is also indicated in normal ovulatory women undergoing controlled ovarian stimulation as part of an *in vitro* fertilization or intracytoplasmic sperm injection cycle.⁴ 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.¹⁻⁴ 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.⁵

Clomiphene citrate tablet is indicated for the treatment of **ovulatory dysfunction in women desiring pregnancy**.⁶ Patients most likely to achieve success with clomiphene therapy include patients with polycystic ovarian syndrome (PCOS), amenorrhea-galactorrhea syndrome, psychogenic amenorrhea, post-oral contraceptive amenorrhea, and certain cases of secondary amenorrhea of undetermined etiology.

Guidelines

An international evidence-based guideline for the management of PCOS was released in 2018.⁷ The guideline was a collaborative effort from the Centre for Research Excellence in PCOS research, the European Society of Human Reproduction and Embryology, the American Society of Reproductive Medicine (ASRM), and professional societies and consumer advocacy groups. The guidelines note letrozole as the first-line pharmacological treatment in women with PCOS and anovulatory infertility and without other infertility factors. Letrozole is used 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 (e.g., FSH) 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 patients who are clomiphene-resistant.

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.⁸ A summary of evidence-based recommendations for the development of global guidance on the management of anovulatory infertility in

women with PCOS also recommend the use of letrozole as first-line therapy (when available and permissible).⁹

The ASRM published a practice committee opinion on clomiphene use in infertile women (2013).¹⁰ Clomiphene is noted to be an effective first-line treatment for the majority of women with anovulatory infertility. Clomiphene is ineffective in women with hypogonadotropic hypogonadism (hypothalamic amenorrhea) in which case the hypothalamic-pituitary-ovarian axis is severely dysfunctional. Clomiphene is also ineffective in women with hypergonadotropic hypogonadism. For women who are resistant to 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 patients include aromatase inhibitors (e.g., letrozole tablets), tamoxifen, insulin-sensitizing agents, ovarian drilling, gonadotropins, and *in vitro* fertilization.

POLICY STATEMENT

This Preferred Specialty Management program has been developed to encourage the use of Preferred Products. Utilization of the follitropin products and clomiphene is not managed by *Prior Authorization* criteria, but is based on whether the patient’s benefit includes infertility coverage. The program directs the patient to try the Preferred Product(s) prior to the approval of a Non-Preferred Product. Requests for Non-Preferred Products (Step 3) will also be reviewed using the exception criteria (below). All approvals are provided for the duration noted below.

Automation: A patient with a history of either clomiphene citrate tablets or the Gonal-f injectable products (including Gonal-f RFF and Gonal-f RFF Redi-ject pens) within the 130-day look-back period is excluded from this Preferred Specialty Management program.

Preferred Products

Step 1: Clomiphene citrate

Step 2: Gonal-f, Gonal-f RFF, Gonal-f RFF Redi-ject

Non-Preferred Products

Step 3: Follistim AQ, Bravelle

RECOMMENDED EXCEPTION CRITERIA

Product	Exception Criteria
Gonal-f, Gonal-f RFF, Gonal-f RFF Redi-ject	<p>1. Approve if the patient meets the following criteria (A <u>or</u> B):</p> <p>A) Approve for 1 year if the patient meets one of the following criteria (i, ii, iii, iv, <u>or</u> v):</p> <ul style="list-style-type: none"> i. Patient has tried clomiphene tablets; OR ii. Patient has tried letrozole tablets for ovulatory dysfunction; OR iii. Patient has previously received and/or is continuing infertility treatment with injectable agents (e.g., patient has tried injectable infertility agents in previous cycles and is re-starting new cycle of treatments); OR iv. Patient has causes of infertility other than ovulatory dysfunction; OR v. The medication is used for the induction of spermatogenesis in a patient with primary or secondary hypogonadism. <p>B) Patient already started on a cycle of treatment with a Gonal-f product: approve for the duration needed to complete the current cycle.</p>

<p>Follistim AQ Bravelle</p>	<ol style="list-style-type: none"> 1. Approve for 1 year if the patient has tried at least one of Gonal-f, Gonal-f RFF, or Gonal-f RFF Redi-ject. 2. For patients who have not tried at least one of the Step 2 preferred follitropin products: offer to review for Gonal-f, Gonal-f RFF, or Gonal-f RFF Redi-ject. 3. Patient already started on a cycle of treatment with Follistim AQ for the induction of spermatogenesis in patients with primary or secondary hypogonadism: approve for 1 year. 4. Patient already started on a cycle of treatment with Follistim AQ or Bravelle: approve for the duration needed to complete the current cycle.
----------------------------------	--

REFERENCES

1. Gonal-f Multi-Dose Vials [prescribing information]. Rockland, MA: EMD Serono, Inc.; December 2020.
2. Gonal-f RFF Vials [prescribing information]. Rockland, MA: EMD Serono, Inc.; May 2018.
3. Gonal-f RFF Redi-ject Pens [prescribing information]. Rockland, MA: EMD Serono, Inc.; January 2014.
4. Follistim AQ Cartridge [prescribing information]. Whitehouse Station, NJ, Merck & Co.; June 2020.
5. Bravelle [prescribing information]. Parsippany, NJ: Ferring Pharmaceuticals Inc.; July 2015.
6. Clomiphene Citrate Tablets [prescribing information]. Chestnut Ridge, NY: Par Pharmaceutical, Inc.; August 2019.
7. Teede HJ, Misso ML, Costello MF, et al. International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018. Available at: https://www.monash.edu/data/assets/pdf_file/0004/1412644/PCOS_Evidence-Based-Guidelines_20181009.pdf. Accessed on February 1, 2021.
8. Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2013;98:4565-4592.
9. Balen AH, Morley LC, Misso M, et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. *Hum Reprod Update.* 2016;22:687-708.
10. Use of clomiphene citrate in infertile women: a committee opinion. The Practice Committee of the American Society for Reproductive Medicine. *Fertil Steril.* 2013;100:341-348.