Cigna National Formulary Coverage Policy

Effective Date..... 4/1/2023
Next Review Date..... 4/1/2024

Preferred Specialty Management Infertility – Follitropins/Clomiphene

Table of Contents

Product Identifier(s)

Effective 1/1/23 to 2/6/23: 108280

Effective 2/7/23: 15005

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. 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.

National Formulary Medical Necessity

Drugs Affected

- Clomiphene Citrate tablets (generic)
- Gonal-f®, Gonal-f® RFF, Gonal-f® RFF Redi-ject (follitropin alfa injection)
- Follistim® AQ (follitropin beta injection)

This Preferred Specialty Management program has been developed to encourage the use of the Preferred Products. Utilization of the follitropin products and clomiphene is not managed by *Prior Authorization* criteria, but is based on whether the individual's benefit includes infertility coverage. The program directs the individual to try the Preferred Products 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.

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

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

Product	Exception Criteria
Gonal-f, Gonal-f RFF, Gonal-f RFF Redi-ject	**1.** Approve if the individual meets the following criteria (A or B): **A)** Approve for 1 year if the individual meets one of the following criteria (i, ii, iii, iv, or v): **i.** Individual has tried clomiphene tablets; OR **ii.** Individual has tried letrozole tablets for ovulatory dysfunction; OR **iii.** 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.** Individual has causes of infertility other than ovulatory dysfunction OR the product is being used for planned oocyte preservation; OR **v.** The medication is used for the induction of spermatogenesis in an individual with primary or secondary hypogonadism. Individual already started on a cycle of treatment with a Gonal-f product: approve for the duration needed to complete the current cycle.
Follistim AQ	**1.** Approve for 1 year if the individual has tried at least one of Gonal-f, Gonal-f RFF, or Gonal-f RFF Redi-ject. **2.** For an individual who has 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.** Individual already started on a cycle of treatment with Follistim AQ for the induction of spermatogenesis in individuals with primary or secondary hypogonadism: approve for 1 year. **4.** Individual already started on a cycle of treatment with Follistim AQ: approve for the duration needed to complete the current cycle.

Conditions Not Covered

Any other exception is considered not medically necessary.

Background

Overview
The Gonal-f products and Follistim AQ are gonadotropins (follicle stimulating hormones [FSH]).[1-5] 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]
Clomiphene citrate tablets are indicated for the treatment of **ovulatory dysfunction in women who desire pregnancy**.[5] 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
American Society for Reproductive Medicine (ASRM) committee opinion (2020) on the use of exogenous gonadotropins for ovulation induction in anovulatory women note that gonadotropin therapy has more risks than oral ovulation induction.[7] The publication states that gonadotropin therapy should only be used by clinicians who have the training and experience to use these products. Most women will respond to ovulation induction with oral medications, but exogenous gonadotropin treatment may be an option in women who fail to respond to lifestyle modifications and oral agents. The ASRM opinion states that there is no significant advantage to using any specific gonadotropin preparation.

An international evidence-based guideline for the management of PCOS was released in 2018.[6] The guideline was a collaborative effort from the Centre for Research Excellence in PCOS research, the European Society of Human Reproduction and Embryology, the 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/m^2). 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.

References

1. Gonal-f Multi-Dose Vials [prescribing information]. Rockland, MA: EMD Serono; December 2020.
2. Gonal-f RFF Vials [prescribing information]. Rockland, MA: EMD Serono; December 2020.
3. Gonal-f RFF Redi-ject Pens [prescribing information]. Rockland, MA: EMD Serono; February 2020.
4. Follistim AQ Cartridge [prescribing information]. Whitehouse Station, NJ: Merck; June 2020.
5. Clomiphene Citrate Tablets [prescribing information]. Chestnut Ridge, NY: Par; May 2021.
6. 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 8, 2023.
7. Use of exogenous gonadotropins for ovulation induction in anovulatory women: a committee opinion. American Society for Reproductive Medicine. *Fertil Steril*. 2020;113(1):66-70.

Revision History

Type of Revision	Summary of Changes	Approval Date
Annual revision	**Gonal-f, Gonal-f RFF, Gonal-f RFF Redi-ject**: Added an exception for planned oocyte preservation.	02/15/2023