PREFERRED SPECIALTY MANAGEMENT POLICY

POLICY: Infertility – Follitropins, Clomiphene Preferred Specialty Management Policy

- Clomid® (clomiphene tablets – Cosette)
- Clomiphene citrate tablets (generic – multiple manufacturers)
- Gonal-f®, Gonal-f® RFF, Gonal-f® RFF Redi-ject (follitropin alfa injection – EMD Serono)
- Follistim® AQ (follitropin beta injection – Organon)

REVIEW DATE: 09/11/2024

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. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. 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.

CIGNA NATIONAL FORMULARY COVERAGE:

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 2023.[6] The guideline recommends that letrozole should be the first-line pharmacological treatment in women with PCOS and anovulatory infertility without other infertility factors. Both metformin and clomiphene could be used in women with PCOS with anovulatory infertility and no other infertility factors. Gonadotropins (e.g., FSH) alone could be considered rather than clomiphene citrate therapy. Gonadotropins could also be second-line pharmacological 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 could also be considered rather than the combination of clomiphene citrate and metformin in patients who are clomiphene-resistant. These guidelines additionally state there appears to be no difference in the clinical efficacy of gonadotropins preparations.

POLICY STATEMENT

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 patient's benefit includes infertility coverage. The program directs the patient 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: Clomid, Clomiphene citrate
Step 2: Gonal-f, Gonal-f RFF, Gonal-f RFF Redi-ject

Non-Preferred Products

Step 3: Follistim AQ

***Infertility – Follitropins, Clomiphene Preferred Specialty Management Policy* non-preferred product(s) is(are) covered as medically necessary when the following non-preferred product exception criteria is(are) met. Any other exception is considered not medically necessary.**

NON-PREFERRED PRODUCT EXCEPTION CRITERIA

Product	Exception Criteria
Gonal-f, Gonal-f RFF, Gonal-f RFF Redi-ject	**1.** Approve if the patient meets ONE of the following (A or B): **A)** Approve for 1 year if the patient meets ONE of the following (i, ii, iii, iv, or v): **i.** Patient has tried Clomid tablets or 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 the product is being used for planned oocyte or embryo preservation; OR **v.** The medication is used for the induction of spermatogenesis in a patient with primary or secondary hypogonadism. **B)** Patient 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 patient has tried at least one of Gonal-f, Gonal-f RFF, or Gonal-f RFF Redi-ject. **2.** For a patient 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.** 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: approve for the duration needed to complete the current cycle.

REFERENCES

1. Gonal-f multi-dose vials [prescribing information]. Rockland, MA: EMD Serono; November 2023.
2. Gonal-f RFF vial [prescribing information]. Rockland, MA: EMD Serono; November 2023.
3. Gonal-f RFF Redi-ject pens [prescribing information]. Rockland, MA: EMD Serono; August 2024.
4. Follistim AQ Cartridge [prescribing information]. Jersey City, NJ: Organon; July 2023.
5. Clomid tablets [prescribing information]. South Plainfield, NJ: Cosette; May 2022.

6. Recommendations from the 2023 International Evidence Based Guideline for the assessment and management of polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2023;108(10):2447-2469.
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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	**Gonal-f, Gonal-f RFF, Gonal-f RFF Redi-ject**: Added an exception for planned oocyte preservation.	02/15/2023
Annual revision	Added "Clomid tablets" to the policy. Added as a Step 1 agent.	02/21/2024
Early Annual Revision	**Gonal-f, Gonal-f RFF, Gonal-f RFF Redi-ject**: Added "or embryo" to the exception regarding the product being used for planned oocyte preservation.	09/11/2024