

UnitedHealthcare Pharmacy
Clinical Pharmacy Programs

Program Number	2021 P 1136-8
Program	Prior Authorization/Notification
Medication	Clomid (clomiphene citrate)*
P&T Approval Date	8/2014, 5/2015, 5/2016, 5/2017, 5/2018, 5/2019, 5/2020, 5/2021
Effective Date	8/1/2021; Oxford only: N/A

1. Background:

Clomiphene citrate is a nonsteroidal fertility agent used to induce ovulation in infrequently ovulating or anovulatory women, including patients with polycystic ovary syndrome (PCOS). It is also used for controlled ovarian stimulation in ovulatory women. The drug is effective at producing ovulation in patients with an intact hypothalamic-pituitary-ovarian axis and with ovaries that are capable of functioning normally. Clomiphene therapy is not effective in patients with primary pituitary or ovarian failure. Dosage should generally not exceed 100 mg daily for 5 days. If ovulation has not occurred after 3 courses of therapy, the patient should be reevaluated. If pregnancy does not occur within a total of 6 cycles, clomiphene should be discontinued as prolonged administration is not recommended.¹⁻⁵

Clomid (clomiphene citrate) is indicated for the treatment of ovulatory dysfunction in women desiring pregnancy. Impediments to achieving pregnancy must be excluded or adequately treated before beginning CLOMID therapy. Those patients most likely to achieve success with clomiphene therapy include patients with polycystic ovary syndrome, amenorrhea-galactorrhea syndrome, psychogenic amenorrhea, certain cases of secondary amenorrhea of undetermined etiology, and post-oral contraceptive amenorrhea.⁶

Clomiphene may be used to evaluate a woman’s ovulation and egg quality in what is referred to as the Clomiphene Challenge Test.⁸⁻⁹ When given early in a woman’s menstrual cycle for 5 days, clomiphene elevates a woman’s follicle-stimulating hormone (FSH) level. On the next day, an FSH blood level that has dropped back to normal is a sign of a normal ovarian reserve and ovulation. An elevated FSH is a sign of low ovarian reserve. Women who have a diminished ovarian reserve can use donor eggs, which greatly improves their chances of giving birth to a healthy child.

2. Coverage Criteria:

<p>A. <u>Ovulation Induction</u></p> <p>1. Clomid will be approved based on all of the following criteria*:</p> <p style="padding-left: 40px;">a. Diagnosis of ovulatory dysfunction</p> <p style="text-align: center;">-AND-</p> <p style="padding-left: 40px;">b. One of the following exists:</p> <p style="padding-left: 80px;">(1) Anovulation</p> <p style="padding-left: 80px;">(2) Oligo-ovulation</p>
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(3) Amenorrhea

-AND-

- c. Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated

-AND-

- d. Infertility is not due to primary ovarian failure

-AND-

- e. For induction of ovulation

Authorization will be issued for 6 months.

B. Controlled Ovarian Stimulation

1. **Clomid** will be approved based on **all** of the following criteria*:

- a. Diagnosis of infertility

-AND-

- b. **One** of the following exists:

- (1) Unexplained infertility
- (2) Endometriosis
- (3) Male factor infertility
- (4) Diminished ovarian reserve
- (5) Unilateral tubal factor infertility

-AND-

- c. For the development of one or more follicles (controlled ovarian stimulation)

-AND-

- d. Will be used in conjunction with intrauterine insemination (IUI)

Authorization will be issued for 6 months.

C. Clomiphene Challenge Test

1. **Clomid** will be approved based on the following criterion*:

- a. To be used to conduct a clomiphene challenge test

Authorization will be issued for 1 month.

D. Male Factor Infertility/Oligospermia [off label]**1. Clomid** will be approved based on **all** of the following criteria*:

a. Diagnosis of one of the following:

- (1) Mild, moderate, or severe male factor infertility
- (2) Oligospermia

-AND-

b. At least **one** of the following exists on at least 2 separate semen analyses obtained at least 4 weeks apart:

- (1) Sperm concentration is < 15 million/ml
- (2) Progressive motility < 40%
- (3) Sperm preparation techniques result in a sperm concentration of < 1 million motile sperm/ml

-AND-

c. Patient condition has not improved despite an adequate trial (two to three months) of positive lifestyle changes (e.g., weight loss, healthy diet, smoking cessation, reduction of alcohol intake).

Authorization will be issued for 6 months.

3. Additional Clinical Rules:

- Notwithstanding Coverage Criteria, UnitedHealthcare may approve initial and re-authorization based solely on previous claim/medication history, diagnosis codes (ICD-10) and/or claim logic. Use of automated approval and re-approval processes varies by program and/or therapeutic class.

*Infertility is typically excluded from coverage for UnitedHealthcare. Please refer to member's specific benefits for coverage determination.

4. References:

1. Gold Standard, Inc. Clomiphene. Clinical Pharmacology [database online]. Available at: <http://www.clinicalpharmacology.com>. Accessed March 30, 2019.
2. ASRM. The Practice Committee of the American Society for Reproductive Medicine: Use of Clomiphene Citrate in Infertile Females: a Committee Opinion. Fertil Steril 2013; 100: 341-8.
3. Badawy A, Elnashar A, Totongy M. Clomiphene citrate or aromatase inhibitors for superovulation in women with unexplained infertility undergoing intrauterine insemination: a prospective randomized trial. Fertil Steril. 2009 Oct;92(4):1355-9.
4. Dovey S, Sneeringer RM, Penzias AS. Clomiphene citrate and intrauterine insemination: analysis of more than 4100 cycles. Fertil Steril 2008;90:2281-6.

5. Lewis V, Queenan J, Hoeger K, et al. Clomiphene citrate monitoring for intrauterine insemination: a randomized trial. *Fertil Steril* 2004; 85: 401-406.
6. Clomid [package insert]. Bridgewater, NJ: Sanofi-Aventis US LLC; July 2017.
7. Infertility and Reproduction Health Center: Clomiphene for Infertility. WebMD. Available at <http://www.webmd.com/infertility-and-reproduction/clomiphene-citrate-for-infertility>. Accessed on March 30, 2018.
8. Hendriks DJ, Mol, Laszlo BJ, Bancsi FJ, et al. The clomiphene citrate challenge test for the prediction of poor ovarian response and nonpregnancy in patients undergoing in vitro fertilization: a systematic review. *Fertil Steril* 2006; 86: 807-818.
9. World Health Organization. WHO Laboratory Manual for the Examination of Human Semen and Semen-Cervical Mucus Interaction. 4th ed. Cambridge: Cambridge University Press; 1999. 1–86.
10. Barratt CLR, Björndal L, DeJonge CJ et al. The diagnosis of male infertility: an analysis of the evidence to support the development of global WHO guidance—challenges and future research opportunities. *Hum Reprod Update*. 2017 Nov; 23(6): 660–680.

Program	Prior Authorization/Notification – Clomid (clomiphene citrate)
Change Control	
8/2014	New program.
5/2015	No change to clinical criteria. Updated background and references.
5/2016	Serophene labeled as discontinued product, removed from background and coverage criteria. Added diminished ovarian reserve and unilateral tubal factor infertility to coverage criteria for controlled ovarian stimulation.
5/2017	Annual review. No change to clinical criteria. Updated references.
5/2018	Annual review. No change to clinical criteria.
5/2019	Annual review. Added male factor infertility to coverage rationale. Updated references.
5/2020	Annual review. No changes to clinical criteria. Updated reference.
5/2021	Annual review. No changes to clinical criteria.