



Horizon BCBSNJ
Medical Necessity Guideline

Section	Drugs
Policy Number	
Effective Date	6/25/04
Review Date	2/24/06, 7/27/07, 9/26/08

Subject:

BRAND NAME	Clomid, Milophene, Serophene
(Generic)	(clomiphene citrate)

IMPORTANT NOTE:

*The purpose of this policy is to provide general information applicable to the administration of outpatient prescription drug benefits that Horizon Blue Cross Blue Shield of New Jersey and Horizon Healthcare of New Jersey, Inc. (collectively "Horizon BCBSNJ") insures or administers. **Outpatient prescription drugs are not covered under all Horizon benefit plans.** If the member's contract benefits differ from the pharmacy guideline, the contract prevails. Although a service, supply drug or procedure may be medically necessary, it may be subject to limitations and/or exclusions under a member's benefit plan. If a service, supply drug or procedure is not covered and the member proceeds to obtain the service, supply drug or procedure, the member may be responsible for the cost. Decisions regarding treatment and treatment plans are the responsibility of the physician. This policy is not intended to direct the course of clinical care a physician provides to a member, and it does not replace a physician's or pharmacist's independent professional clinical judgment or duty to exercise special knowledge and skill in the treatment of Horizon BCBSNJ members. Horizon BCBSNJ is not responsible for, does not provide, and does not hold itself out as a provider of medical care. The physician remains responsible for the quality and type of health care services provided to a Horizon BCBSNJ member.*

Horizon BCBSNJ pharmacy guidelines do not constitute medical advice, authorization, certification, approval, explanation of benefits, offer of coverage, contract or guarantee of payment.

FDA-APPROVED INDICATIONS

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 clomiphene citrate therapy. Those patients most likely to achieve success with clomiphene therapy include patients with polycystic ovary, amenorrhea-galactorrhea syndrome, psychogenic amenorrhea, post-oral-contraceptive amenorrhea, and certain cases of secondary amenorrhea of undetermined etiology.

Properly timed coitus in relationship to ovulation is important. A basal body temperature graph or other appropriate tests may help the patient and her physician determine if ovulation occurred. Once ovulation has been established, each course of clomiphene citrate should be started on or about the 5th day of the cycle. Long-term cyclic therapy is not recommended beyond a total of about six cycles (including three ovulatory cycles).

Clomiphene citrate is indicated only in patients with demonstrated ovulatory dysfunction who meet the following described conditions:

- Patients who are not pregnant
- Patients without ovarian cysts, clomiphene citrate should not be used in patients with ovarian enlargement except those with polycystic ovary syndrome. Pelvic examination is necessary prior to the first and each subsequent course of clomiphene citrate treatment
- Patients without abnormal vaginal bleeding. If abnormal vaginal bleeding is present, the patients should be carefully evaluated to ensure that neoplastic lesions are not present.
- Patients with normal liver function

In addition, patients selected for clomiphene citrate therapy should be evaluated in regard to the following:

- Estrogen levels: Patients should have adequate levels of endogenous estrogen, as estimated from vaginal smears, endometrial biopsy, assay of urinary estrogen, or from bleeding in response to progesterone, reduced estrogen levels, while less favorable, do not preclude successful therapy.
- Primary pituitary or ovarian failure: Clomiphene citrate therapy cannot be expected to substitute for specific treatment of other causes of ovulatory failure.
- Endometriosis and endometrial carcinoma: the incidence of endometriosis and endometrial carcinoma increases with age, as does the incidence of ovulatory disorders. Endometrial biopsy should always be performed prior to clomiphene citrate therapy in this population.
- Other impediments to pregnancy: impediments to pregnancy can include thyroid disorders, adrenal disorders, hyperprolactinemia, and male factor infertility.
- Uterine fibroids: caution should be exercised when using clomiphene citrate in patients with uterine fibroids due to the potential for further enlargement of the fibroids.

There are no adequate or well-controlled studies that demonstrate the effectiveness of clomiphene citrate in the treatment of male infertility. In addition, testicular tumors and gynecomastia have been reported in males using clomiphene. The cause and effect relationship between reports of testicular tumors and the administration of clomiphene citrate is not known.

Although the medical literature suggests various methods there is no universally accepted standard regimen for combined therapy (i.e., Clomiphene citrate in conjunction with other ovulation –inducing drugs). Similarly, there is no standard clomiphene citrate regimen for ovulation induction in vitro fertilization programs to produce ova for fertilization and reintroduction, therefore clomiphene citrate is not recommended for these uses

Medical Necessity Guideline:

1. The following questionnaire may be used to determine medical necessity of Clomiphene prescriptions.

<u>CRITERIA FOR APPROPRIATENESS</u>		
1. Is the patient female? [If the answer to this question is no, then no further questions are required.]	Yes	No
2. Does the patient have the diagnosis of infertility? [If the answer to this question is no, then no further questions required.]	Yes	No
3. Has pregnancy been excluded as confirmed by a negative urine or serum pregnancy test?	Yes	No
4. Does the patient have any of the following contraindications to clomiphene therapy? Ovarian Cysts-excluding polycystic ovarian syndrome Abnormal vaginal bleeding Abnormal liver function or history of liver disease Hypersensitivity	Yes	No
5. Does the patient have a diagnosis of primary ovarian failure?	Yes	No
6. Will the patient be undergoing intrauterine insemination (IUI)? [If the answer to this question is no, then skip to question 8.]	Yes	No
7. Is the patient less than 45 years of age? [If the answer is no, then please forward request to Horizon Pharmacy Service pharmacy_services@horizonblue.com . When Horizon approves please proceed to question 12.] [If the answer is yes, then skip to question 12.]	Yes	No
8. Is clomiphene treatment part of an Assisted Reproductive Technology (ART) program? (e.g., IVF, GIFT, ZIFT)? [If the answer to this question is yes, then no further questions required.]	Yes	No

9. Is clomiphene being prescribed for a Clomiphene Citrate Challenge Test? [If the answer to this question is yes, then skip to question 12.]	Yes	No
10. Is or will the patient be undergoing ovulation induction? [If the answer to this question is no, then no further questions required.]	Yes	No
11. Was the partner of the patient found to be fertile?	Yes	No
12. Is this request for more than 10 tablets per 30 days?	Yes	No
13. Has the patient received at least 3 months of therapy with clomiphene?	Yes	No

Guidelines for Approval							
Duration of Approval 6 months		Quantity for Approval Up to 10 tablets per month for a maximum of 3 months for Sets 1, 2 and 3				Quantity for Approval – 10 tablets one time only for Set 4	
Set 1 – IUI (< 45)		Set 2 – IUI (≥ 45)		Set 3 – Ovulation Induction		Set 4 – CCC Test (one month only)	
Yes to questions	No to questions	Yes to questions	No to questions	Yes to questions	No to questions	Yes to questions	No to questions
1	4	1	4	1	4	1	4
2	5	2	5	2	5	2	5
3	12	3	7	3	6	3	6
6	13	6	12	10	8	9	8
7			13	11	9		12
					12		13
					13		

LIMIT CRITERIA	
clomiphene (Clomid) 50mg tablet: 500mg (10 tablets) per cycle (25 days)/3 prescription fills per pharmacy history	
<i>The duration of 25 days is used because a cycle is denoted as 30 days. more than 3 cycles</i>	No

Horizon BCBSNJ Pharmacy Guideline Development Process: This Horizon BCBSNJ Pharmacy Guideline (the “Pharmacy Guideline”) has been developed by Horizon BCBSNJ’s Pharmacy Drug Policy Subcommittee, Clinical Issues Subcommittee, and Quality Improvement Committee which include practicing physicians and pharmacists. This guideline is consistent with generally accepted standards of medical and pharmacy practice, and reflects Horizon BCBSNJ’s view of the subject health care services, supplies drugs or procedures, and in what circumstances they are deemed to be medically necessary or experimental/ investigational in nature. This Pharmacy Guideline also considers whether and to what degree the subject health care services, supplies or procedures are clinically appropriate, in terms of type, frequency, extent, site and duration and if they are considered effective for the illnesses, injuries or diseases discussed. Where relevant, this Pharmacy Guideline considers whether the subject prescription drugs are being requested primarily for the convenience of the covered person or the health care provider. It may also consider whether the prescription drugs are more costly than alternative prescription drugs that are at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the relevant illness, injury or disease. In reaching its conclusion regarding what it considers to be the generally accepted standards of medical and pharmacy practice, Horizon BCBSNJ reviews and considers the following: all credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, physician and health care provider specialty society recommendations, the views of physicians and health care providers practicing in relevant clinical areas (including, but not limited to, the prevailing opinion within the appropriate specialty), the findings and directives of the Food and Drug Administration and any other relevant factor as determined by applicable State and Federal laws and regulations.

RATIONALE

The intent of the criteria is to ensure patients follow selection elements noted in labeling and accepted practice guidelines, and to reduce inappropriate use.

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 clomiphene citrate therapy. Those patients most likely to achieve success with clomiphene therapy include patients with polycystic ovary syndrome, amenorrhea-galactorrhea syndrome, psychogenic amenorrhea, post-oral-contraceptive amenorrhea, and certain cases of secondary amenorrhea of undetermined etiology. Clomiphene citrate is indicated only in patients with demonstrated ovulatory dysfunction who are not pregnant, do not have ovarian cysts, do not have abnormal vaginal bleeding, and have normal liver function. In addition, patients selected for clomiphene citrate therapy should be evaluated in regard to estrogen levels, primary pituitary or ovarian failure, endometriosis and endometrial carcinoma, other impediments to pregnancy (e.g., thyroid disorders, adrenal disorders, hyperprolactinemia, and male factor infertility), and uterine fibroids.¹⁻⁶

Although the medical literature suggests various methods there is no universally accepted standard regimen for combined therapy (i.e., clomiphene citrate in conjunction with other ovulation-inducing drugs). Similarly, there is no standard clomiphene citrate regimen for ovulation induction in an in vitro fertilization program to produce ova for fertilization and reintroduction. Therefore clomiphene citrate is not recommended for this use.¹⁻⁶

In order to be considered for approval, a determination should be made that the female patient has a diagnosis of infertility. An evaluation should be made to ensure that the patient is not pregnant, does not have a diagnosis of primary ovarian failure, does not have any contraindications to therapy, and the patient's partner has been determined to be fertile. Clomiphene also will not be considered for female patients requiring ovulation induction that is part of an Assisted Reproductive Technologies (ART) program. The patient must be monitored during therapy on a regular basis.¹⁻⁶

Clomiphene therapy is usually started at a dose of 50 mg daily for a maximum for 5 days per cycle. If lower dosages are not successful in inducing ovulation, the dose may be increased in 50 mg increments up to a maximum of 150 mg. Doses of clomiphene greater than 150 mg are rarely beneficial and increase the risk of adverse events. Long-term cyclic therapy is not recommended beyond a total of about six cycles (including three ovulatory cycles). In general, if a dosage of 150 mg is not successful, alternate therapy should be considered.¹⁻⁶

Additionally, clomiphene has been used for the treatment of oligospermia in male patients. However, there are no adequate or well-controlled studies that demonstrate the effectiveness of clomiphene citrate in the treatment of male infertility. The current guidelines from the American Academy of Clinical Endocrinology do not recommend its use.^{1,7}

Horizon BCBSNJ has chosen to allow coverage of clomiphene for intrauterine insemination (IUI). The client has requested that all requests for patients undergoing IUI who are 45 years of age or older be sent to Horizon Pharmacy Services to verify whether the patient has coverage for this indication. If the patient qualifies for coverage, Horizon will contact CVS Caremark to proceed with the clinical questions in the criteria. If the patient does not qualify for coverage, Horizon will send a denial letter to the physician and inform CVS Caremark of this decision.

Horizon BCBSNJ has determined that if the patient meets the prior authorization requirements for fertility, a dispensing limit of 10 tablets per 30 days will be applied. Additionally, the client will allow up to a total of 3 months of therapy. The client has also chosen to allow coverage of up to 10 tablets one time only for use in the Clomiphene Citrate Challenge Test.

ADDITIONAL INFORMATION

Dosage and Administration:

General Considerations

The workup and treatment of candidates for clomiphene citrate therapy should be supervised by physicians experienced in management of gynecologic or endocrine disorders. Patients should be chosen for therapy with

clomiphene citrate only after careful diagnostic evaluation. The plan of therapy should be outlined in advance. Impediments to achieving the goal of therapy must be excluded or adequately treated before beginning clomiphene citrate. The therapeutic objectives should be balanced with potential risks and discussed with the patient and others involved in the achievement of a pregnancy.

Ovulation most often occurs from 5 to 10 days after a course of clomiphene citrate. Coitus should be timed to coincide with the expected time of ovulation. Appropriate tests to determine ovulation may be useful during the time.

Recommended Dosage

Treatment of the selected patient should begin with a low dose, 50 mg (one tablet) daily for 5 days. The dose should be increased only in those patients who do not ovulate in response to cyclic 50-mg clomiphene citrate. A low dosage or duration of treatment course is particularly recommended if unusual sensitivity to pituitary gonadotropin is suspected, such as in patients with polycystic ovary syndrome.

The patient should be evaluated carefully to exclude pregnancy, ovarian enlargement, or ovarian cyst formation between each treatment cycle.

If progestin-induced bleeding is planned, or if spontaneous uterine bleeding occurs prior to therapy, the regimen of 50 mg daily for 5 days should be started on or about the 5th day of the cycle. Therapy may be started at any time in the patient who has had no recent uterine bleeding. When ovulation occurs at this dosage, there is no advantage to increasing the dose in subsequent cycles of treatment.

If ovulation does not appear to occur after the first course of therapy, a second course of 100 mg daily (two 50-mg tablets given as a single dose) for 5 days should be given. This course may be started as early as 30 days after the previous one after precautions are taken to exclude the presence of pregnancy. Increasing the dosage or duration of therapy beyond 100mg per day for 5 days is not recommended.

The majority of patients who are going to ovulate will do so after the first course of therapy. If ovulation does not occur after three course of therapy, further treatment with clomiphene citrate is not recommended and the patient should be reevaluated. If the ovulatory responses occur, but pregnancy has not been achieved, further treatment is not recommended. If menses does not occur after an ovulatory response, the patient should be reevaluated.

Long-term cyclic therapy is not recommended beyond a total of about six cycles.

CONTRAINDICATIONS/WARNINGS/PRECAUTIONS

Contraindications:

Hypersensitivity

Clomiphene is contraindicated in patients with a known hypersensitivity or allergy to clomiphene citrate or to any of its ingredients.

Pregnancy

Clomiphene should not be administered during pregnancy. Pregnancy Category: X.

To avoid inadvertent clomiphene administration during early pregnancy, appropriate tests should be utilized during each treatment cycle to determine whether ovulation occurs. The patient should be evaluated carefully to exclude pregnancy, ovarian enlargement, or ovarian cyst formation between each treatment cycle. The next course of therapy should be delayed until these conditions have been excluded.

Fetal/Neonatal Anomalies and Mortality

The following fetal abnormalities have been reported subsequent to pregnancy following ovulation induction therapy with clomiphene during clinical trials: Congenital heart lesions, Down syndrome, club foot, congenital gut lesions, conjoined twins and teratomatous malformation, congenital hip, hemangioma, undescended testicles, polydactyly, hypospadias, microcephaly, harelip and cleft palate, patent ductus arteriosus, amaurosis, arteriovenous fistula, inguinal hernia, umbilical hernia, syndactyly, pectus excavatum, myopathy, dermoid cyst of scalp, omphalocele, spina bifida occulta, ichthyosis, and persistent lingual frenulum. Neonatal death and fetal death/stillbirth in infants with birth defects have also been reported. In addition, reports of birth anomalies have been received during postmarketing surveillance.

Liver Disease

Clomiphene therapy is contraindicated in patients with liver disease or a history of liver dysfunction.

Abnormal Uterine Bleeding

Clomiphene is contraindicated in patients with abnormal uterine bleeding of undetermined origin.

Ovarian Cysts

Clomiphene is contraindicated in patients with ovarian cysts or enlargement not due to polycystic ovarian syndrome.

Other

Clomiphene is contraindicated in patients with uncontrolled thyroid or adrenal dysfunction or in the presence of an organic intracranial lesion such as pituitary tumor.

Warnings:

Visual Symptoms

Patients should be advised that blurring or other visual symptoms such as spots or flashes (scintillating scotomata) may occasionally occur during therapy with clomiphene. These visual symptoms increase in incidence with increasing total dose or therapy duration and generally disappear within a few days or weeks after clomiphene is discontinued. Patients should be warned that these visual symptoms may render such activities as driving a car or operating machinery more hazardous than usual, particularly under conditions of variable lighting.

Ophthalmologically definable scotomata and retinal cell function changes have also been reported.

Ovarian Hyperstimulation Syndrome

Ovarian hyperstimulation syndrome (OHSS) has been reported in patients receiving clomiphene citrate therapy for ovulation induction. In some cases OHSS occurred following cyclic use of clomiphene therapy or when clomiphene was used in combination with gonadotropins. Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with ovarian hyperstimulation syndrome.

To minimize the hazard associated with occasional abnormal ovarian enlargement associated with clomiphene therapy, the lowest dose consistent with expected clinical results should be used. Some patients with polycystic ovary syndrome who are unusually sensitive to gonadotropin may have an exaggerated response to usual doses of clomiphene. Therefore, patients with polycystic ovary syndrome should be started on the lowest recommended dose and shortest treatment duration for the first course of therapy.

Precautions:

Careful attention should be given to the selection of candidates for clomiphene therapy. Pelvic examination is necessary prior to clomiphene treatment and before each subsequent course.

Information for Patients

The purpose and risks of clomiphene therapy should be presented to the patient before starting treatment. It should be emphasized that the goal of clomiphene therapy is ovulation for subsequent pregnancy. The physician should counsel the patient with special regard to the following potential risks:

- Visual Symptoms
- Abdominal/Pelvic Pain or Distention
- Multiple Pregnancy
- Pregnancy Wastage and Birth Anomalies

Ovarian Cancer

Prolonged use of clomiphene citrate tablets may increase the risk of a borderline or invasive ovarian tumor.

REFERENCES

1. Clomiphene Citrate product information. TEVA Pharmaceuticals. revised February 2003.
2. Clomid product information. Merrell Pharmaceuticals, Inc (Subsidiary of Aventis Pharmaceuticals, Inc). June 2000.

3. Serophene product information. Serono, Inc. December 2002.
4. Clinical Management Guidelines for Obstetrician-Gynecologists. Management of Infertility Caused by Ovarian Dysfunction. ACOG Practice Bulletin No. 34. February 2002. 99:347-358.
5. Institute for Clinical Systems Improvement (ICSI). Diagnosis and management of infertility. July 2004. www.icsi.org.
6. Cahill, DJ. Wardle, PG. Clinical Review. Management of infertility. British Medical Journal.2002; 125:26-32.
7. American Association of clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients-2002 updates. Endocrine Practice 2002. Nov/Dec; 8(6): 439-456.
8. American Hospital Formulary Service. American Society of Health-System Pharmacists. 2005.
9. USPDI Drug Information for Healthcare Professionals. MICROMEDEX Thomson Healthcare. 2005.
10. Brigham and Women's Hospital. Infertility: A Guide to Evaluation, Treatment, and Counseling. 2003. www.brighamandwomens.org.
11. MICROMEDEX Thomson Healthcare. MICROMEDEX Inc. Greenwood Village, CO. March 2006.

Pharmacy Guidelines can be highly technical and are designed for use by the Horizon BCBSNJ professional staff in making coverage determinations. Members referring to this policy should discuss it with their treating physician or pharmacist, and should refer to their specific benefit plan for the terms, conditions, limitations and exclusions of their coverage.

This Horizon BCBSNJ Pharmacy Guideline is proprietary. It is to be used only as authorized by Horizon BCBSNJ and its affiliates. The contents of this Pharmacy Guideline are not to be copied, reproduced or circulated to other parties without the express written consent of Horizon BCBSNJ. The contents of this Pharmacy Guideline may be updated or changed without notice, unless otherwise required by law and/or regulation. However, benefit determinations are made in the context of Pharmacy Guidelines existing at the time of the decision and are not subject to later revision as the result of a change in Pharmacy Guideline.