Clomiphene Citrate Tablets, USP

**DESCRIPTION**

Clomiphene Citrate Tablets, USP is an orally administered, nonsteroidal, ovulatory stimulant designed chemically as 2-p-(2-ethylhexyl)phenyl)-N,N-dimethyl-1,3-propanediamine citrate. It occurs as a white or off-white amorphous powder having a molecular formula of C26H28CIN O • C6H8 O7 and a molecular weight of 598.10. It is represented structurally as:

![Chemical Structure of Clomiphene Citrate](https://example.com/structure.png)

Clomiphene citrate is a white to pale yellow, essentially odorless, crystalline powder. It is freely soluble in methanol; soluble in ethanol, water, and chloroform; and insoluble in other.

Clomiphene citrate is a mixture of two geometric isomers (cis [zuclofen] and trans [enclomiphene]) containing between 30% and 50% transdienens to achieving potency must be excluded.

Each off-white debossed tablet contains 50 mg clomiphene citrate USP. The tablet also contains the following inactive ingredients: corn starch, lactose monohydrate, magnesium stearate, pregelatinized starch, and docusate.

**CLINICAL PHARMACOLOGY**

**Action**

Clomiphene citrate is a drug of considerable pharmacologic potency. Since care selection and proper management of the patient, clomiphene citrate has been demonstrated to be a useful therapy for the anovulatory patient desiring pregnancy.

Clomiphene citrate is capable of interacting with estrogen-receptor-containing tissues, including the hypothalamus, pituitary, ovary, endometrium, vagina, and cervix. It may compete with estrogen for estrogen-receptor-binding sites and may delay replenishment of intracellular estrogen receptors. Clomiphene citrate induces in a series of endocrine events culminating in a preovulatory gonadotropin surge and subsequent follicular rupture. This first endocrine event in response to a course of clomiphene therapy is an increase in the release of pituitary gonadotropins. This initiates steroidogenesis and folliculogenesis, resulting in growth of the ovarian follicles and release of ova (see Clomiphene Administration).

Available data suggest that both the estrogenic and antiestrogenic properties of clomiphene may participate in the initiation of ovulation. The two clomiphene isomers have been found to have mixed estrogenic and antiestrogenic effects, which may vary from one species to another. Some data suggest that zuclofen has greater estrogenic activity than enclomiphene.

Clomiphene citrate has no apparent progestational, endocrine, or antiandrogenic effects and does not appear to interfere with pituitary-adenal or pituitary-thyroid function, although there is no evidence of a "carryover effect" of clomiphene citrate, spontaneous ovulatory menstrual cycles have been noted in some patients after clomiphene citrate therapy.

Clomiphene citrate is a potentially effective ovulating agent in a variety of patients, including those with a history of previous spontaneous cycles. It is effective in ovulating a day or two before the expected ovulatory day. In some studies, clomiphene citrate has been utilized in the treatment of patients with anovulatory dysfunction, including those with polycystic ovarian syndrome, anovulatory infertility, and those with secondary amenorrhea.

**Pharmacokinetics**

Clomiphene citrate is a weak base that combines with citric acid to form a slightly soluble diester in the gastrointestinal tract. It is rapidly absorbed and has a peak serum level around 100 minutes after ingestion. The absorption rate is not affected by food. The drug is bound to serum proteins to a small extent. It is metabolized in the liver and excreted in the urine as the citrate and unconjugated metabolites. The elimination half-life is approximately 9 days. The drug is not eliminated by hemodialysis.

**Indications**

Clomiphene citrate is indicated for the treatment of ovulatory dysfunction in female infertility. It is used primarily for inducing ovulation in patients with pituitary adenomas, nasopharyngeal carcinoma, and breast cancer. It is also used to induce ovulation in women with polycystic ovary syndrome (PCOS). It is not recommended for treatment of ovulatory dysfunction in women with polycystic ovary syndrome (PCOS) because of the risk of ovarian hyperstimulation syndrome (OHSS).

**Usage**

Clomiphene citrate is used to induce ovulation in women with polycystic ovary syndrome (PCOS). It is not recommended for treatment of ovulatory dysfunction in women with polycystic ovary syndrome (PCOS) because of the risk of ovarian hyperstimulation syndrome (OHSS).

**Contraindications**

Clomiphene citrate is contraindicated in patients with uncontrolled thyroid or adrenal dysfunction or in the presence of an organic intracranial lesion such as pituitary tumor (see INDICATIONS AND USAGE). Clomiphene citrate is contraindicated in patients with uncontrolled thyroid or adrenal dysfunction or in the presence of an organic intracranial lesion such as pituitary tumor (see INDICATIONS AND USAGE).

**Warnings**

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**Precautions**

Clomiphene citrate is contraindicated in patients with uncontrolled thyroid or adrenal dysfunction or in the presence of an organic intracranial lesion such as pituitary tumor (see INDICATIONS AND USAGE).

**Adverse Reactions**

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**Adverse Reaction**

**Adverse Event**

- Ovarian Enlargement (13.6)
- Ovarian Fluid (10.4)
- Nausea and Vomiting (5.6)
- Breast Pain (2.2)
- Visual Symptoms (2.1)
- Blurred vision, light sensitivity, waves, flashes, unspesific visual complaints, photophobia, diplopia, scotomata, headaches
- Abnormal Vaginal Bleeding (1.5)
- Familial spottings, amenorrhagia

**Drug Interactions**

Drug interactions with clomiphene citrate have not been documented.

**Precautionary Maturation, Impairment of Fertility**

Long-term toxicity studies in animals have not been performed to evaluate the carcinogenic potential of clomiphene citrate. Oral administration of clomiphene citrate to male rats at doses of 0.3 or 1 mg/kg/day caused decreased fertility, while higher doses caused temporary infertility. Oral doses of 0.1 mg/kg in female rats temporally interrupted the normal cyclic vaginal smear pattern and prevented conception. Doses of 0.3 mg/kg/day slightly reduced the number of ovulated ova and corpora lutea, while 3 mg/kg/day inhibited ovulation.

**Fetal Risk Summary**

(Females should be counseled about the potential for drug exposure.)

Available animal data do not suggest an increased risk for congenital anomalies above the background population risk. However, animal reproductive toxicity studies showed increased embryo-fetal loss and structural malformations in offspring. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks to the fetus.

**Clinical Considerations**

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

**Animal Data**

Oral administration of clomiphene citrate to pregnant rats during organogenesis at doses of 1.0 mg/kg/day resulted in increased maternal mortality, increased resorptions and dead fetuses, dystocia, and delayed labor. At 8 mg/kg/day, increased maternal mortality, single doses of 50 mg/kg caused fetal cataracts, while 200 mg/kg caused cleft palate. Following injection of clomiphene citrate 2 mg/kg to mice and rats during pregnancy, the offspring exhibited metabolic changes of the reproductive tract. Newborn mice and rats injected during the first few days of life also developed metabolic-stress changes in utero and vaginal mucosa, as well as premature vaginal opening and anovulatory ovaries. These findings are similar to the abnormal reproductive behavior and sterility described with other estrogens and antiestrogens. In rabbits, some temporary bone alterations were seen in fetuses from dams given oral doses of 20 or 40 mg/kg/day during pregnancy, but not following 8 mg/kg/day. No permanent malformations were observed in those studies. Also, reusus monkeys given oral doses of 1.5 to 4.5 mg/kg/day for various periods during pregnancy did not have any abnormal offspring.

**Dosage**

Oral LD₅₀: The acute oral LD₅₀ of clomiphene citrate is 1700 mg/kg in mice and 750 mg/kg in rats. The toxic dose in humans is not known.

Dialysis: Not known if clomiphene citrate is dialyzable.

**Drug Abuse and Dependence**

Tolerance, abuse, or dependence with clomiphene citrate has not been reported.

**Overdosage**

**Signs and Symptoms**

Side effects accompanying acute overdose of clomiphene citrate have not been reported. The extent of overdosage as a result of the usual therapeutic dose during clomiphene citrate therapy include nausea, vomiting, vasomotor flushes, visual blurring, spots or flashes, scotomata, ovarian enlargement with pelvic or abdominal pain. (See CONTRAINDICATIONS: Ovarian Cyst.)