**DESCRIPTION**

Clomiphene citrate is an orally administered, nonsteroidal ovulatory stimulant. It is a white to pale yellow, essentially odorless, crystalline powder. Its molecular formula is C_21_ H_26_ C_2_ N_2_ O_5_ and its molecular weight is 359.46. It is freely soluble in methanol; soluble in ethanol; slightly soluble in water and is insoluble in chloroform, benzene, and ether.

**PHARMACOLOGY**

Clomiphene citrate has no direct effect on the ovary. It is a weak antianabolic agent. Its principal effects are on the hypothalamus and the anterior pituitary gland. By inhibiting hypothalamic release of gonadotropin-releasing hormone (GnRH), clomiphene citrate blocks the normal inhibitory feedback of estrogen on GnRH secretion. This leads to increased release of gonadotropins, which stimulates follicle development. Clomiphene citrate is a weak antiestrogen and possesses some estrogenic activity.

**PHARMACOKINETICS**

Clomiphene citrate is absorbed from the gastrointestinal tract. It is well absorbed after oral administration, and peak plasma levels occur within 3-5 hours. The drug is extensively metabolized in the liver and is excreted in the urine as conjugates of the parent compound and its metabolites. The plasma half-life is approximately 1 hour. The drug is distributed into body fluids and is found in the breast milk. Clomiphene citrate is metabolized by the liver to its active metabolite, theophylline, and its inactive metabolite, theophylline-1,3-dihydroxy. Clomiphene citrate is contraindicated in patients receiving selective serotonin reuptake inhibitors (SSRIs) because of the risk of serotonin syndrome.

**CLINICAL PHARMACOLOGY**

**Indications**

Clomiphene citrate is used in the treatment of ovulatory dysfunction in women with amenorrhea or oligomenorrhea, secondary amenorrhea, and infertility. It is also used in the treatment of male infertility.

**Contraindications**

Clomiphene citrate is contraindicated in patients with a history of uterine bleeding, including endometrial cancer, adenomyosis, and endometriosis. It is also contraindicated in patients with a history of uterine fibroids, uterine polyps, or uterine leiomyomas. Clomiphene citrate is contraindicated in patients with a history of ovarian hyperstimulation syndrome, multiple births, and dizygotic twins. Clomiphene citrate is also contraindicated in patients with a history of hypertension, hyperlipidemia, or hypercholesterolemia.

**Warnings**

Clomiphene citrate is associated with increased risk of multiple births, especially triplet or higher order births. The overall risk of multiple births is greater than that reported for the general population.

**Adverse Reactions**

The most common adverse reactions associated with clomiphene citrate are nausea, vomiting, diarrhea, weight gain, and polyuria. Other adverse reactions include abdominal pain, breast tenderness, headache, hot flashes, and fluid retention.

**Interactions**

Clomiphene citrate is a weak inhibitor of the cytochrome P450 3A4 enzyme. It may increase the serum levels of other drugs that are also metabolized by this enzyme. Clomiphene citrate is also a weak inhibitor of the CYP2C9 enzyme. It may increase the serum levels of other drugs that are also metabolized by this enzyme.

**Dosage and Administration**

Clomiphene citrate is usually administered in a dosage of 50-150 mg per day, orally, for 5 days during the follicular phase of the menstrual cycle. The dosage may be increased to 200 mg per day for a total of 10 days if needed. Patients should be instructed to resume normal sexual activity after treatment. The duration of treatment should be individualized based on the patient's response.

**Clinical Studies**

During clinical investigations, 7578 patients received clomiphene citrate, some of whom had impaired rates of ovulation or reduced rates of fertilization. In clinical trials, ovulation rates varied from approximately 30% to 50% of treated patients. The pregnancy rate per ovulation was 9-11% per cycle. The overall pregnancy rate per treatment cycle was 25%.

**Pharmacotherapeutic Group**

Selective estrogen receptor modulator (SERM)

**Reference**

The information provided is for educational purposes only and is not intended to replace professional medical advice. The medical use and usage of clomiphene citrate should be individualized based on the patient's response.

**Suggested Reading**


**Table 1: Outcome of Pregnancy in Clinical Trials (n=2368)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total Number of Pregnancies</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>681</td>
<td></td>
</tr>
<tr>
<td>Spontaneous Abortion</td>
<td>431</td>
<td>96.2%</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

| Live Births           |                           |               |
| Single Births         | 169                        | 98.16%        |
| Multiple Births       | 165                        | 85.25%        |

**INDICATIONS AND USAGE**

Clomiphene citrate tablets USP is indicated for the treatment of ovulatory dysfunction in women desiring pregnancy. The drug is administered in a dosage of 50-150 mg per day, orally, for 5 days during the follicular phase of the menstrual cycle. The dosage may be increased to 200 mg per day for a total of 10 days if needed. Patients should be instructed to resume normal sexual activity after treatment. The duration of treatment should be individualized based on the patient's response.

**CONTRAINDICATIONS**

Clomiphene citrate is contraindicated in patients with a history of uterine bleeding, including endometrial cancer, adenomyosis, and endometriosis. It is also contraindicated in patients with a history of ovarian hyperstimulation syndrome, multiple births, and dizygotic twins. Clomiphene citrate is also contraindicated in patients with a history of hypertension, hyperlipidemia, or hypercholesterolemia.

**ADVERSE REACTIONS**

The most common adverse reactions associated with clomiphene citrate are nausea, vomiting, diarrhea, weight gain, and polyuria. Other adverse reactions include abdominal pain, breast tenderness, headache, hot flashes, and fluid retention.

**INTERACTIONS**

Clomiphene citrate is a weak inhibitor of the cytochrome P450 3A4 enzyme. It may increase the serum levels of other drugs that are also metabolized by this enzyme. Clomiphene citrate is also a weak inhibitor of the CYP2C9 enzyme. It may increase the serum levels of other drugs that are also metabolized by this enzyme.

**DOSAGE AND ADMINISTRATION**

Clomiphene citrate is usually administered in a dosage of 50-150 mg per day, orally, for 5 days during the follicular phase of the menstrual cycle. The dosage may be increased to 200 mg per day for a total of 10 days if needed. Patients should be instructed to resume normal sexual activity after treatment. The duration of treatment should be individualized based on the patient's response.

**CLINICAL STUDIES**

During clinical investigations, 7578 patients received clomiphene citrate, some of whom had impaired rates of ovulation or reduced rates of fertilization. In clinical trials, ovulation rates varied from approximately 30% to 50% of treated patients. The pregnancy rate per ovulation was 9-11% per cycle. The overall pregnancy rate per treatment cycle was 25%.

**Pharmacotherapeutic Group**

Selective estrogen receptor modulator (SERM)

**Reference**

The information provided is for educational purposes only and is not intended to replace professional medical advice. The medical use and usage of clomiphene citrate should be individualized based on the patient's response.

**Suggested Reading**


To minimize the hazard associated with occasional ovarian enlargement associated with clomiphene citrate therapy, the lowest dose consistent with effectiveness should be used. Ovarian enlargement is a common but not invariable accompaniment of the administration of the recommended dose of clomiphene citrate. Some patients, particularly those with a history of benign or malignant neoplasms, may occasionally experience considerable ovarian enlargement that may be associated with discomfort.

Information for Patients: The known and potential risks of clomiphene citrate therapy should be presented to the patient before each subsequent course (see CONTRAINDICATIONS AND WARNINGS).

Pregnancy and Breastfeeding: Pregnancy should be avoided in females receiving clomiphene citrate therapy. Pregnancy outcome data are discussed in the subsection-INDICATIONS AND USAGE. Pregnancy: Instruct the patient that pregnancy must be avoided while taking clomiphene citrate (see CONTRAINDICATIONS AND WARNINGS). Nursing Mothers: It is not known whether clomiphene citrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when clomiphene citrate is administered to a nursing woman. In patients, clomiphene citrate may reduce lactation.

Ovarian Cancer: Postmenopausal use of clomiphene citrate tablets USP may increase the risk of a borderline or invasive ovarian tumor (see ADVERSE REACTIONS). ADVERSE REACTIONS Clinical Trial Adverse Events: clomiphene citrate, at recommended dosages, is generally well-tolerated. Adverse reactions usually have been mild and transitory and have disappeared promptly after treatment has been discontinued. Adverse experiences reported in patients treated with clomiphene citrate during clinical studies are shown in Table 1.

Table 1. Incidence of Adverse Events in Clinical Studies (Events Greater than or Equal to 1% in n = 8292)

<table>
<thead>
<tr>
<th>Event</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian Enlargement</td>
<td>13.6</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>2.0</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>2.2</td>
</tr>
<tr>
<td>Breast Complaints</td>
<td>2.2</td>
</tr>
<tr>
<td>Visual Symptoms</td>
<td>1.5</td>
</tr>
<tr>
<td>Varicose Veins</td>
<td>1.3</td>
</tr>
<tr>
<td>Abnormal Uterine Bleeding</td>
<td>1.3</td>
</tr>
<tr>
<td>Hematoma</td>
<td>0.8</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>0.8</td>
</tr>
</tbody>
</table>

In includes 498 patients whose reports may have been duplicated in the event of overdose, appropriate supportive measures should be employed (see OVERDOSAGE). Drug Interactions: Drug interactions with clomiphene citrate have not been documented.

Cardiovascular: Angina pectoris, arrhythmias, edema, heart failure, hypotension, hypertension, myocardial infarction, stroke.

Dermatologic: Alopecia, acne, pruritus, contact dermatitis, dermatitis herpetiformis, erythema, erythema multiforme, hyperpigmentation, hypertrichosis, pityriasis, psoriasis, pemphigus, urticaria, vitiligo.

Endocrine: Amenorrhea, anovulation, galactorrhea, gynecomastia, hirsutism, intermenstrual bleeding, menopause, menstrual disorders, secondary amenorrhea.

Gastrointestinal: Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gastritis, gastroesophageal reflux disease, irritable bowel syndrome, nausea, vomiting.

Genitourinary: Amenorrhea, anovulation, oligospermia, ovulation, uterine bleeding, vaginal bleeding.

Hematologic: Anemia, aplastic anemia, asymptomatic neutropenia, leukopenia, neutropenia, thrombocytopenia.

Metabolic: Edema, fluid retention, gout, hypercholesterolemia, hyperglycemia, hyperlipidemia, hyperuricemia, hypokalemia, hypomagnesemia, hypophosphatemia, hyperuricemia, weight gain.

Neuromuscular and skeletal: Arthralgia, back pain, fractures, pain in muscles, rhabdomyolysis, muscle spasm.

Ophthalmic: Amblyopia, eyelid swelling, epiphora, exophthalmos, glaucoma, optic atrophy, retinal hemorrhage, retinal detachment, retinitis, retinopathy, strabismus.

Respiratory: Asthma, bronchitis, cough, dyspnea, emphysema, hyperventilation, laryngitis, pneumonia, pulmonary embolism, respiratory distress, rhinitis, sinusitis.

Skin: Acne, allergic reaction, dermatitis, dermatitis herpetiformis, erythema, erythema multiforme, erythema nodosum, hypertrichosis, pruritus, urticaria.

Central Nervous System: Migraine headache, parasthesia, seizures, stroke, syncope.

Other: Anxiety, irritability, mood changes, psychosis.

Drug Interactions: Drug interactions with clomiphene citrate have not been documented.

Central Nervous System: Migraine headache, parasthesia, seizures, stroke.

Dermatologic: Alopecia, acne, pruritus, contact dermatitis, dermatitis herpetiformis, erythema, erythema multiforme, hyperpigmentation, hypertrichosis, pityriasis, psoriasis, pemphigus, urticaria, vitiligo.

Gastrointestinal: Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gastritis, gastroesophageal reflux disease, irritable bowel syndrome, nausea, vomiting.

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