Serophene
Clomiphene Citrate Tablets

Presentation

Clomiphene citrate 50 mg in a round, flat, bevel-edged tablet of approximately 8 mm diameter. It is scored on one side and embossed S on the other.

Uses

Actions

Clomiphene citrate, an orally administered, non-steroidal agent, may induce ovulation in selected anovulatory women.

Clomiphene citrate is a drug of considerable pharmacological potency. Careful evaluation and selection of the patient and close attention to the timing of the dose is mandatory prior to treatment with clomiphene citrate. Conservative selection and management of the patient contribute to successful therapy of anovulation.

Clomiphene citrate induces ovulation in most selected anovulatory patients. The various criteria for ovulation include: an ovulation peak of oestrogen excretion followed by a biphasic basal body temperature curve; urinary excretion of pregnanediol at post-ovulatory levels and, endometrial histologic findings characteristic of the luteal phase.

A review of eleven publications appearing between 1964 and 1978 showed that pregnancy occurred in 35% of 5154 patients with ovulatory dysfunction who received clomiphene citrate.

Pregnancies following Clomiphene Citrate\(^a\) (No. of patients studied - 5154)

<table>
<thead>
<tr>
<th>Patients Ovulating(^b)</th>
<th>75 % (50-94%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulatory Cycles</td>
<td>53 % (33-69%)</td>
</tr>
<tr>
<td>Patients Pregnant</td>
<td>35 % (11-52%)</td>
</tr>
<tr>
<td>Patients Pregnant</td>
<td>46 % (22-61%)</td>
</tr>
<tr>
<td>Patients Ovulating Live Births</td>
<td>86 % (74-99.8%)</td>
</tr>
<tr>
<td>Abortions</td>
<td>14 % (0.2-26%)</td>
</tr>
<tr>
<td>Single Births</td>
<td>90 % (67-100%)</td>
</tr>
<tr>
<td>Surviving</td>
<td>99 % (98.2-100%)</td>
</tr>
<tr>
<td>Multiple Births</td>
<td>10 % (0-33%)</td>
</tr>
<tr>
<td>Surviving</td>
<td>96 % (82-100%)</td>
</tr>
</tbody>
</table>

\(a\) Includes patients receiving other than recommended dosage regimen.
\(b\) average from studies.

Clomiphene citrate therapy appears to mediate ovulation through increased output of pituitary gonadotropins. These stimulate the maturation and endocrine activity of
the ovarian follicle which is followed by the development and function of the corpus luteum. Increased urinary excretion of gonadotropins and oestrogen suggest involvement of the pituitary.

**Pharmacokinetics**

There is very little data available concerning the pharmacokinetics of clomiphene citrate. What little data is available may be summarised as follows:

Studies with $^{14}$C-labelled clomiphene citrate have shown that it is readily absorbed orally in humans, and is excreted principally in the faeces. An average of 51% of the administered dose was excreted after 5 days. After intravenous administration 37% was excreted in 5 days. The appearance of $^{14}$C in the faeces six weeks after administration suggests that the remaining drug and/or metabolites are slowly excreted from a sequestered enterohepatic recirculation pool.

After a single 50 mg dose peak concentrations of 8-9 ng/mL are achieved after 6 to 7 hours for the z-isomer. The area under the curve measured over 336 hours was approximately 650 ng/mL/h.

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**Indications**

Clomiphene citrate is indicated for the treatment of ovulatory failure in patients desiring pregnancy, and whose husbands are fertile and potent. Impediments to this goal must be excluded or adequately treated before beginning therapy.

Administration of clomiphene citrate is indicated only in patients with demonstrated ovulatory dysfunction and in whom the following conditions apply:

1. Normal liver function.
2. Physiologic indications of normal endogenous oestrogen (as estimated from vaginal smears, endometrial biopsy, assay of urinary oestrogen, or from bleeding in response to progesterone). Reduced oestrogen levels, while less favourable do not prevent successful therapy.
3. Clomiphene citrate therapy is not effective for those patients with primary pituitary or ovarian failure. It cannot substitute for appropriate therapy of other disturbances leading to ovulatory dysfunction, eg., diseases of the thyroid or adrenals.
4. Particularly careful evaluation prior to clomiphene citrate therapy should be done in patients with abnormal uterine bleeding. It is most important that neoplastic lesions are detected.

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**Dosage and Administration**

**General Considerations**

Physicians experienced in managing gynecologic or endocrine disorders should supervise the work-up and treatment of candidate patients for clomiphene citrate therapy. Patients should be chosen for clomiphene citrate therapy only after careful
diagnostic evaluation (see **Indications**). 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. In determining a starting dose schedule, efficacy must be balanced against potential side effects.

For example, the available data so far suggests that ovulation and pregnancy are slightly more attainable with 100 mg/day for 5 days than with 50 mg/day for 5 days. As the dosage is increased, however, ovarian overstimulation and other side effects may be expected to increase.

Although the data do not yet establish a relationship between dose level and multiple births, it is reasonable that such a correlation exists on pharmacologic grounds.

For these reasons, treatment of the usual patient should initiate with a 50 mg daily dose for 5 days. The dose may be increased only in those patients who do not respond to the first course (see Recommended Dosage).

Special treatment with lower dosage over shorter duration is particularly recommended if unusual sensitivity to pituitary gonadotropin is suspected including patients with polycystic ovary syndrome (PCOS; see Contraindications).

**Recommended Dosage**

The recommended dosage for the first course of clomiphene citrate is 50 mg (1 tablet) daily for 5 days. Therapy may be started at any time if the patient has had no recent uterine bleeding. If progestin-induced bleeding is intended, 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 fifth day of the cycle. When ovulation occurs at this dosage, there is no advantage to increasing in dose in subsequent cycles of treatment.

If ovulation does not appear to have occurred after the first course of therapy, a second course of 100 mg daily (two 50 mg tablets given as a single daily dose) for 5 days may be started. This course may begin as early as 30 days after the previous one. Increasing the dosage or duration of therapy beyond 100 mg/day for 5 days should not be undertaken. Maximum number of cycles under clomiphene therapy is 6 cycles.

The majority of patients who respond do so during the first course of therapy, and 3 courses constitute an adequate therapeutic trial. If ovulatory menses do not occur, the diagnosis should be re-evaluated. Treatment beyond this is not recommended in the patient who does not exhibit evidence of ovulation.

**Pregnancy**

Properly timed coitus is very important for good results. For regularity of cyclic ovulatory response it is also important that each course of clomiphene citrate be started on or about the fifth day of the cycle, once ovulation has been established. As with other therapeutic modalities, Serophene therapy follows the rule of
diminishing returns, such that likelihood of conception diminishes with each succeeding course of therapy.

If pregnancy has not been achieved after 3 ovulatory responses to Serophene, further treatment is not generally recommended.

**Contraindications**

1. Uncontrolled thyroid or adrenal dysfunction
2. An organic intracranial lesion such as pituitary tumour
3. Liver disease or a history of liver dysfunction
4. Abnormal uterine bleeding of undetermined origin
5. Ovarian cysts or enlargement not due to polycystic ovary syndrome
6. Ovarian insufficiency of hypergonadotrophic or hyperprolactinaemic origin
7. Cancer of genital organs
8. Endometriosis: endometriosis may be aggravated by elevated oestradiol levels associated with ovulation induction
9. Thrombophlebitis
10. Occurrence of visual disorders during previous treatment with clomiphene
11. Pregnancy and lactation: Although no direct effect of clomiphene citrate therapy on the human foetus has been seen, clomiphene citrate should not be administered in cases of suspected pregnancy as such effects have been reported in animals. To prevent inadvertent clomiphene citrate administration during early pregnancy, the basal body temperature should be recorded throughout all treatment cycles; and therapy should be discontinued if pregnancy is suspected. If the basal body temperature following clomiphene citrate is biphasic and is not followed by menses the possibility of an ovarian cyst and/or pregnancy should be excluded. Until the correct diagnosis has been determined, the next course of therapy should be delayed.
12. Known hypersensitivity or allergy to clomiphene and any of the excipients

**Warnings and Precautions**

*Pre-treatment Diagnosis*
Careful evaluation should be given to candidates for clomiphene citrate therapy. A complete pelvic examination should be performed prior to treatment and repeated
before each subsequent course. Clomiphene citrate should not be given to patients with an ovarian cyst, as further ovarian enlargement may result.

Since the incidence of endometrial carcinoma and of ovulatory disorders increases with age, endometrial biopsy should always exclude the former as causative in such patients. If abnormal uterine bleeding is present, full diagnostic measures are necessary.

**Pregnancy**
Serophene is contraindicated during pregnancy and lactation.

It is essential before any treatment cycle to confirm that the patient is not pregnant (confirmation by β-hCG pregnancy test). In published pharmacological studies, an elimination time up to one month was observed after a single dose of clomiphene citrate. These data suggest that some active drug may remain in the body during early pregnancy in women who conceive in the menstrual cycle of clomiphene citrate therapy. Patient should be informed that the foetus might be exposed to the active substance in early development. The exact exposure is not known.

*In vitro* genotoxicity and *in vivo* genotoxicity testing in rats showed genotoxic effects. From the limited available data in humans, there is no evidence of an increased risk of congenital malformations associated with clomiphene treatment.

**Visual Symptoms**
Occasionally, visual disorders can appear during or just after treatment with clomiphene. Up to now have been observed: visual acuity decrease, blurred vision, scotoma, photophobia, diplopia, peripheral visual field loss, spatial distortion and rarely, optical nerve neuropathy. These symptoms appear more frequently with an increase of the total dose of Serophene and they disappear generally in a few days or in a few weeks after stopping treatment. Symptoms often first appear or are accentuated with exposure to a more brightly lit environment. Their pathophysiological mechanism is not yet established and these symptoms have no predictive value on the evolution of the ophthalmologic disorder. In case of visual disorder, Serophene should be discontinued and an ophthalmic evaluation should be made.

Patients should be warned that blurring and other visual symptoms may render activities such as driving or operating machinery more hazardous than usual, particularly under conditions of variable lighting.

**Ovarian Cyst and Ovarian Enlargement**
An ovarian cyst can grow under clomiphene citrate. It is essential before any treatment cycle to confirm there is no ovarian cyst (except PCOS; see **PRECAUTIONS, Polycystic Ovary Syndrome**). To minimise the hazard associated with the occasional abnormal ovarian enlargement during Serophene therapy (see **ADVERSE EFFECTS**), the lowest dose producing good results should be chosen. Maximal enlargement of the ovary, whether abnormal or physiological, does not occur until several days after discontinuation of clomiphene citrate. Patients should be instructed to inform their physician immediately if they experience abdominal or pelvic pain, malaise, a feeling of tension and/or weight gain, as these symptoms can be indicative of ovarian cyst growth.
The patient complaining of pelvic pain after receiving Serophene should be examined carefully. If enlargement of the ovary occurs, Serophene therapy should be withheld until the ovaries have returned to pretreatment size, and the dosage or duration of the next course should be reduced.

The ovarian enlargement and cyst formation following Serophene therapy usually regress spontaneously within a few days or weeks after discontinuing treatment. Therefore, unless a strong indication for laparoscopy (or laparotomy) exists, such cystic enlargement should always be managed conservatively.

**Ovarian Hyperstimulation Syndrome**

The ovarian hyperstimulation syndrome (OHSS) has been reported to occur in patients receiving Serophene therapy for ovulation induction. In some cases, OHSS occurred following cyclic use of Serophene therapy or when Serophene was used in combination with gonadotropins. OHSS is a medical event distinct from uncomplicated ovarian enlargement. Symptoms usually appear 3-6 days after ovulation or hCG administration. In order to decrease the risk of this syndrome, treatment should start with the lowest effective dose.

The clinical signs of this syndrome in severe cases can include gross ovarian enlargement, gastrointestinal symptoms, ascites, dyspnea, oliguria and pleural effusion. In addition, the following symptoms have been reported in association with this syndrome: pericardial effusion, anasarca, hydrothorax, acute abdomen, hypotension, renal failure, pulmonary oedema, intraperitoneal and ovarian hemorrhage, deep venous thrombosis, torsion of the ovary and acute respiratory distress. The early warning signs of OHSS are abdominal pain and distension, nausea, vomiting, diarrhoea and weight gain. Elevated urinary steroid levels, varying degrees of electrolyte imbalance, hypovolemia, haemoconcentration and hypoproteinemia may occur. Death due to hypovolemic shock, hemoconcentration or thromboembolism has occurred.

Due to fragility of enlarged ovaries in severe cases, abdominal and pelvic examination should be performed very cautiously. If conception results, rapid progression to the severe form of the syndrome may occur. Therapy varies from rest and observation in mild forms of OHSS to hospitalisation with conservative treatment concentrating on restoring blood volume and preventing shocks.

**Polycystic Ovary Syndrome**

Some patients with PCOS who are unusually sensitive to gonadotrophins may have an exaggerated response to usual doses of Serophene. Therefore, patients with PCOS should be started on the lowest recommended dose and shortest treatment duration for the first course of therapy.

**Multiple Pregnancy**

In the reviewed publications, the incidence of multiple pregnancy was increased during those cycles in which clomiphene citrate was given. Among the 1803 pregnancies on which the outcome was reported, 90% were single and 10% twins. Less than 1% of the reported deliveries resulted in triplets or more. Of these multiple pregnancies, 96-99% resulted in the births of live infants. The patient and
her husband should be advised of the frequency and potential hazards of multiple pregnancy before starting treatment.

**Ectopic Pregnancy**
There is an increased chance of ectopic pregnancy (including tubal and ovarian sites) in women who conceive following clomiphene citrate therapy. Multiple pregnancies, including simultaneous intrauterine and extrauterine pregnancies, have been reported.

**Pregnancy Wastage and Birth Anomalies**
The physician should explain so that the patient understands the assumed risk of any pregnancy whether the ovulation was induced with the aid of clomiphene citrate or occurred naturally.

The patient should be informed of the greater pregnancy risks associated with certain characteristics or conditions of any pregnant woman; e.g. age of female and male partner, history of spontaneous abortions, Rh genotype, abnormal menstrual history, infertility history (regardless of cause), organic heart disease, diabetes, exposure to infectious agents such as rubella, familial history of birth anomaly, and other risk factors that may be pertinent to the patient for whom clomiphene citrate is being considered. Based upon evaluation of the patient, genetic counselling may be indicated.

**Uterine Fibroids**
Caution should be exercised when using clomiphene citrate in patients with uterine fibroids due to potential for further enlargement of the fibroids.

**Ovarian Cancer**
It is unknown whether clomiphene citrate increases the risk of ovarian carcinoma. Rare cases of ovarian cancer have been observed after drug treatment of infertility. Infertility is a primary risk factor for ovarian cancer; however, some epidemiology data suggest that prolonged use of Serophene may increase the risk of ovarian tumour. As a precaution, clomiphene should not normally be used for more than 3 cycles.

**Hypertriglyceridaemia**
Cases of hypertriglyceridaemia have been reported in the post-marketing experience with clomiphene citrate (see Adverse Effects). Pre-existing or family history of hyperlipidaemia and use of higher than recommended dose and/or longer duration of treatment with clomiphene citrate are associated with risk of hypertriglyceridaemia.

**Adverse Effects**

Serophene at recommended dosages is generally well tolerated. Adverse reactions are usually mild and transient and most disappear promptly after treatment has been discontinued.

Incidence and severity of adverse reactions tend to be related to dose and duration of treatment.
The adverse reactions reported below are classified according to frequency of occurrence as follows:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>&gt; 1/10</td>
</tr>
<tr>
<td>Common</td>
<td>1/100 – 1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>1/1,000 – 1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>1/10,000 – 1/1,000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt;1/10,000</td>
</tr>
</tbody>
</table>

**Adverse events in clinical trials**

The following frequencies of adverse events have been recorded in 5836 patients treated with clomiphene citrate (Kistner, 1973)\(^1\). Only those events whose frequency was 1% or higher are reported below.

**Central nervous system disorders**

Common: Nervousness and insomnia, headache, dizziness and lightheadedness

**Visual disorders**

Common: Visual symptoms (blurred vision, lights, floaters, waves, unspecified visual complaints, photophobia, diplopia, scotomata, phosphene)

**Vascular disorders**

Very common: Vaso-motor flushes

**Gastrointestinal disorders**

Common: Nausea and vomiting

**Reproductive system and breast disorders**

Very common: Ovarian enlargement

Common: Breast discomfort, abnormal uterine bleeding (intermenstrual spotting, menorrhagia)

**Body as a Whole**

Common: Abdominal-pelvic discomfort/distension/bloating (may resemble ovulatory (mittelschmerz) or premenstrual phenomena or that due to ovarian enlargement)

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\(^1\) Kistner RW. The use of clomiphene citrate in the treatment of anovulation. Semin Drug Treat 1973; 3:159-76.
**Post-marketing adverse reactions**

Among the adverse experiences reported spontaneously with Serophene, the following are deemed to have a possible causal relationship with Serophene.

**Visual disorders:** Abnormal accommodation, blurred vision, photopsia, cataract, eye pain, macular oedema, optic neuritis

**Vascular disorders:** Thrombophlebitis

**Gastrointestinal disorders:** Nausea, vomiting, constipation, diarrhoea, acute pancreatitis

**Hepatic disorders:** Increase in transaminases

**Metabolism and nutrition disorders:** Hypertriglyceridaemia

**Neoplasms:** Ovarian cancer (rare cases observed after treatment for infertility)

**Reproductive and breast disorders:** Endometriosis, heavier menses, ovarian enlargement or cysts

**Ovarian Enlargement**

When clomiphene citrate is administered at the recommended dose, abnormal ovarian enlargement (see Warnings and Precautions) is infrequent, although the usual cyclic variation in ovarian size may be exaggerated. Similarly, mid-cycle ovarian pain (mittelschmerz) may be accentuated. With prolonged or higher dosage, ovarian enlargement and cyst formation (usually luteal) may occur more often and the luteal phase of the cycle may be prolonged. Patients with PCOS may be unusually sensitive to clomiphene therapy.

Rare occurrences of massive ovarian enlargement have been reported, for example in a patient with PCOS whose clomiphene citrate therapy consisted of 100 mg daily for 14 days. Since abnormal ovarian enlargement usually regresses spontaneously, most of these patients should be treated conservatively.

**Visual Symptoms**

The incidence of visual symptoms (see Warnings and Precautions for further recommendations), usually described as ‘blurring’ or spots or flashes (scintillating scotomata), correlates with increasing total dose. The symptoms disappear within a few days or weeks after clomiphene citrate is discontinued. This may be due to intensification and/or prolongation of after-images. Symptoms often appear first, or are accentuated, upon exposure to a more brightly lit environment.

While measured visual acuity has not generally been affected, in one patient taking 200 mg daily, visual blurring developed on the seventh day of treatment, and progressed to severe diminution of visual acuity by the tenth day. No other abnormality was coincident, and the visual acuity was normal by the third day after
treatment was stopped. Ophthalmologically definable scotomata and electroretinographic retinal function changes have also been reported.

**BSP Laboratory Studies**
Greater than 5% retention of sulfobromophthalein (BSP) has been reported in approximately 10 to 20% of patients in whom it was measured. Retention was usually minimal but was elevated during prolonged clomiphene citrate administration or with apparently unrelated liver disease. In some patients, pre-existing BSP retention decreased even though clomiphene citrate therapy was continued. Other liver function tests were usually nominal.

**Other Laboratory Studies**
Clomiphene citrate has not been reported to cause a significant abnormality in hematologic or renal tests, in protein bound iodine, or in serum cholesterol levels.

**Foetal and Congenital Anomalies**
Of 1803 births following clomiphene citrate administration, 45 infants with birth defects were reported for a cumulative rate of 2.5%.

Six cases of Down's Syndrome, one neonatal death with multiple malformations and one case each of the following were reported: extropia, club foot, tibial torsion, blocked tear duct and hemangioma. The other congenital abnormalities were not described. The investigators did not report that these were presumed to be due to therapy. Although isolated cases of congenital anomalies have been observed after treatment with Serophene, Serophene has not been shown to alter the incidence of congenital anomalies observed in the offspring of women with fertility problems. The cumulative rate of congenital abnormalities does not exceed that reported in the general population.

**Interactions**
None known.

**Overdosage**
The effects of an overdose of SEROPHENE are unknown, nevertheless, one could expect ovarian hyperstimulation syndrome to occur, which is further described under "Adverse Reactions".

Advise your patients to immediately contact their doctor or the Poisons Information Centre (in Australia telephone 131 126, in New Zealand telephone 0800 764 766) if they are concerned that they have given themselves too much Serophene.

**Pharmaceutical Precautions**
Protect from light and moisture. Store at room temperature. Keep out of reach of children.
**Medicine Classification**

Prescription medicine

**Package Quantities**

Serophene is available as 50 mg scored white tablets packaged in blister of 10 tablets.

**Further Information**

Clomiphene citrate is designated chemically as 2-[p-(2-chloro-1,2-diphenylvinyl) phenoxy] triethylamine dihydrogen citrate.

The chemical formula and molecular weight are $C_{26}H_{28}ClNO$, $C_6H_8O_7$ and 598.1 respectively. One molecule of citric acid is chemically bound with one molecule of the organic base, clomiphene.

Clomiphene citrate is a chemical analog of other triarylethylene compounds such as chlorotrianisene and the cholesterol inhibitor, triparanol.

Clomiphene citrate is a mixture of both Z ('trans-' form) and E ('cis-' form) isomers. The Z-isomer is active.

**Name and Address**

Serophene is supplied in New Zealand by:

Healthcare Logistics  
58 Richard Pearse Drive  
Airport Oaks, Auckland

Serophene is supplied in Australia by:

Merck Serono Australia Pty Ltd  
3-4/25 Frenchs Forest Rd  
Frenchs Forest NSW 2086

**Date of Preparation**

21 August 2015