

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)

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

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 ¹⁴C-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 ¹⁴C 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.

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.

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 (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 150 mg/day for 5 days should not be undertaken.

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

Pregnancy

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.

Liver Disease

Patients with liver disease or a history of liver dysfunction should not receive clomiphene citrate therapy.

Abnormal Uterine Bleeding

Clomiphene citrate is contraindicated in patients with abnormal uterine bleeding.

Ovarian Cysts and Endometriosis

Use of Serophene is contraindicated when pre-existing endometriosis and ovarian cysts are present, since endometriosis may be aggravated by elevated oestradiol levels associated with ovulation induction.

Warnings and Precautions

Visual Symptoms

Patients should be warned that blurring and/or other visual symptoms may occur occasionally with clomiphene citrate therapy. These may make activities such as driving or operating machinery more hazardous than usual particularly under conditions of variable lighting. While their significance is not yet understood (see Adverse Reactions), patients having any visual symptoms, should discontinue treatment and have a complete ophthalmologic evaluation.

Diagnosis Prior to Clomiphene Citrate Therapy

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.

Ovarian Overstimulation during Treatment with Clomiphene Citrate

To minimise the hazard associated with the occasional abnormal ovarian enlargement during clomiphene citrate therapy (see Adverse Reactions), The lowest dose producing good results should be chosen. Some patients with polycystic ovary syndrome are unusually sensitive to gonadotropin and may have an exaggerated response to usual doses of clomiphene citrate.

Maximal enlargement of the ovary, whether abnormal or physiologic, does not occur until several days after discontinuation of clomiphene citrate. The patient complaining of pelvic pains after receiving clomiphene citrate should be examined carefully.

If enlargement of the ovary occurs, clomiphene citrate 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 clomiphene citrate therapy regress spontaneously within a few days or weeks after discontinuing treatment. Therefore, unless a strong indication for laparotomy exists, such cystic enlargement always should be managed conservatively.

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.

Adverse Effects

Symptoms

Side effects are not prominent at the recommended dosage of clomiphene citrate and infrequently interfere with treatment. Side effects tend to occur more frequently at higher doses and in the longer treatment courses used in some early studies.

The more common side effects and the percent of patients experiencing them include vasomotor flushes (11%), abdominal discomfort (7.4%) abnormal uterine bleeding (0.5%), ovarian enlargement (14%) breast tenderness (2.1%) and visual symptoms (1.6%). The vasomotor symptoms resemble menopausal hot flushes, and are not usually severe. They promptly disappear after treatment is discontinued. Abdominal discomfort may resemble ovulatory (mittelschmerz) or premenstrual phenomena, or that due to ovarian enlargement. In addition, nausea and vomiting (2.1%), nervousness and insomnia (1.9%), headache (1%), dizziness and light-headedness (1%), increased urination (0.9%), depression and fatigue

(0.8%), urticaria and allergic dermatitis (0.6%), weight gain (0.4%), and reversible hair loss (0.3%) have been reported.

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 polycystic ovary disease may be unusually sensitive to clomiphene therapy.

Rare occurrences of massive ovarian enlargement have been reported, for example in a patient with polycystic ovary syndrome 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.

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.

Birth Defects

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. 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

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