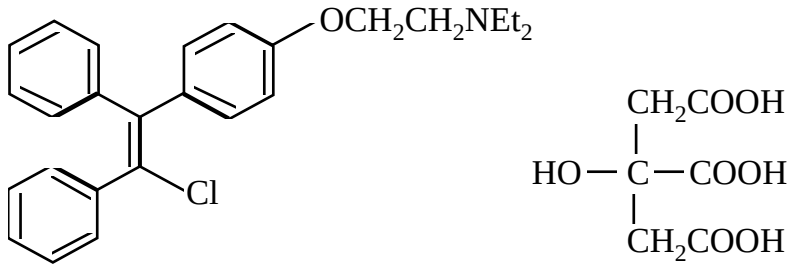
PRODUCT INFORMATION

SEROPHENE

NAME OF DRUG

SEROPHENE (clomiphene citrate)
Clomiphene citrate exists as a mixture of E and Z isomers. The Z-isomer of clomiphene citrate is represented structurally as:



DESCRIPTION

Each scored white tablet contains clomiphene citrate USP 50 mg and lactose 57.75 mg, sodium starch glycollate 8.5 mg, maize starch 17.25 mg, microcrystalline cellulose 25.25 mg, silica 3.25 mg and magnesium stearate 3.0mg as excipients. Clomiphene citrate is designated chemically as 2-[p-(2-chloro-1,2-diphenylvinyl) phenoxy] triethylamine dihydrogen citrate. It is white to pale yellow, essentially odourless. It is slightly soluble in water and chloroform, freely soluble in methanol, sparingly soluble in alcohol, insoluble in ether.

Molecular weight: 598.09
CAS: 911-45-5 (clomiphene) 50-41-9 (citrate)

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

PHARMACOLOGY

Actions: The stimulation of an ovulatory response to cyclic SEROPHENE therapy is believed to be related to its anti-oestrogenic properties; by apparently competing with oestrogen for binding sites at the hypothalamic level, it causes increased secretion of follicle stimulating hormone (FSH) and luteinising hormone (LH), with subsequent ovarian stimulation, resulting in maturation of the ovarian follicle and development of the corpus luteum. Involvement of the pituitary is indicated by increased urinary excretion of gonadotrophins and the ovarian response is manifested by increased urinary oestrogen excretion.

Ovulation most frequently occurs 6 - 12 days after a course of SEROPHENE. Coitus should be timed, with this in mind, to coincide with the expected time of ovulation. Spontaneous ovulatory menses have been noted after clomiphene therapy in some patients. However, there is no evidence of “carry over effect” of clomiphene. Fertile patients with polycystic ovulatory

syndrome who have not responded to wedge resection of the ovary may respond to SEROPHENE.

Suggested criteria for ovulation following SEROPHENE may include: an ovulatory peak of oestrogen excretion followed by biphasic basal body temperature curve; urinary excretion of pregnanediol at post-ovulatory levels and endometrial histological findings characteristic of the luteal phase.

Pharmacokinetics: 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.

INDICATIONS

SEROPHENE is indicated in the treatment of ovulatory failure in patients desiring pregnancy, whose partners have adequate sperm and who have potentially functional hypothalamic-hypophyseal ovarian systems and adequate endogenous oestrogens. Impediments to this goal must be excluded or adequately treated before beginning therapy. Administration of SEROPHENE is indicated only in patients with demonstrated ovulatory dysfunction and in whom the following conditions apply:

1. Demonstration of normal liver function.
2. Physiological indications of normal or near normal endogenous oestrogen levels should be present (as estimated from vaginal smears, endometrial biopsy, assay of urinary or serum 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 in patients with primary pituitary or ovarian failure. It cannot substitute for appropriate therapy of other disturbances leading to ovulatory dysfunction, e.g. diseases of the thyroid or adrenals.
4. Patients with abnormal uterine bleeding should be thoroughly evaluated prior to initiating clomiphene citrate therapy. It is most important that neoplastic lesions are detected.

CONTRAINDICATIONS

SEROPHENE is contraindicated in patients who have:

1. Uncontrolled thyroid or adrenal dysfunction
2. An organic intracranial lesion such as a 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 ovarian syndrome
6. Mental depression
7. Thrombophlebitis
8. Visual disturbances: Blurring or other visual symtoms may occur with SEROPHENE treatment. If they do occur, SEROPHENE should be discontinued and a complete ophthalmic evaluation should be made. No further courses of SEROPHENE should be administered.

SEROPHENE is also contraindicated in pregnancy and lactation.

PRECAUTIONS

Diagnosis prior to clomiphene citrate therapy: Candidates for SEROPHENE therapy must be thoroughly evaluated prior to commencing therapy. Dilatation and curettage or hysteroscopy should always be performed for diagnosis before starting therapy with SEROPHENE. A pelvic examination should be repeated before each subsequent course. SEROPHENE 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 possibility of endometrial neoplasm. If abnormal uterine bleeding is present, full diagnostic measures are necessary.

Ovarian enlargement: To minimise the hazard associated with the occasional abnormal ovarian enlargement during SEROPHENE therapy (see **Adverse Reactions**), the lowest dose producing good results should be chosen. Some patients with polycystic ovarian disease are unusually sensitive to gonadotrophins and may have an exaggerated response to usual doses of SEROPHENE. Maximal enlargement of the ovary, whether abnormal or physiological, does not occur until several days after discontinuation of clomiphene citrate. The patient complaining of pelvic pains 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 regress spontaneously within a few days or weeks after discontinuing treatment. Therefore, unless a strong indication for laparoscopy (or laparatomy) exists, such cystic enlargement should always be managed conservatively.

Ovarian Hyperstimulation Syndrome: Ovarian Hyperstimulation Syndrome (OHSS) has been reported to occur in patients receiving drug therapy for ovulation induction, including in rare (between 1/10 000 and 1/1000) patients receiving SEROPHENE therapy. OHSS is a medical event distinct from uncomplicated ovarian enlargement. (See **'Symptoms and treatment of ovarian hyperstimulation syndrome'** below for further information).

Multiple Pregnancy: Before starting treatment, patients should be advised of the possibility and potential hazards of multiple pregnancy if conception occurs following SEROPHENE therapy.

Occupational hazards: Patients should be warned that blurring and other visual symptoms, especially under conditions of variable lighting, which increase the hazards of operating machinery or driving a car, may occur during therapy with SEROPHENE.

Use in Pregnancy: (Category B3)
Even though there is no evidence that SEROPHENE has a harmful effect on human foetuses it does damage rabbit and rat foetuses when given in high doses to the pregnant animal. Therefore, SEROPHENE should not be administered during pregnancy.

To prevent inadvertent SEROPHENE administration during early pregnancy, careful pelvic examination must be done prior to each course of therapy, the basal body temperature (BBT) should be recorded throughout all treatment cycles, and the patient should be carefully observed

to determine whether ovulation has occurred. If the basal temperature following SEROPHENE is biphasic and is not followed by menses, the patient should be examined carefully for the presence of an ovarian cyst and should have a pregnancy test. The next course of therapy should be delayed until the possibility of pregnancy has been excluded.

Use in lactation:
SEROPHENE is contraindicated in lactating women.

Use in Elderly and Children: SEROPHENE is not indicated for use in the elderly or in children.

Drug Interactions
There are no known interactions.

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

Other Laboratory Studies: SEROPHENE has not been reported to cause a significant abnormality in haematological or renal tests, in protein bound iodine or in serum cholesterol levels.

ADVERSE REACTIONS
Adverse reactions are not prominent at the recommended dosage of SEROPHENE, and infrequently interfere with treatment. Incidence and severity of reactions tend to be related to dose and duration of treatment and are usually reversible after SEROPHENE therapy is discontinued.

The most frequent adverse reactions include ovarian enlargement (approximately 1 in 7 patients), vasomotor flushes resembling menopausal symptoms which are not usually severe and promptly disappear after treatment is discontinued (approximately 1 in 10 patients), and abdominal discomfort (approximately 1 in 15 patients). Other reactions include visual symptoms, abdominal distention, bloating, pain or soreness. If visual symtoms occur, stop treatment and perform a complete ophthalmological evaluation.

Adverse reactions which occur less frequently (approximately 1 in 50 patients or more) include breast tenderness, nausea and vomiting, nervousness and insomnia. Other adverse effects which occur in less than 1 in 100 patients include headache, dizziness and lightheadedness, increased urination, depression, fatigue, urticaria and allergic dermatitis, abnormal uterine bleeding, weight gain, ovarian cysts, ovarian hyperstimulation syndrome (see below for further information) and reversible hair loss.

Thromboembolic events, such as pulmonary embolism, arterial occlusion, and phlebitis have been reported rarely (ie. between 1/10 000 and 1/1000) in patients treated with clomiphene citrate. It is not clear what, if any, relationship these events have to SEROPHENE therapy.

When SEROPHENE is administered at the recommended dose, abnormal ovarian enlargement (see **Precautions**) is infrequent, although the usual cyclic variation in ovarian size may be exaggerated. Similarly, mid-cycle ovarian pain 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 SEROPHENE. Rare occurrences of massive ovarian enlargement have been reported, for example, in a patient with polycystic ovary disease whose clomiphene citrate therapy consisted of 100 mg daily for 14 days.

Visual symptoms: Visual symptoms, usually described as "blurring" or spots or flashes, increase in incidence with increasing total dose and disappear within a few days or weeks after SEROPHENE is discontinued. Other visual symptoms which may occur include diplopia, phosphenes, photophobia, decreased visual acuity, loss of peripheral vision and spatial distortion. 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 had not generally been affected in one patient taking 200 mg daily, visual blurring developed on the 7th day of treatment and progressed to severe diminution of visual acuity by the 10th day. No other abnormality was co-incident 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.

Birth Defects: From 2339 births following clomiphene citrate administration, 58 infants with birth defects were reported for a cumulative rate of 2.5%. Reported defects were congenital heart lesions (8 infants), Down's Syndrome (5 infants), club foot (4 infants), congenital gut lesions (4 infants), hypospadias (3 infants), microcephaly (2 infants), harelip and cleft palate (2 infants), congenital hip (2 infants), polydactyl (2 sets of twins), conjoined twins with teratomatous malformation, patent ductus arteriosus, amaurosis (blindness), arteriovenous fistula, inguinal hernia, umbilical hernia, syndactyly, pectus excavatum, myopathy, dermoid cyst of scalp, omphalocele, spina bifida occulta, ichthyosis, persistent lingual fraenulum and 7 infants with multiple somatic defects. The cumulative rate of congenital abnormalities does not exceed that reported in the general population.

Multiple pregnancies often result from induction of ovulation and are the main determinant of the outcome of the pregnancies and of the health of the neonates. The majority of multiple conceptions have been found to be twins.

SYMPTOMS AND TREATMENT OF OVARIAN HYPERSTIMULATION SYNDROME

Ovarian hyperstimulation syndrome is a serious and sometimes fatal complication of follicular stimulation therapy. In the WHO Technical Report Series No. 514 it is classified into 3 grades.

Grade 1: Variable ovarian enlargement, sometimes associated with small cysts. Laboratory findings include urinary oestrogen levels of over 150 microgram/24 hours and pregnanediol excretion titres of over 10 mg/24 hours. Symptoms are minor.

Grade 2: Patients in this category have additional symptoms of a variable nature. They include abdominal distension, nausea, vomiting and diarrhoea. Careful medical observation is required and appropriate symptomatic treatment is indicated.

Grade 3: These patients are characterised by having large ovarian cysts, ascites, and sometimes hydrothorax. Haemoconcentration with increased blood viscosity and coagulation abnormalities may appear.

Symptoms first appear 2 to 4 days after the ovulation dose of hCG, increase for about a week, remain constant for the second week and then subside quite rapidly in the course of the third week.

Haemoconcentration should be thoroughly assessed by:
(1) fluid intake and output
(2) weight
(3) haematocrit
(4) serum and urinary electrolytes, and
(5) urine specific gravity

These determinations should be performed daily or more often if indicated. Should the haematocrit rise dangerously, the patient should be given an infusion of heparin. Continue the infusion for 1 to 2 weeks.

Generally treatment is symptomatic and consists of bed rest, fluid and electrolyte replacement and analgesics if necessary.

Hospitalisation is recommended for patients demonstrating the mild to severe form and required for patients with symptoms of severe hyperstimulation.

The pathological changes associated with the hyperstimulation syndrome are explicable on the basis of protein, particularly albumin, shifting from the plasma to the peritoneal cavity.

A dangerous downward spiral of hypovolaemia, haemoconcentration and circulatory failure ensues with the attendant risks of thrombosis and renal failure. This process can be interrupted by increasing the plasma colloid osmotic pressure with human serum albumin and by removing protein from the peritoneal cavity by paracentesis.

Care should be taken during manual examination not to rupture ovarian cysts and intercourse should be prohibited because of this risk. Should ovarian cysts rupture and bleeding become such that surgery is required, the conservative approach with partial resection of the ovary or ovaries is generally adequate.

The risk of precipitating the syndrome may be greatly reduced by adequate patient monitoring during therapy.

DOSAGE AND ADMINISTRATION

General considerations: Physicians experienced in managing gynaecological or endocrinological disorders should supervise the work-up and treatment of candidate patients for SEROPHENE therapy. Patients should be chosen for SEROPHENE therapy only after thorough diagnostic evaluation (see **Indications**). The plan of therapy should be outlined in advance.

In determining a starting dose schedule, efficacy must be balanced against potential adverse effects. For example, the available data so far suggest 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 hyperstimulation and other adverse 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 pharmacological 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 a lower dosage over a shorter duration is particularly recommended if unusual sensitivity to pituitary gonadotrophin is suspected, including patients with polycystic ovary disease (see **Precautions**).

The recommended dosage for the first course of SEROPHENE 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 the 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. The dosage or duration of therapy should not be increased beyond 150 mg/day for 5 days.

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.

Properly timed coitus is very important for good results. For regularity of cyclic ovulatory response it is also important that each course of SEROPHENE 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 clomiphene treatment is not generally recommended.

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.

PRESENTATION

SEROPHENE (clomiphene citrate) 50 mg scored white tablets are supplied in blister packs of 10 tablets.

NAME AND ADDRESS OF THE SPONSOR

Serophene is supplied in Australia by:
Merck Serono Australia Pty Ltd
3-4/25 Frenchs Forest Rd
Frenchs Forest NSW 2086

Serophene is supplied in New Zealand by:
Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks, Auckland

TGA Approved: 20 August 1996

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