PRODUCT MONOGRAPH

SEROPHENE®

Clomiphene Citrate Tablets, USP 50 mg

OVULATORY AGENT

EMD Serono Canada Inc.
2695 North Sheridan Way, Suite 200
Mississauga, Ontario L5K 2N6
Canada

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NAME OF DRUG

SEROPHENE®

Clomiphene Citrate Tablets, USP 50 mg

PHARMACOLOGIC CLASSIFICATION

Ovulatory Agent

ACTIONS

Serophene (clomiphene citrate) is an orally-administered, non-steroidal agent which may induce ovulation in anovulatory women in appropriately selected cases[1-24].

Mechanism of Action

The stimulation of an ovulatory response to cyclic Serophene therapy is believed to be related to its antiestrogenic properties; by competing with estrogen for binding sites at the hypothalamic level, it may cause increased secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), with subsequent ovarian stimulation and preovulatory LH surge, resulting in maturation of the ovarian follicle and development of the corpus luteum. The involvement of the pituitary is indicated by increased urinary excretion of gonadotropins and by the response of the ovary as manifested by increased urinary estrogen excretion. Following therapy with Serophene**,** presumptive signs of ovulation resemble those associated with normal menstrual cycle. It should be noted, however, that during drug administration and for several days thereafter, the effects of endogenous estrogen on the vaginal mucosa and cervical mucus are inhibited[25].
Suggested criteria for ovulation following Serophene may include the ovulatory peak of estrogen excretion, a biphasic basal body temperature curve, urinary excretion of pregnanediol at postovulatory of higher levels, and endometrial histologic findings characteristic of the luteal phase. In most patients, ovulation appears to occur from 6 to 12 days after completion of therapy at recommended dosage. A review of fourteen publications appearing between 1964 and 1983 showed that an ovulatory response occurred in 74% of 8,228 patients with ovulatory dysfunction who received clomiphene citrate. Successful therapy characterized by pregnancy occurred in 31% of the 8,228 patients[1,25-27].

Pregnancies following clomiphene citrate USP*.

Author	No. of Patients	Ovulation Rate	Pregnancy Rate
Gysler et al. (1982)	428	85.3	42.8
Hummond et al. (1983)	159	86.0	49.0
Kase et al. (1967)	81	60.5	25.9
Kistner (1965)	50	96.0	26.0
MacGregor et al. (1968)	6,714	70.0	32.7
Murray & Osmond-Clarke (1971)	328	66.5	25.0
O'Herlity et al. (1981)	30	70.0	27.0
Pildes (1965)	36	50.0	11.1
Rabau et al. (1967)	101	62.6	33.6
Rust et al. (1974)	105	91.4	38.1
Seegar-Jones & Moraes-Ruehsen (1967)	73	83.0	30.1
Spellacy & Cohen (1967)	35	80.0	20.0
Sutaria et al. (1980)	51	64.7	31.4
Whitelow et al. (1964)	37	72.9	45.9
TOTAL	8,828	74.21	31.33

* The reported data included patients receiving other than recommended dosage regimen.

INDICATIONS

Serophene (clomiphene citrate) 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 estrogens. Impediments to this goal must be excluded or adequately treated before beginning therapy. The workup and treatment of candidates for Serophene therapy should be supervised by physicians experienced in management of gynecologic or endocrine disorders. The workup of the patient must begin with a careful and detailed history of menstrual and reproductive function, and a complete physical examination. It should be followed by a selective and careful laboratory investigation, based on historical and physical findings.

The following considerations are appropriate for selection of patients:

1. If any doubt exists as to the presence of early pregnancy, Serophene therapy should be withheld until a diagnosis of pregnancy has been excluded.
2. The partner's potential fertility and potency should be ascertained by semen analysis and other indicated examinations.

3. Mechanical impediments to conception, such as tubal obstruction, should be excluded or adequately treated before undertaking Serophene therapy.

4. The diagnosis of ovulatory dysfunction should be established by such standard techniques as basal body temperature curves, serial vaginal smears, cervical mucus, endometrial biopsy, and pregnanediol determination.

5. Appropriate diagnostic measures should be undertaken to exclude primary pituitary failure or primary ovarian failure. Intact pituitary and ovaries are required for successful therapy. Ovulatory dysfunction in the presence of abnormally high levels of pituitary gonadotropins is indicative of ovarian failure, and patients in this category cannot be expected to respond to Serophene. Adequacy of endogenous estrogen, as estimated by vaginal smears, cervical mucus, endometrial biopsy, or urinary estrogen determination, furnishes a measure of ovarian function and indirectly of pituitary function. Bleeding after progesterone administration (progesterone alone, not combined with estrogen) furnishes evidence of an adequate level of endogenous estrogen. A good level of endogenous estrogen provides a favourable prognosis for treatment with Serophene. A reduced estrogen level, although less favourable, does not always preclude successful therapy.

6. Patients with abnormal or excessive bleeding should have particularly careful evaluation prior to Serophene therapy. It is most important to ensure that neoplastic lesions are not overlooked.

7. Clinical evaluation of liver function should always precede Serophene therapy.

8. When disorders such as diabetes, adrenal disease, or thyroid disease are identified during investigation, specific treatment should be undertaken and subfertility therapy reconsidered only after the underlying disorder has been adequately treated. Serophene cannot be expected to be a substitute for specific therapy of these conditions.

CONTRAINDICATIONS

Pregnancy
Serophene (clomiphene citrate) should not be administered during pregnancy since studies in rats and rabbits have shown clomiphene to be teratogenic (see **"**REPRODUCTION STUDIES**"**). Studies in humans have not been done. However, there have been reports of congenital malformations and fetal death associated with clomiphene administration in humans, although a direct causal relationship has not been established. To prevent inadvertent Serophene administration during early pregnancy,

careful pelvic examination must be done prior to each course of therapy, the basal body temperature must be recorded throughout all treatment cycles,
and the patient should be carefully observed to determine whether ovulation has occurred. If the basal body 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.

Medical Problems
Serophene should not be used when the following medical problems exist (reasons given where appropriate):

Liver disease - Serophene therapy is contraindicated in patients with active liver disease of history of hepatic function impairment.

Abnormal bleeding - Serophene is contraindicated in patients with abnormal bleeding of undetermined origin. (Careful evaluation is recommended; neoplastic lesions should not be overlooked). Serophene is not indicated for the management of menstrual disorders. Fibroid tumours of the uterus.

Ovarian cyst - Serophene should not be given in the presence of an ovarian cyst, since further enlargement of the ovary may occur.

Mental depression.

Thrombophlebitis.

WARNINGS

Visual Symptoms
Patients should be advised that blurring or other visual symptoms, dizziness or light-headedness may occasionally occur during therapy with Serophene (clomiphene citrate). Patients should be warned that visual symptoms may render such activities as driving a car or operating machinery more hazardous than usual, particularly under conditions of variable lighting. The significance of these visual symptoms is not yet understood (see “ADVERSE REACTIONS”). If the patient has any visual symptoms, treatment should be discontinued and complete ophthalmologic evaluation carried out.

PRECAUTIONS
Diagnosis prior to Serophene therapy:
Careful attention should be given to diagnosis in candidates for Serophene (clomiphene citrate) therapy. Complete pelvic examination including cervical cytology is mandatory prior to treatment, and pelvic examination should be repeated before each subsequent course. Serophene should not be given in the presence of an ovarian cyst, since further enlargement of the ovary may occur.

Patients in later reproductive life have a greater tendency to endometrial carcinoma as well as a higher incidence of anovulatory disorders. Dilation and curettage should always be done for diagnosis before starting Serophene therapy in such patients. If abnormal bleeding is present, full diagnostic measures are mandatory.

Overstimulation of the ovary during Serophene therapy:
In order to minimize the hazard associated with the occasional abnormal ovarian enlargement associated with Serophene (clomiphene citrate) therapy (see "ADVERSE REACTIONS"), the lowest dose consistent with expectation of good results should be used. The patient should be advised of the possibility of ovarian cyst formation and should be instructed to return for repeat pelvic examination between 2 and 3 weeks after starting each course of treatment. Some patients with polycystic ovarian syndrome who are unusually sensitive to gonadotropin may have an exaggerated response to usual doses of Serophene. It should be borne in mind that maximal enlargement of the ovary, whether physiologic or abnormal, does not occur until several days after discontinuation of the recommended dose of Serophene. The patient who complains of pelvic pain after receiving Serophene should be examined with care. If enlargement of the ovary occurs, additional Serophene therapy should not be given until the ovaries have returned to pretreatment size, and the dosage or duration of the next course should be reduced. Experience has shown that the ovarian enlargement and cyst formation associated with Serophene therapy regress spontaneously within a few days or weeks after discontinuing treatment. Unless surgical indication for laparotomy exists, such cystic enlargement should always be managed conservatively.

Multiple Pregnancy
The incidence of multiple pregnancy (including triplets, quadruplets and quintuplets) has been increased up to tenfold when conception takes place during a cycle in which clomiphene citrate therapy is given. During clinical studies, 353 infants were born of 163 multiple pregnancies. Of these infants, 293 survived, including 27 of 62 infants from triplet, quadruplet and quintuplet pregnancies. The patient and her partner should be advised of the frequency and potential hazards of multiple pregnancy before starting treatment.

Diagnostic Interference
Plasma desmosterol concentrations (only with long-term use, possibly indicating interference with cholesterol synthesis) and
Plasma transcortin concentrations and
Serum thyroxine concentrations and
Sex hormone-binding globulin concentrations and
Sulfobromophthalein (BSP) retention (indicating hepatotoxicity) and
Thyroxine-binding globulin (TBG) concentrations (may be increased).

Carcinogenicity
Two cases of bilateral breast carcinoma in women treated with clomiphene have been reported.

Patient check-ups
The following procedures may be especially important in patient monitoring (other tests[24] may be warranted in some patients, depending on condition):

Complete pelvic examination for evaluation of ovarian size (recommended prior to each course of treatment with clomiphene)

Daily basal body temperature and
Estrogen excretion determinations and
Histological studies of luteal phase endometrium and
Serum progesterone concentrations and
Urinary excretion of pregnanediol (recommended during or after a cycle of clomiphene treatment to determine whether ovulation has occurred).

Endometrial biopsy (recommended prior to initiation of clomiphene treatment in older patients to rule out the presence of endometrial carcinoma).

Liver function tests (recommended prior to initiation of therapy with clomiphene).

Ophthalmologic, including slit-lamp, examination (recommended if treatment with clomiphene is continued for more than 1 year).

ADVERSE REACTIONS

Note: At recommended dosage, adverse reactions are usually rare. Incidence and severity of adverse reactions tend to be related to dose and duration of treatment and are usually reversible after clomiphene therapy is discontinued.

Use of clomiphene is associated with an increased incidence of multiple pregnancies and, therefore, possible premature deliveries. Clomiphene may cause a decrease in cervical mucus which may interfere with response.

The following adverse reactions have been selected on the basis of their potential clinical significance (possible cause in parentheses where appropriate - not necessarily inclusive).

Those indicating need for medical attention:
Incidence more frequent than 5%:

- Abdominal discomfort (bloating, stomach or pelvic pain) may be most often related to ovulatory or premenstrual phenomena, to ovarian enlargement or to enlargement of fibroids.

At recommended dosage, abnormal ovarian enlargement (see also “PRECAUTIONS”) is

infrequent, although the usual cyclic variations in ovarian size may be exaggerated. Similarly, cyclic ovarian pain (mittelschmerz) may be accentuated. With higher or prolonged dosage, more frequent ovarian enlargement and cyst formation (usually luteal) may occur, and the luteal phase of the cycle may be prolonged. Rare instances of massive ovarian enlargement are on record. Southam and Janovski[28] described such an instance in a patient with polycystic ovarian syndrome whose clomiphene citrate therapy consisted of 100 mg daily for 14 days. Abnormal ovarian enlargement usually regresses spontaneously, and while laparotomy was performed on several such patients, investigators believe most of these patients should have been treated conservatively.

Note: Maximum ovarian enlargement occurs several days after clomiphene therapy is discontinued.

- Blurred vision (ocular toxicity).

Visual symptoms (see also WARNINGS for further recommendations) described usually as "blurring" or spots or flashes, disappear within a few days or weeks after Serophene (clomiphene citrate) is discontinued. These symptoms appear to be due to intensification and prolongation of after-images. Symptoms often first appear or are accentuated with exposure to a more brightly lit environment. While measured visual acuity has not generally been affected, one patient taking 200 mg daily developed visual blurring on the seventh day of treatment, which progressed to severe diminution of visual acuity by the tenth day. No other abnormality was found and the visual acuity returned to normal on the third day after treatment was stopped. Another patient treated during the clinical studies developed scotomata during prolonged Serophene administration, which disappeared on placebo[29]. Monolateral exophthalmos associated with laboratory evidence of hyperthyroidism was observed in one patient concomitant with completion of the third course of clomiphene citrate. In a 34 year-old patient who had taken 3 courses of clomiphene citrate, slit-lamp microscopic examination showed a mild amount of posterior cortical subcapsular opacity in each eye. Ophthalmoscopic examination revealed normal findings. The ocular diagnosis was posterior cortical senile cataracts.

- Yellowing of eyes and skin (hepatotoxicity).

<u>Those indicating need for medical attention only if they continue or are bothersome:</u>

Incidence more frequent than 10%:

- Hot flashes - The vasomotor symptoms resemble long menopausal "hot flashes" are not usually severe and disappear promptly after treatment is discontinued.

Incidence less frequent or rare: 1 to 2%
- Breast discomfort
- Dizziness or lightheadedness
- Headache
- Heavy menstrual periods or bleeding between periods

- Mental depression, nervousness, restlessness, sleeplessness, or tiredness
- Nausea or vomiting.

Other less frequently reported symptoms during therapy have included: urticaria or allergic dermatitis, weight gain, increased urinary frequency or volume, constipation or diarrhea; moderate, reversible hair loss has been reported in a few patients, primarily on continuous therapy.

Serophene has not been reported to cause significant abnormality in the hematologic or renal systems, in protein bound iodine, or in serum cholesterol. Analysis by gas liquid chromatography (GLC) of serum sterols from patients on prolonged, continuous administration of Serophene yields a peak compatible with an elevated level of desmosterol. This peak is indicative of an interference with cholesterol synthesis. However, the serum sterol GLC pattern from patients receiving recommended doses of Serophene is not significantly altered.

Sulfobromophthalein (BSP) retention of greater than 5% has been reported in 32 of 141 patients in whom it was measured, including 5 of 43 patients who received approximately the dose of clomiphene citrate now recommended. Retention was usually minimal unless associated with prolonged continuous clomiphene citrate administration or with apparently unrelated live disease. In some patients, pre-existing BSP retention decreased even though clomiphene citrate therapy was continued. Other liver function tests were usually normal. In a later study in which patients were given 6 consecutive monthly courses of clomiphene citrate (100 mg daily for 3 days) or matching placebo, BSP tests were done on 94 patients. Values in excess of 5% retention were recorded in 11 patients, 6 of whom had received drug and 5 placebo. One patient developed jaundice on the nineteenth day of treatment (50 mg/day); liver biopsy revealed bile stasis without evidence of hepatitis.[16] A male prison subject who received 200 mg daily for 77 days developed the clinical picture of infectious hepatitis; his cellmate was discovered to have had infectious hepatitis four months earlier.

Ovarian cancer has been reported in a very small number of infertile women who have been treated with fertility drugs. A causal relationship between treatment with fertility drugs and ovarian cancer has not been established.

Birth Defects

From 2,339 completed pregnancies associated with clomiphene citrate administration, 58 birth defects have been reported, for a cumulative rate of 2.5%. They have been reported in 4 conceptions in the abortion/stillbirth category, 14 of 353 infants from multiple pregnancies, and 39 of 1,676 infants from single pregnancies. Three live-born infants failed to survive.

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), polydactyly (both 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 frenulum, and 7 infants with multiple somatic defects.

Eight of the entire group of 58 infants were born to 7 of 153 mothers who received a course of clomiphene citrate during the first 6 weeks after conception.

An interval of 4, 4, and 10 months respectively elapsed between the last clomiphene citrate therapy and conception in 3 mothers. In a fourth mother, conception occurred during a subsequent ovulation induced by gonadotropin therapy.

The cumulative rate of congenital abnormalities does not exceed that reported in the general population[2,30].

TREATMENT OF OVERDOSAGE

There is no known antidote, but gastric lavage should be performed.

PATIENT CONSULTATION

Consider advising the patient on the following:

Before using this medication:

Possibility of multiple pregnancy
See also PRECAUTIONS.

Proper use of this medication:

Compliance with therapy; clarification of schedule; taking at the same time every day to aid in remembering each dose.

Missed dose: Taking as soon as possible; doubling dose if not remembered until time of next dose; checking with physician if more than one dose missed.

Precautions while using this medication:

Importance of not taking medication while pregnant; importance of close monitoring by physician.

Importance of following physician's instructions for recording of temperature and timing of intercourse.

Caution when driving or doing jobs requiring alertness because of visual disturbances, dizziness, or lightheadedness.

Adverse reactions:

See ADVERSE REACTIONS.

GENERAL DOSING INFORMATION

Patients receiving clomiphene should be under supervision of a physician experienced in the treatment of gynecologic or endocrine disorders. Patients should be chosen for therapy with Serophene (clomiphene citrate) 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 Serophene.
Patients who have been hypoestrogenic for prolonged periods may require pretreatment with estrogen to provide a more normal endometrium for ovum implantation. Estrogen therapy should be discontinued immediately before initiation of clomiphene citrate.

In some patients, a single injection of 5,000 to 10,000 USP units of human chorionic gonadotropin (hCG) is given 3 to 7 days after the last dose of clomiphene to stimulate the midcycle LH surge which results in ovulation.

Many patients will respond to 50 mg of Serophene (clomiphene citrate) daily for 5 days (see"RECOMMENDED DOSAGE"). In the determination of a recommended starting dose schedule, efficacy must be balanced against potential adverse reactions. For example, the data available so far suggest that ovulation and pregnancy are slightly more attainable on 100 mg/day for 5 days than on 50 mg/day for 5 days. As the dosage is increased, however, ovarian overstimulation and other adverse reactions may be expected to increase. Furthermore, although the data does not yet establish a relationship between dosage and multiple births, it would seem reasonable on pharmacologic grounds that such a relationship does exist. For these reasons, it would seem prudent to begin the treatment of the usual patient with a lower dose, 50 mg daily for 5 days, and to increase the dose only in those patients who do not respond to the first course (see "RECOMMENDED DOSAGE").

Patients with unusual sensitivity to pituitary gonadotropins (for example, those with polycystic ovarian syndrome) may require a lower dosage or shorter duration of clomiphene therapy. Use of clomiphene is not recommended in patients with ovarian cysts because further enlargement may occur. A patient's report of abdominal pain during clomiphene therapy indicates immediate pelvic examination. If ovarian enlargement or cyst formation has occurred, it is recommended that clomiphene therapy be withdrawn until the ovaries have returned to pretreatment size, usually within a few days or weeks. Dosage and duration of the next course of clomiphene should be reduced. If the patient receiving clomiphene experiences any visual disturbances, it is recommended that clomiphene therapy be withdrawn and a complete ophthalmologic examination

performed. Ocular adverse reactions usually disappear within a few days or weeks after the last dose of clomiphene.
The majority of patients who are going to respond will respond to the first course of therapy, and 3 courses should constitute an adequate therapeutic trial[2]. Treatment beyond this is not recommended in the patient who does not exhibit evidence of ovulation. If ovulatory menses does not occur after 3 to 4 cycles of clomiphene therapy at the maximum dose, or pregnancy after a treatment-free interval of 3 to 6 months, the diagnosis should be reevaluated.

Pregnancy

In most patients, ovulation appears to occur from 6 to 12 days after completion of therapy. For regularity of cyclic ovulatory response, it is also important that each course of Serophene be started on or about the fifth cycle day, once ovulation has been established. The importance of properly timed coitus cannot be over-emphasized. Conception should be attempted by having intercourse every other day, starting within 48 hours before ovulation.

If a cycle of Serophene is followed by a biphasic course of basal body temperature and menses do not ensue, the next cycle of Serophene should be delayed until it is confirmed that the patient is not pregnant.

In common 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 recommended. Patients should be advised of the possibility of multiple pregnancy and its potential hazards if conception occurs during a cycle in which Serophene is given.

RECOMMENDED DOSAGE

Serophene (clomiphene citrate) tablets.

Usual adult dose: Oral, 50 mg (1 tablet) a day for five days, starting on the fifth day of the menstrual cycle, if bleeding occurs or at any time in the patient who has had no recent uterine bleeding. If ovulation without conception occurs, this cycle is repeated until conception or for three or four cycles. When ovulation occurs at the regimen of 50 mg daily for 5 days, there is no advantage to increasing the dose in subsequent cycles of treatment. If ovulation does not occur, the dose is increased to 100 mg a day for five days (starting as early as 30 days after the previous course), repeated if ovulation without conception occurs. Some patients require up to 250 mg/day to induce ovulation.

Note: The majority of patients who are going to respond will respond to the first course of therapy, and 3 courses should constitute an adequate therapeutic trial[2]. If ovulatory menses do not occur after 3 cycles of clomiphene therapy at the maximum dose, or pregnancy after a treatment-free interval of 3 to 6 months, the diagnosis should be

reevaluated. Treatment beyond this is not recommended in the patient who does not exhibit evidence of ovulation.
Usual adult prescribing limits: Doses over 100 mg a day for five days have been associated with a higher incidence of adverse reactions, and patients receiving these doses should be carefully monitored.

AVAILABILITY

Serophene (clomiphene citrate) is available as 50 mg scored white tablets, packaged in bottles of 50 and blister packs of 10.

Storage

Preserve in well-closed containers, protected from light, between 15-30°C.

CHEMISTRY

Clomiphene Citrate

Molecular Formula: $C_{26}H_{28}ClNO.C_6H_8O_7$

Molecular Weight: 598.09
Chemical Name: 2-[p-(2-chloro-1,2-diphenylvinyl) phenoxy]
triethylamine dihydrogen citrate.

Description: Clomiphene citrate 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.

PHARMACOLOGY

Clomiphene citrate is absorbed from the gastrointestinal tract and slowly excreted through the liver into the bile. The biological half life is reported to be 5 days. Enterohepatic recirculation takes place.

Serophene (clomiphene citrate) was found to inhibit endogenous pituitary gonadotropic activity in rats based on organ weight indices, but did not block superovulation produced in immature female rats by pregnant mare's serum and chorionic gonadotropin. It also produced a reversible anti-fertility effect in both male and female rats. In immature female mice, Serophene acted both as a weak estrogen, judged by its uterotrophic effect, and as antiestrogen because of its antagonism to the uterotrophic effect of estradiol monobenzoate. Serophene had no progestational, androgenic, or anti-androgenic effects and appeared not to interfere with pituitaryadrenal or pituitary-thyroid function. In rats and dogs, a dose-dependent decrease in plasma cholesterol and total sterols, and an increase in desmosterol were observed after higher doses.

Studies with C-14 labelled clomiphene citrate in rats indicate that is readily absorbed after oral administration and is excreted principally in the feces. Rats with biliary fistulas excreted the C-14 label in the bile, and enterohepatic recirculation was demonstrated. Low levels of C-14 were observed in pituitary and testis of both rats and monkeys, whereas the ovary had levels close to the median value of tissues examined.

BIOAVAILABILITY

In a 3-way cross-over study in healthy fasting female subjects, comparison of the plasma concentration versus time curves by repeated measures, ANOVA showed that there is no significant difference among clomiphene citrate tablets manufactured by Merrell Dow Pharmaceutical Inc., U.S.A.: Merrell Canada; and Serono Labs Inc. (Serophene tablets) with regard to the blood levels they produce. Comparison of the pharmacokinetic parameters $AUC_{(0\text{-}24h)}$, $AUC_{(0\text{-}336\,h)}$, T_{max}, and C_{max} by ANOVA testing showed that there were no significant effects due to treatment. This, it can be concluded that the products are equivalent with regard to the rate and extent of absorption[34].

TOXICOLOGY

High levels of C-14 were found in the ocular tissue after intravenous administration in rats, dogs, and monkeys. In rats, the acute LD_{50} was 5750 mg/kg on oral administration and 530 mg/kg I.P. The acute LD_{50} in mice was 1700 mg/kg orally, 390 mg/kg I.P.; and 86 mg/kg I.V. Convulsions occurred in dogs after infusion of 40 to 62 mg/kg and the animals died of respiratory failure at 112 and 121 mg/kg. In chronic toxicity studies, clomiphene citrate was administered at various dose levels to rats and dogs for as long as 53 weeks. Some decrease in growth rate and food consumption was observed at all dose levels in rats but not in dogs. No significant hematologic changes were observed, and in the dog, serum transaminase, alkaline phosphatase, bilirubin, glucose, blood urea

nitrogen levels, and urinalysis were within normal limits. Changes in the reproductive system compatible with inhibition of gonadotropin were observed in both species. Thinning of fur occurred in rats receiving 5 to 40 mg/kg/day for 53 weeks, with incidence related to dose and duration of therapy. Subcapsular cataracts occurred in 4 of 29 rats (but not in dogs) receiving 40 mg/kg/day, which were sacrificed at 53 weeks; in one of these animals, opacities had first appeared at 31 weeks. No cataracts were observed in rats receiving 15 mg/kg and 5 mg/kg for 53 weeks. At the end of 53 weeks, one dog exhibited an eye derangement in the form of a granular, dot-like opacity.

REPRODUCTION STUDIES

After oral administration of clomiphene citrate to pregnant rats during the interval of organogenesis in doses of 1.6 to 200 mg/kg/day, malformations were observed in the pups from one of five liters in the group receiving 8 mg/kg/day. Higher oral doses (40-200 mg/kg/day(inhibited fetal development and only one litter (normal) was born. Subcutaneous administration of clomiphene citrate to pregnant rats on one day (12th) during the period of organogenesis resulted in a dose-dependent increase in the incidence of malformations in doses of 1.0 to 1,000 mg/kg. In rabbits, deformed fetuses were seen following oral doses of 20 and 40 mg/kg/day from the eighth through the fifteenth day of a 32-day gestation. None was seen after the oral dose of 8 mg/kg/day.

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