PACKAGE INSERT FOR FERTOMID-50 TABLETS

Scheduling Status
S4

Proprietary Name (and dosage form)
FERTOMID - 50 (TABLETS)

Composition
Each tablet contains Clomiphene citrate 50 mg

Pharmacological Classification
A18.8 Ovulation controlling agents

Pharmacological Action
Clomiphene has both oestrogenic and anti-oestrogenic properties. It exerts its therapeutic effects by stimulating the secretion of pituitary gonadotrophic hormones which results ultimately in increased gametogenesis and steriodogenesis in the ovaries. Ovarian stimulation culminates in ovulation.

Pharmacokinetics: Clomiphene is well absorbed after oral administration and is cleared slowly from the plasma. The plasma half-life ($t_{½}$) is from 5 - 7 days due to the high-affinity plasma protein binding, enterohepatic re-circulation and accumulation in fatty tissues. Clomiphene is metabolised to derivatives with anti-oestrogen activity.

Indications
Fertomid 50 is indicated in the treatment of an ovulation and oligo-ovulation in patients desiring pregnancy, whose hypothalamic-hypophyseal-ovarian systems are functional and who have adequate endogenous oestrogen.

Contra-Indications
Pregnancy; patients with liver disease or a history of liver dysfunction, endometrial carcinoma, ovarian cysts (other than polycystic ovary), undiagnosed abnormal uterine bleeding, pituitary failure, Hypersensitivity to Clomiphene, active thrombophlebitis, mental depression.

Warnings
To avoid inadvertent Clomiphene administration during early pregnancy, the basal body temperature should be recorded throughout to determine whether ovulation occurs. If the basal body temperature following Clomiphene therapy is biphasic and not followed by menses, the possibility of an ovarian cyst, and/or pregnancy should be excluded until the correct diagnosis can be determined. The next course of therapy should be delayed.

Dosage and Directions for use:
Careful evaluation and selection of patients and close attention to dosage instructions, contra-indications and side-effects is important. The recommended dose for the first course of Fertomid 50 is 1 tablet (50 mg) daily for 5 days. Therapy may be started at any time in the patient who has had no recent bleeding. If progestin-induced bleeding is planned, or if spontaneous bleeding occurs before 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 appears not to have occurred after the first course of therapy, a second course of 100 mg daily (two tablets given as a single dose) for 5 days should be given. This course may be started as early as 30 days after the previous one.

Most patients who are going to respond to Clomiphene therapy will respond to the first course of therapy and three courses of therapy is considered an adequate trial for the Clomiphene to have an effect. If ovulation menses has not yet occurred, the diagnosis should be re-evaluated. Treatment beyond the three courses is not recommended in patients who do not exhibit evidence of ovulation. Ovulation normally occurs from days 6 - 12 after a course of Fertomid 50 and the important of correctly

time coitus must be emphasized. Once ovulation has been established, to maintain regular cyclic ovulation it is important that each course of Fertomid 50 is started on or about the fifth cycle day.

The long-term safety of Clomiphene citrate has not been established. Since most patients will ovulate following 3 courses of Fertomid 50, the long-term use of Fertomid 50 is not recommended that is beyond a total of about 6 cycle (including 3 ovulatory cycles).

Side-effects and special precautions:
Side-effects with Clomiphene citrate generally appear to be dose-related. The most common side effects reported are reversible ovarian enlargement and cyst formation, vasomotor flushes resembling menopausal symptoms and abdominal or pelvic discomfort or pain sometimes with nausea or vomiting. Breast tenderness, abnormal uterine bleeding, weight gain, headache, and increased urinary flow have also been reported. Transient eye disturbances such as blurring of vision, spots or fashes (scintillating scotomata) may occur and there have been rare reports of cataracts. Skin reactions such as allergic rashes and urticaria have occasionally been reported and reversible hair loss has been reported rarely. Hydatidiform mole formation has been associated with Clomiphene administration. There have been reports of conditions such as syncope/fainting, cerebrovascular accident, central thrombosis, psychotic reactions including paranoid psychosis, neurologic impairment, disorientation and speech disturbance.

Central nervous system disturbances have included dizziness, lightheadedness, nervous tension, fatigue, vertigo, insomnia and depression. Abnormalities in liver function test have sometimes been reported.

Following therapy with Fertomid 50 there is an increased risk of multiple births.

The patient should be warned that visual symptoms may render driving a car or operating machinery may be more hazardous than usual, particularly under conditions of vague lighting. Ophthalmologically definable scotomata and retinal cell function (electroretinographic) changes have been reported. If visual symptoms occur, Fertomid 50 should be discontinued and a complete ophthalmological evaluation should be made. No further courses of Fertomid 50 must be administered.

The patient should also be instructed to report any abdominal or pelvic pain as this may indicate the presence or enlargement of ovarian cysts. If abnormal enlargement occurs, Clomiphene citrate should not be given until the ovaries have returned to pre-treatment size. The ovarian enlargement and cyst formation associated with Clomiphene therapy usually regress spontaneously within a few days or weeks after discontinuing the treatment. Most of these patients should be managed conservatively. The dosage and/or duration of the next doses should be reduced. Patients with polycystic ovaries undergoing therapy with Clomiphene should receive the lowest doses possible to prevent further enlargement or cyst formation. Prolonged courses of treatment are not recommended.

Safety in lactation has not been established.

Known symptoms of over dosage and particulars of its treatment:
The signs and symptoms of over dosage are nausea, vomiting, vasomotor flushes, visual blurring or flashes; scotomata; ovarian enlargement with pelvic or abdominal pain. The maximum enlargement of the ovaries may not occur until several days after discontinuation of the Clomiphene therapy. Female patients who are capable of reproduction who have taken an overdose of Clomiphene require observation for 2 to 3 weeks in case of ovarian enlargement. Gastric lavage is recommended. Further treatment is supportive and symptomatic.

Identification:
White circular tablets with flat faces bevelled edges, '50' embossed on one side and a cental break line on the other side.

Presentation:
Fertomid 50 Tablets are available in cartons of 10 blister packed tablets.

Storage Instructions:
Store below 30°C. Keep in carton. Protect from light.
Keep out of reach of children.

Registration number:

Name and business address of applicant:
Cipla-Medpro (Pty) Limited