FERTOMID Tablets (Clomiphene citrate)

Composition

FERTOMID 25
Each tablet contains
Clomiphene citrate...25 mg
FERTOMID 50
Each tablet contains
Clomiphene citrate...50 mg
FERTOMID 100
Each tablet contains
Clomiphene citrate...100 mg

Dosage Form

Tablets for oral use.

Pharmacology

Pharmacodynamics

Clomiphene citrate is a drug of considerable pharmacologic potency. With careful selection and proper management of the patient, clomiphene citrate has been demonstrated to be a useful therapy for the anovulatory patient desiring pregnancy.

Clomiphene citrate is capable of interacting with oestrogen-receptor-containing tissues, including the hypothalamus, pituitary, ovary, endometrium, vagina, and cervix. It may compete with oestrogen for oestrogen-receptor-binding sites and may delay replenishment of intracellular oestrogen receptors. Clomiphene citrate initiates a series of endocrine events culminating in a preovulatory gonadotropin surge and subsequent follicular rupture. The first endocrine event in response to a course of clomiphene citrate therapy is an increase in the release of pituitary gonadotropins. This initiates steroidogenesis and folliculogenesis, resulting in growth of the ovarian follicle and an increase in the circulating level of oestradiol. Following ovulation, plasma progesterone and oestradiol rise and fall as they would in a normal ovulatory cycle.

Available data suggest that both the oestrogenic and anti-oestrogenic properties of clomiphene may participate in the initiation of ovulation. The two clomiphene isomers have been found to have mixed oestrogenic and anti-oestrogenic effects, which may vary from one species to another. Some data suggest that zuclomiphene has greater oestrogenic activity than enclomiphene.

Clomiphene citrate has no apparent progestational, androgenic or anti-androgenic effects and does not appear to interfere with pituitary-adrenal or pituitary-thyroid function.
Although there is no evidence of a 'carryover effect' of clomiphene citrate, spontaneous ovulatory menses have been noted in some patients after clomiphene citrate therapy.

### Pharmacokinetics

Based on early studies with $^{14}$C-labeled clomiphene citrate, the drug was shown to be readily absorbed orally in humans and excreted principally in the faeces. Cumulative urinary and faecal excretion of the $^{14}$C averaged about 50% of the oral dose and 37% of an intravenous dose after 5 days. Mean urinary excretion was approximately 8% with faecal excretion of about 42%. A mean rate of excretion of 0.73% per day of the $^{14}$C dose after 31 to 35 days and 0.45% per day of the $^{14}$C dose after 42 to 45 days was present in the faeces. The remaining drug/metabolites may be slowly excreted from a sequestered enterohepatic recirculation pool. Some $^{14}$C label was still present in the faeces 6 weeks after administration. Subsequent single-dose studies in normal volunteers showed that zuclomiphene (cis) has a longer half-life than enclomiphene (trans). Detectable levels of zuclomiphene persisted for longer than a month in these subjects. This may be suggestive of stereo-specific enterohepatic recycling or sequestering of the zuclomiphene. Thus, it is possible that some active drug may remain in the body during early pregnancy in women who conceive in the menstrual cycle during clomiphene citrate therapy.

### Indications

FERTOMID is indicated for the treatment of ovulatory dysfunction in women desiring pregnancy. Impediments to achieving pregnancy must be excluded or adequately treated before beginning FERTOMID. Those patients most likely to achieve success with FERTOMID include patients with polycystic ovary syndrome (PCOS), amenorrhoea-galactorrhoea syndrome, psychogenic amenorrhea, post-oral-contraceptive amenorrhoea, and certain cases of secondary amenorrhea of undetermined aetiology. Properly timed coitus in relationship to ovulation is important. A basal body temperature graph or other appropriate tests may help the patient and her physician determine if ovulation occurred. Once ovulation has been established, each course of FERTOMID should be started on or about the day 5 of the cycle. Long-term cyclic therapy is not recommended beyond a total of about six cycles (including three ovulatory cycles).

### Male infertility

FERTOMID increases spermatogenesis and is useful in oligospermia and asthenospermia. FERTOMID is indicated only in patients with demonstrated ovulatory dysfunction who meet the conditions described below:

- Patients who are not pregnant.

  **Patients without Ovarian Cysts**: FERTOMID should not be used in patients with ovarian enlargement except those with PCOS. Pelvic examination is necessary prior to the first and each subsequent course of FERTOMID treatment.

  **Patients without Abnormal Vaginal Bleeding**: If abnormal vaginal bleeding is present, the patient should be carefully evaluated to ensure that neoplastic lesions are not present.

- Patients with normal liver function.

In addition, patients selected for FERTOMID therapy should be evaluated in regard to the following:

- **Oestrogen Levels**: Patients should have adequate levels of 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 preclude successful therapy.

- **Primary Pituitary or Ovarian Failure**: FERTOMID cannot be expected to substitute for specific treatment of other causes of ovulatory failure.
**Endometriosis and Endometrial Carcinoma:** The incidence of endometriosis and endometrial carcinoma increases with age as does the incidence of ovulatory disorders. Endometrial biopsy should always be performed prior to clomiphene citrate therapy in this population.

**Other Impediments to Pregnancy:** Impediments to pregnancy can include thyroid disorders, adrenal disorders, hyperprolactinaemia, and male factor infertility.

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

There are no adequate or well-controlled studies that demonstrate the effectiveness of clomiphene citrate in the treatment of male infertility. In addition, testicular tumours and gynaecomastia have been reported in males using clomiphene. The cause and effect relationship between reports of testicular tumours and the administration of clomiphene citrate is not known.

Although the medical literature suggests various methods, there is no universally accepted standard regimen for combined therapy (i.e., clomiphene citrate in conjunction with other ovulation-inducing drugs). Similarly, there is no standard clomiphene citrate regimen for ovulation induction in *in vitro* fertilization programs to produce ova for fertilization and reintroduction. Therefore, clomiphene citrate is not recommended for these uses.

### Dosage And Administration

#### General Considerations

The workup and treatment of candidates for clomiphene citrate therapy should be supervised by physicians experienced in management of gynaecologic or endocrine disorders. Patients should be chosen for therapy with clomiphene citrate only after careful diagnostic evaluation. 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. The therapeutic objective should be balanced with potential risks and discussed with the patient and others involved in the achievement of a pregnancy.

Ovulation most often occurs from 5 to 10 days after a course of clomiphene citrate. Coitus should be timed to coincide with the expected time of ovulation. Appropriate tests to determine ovulation may be useful during this time.

#### Recommended Dosage

Treatment of the selected patient should begin with a low dose, 50 mg daily (1 tablet) for 5 days, starting within the first 5 days of spontaneous or induced menstrual bleeding. The dose should be increased only in those patients who do not ovulate in response to cyclic FERTOMID 50. A low dosage or duration of treatment course is particularly recommended if unusual sensitivity to pituitary gonadotropin is suspected, such as in patients with PCOS.

The patient should be evaluated carefully to exclude pregnancy, ovarian enlargement, or ovarian cyst formation between each treatment cycle. If progestin-induced bleeding is planned, 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 day 5 of the cycle. Therapy may be started at any time in the patient who has had no recent uterine bleeding. 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 occur after the first course of therapy, a second course of FERTOMID 100 daily for 5 days should be given, starting within the first 5 days of spontaneous or induced menstrual bleeding. This course may be started as early as 30 days after the previous one after precautions are taken to exclude the presence of pregnancy. Increasing the dosage or duration of therapy beyond 100 mg/day for 5 days is not recommended.

The majority of patients who are going to ovulate will do so after the first course of therapy. If ovulation does not occur after three courses of therapy, further treatment with FERTOMID is not recommended and the patient should be re-
evaluated. If three ovulatory responses occur, but pregnancy has not been achieved, further treatment is not recommended. If menses does not occur after an ovulatory response, the patient should be re-evaluated. Long-term cyclic therapy is not recommended beyond a total of about six cycles.

### Male Infertility

A dose of one tablet of FERTOMID 25 daily for 25 days followed by a rest period of 5 days for 3 months.

### Contraindications

#### Hypersensitivity

Clomiphene citrate is contraindicated in patients with a known hypersensitivity or allergy to clomiphene citrate or to any of its ingredients.

#### Pregnancy

Pregnancy Category X.

Clomiphene citrate use in pregnant women is contraindicated as it does not offer benefit in this population. Available human data do not suggest an increased risk for congenital anomalies above the background population risk when used as indicated. Although no causative evidence of a deleterious effect of clomiphene citrate therapy on the human foetus has been established, there have been reports of birth anomalies which, during clinical studies, occurred at an incidence within the range reported for the general population. Animal reproductive toxicology studies showed increased embryo-foetal loss and structural malformations in offspring. There is evidence that clomiphene citrate has a deleterious effect on rat and rabbit foetuses when given in high doses to the pregnant animal.

To avoid inadvertent clomiphene citrate administration during early pregnancy, appropriate tests should be utilized during each treatment cycle to determine whether ovulation occurs. The patient should be evaluated carefully to exclude pregnancy, ovarian enlargement, or ovarian cyst formation between each treatment cycle. The next course of clomiphene citrate therapy should be delayed until these conditions have been excluded. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks to the foetus.

#### Foetal/Neonatal Anomalies and Mortality

The following foetal abnormalities have been reported subsequent to pregnancies following ovulation induction therapy with clomiphene citrate during clinical trials. Each of the following foetal abnormalities was reported at a rate of <1% (experiences are listed in order of decreasing frequency): Congenital heart lesions, Down’s syndrome, club foot, congenital gut lesions, hypospadias, microcephaly, harelip and cleft palate, congenital hip, haemangioma, undescended testicles, polydactyly, conjoined twins and teratomatous malformation, patent ductus arteriosus, amaurosis arteriovenous fistula, inguinal hernia, umbilical hernia, syndactyly, pectus excavatum, myopathy, dermoid cyst of scalp, omphalocele, spina bifida occulta, ichthyosis, and persistent lingual frenulum. Neonatal death and foetal death/stillbirth in infants with birth defects have also been reported at a rate of <1%. The overall incidence of reported birth anomalies from pregnancies associated with maternal clomiphene citrate ingestion during clinical studies was within the range of that reported for the general population.

In addition, reports of birth anomalies have been received during post-marketing surveillance of clomiphene citrate.

#### Liver Disease

Clomiphene citrate is contraindicated in patients with liver disease or a history of liver dysfunction.
Abnormal Uterine Bleeding

Clomiphene citrate is contraindicated in patients with hormone-dependent tumours or in patients with abnormal uterine bleeding of undetermined origin.

Ovarian Cysts

Clomiphene citrate is contraindicated in patients with ovarian cysts or enlargement not due to PCOS. Patients should be evaluated for the presence of ovarian cyst prior to each course of treatment.

Other

Clomiphene citrate is contraindicated in patients with the following:
- Uncontrolled thyroid
- Adrenal dysfunction
- In the presence of an organic intracranial lesion such as pituitary tumour

Warnings And Precautions

General

Careful attention should be given to the selection of candidates for clomiphene citrate therapy. Pelvic examination is necessary prior to clomiphene citrate treatment and before each subsequent course.

Good levels of endogenous oestrogen (as estimated from vaginal smears, endometrial biopsy, assay of urinary oestrogen, or endometrial bleeding in response to progesterone) provide a favourable prognosis for ovulatory response induced by clomiphene citrate. A low level of oestrogen, although clinically less favourable, does not preclude successful outcome of therapy. Clomiphene citrate therapy is ineffective in patients with primary pituitary or primary ovarian failure. Clomiphene citrate therapy cannot be expected to substitute for specific treatment of other causes of ovulatory failure, such as thyroid or adrenal disorders. For hyperprolactinaemia there is other preferred specific treatment. Clomiphene citrate is not a first-line treatment for low weight-related amenorrhoea, with infertility, and has no value if a high follicle-stimulating hormone (FSH) blood level is observed following an early menopause.

Visual Symptoms

Patients should be advised that blurring or other visual symptoms such as spots or flashes (scintillating scotomata) may occasionally occur during therapy with clomiphene citrate. These visual symptoms increase in incidence with increasing total dose or therapy duration and generally disappear within a few days or weeks after clomiphene citrate is discontinued. However, prolonged visual disturbances have been reported after clomiphene citrate has been discontinued and these disturbances may be irreversible. Patients should be warned that these visual symptoms render such activities as driving a car or operating machinery more hazardous than usual, particularly under conditions of variable lighting. Onset is gradual.

These visual symptoms appear to be due to intensification and prolongation of after-images. Symptoms often first appear or are accentuated with exposure to a brightly lit environment. While measured visual acuity usually has not been affected, a study patient taking 200 mg clomiphene citrate daily developed visual blurring on the day 7 of treatment, which progressed to severe diminution of visual acuity by the day 10. No other abnormality was found, and the visual acuity returned to normal on the day 3 after treatment was stopped.

Ophthalmologically definable scotomata and retinal cell function (electroretinographic) changes have also been reported. A patient treated during clinical studies developed phosphenes and scotomata during prolonged clomiphene citrate administration, which disappeared by the day 32 after stopping therapy.
Post-marketing surveillance of adverse events has also revealed other visual signs and symptoms during clomiphene citrate therapy. While the aetiology of these visual symptoms is not yet understood, patients with any visual symptoms should discontinue treatment and have a complete ophthalmological evaluation carried out promptly.

Ovarian Hyperstimulation Syndrome
The ovarian hyperstimulation syndrome (OHSS) has been reported to occur in patients receiving clomiphene citrate for ovulation induction. In some cases, OHSS occurred following cyclic use of clomiphene citrate or when clomiphene citrate was used in combination with gonadotropins. Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with OHSS.

OHSS is a medical event distinct from uncomplicated ovarian enlargement. It may progress rapidly (within 24 hours to several days) to become a serious medical event. The clinical signs of this syndrome in severe cases can include gross ovarian enlargement, gastrointestinal symptoms, ascites, dyspnoea, 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 haemorrhage, deep venous thrombosis, torsion of the ovary, and acute respiratory distress. The early warning signs of OHSS are abdominal pain and distention, nausea, vomiting, diarrhoea, and weight gain. Elevated urinary steroid levels, varying degrees of electrolyte imbalance, hypovolaemia, haemoconcentration, and hypoproteinaemia may occur. Death due to hypovolaemic shock, haemoconcentration, 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.

To minimize the hazard associated with occasional abnormal ovarian enlargement associated with clomiphene citrate, the lowest dose consistent with expected clinical results should be used. The patient should be instructed to inform the physician of any abdominal or pelvic pain, weight gain, discomfort or distension after taking clomiphene citrate. Maximal enlargement of the ovary, whether physiologic or abnormal, may not occur until several days after discontinuation of the recommended dose of clomiphene citrate. Some patients with PCOS who are unusually sensitive to gonadotropin may have an exaggerated response to usual doses of clomiphene citrate. Therefore, patients with PCOS should be started on the lowest recommended dose and shortest treatment duration for the first course of therapy.

If enlargement of the ovary occurs, additional clomiphene citrate should not be given until the ovaries have returned to pre-treatment size, and the dosage or duration of the next course should be reduced. Ovarian enlargement and cyst formation associated with clomiphene citrate usually regress spontaneously within a few days or weeks after discontinuation treatment. The potential benefit of subsequent clomiphene citrate therapy in these cases should exceed the risk. Unless surgical indication for laparotomy exists, such cystic enlargement should always be managed conservatively.

A causal relationship between ovarian hyperstimulation and ovarian cancer has not been determined. However, because a correlation between ovarian cancer and nulliparity, infertility and age has been suggested, if ovarian cysts do not regress spontaneously, a thorough evaluation should be performed to rule out the presence of ovarian neoplasia.

Ovarian Cancer
Prolonged use of clomiphene citrate may increase the risk of a borderline or invasive ovarian tumour.

Lactose Intolerance
Each tablet of this medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Patient Information
The purpose and risks of clomiphene citrate therapy should be presented to the patient before starting treatment. It
should be emphasized that the goal of clomiphene citrate therapy is ovulation for subsequent pregnancy. The physician should counsel the patient with special regard to the following potential risks:

* **Visual Symptoms**
  Advise that blurring or other visual symptoms occasionally may occur during or shortly after clomiphene citrate therapy. It should be made clear that, in some instances, visual disturbances may be prolonged and, possibly, irreversible. Warn that the visual symptoms render such activities as driving a car or operating machinery more hazardous than usual, particularly under conditions of variable lighting. The patient should be instructed to inform the physician whenever any unusual visual symptoms occur. If the patient has any visual symptoms, treatment should be discontinued and complete ophthalmologic evaluation performed.

* **Abdominal/Pelvic Pain or Distention**
  Ovarian enlargement may occur during or shortly after therapy with clomiphene citrate. To minimize the risks associated with ovarian enlargement, the patient should be instructed to inform the physician of any abdominal or pelvic pain, weight gain, discomfort, or distention after taking clomiphene citrate.

* **Metabolism Disorders**
  Cases of hypertriglyceridaemia have been reported. 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 a risk of hypertriglyceridaemia. Periodic monitoring of plasma triglycerides may be indicated in these patients.

* **Multiple Pregnancy**
  Inform the patient that there is an increased chance of multiple pregnancy, including bilateral tubal pregnancy and coexisting tubal and intrauterine pregnancy, when conception occurs in relation to clomiphene citrate therapy. The potential complications and hazards of multiple pregnancy should be explained.

* **Spontaneous Abortion and Congenital Anomalies**
  Inform the patient that the available data suggest no increase in the rates of spontaneous abortion (miscarriage) or congenital anomalies with maternal clomiphene citrate use compared to rates in the general population. During clinical investigation, the experience from patients with known pregnancy outcome shows a spontaneous abortion rate of 20.4% and stillbirth rate of 1.0%. Among the birth anomalies spontaneously reported as individual cases since commercial availability of clomiphene citrate, the proportion of neural tube defects has been high among pregnancies associated with ovulation induced by clomiphene citrate, but this has not been supported by data from population-based studies.

* **Pregnancy Wastage and Birth Anomalies**
  The physician should explain so that the patient understands the assumed risk of any pregnancy, whether ovulation was induced with the aid of clomiphene citrate or occurred naturally. The patient should be informed of the greater 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, 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 the evaluation of the patient, genetic counselling may be indicated.
  Population-based reports have been published on possible elevation of risk of Down's Syndrome in ovulation induction cases and of increase in trisomy defects among spontaneously aborted foetuses from subfertile women receiving ovulation-inducing drugs (no women with clomiphene citrate alone and without additional inducing drug). However, as yet, the reported observations are too few to confirm or not confirm the presence of an increased risk that would justify amniocentesis other than for the usual indications because of age and family history.
  The experience from patients of all diagnosis during clinical investigation of clomiphene citrate showed the following: a pregnancy (single and multiple) wastage or foetal loss rate of 21.4% (abortion rate of 19.0%); ectopic pregnancies,
1.18%; hydatidiform mole, 0.17%; foetus papyraceous, 0.04%; and of pregnancies with one or more stillbirths, 1.01%.

Clomiphene citrate therapy after conception was reported for 158 of the 2,369 delivered and reported pregnancies in the clinical investigations. Of these 158 pregnancies, 8 infants (born of 7 pregnancies) were reported to have birth defects. There was no difference in reported incidence of birth defects whether clomiphene citrate was given before the day 19 after conception or between the days 20 and 35 after conception. This incidence is within the anticipated range of the general population.

Clomiphene citrate should be used with caution:
- in patients with uterine fibroids, because of the risk of further enlargement of the fibroids;
- in patients suffering from mental depression, because of the risk of exacerbation; and,
- in patients with or susceptible to thrombophlebitis.

Drug Interactions

Drug interactions with clomiphene citrate have not been documented.

Pregnancy

Pregnancy Category X

Use of clomiphene citrate during pregnancy is contraindicated.

Human data

The available human data from epidemiologic studies do not show any apparent cause and effect relationship between clomiphene citrate periconceptual exposure and an increased risk of overall birth defects, or any specific anomaly. However, due to the small number of cases of congenital anomalies occurring in clomiphene citrate treated women, these epidemiologic studies were only able to rule out large differences in risk. The studies did not consider factors associated with female subfertility and were unable to adjust for other important confounders. In addition, available data do not support an increased rate of spontaneous abortion among subfertile women treated with clomiphene citrate for ovulation induction.

Lactation

It is not known whether clomiphene citrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if clomiphene citrate is administered to a nursing woman. In some patients, clomiphene citrate may reduce/suppress lactation.

Undesirable Effects

Symptoms/Signs/Conditions: Adverse effects appeared to be dose-related, occurring more frequently at the higher dose and with the longer courses of treatment used in investigational studies. At recommended dosage, adverse effects are not prominent and infrequently interfere with treatment.

During the investigational studies, the more commonly reported adverse effects included ovarian enlargement (13.6%), vasomotor flushes (10.4%), abdominal-pelvic discomfort (distention, bloating) (5.5%), nausea and vomiting (2.2%), breast discomfort (2.1%), visual symptoms (1.5%), headache (1.3%) and intermenstrual spotting or menorrhagia (1.3%).

Ovarian Enlargement: At recommended dosage, abnormal ovarian enlargement is infrequent although the usual cyclic variation 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 may occur, and the luteal phase of the cycle may be prolonged.

Rare instances of massive ovarian enlargement are recorded. Such an instance has been described in a patient with PCOS whose clomiphene citrate therapy consisted of 100 mg daily for 14 days. Abnormal ovarian enlargement usually
recesses spontaneously; most of the patients with this condition should be treated conservatively.

Eye/Visual Symptoms: Symptoms described usually as ‘blurring’ or spots or flashes (scintillating scotomata) increase in incidence with increasing total dose.

These symptoms appear to be due to intensification and prolongation of after-images. After-images as such have also been reported. Symptoms often first appear or are accentuated with exposure to bright-light environment. Ophthalmologically definable scotomata, phosphenes and reduced visual acuity have been reported. There are rare reports of cataracts and optic neuritis. These visual disturbances are usually reversible. However, cases of prolonged visual disturbance have been reported, including after clomiphene citrate have been discontinued. The visual disturbances may be irreversible, especially with increased dosage or duration of therapy.

Genitourinary: There are reports of new cases of endometriosis and exacerbation of pre-existing endometriosis during clomiphene citrate therapy. Multiple pregnancies, including simultaneous intrauterine and extraterine pregnancies, have been reported. There is an increased chance of ectopic pregnancy in women who conceive following clomiphene citrate therapy.

Tumours/Neoplasms: Isolated reports have been received on the occurrence of endocrine-related or dependent neoplasms or their aggravation.

Central Nervous System (CNS): Convulsions have been reported; patients with a history of seizures may be predisposed. In investigational patients, CNS symptoms/signs, conditions of dizziness, light-headedness/vertigo (0.9%), nervous tension/insomnia (0.8%) and fatigue/depression (0.7%) were reported. After prescription availability, there were isolated additional reports of these conditions and also reports of other conditions such as syncope/fainting, cerebrovascular accident, cerebral thrombosis, psychotic reactions, including paranoid psychosis, neurologic impairment, disorientation and speech disturbance.

Dermatoses: Dermatitis and rash were reported by investigational patients. Conditions such as rash and urticaria were the most common ones reported after prescription availability but also reported were conditions such as allergic reaction, erythema multiforme, ecchymosis and angioneurotic oedema. Hair thinning (alopecia) has been reported very rarely.

Liver Function: Bromsulphalein (BSP) retention of greater than 5% was reported in 32 of 141 patients in whom it was measured, including 5 of 43 patients who took approximately the dose of clomiphene citrate now recommended. Retention was usually minimal unless associated with prolonged continuous clomiphene citrate administration or with apparently unrelated liver disease. Other liver function tests were usually normal. In a later study in which patients were given 6 consecutive monthly courses of clomiphene citrate (50 or 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 taken the drug while 5 had placebo. In a separate report, 1 patient taking 50 mg of clomiphene citrate daily developed jaundice on day 19 of treatment; liver biopsy revealed bile stasis without evidence of hepatitis.

Metabolism Disorders: Hypertriglyceridaemia (frequency: not known), in some cases with pancreatitis, has been observed in patients with pre-existing or a family history of hypertriglyceridaemia and/or with dose and duration of treatment exceeding the label recommendations.

Clinical Trial Adverse Events

Clomiphene citrate, at recommended dosages, is generally well tolerated. Adverse reactions usually have been mild and transient and most have disappeared promptly after treatment has been discontinued. Adverse experiences reported in patients treated with clomiphene citrate during clinical studies are shown in the table.

Incidence of Adverse Events in Clinical Studies (Events >1%; n = 8,029*)

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<thead>
<tr>
<th>Adverse Event</th>
<th>%</th>
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<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Ovarian enlargement</td>
<td>13.6</td>
</tr>
<tr>
<td>Vasomotor flushes</td>
<td>10.4</td>
</tr>
<tr>
<td>Abdominal-pelvic discomfort/distention/bloating</td>
<td>5.5</td>
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<tr>
<td>Nausea and vomiting</td>
<td>2.2</td>
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<tr>
<td>Breast discomfort</td>
<td>2.1</td>
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<tr>
<td>Visual symptoms-blurred vision, lights, floaters, waves, unspecified visual complaints, photophobia, diplopia, scotomata, phosphenes</td>
<td>1.5</td>
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<tr>
<td>Headache</td>
<td>1.3</td>
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<tr>
<td>Abnormal uterine bleeding-intermenstrual spotting, menorrhagia</td>
<td>1.3</td>
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*Includes 498 patients whose reports may have been duplicated in the event totals and could not be distinguished as such. Also, excludes 47 patients who did not report symptom data.

The following adverse events have been reported in <1% of patients in clinical trials: acute abdomen, appetite increase, constipation, dermatitis or rash, depression, diarrhoea, dizziness, fatigue, hair loss/dry hair, increased urinary frequency/volume, insomnia, light-headedness, nervous tension, vaginal dryness, vertigo, weight gain/loss.

Patients on prolonged clomiphene citrate therapy may show elevated serum levels of desmosterol. This is most likely due to a direct interference with cholesterol synthesis. However, the serum sterols in patients receiving the recommended dose of clomiphene citrate are not significantly altered. Ovarian cancer has been infrequently reported in patients who have received fertility drugs. Infertility is a primary risk factor for ovarian cancer; however, epidemiology data suggest that prolonged use of clomiphene may increase the risk of a borderline or invasive ovarian tumour.

Post Marketing Adverse Events

The following adverse experiences were reported spontaneously with clomiphene citrate. The cause and effect relationship of the listed events to the administration of clomiphene citrate is not known:

**Dermatologic:** Acne, allergic reaction, erythema, erythema multiforme, erythema nodosum, hypertrichosis, pruritus, urticaria.

**CNS:** Migraine headache, paraesthesia, seizure, stroke, syncope.

**Psychiatric:** Anxiety, irritability, mood changes, psychosis.

**Visual Disorders:** Abnormal accommodation, cataract, eye pain, macular oedema, optic neuritis, photopsia, posterior vitreous detachment, retinal haemorrhage, retinal thrombosis, retinal vascular spasm, temporary loss of vision, possibly irreversible.

**Cardiovascular:** Arrhythmia, chest pain, oedema, hypertension, palpitation, phlebitis, pulmonary embolism, shortness of breath, tachycardia, thrombophlebitis.

**Musculoskeletal:** Arthralgia, back pain, myalgia.

**Gastrointestinal:** Pancreatitis.

**Hepatic:** Transaminases increased, hepatitis.

**Neoplasms:** Liver (hepatic haemangiosarcoma, liver cell adenoma, hepatocellular carcinoma); breast (fibrocystic disease, breast carcinoma); endometrium (endometrial carcinoma); nervous system (astrocytoma, pituitary tumour, prolactinoma, neurofibromatosis, glioblastoma multiforme, brain abscess); ovary (luteoma of pregnancy, dermoid cyst of the ovary, ovarian carcinoma); trophoblastic (hydatiform mole, choriocarcinoma); miscellaneous (melanoma, myeloma, perianal cysts, renal cell carcinoma, Hodgkin’s lymphoma, tongue carcinoma, bladder carcinoma).
Genitourinary: Endometriosis, ovarian cyst (ovarian enlargement or cysts could, as such, be complicated by adnexal torsion), ovarian haemorrhage, tubal pregnancy, uterine haemorrhage, reduced endometrial thickness.

Body as a Whole: Fever, tinnitus, weakness.

Other: Leucocytosis, thyroid disorder.

Foetal/neonatal Anomalies:
- Abnormal bone development: skeletal malformations of the skull, face, nasal passages, jaw, hand, limb (ectromelia, including amelia, hemimelia, and phocomelia), foot (clubfoot), spine, and joints
- Cardiac abnormalities: septal heart defects, muscular ventricular septal defect, patent ductus arteriosus, tetralogy of Fallot, and coarctation of the aorta
- Chromosomal disorders: Down’s syndrome
- Ear abnormalities and deafness
- Gastrointestinal tract abnormalities: cleft lip and palate, imperforate anus, tracheoesophageal fistula, diaphragmatic hernia, omphalocele
- Genitalia abnormalities: hypospadias, cloacal extrophy
- Lung tissue malformations
- Malformations of the eye and lens (cataract)
- Neoplasms: neuroectodermal tumor, thyroid tumour, hepatoblastoma, lymphocytic leukaemia
- Nervous system abnormalities: neural tube defects (anencephaly, meningomyelocele), microcephaly, and hydrocephalus
- Renal abnormalities: renal agenesis and renal dysgenesis
- Others: dwarfism, mental retardation

**Overdosage**

**Signs and Symptoms**

Toxic effects accompanying acute overdosage of clomiphene citrate have not been reported but the number of overdose cases recorded is small. In the event of overdose, appropriate supportive measures should be employed. Signs and symptoms of overdosage as a result of the use of more than the recommended dose during clomiphene citrate therapy include nausea, vomiting, vasomotor flushes, visual blurring, spots or flashes, scotomata, ovarian enlargement with pelvic or abdominal pain.

**Oral LD₅₀**

The acute oral LD₅₀ of clomiphene citrate is 1,700 mg/kg in mice and 5,750 mg/kg in rats. The toxic dose in humans is not known.

**Dialysis**

It is not known if clomiphene citrate is dialysable.

**Treatment**

In the event of overdose, appropriate supportive measures should be employed in addition to gastrointestinal decontamination.

**Storage And Handling Instructions**

Store in cool and dark place.
Packaging Information

FERTOMID 25 ..........................10 tablets in a blister pack
FERTOMID 50 ..........................10 tablets in a blister pack
FERTOMID 100 ............................5 tablets in a blister pack

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FERTOMID Tablets

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