Package Insert

1. Product name

Ova-mit 50 mg tablets

2. Name and Strength of Active Ingredient

Each tablet contains clomifene citrate 50 mg.

3. Product description

Tablet.

Light orange, round, flat scored tablets with Remedica's logo on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. Pharmacological Properties

Pharmacodynamics

Pharmacotherapeutic group: Sex hormones and modulators of the genital system; Gonadotropins and other ovulation stimulants, ATC code: G03GB02

Mechanism of action
The ovulatory response to cyclic clomifene citrate tablets therapy is mediated through increased output of pituitary gonadotrophins, which in turn stimulates the maturation and endocrine activity of the ovarian follicle.

Pharmacodynamic effects
Clomifene citrate tablets is a triarylethylene compound (related to chlorotrianisene and triparanol). It is a non-steroidal agent which stimulates ovulation in a high percentage of appropriately selected an ovulatory women.

Pharmacokinetics

Orally administered ^{14}C labelled clomifene citrate was readily absorbed when administered to humans. Cumulative excretion of the ^{14}C label by way of urine and faeces averaged about 50% of the oral dose after 5 days in 6 subjects, with mean urinary excretion of 7,8% and mean faecal excretion of 42,4%. A mean rate of excretion of 0,73% per day of the ^{14}C dose after 31 days to 35 days and 0,45% per day of the ^{14}C dose after 42 days to 45 days

was seen in faecal and urine samples collected from 6 subjects for 14 to 53 days after clomifene citrate ^{14}C administration. The remaining drug/metabolites may be slowly excreted from a sequestered enterohepatic recirculation pool.

When Ova-mit is administered over prolonged periods it may interfere with cholesterol synthesis. Patients on prolonged therapy may show elevated blood levels of desmosterol.

5. Clinical Particulars

Indications

Ova-mit is indicated for the treatment of ovulatory failure in women desiring pregnancy.

Good levels of endogenous oestrogen provide a favourable prognosis for ovulatory response induced by Ova-mit, Ova-mit therapy is ineffective in patients with primary pituitary or primary ovarian failure.

Posology and method of administration

Adults only:
The recommended dose for the first course of Ova-mit is 50 mg (1 tablet) daily for 5 days. Therapy may be started at any time in the patient who has had no recent uterine bleeding. If progestin-induced bleeding is planned, or if spontaneous uterine 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 50 mg tablets given as a single daily dose) for 5 days should be given. This course may be started as early as 30 days after the previous one. Increase of the dosage or duration of therapy beyond 100 mg/day for 5 days should not be undertaken.

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. If ovulatory menses have not yet occurred, the diagnosis should be re-evaluated. Treatment beyond this is not recommended in the patient who does not exhibit evidence of ovulation.

Pregnancy:
The importance of properly timed coitus cannot be over-emphasised (i.e. at about the time of ovulation). For regularity of cyclic ovulatory response it is also important that each course of Ova-mit be started on or about the fifth cycle day, once ovulation has been established. Ova-mit therapy follows the rule of diminishing returns, such that likelihood of conception diminishes with each succeeding course of therapy. Before starting treatment, patients and their male partners should be advised of the possibility of multiple pregnancy and its potential hazards if conception occurs in relation to Ova-mit therapy.

Long-term cyclic therapy
Not recommended.

Efficacy and safety of clomifene for more than 6 treatment cycles have not been demonstrated.

Method of Administration
Oral administration.

Contraindications

Pregnancy:
Ova-mit is not indicated during pregnancy. Although there is no evidence that clomifene citrate tablets have a harmful effect on the human foetus, there is evidence that clomifene citrate tablets have a deleterious effect on rat and rabbit foetuses when given in high doses to the pregnant animal. Ova-mit should not be administered during pregnancy. To avoid inadvertent Ova-mit administration during early pregnancy, appropriate tests should be utilised during each treatment cycle to determine whether ovulation occurs. The patient should have a pregnancy test before the next course of Ova-mit therapy.

Liver disease:
Ova-mit therapy is contraindicated in patients with active liver disease, a history of liver dysfunction or a family or personal history of disorders of bilirubin metabolism.

Ovarian dysgenesis:
Ova-mit is contraindicated in patients with ovarian dysgenesis, menopause or any state in which a response could not be expected.

Abnormal uterine bleeding:
Ova-mit is contraindicated in patients with hormone-depended tumours or in patients with abnormal uterine bleeding of undetermined origin.

Ovarian cyst:
Ova-mit tablets should not be given in the presence of an ovarian cyst, except polycystic ovary, since further enlargement of the cyst may occur. Patients should be evaluated for the presence of ovarian cyst prior to each course of treatment.

Warnings and Precautions

Warnings:

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

Ovarian Hyperstimulation Syndrome:
Ovarian Hyperstimulation Syndrome (OHSS) has been reported in patients receiving clomifene citrate therapy for ovulation induction. In some cases, OHSS occurred following the cyclic use of clomifene citrate therapy or when clomifene citrate was used in combination with gonadotropins. Rare cases of severe forms of OHSS have been reported where the following symptoms have occurred during clomifene citrate therapy: pericardial effusion, anasarca, hydrothorax, acute abdomen, renal failure, pulmonary oedema, ovarian haemorrhage, deep venous thrombosis, torsion of the ovary and acute respiratory distress. If conception results, rapid progression to the severe form of the syndrome may occur.

To minimise the hazard of the abnormal ovarian enlargement associated with clomifene citrate therapy, the lowest dose consistent with expectation of good 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 Ova-mit. Maximal enlargement of the ovary may not occur until several days after discontinuation of the course of Ova-mit. Some patients with polycystic ovary syndrome who are unusually sensitive to gonadotropin may have an exaggerated response to usual doses of Ova-mit.

The patient who complains of abdominal or pelvic pain, discomfort, or distension after taking Ova-mit should be examined because of the possible presence of an ovarian cyst or other cause. Due to fragility of enlarged ovaries in severe cases, abdominal and pelvic examination should be performed very cautiously. If abnormal enlargement occurs Ova-mit should not be given until the ovaries have returned to pre-treatment size. Ovarian enlargement and cyst formation associated with Ova-mit therapy usually regress spontaneously within a few days or weeks after discontinuing treatment. Most of these patients should be managed conservatively. The dosage and/or duration of the next course of treatment should be reduced.

Visual Symptoms:
Patients should be advised that blurring or other visual symptoms such as spots or flashes (scintillating scotomata) may occasionally occur during or shortly after therapy with Ova-mit.

The patient should be instructed to inform the physician whenever any unusual visual symptoms occur. These visual disturbances are usually reversible; however, cases of prolonged visual disturbance have been reported including after clomifene citrate tablet discontinuation. The visual disturbances may be irreversible especially with increased dosage or duration of therapy (See section Undesirable effects). 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 understood. If the patient has any visual symptoms, treatment should be discontinued and ophthalmologic evaluation performed.

Precautions:

Cases of hypertriglyceridemia have been reported (see section Undesirable effects) in the post-marketing experience with clomifene citrate tablets. Pre-existing or family history of hyperlipidemia and use of higher than recommended dose and/or longer duration of treatment with Ova-mit are associated with risk of hypertriglyceridemia. Periodic monitoring of plasma triglycerides may be indicated in these patients.

Treatment with Ova-mit should only be undertaken by a specialist having available the appropriate facilities for close supervision of clinical and laboratory responses. The patient's physical state and the aetiological diagnosis should be carefully investigated prior to this therapy. Any pre-existent endocrine defect or other cause of infertility in patients or partner should be examined and treated prior to this therapy.

Multiple Pregnancy:
There is an increased chance of multiple pregnancy when conception occurs in relationship to Ova-mit therapy. During the clinical investigation studies, the incidence of multiple pregnancy was 7.9% (186 of 2369 clomifene citrate associated pregnancies on which outcome was reported). Among these 2369 pregnancies, 165 (6.9%) twin, 11 (0.5%) triplet, 7 (0.3%) quadruplet and 3 (0.13%) quintuplet. Of the 165 twin pregnancies for which sufficient information was available, the ratio of monozygotic twins was 1:5.

Ectopic Pregnancy:
There is an increased chance of ectopic pregnancy (including tubal and ovarian sites) in women who conceive following Ova-mit therapy. Ectopic pregnancy associated with clomifene citrate involves a multiple pregnancy with coexisting extrauterine and intrauterine gestations.

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

Pregnancy Wastage and Birth Anomalies:
The overall incidence of reported birth anomalies from pregnancies associated with maternal clomifene citrate ingestion (before or after conception) during the investigational studies was within the range of that reported in the published references for the general population. Among the birth anomalies spontaneously reported in the published literature as individual cases, the proportion of neural tube defects has been high among pregnancies associated with ovulation induced by clomifene citrate, but this has not been supported by data from population based studies.

The physician should explain so that the patient understands the assumed risk of any pregnancy whether the ovulation was induced with the aid of Ova-mit or occurred naturally.

The patient should be informed of the greater pregnancy 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 (regardless of cause), 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 Ova-mit 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 clomifene 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 clomifene citrate shows 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%.

Clomifene citrate therapy after conception was reported for 158 of the 2369 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 clomifene citrate was given before the 19^{th} day after conception or between the 20^{th} and 35^{th} day after conception. This incidence is within the anticipated range of general population.

Ovarian Cancer:
There have been rare reports of ovarian cancer with fertility drugs; infertility itself is a primary risk factor.

Patients with rare hereditary problems of fructose/galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Interactions with other medicaments

None stated.

Pregnancy and Lactation

Ova-mit is not indicated during pregnancy. See contraindications (*See section Contraindications*).

Lactation
It is not known whether Clomifene Citrate is excreted in human milk. Clomifene may reduce lactation.

Undesirable effects

The following CIOMS frequency rating is used, when applicable: *Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥ 1/10,000 to ≤ 1/1,000); very rare (≥ 1/10,000); not known (cannot be estimated from the available data).*

	Very common	Common	Uncommon	Rare	Not known
Eye disorders		Visual symptoms: blurring, spots, flashes (scintillating scotomata), after images		Cataracts, Optic neuritis	Scotomata, phosphenes, reduced visual acuity
Cardiac disorders					Tachycardia, palpitations
Pregnancy, puerperium and perinatal conditions					Multiple pregnancies, Simultaneous intrauterine and extra uterine pregnancies, ectopic pregnancy
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)					Endocrine related or dependent tumors/neoplasms (see section Warnings and precautions)
Nervous system disorders		Headache	Dizziness, Light-headedness/ vertigo, Nervous tension /insomnia, Fatigue	Seizures	Syncope/fainting, Cerebrovascular accident, Cerebral thrombosis Neurologic impairment, Disorientation and speech disturbance, Transient paraesthesia
Psychiatric disorders			Depression		Paranoid psychosis
Vascular disorders	Flushing				
Hepatobiliary disorders					Impaired hepatocellular function: abnormal bromosulphalein test (see below) ,

					Jaundice
Gastrointestinal disorders		Nausea, Vomiting, Distension, Bloating			Pancreatitis
Skin and subcutaneous tissue disorders					Urticaria, Dermatitis/rash, Alopecia Erythema multiform, Ecchymosis, Angioneurotic oedema
Reproductive system and breast disorders	Ovarian enlargement	Breast discomfort, Inter-menstrual spotting or menorrhagia			Endometriosis, exacerbation of pre-existing endometriosis reduced endometrial thickness, Massive ovarian enlargement
Metabolism and nutrition disorders					Hypertriglyceridemia
Immune System Disorders					Allergic reaction

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

Reproductive system and breast disorders:
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 polycystic ovary syndrome whose clomifene citrate therapy consisted of 100 mg daily for 14 days. Abnormal ovarian enlargement usually regresses spontaneously; most of the patients with this condition should be treated conservatively.

Eye disorders:
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. These are rare reports of cataracts and optic neuritis.

These visual disturbances are usually reversible. However, cases of prolonged visual disturbances have been reported, including after clomifene citrate discontinuation. The visual disturbances may be irreversible, especially with increased dosage or duration of therapy (See section 4).

Tumours/neoplasms:
Isolated reports have been received on the occurrence of endocrine-related or dependent neoplasms of their aggravation. Ovarian cancer: see section Warnings and precautions.

Central nervous system:
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 disturbances.

Hepatobiliary disorders:
Increased transaminases have been reported.

The Bromsulphalein test (BSP) is a test of liver function based on the removal of a known quantity of Brom-sulphalein from the blood in a measured period of time. Normal values are less than 5% retention at the end of 45 minutes with an intravenous dose of 5 mg/kg body weight. It is a useful test of hepatocellular disease and detoxifying ability but is not applicable in the presence of extra-hepatic or intrahepatic obstructive jaundice.

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 clomifene citrate tablets now recommended. Retention was usually minimal unless associated with prolonged continuous clomifene 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 clomifene citrate tablets (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 drug and 5 placebo.

In a separate report, one patient taking 50 mg clomifene citrate tablets daily developed jaundice on the 19th day of treatment; liver biopsy revealed bile stasis without evidence of hepatitis.

Metabolism Disorders:
Hypertriglyceridemia in some cases with pancreatitis, has been observed in patients with pre-existing or a family history of hypertriglyceridemia and/or with dose and duration of treatment exceeding the label recommendations.

Symptoms and treatment of overdose

Toxic effects of acute overdosage of clomifene 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.

6. Pharmaceutical Particulars

Storage conditions

Do not store above 30°C. Protect from light and moisture.

Shelf-life

60 months.

Pack size available

PVC/Aluminium blisters. Pack size of 10 and 1000 tablets.

7. Manufacturer

Remedica Ltd.
Aharnon Street, Limassol Industrial Estate, 3056 Limassol, Cyprus

8. Date of revision of the text

06/2022

For internal use only: my-pi-ova-mit-tabs-a0