Ovafin®

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(Clomifene Citrate)

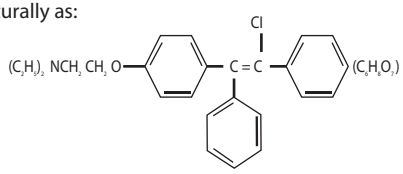
QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Clomifene Citrate (BP).....50 mg

DESCRIPTION

Ovafin (Clomifene Citrate) is an orally administered, nonsteroidal, ovulatory stimulant designated chemically as 2-[p- (2-chloro-1, 2 - diphenylvinyl) phenoxy] triethylamine Citrate (1:1). It has the molecular formula of $C_{26}H_{28}ClNO \cdot C_6H_8O_7$ and a molecular weight of 598.09. It is represented structurally as:



Clomifene Citrate is a white to pale yellow, essentially odorless, crystalline powder. It is freely soluble in methanol; soluble in ethanol; slightly soluble in acetone, water, and chloroform; and insoluble in ether.

CLINICAL INFORMATION

Indications

Ovafin (Clomifene Citrate) is indicated for the treatment of ovulatory dysfunction in women desiring pregnancy. Impediments to achieving pregnancy must be excluded or adequately treated before beginning Ovafin (Clomifene Citrate) therapy. Those patients most likely to achieve success with Clomifene therapy include patients with polycystic ovary syndrome (see Warnings & Precautions; Ovarian Hyperstimulation Syndrome), amenorrhea - galactorrhea syndrome, psychogenic amenorrhea, post-oral-contraceptive amenorrhea, and certain cases of secondary amenorrhea of undetermined etiology.

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 Ovafin (Clomifene Citrate) should be started on or about the 5th day of the cycle. Long-term cyclic therapy is not recommended beyond a total of about six cycles (including three ovulatory cycles) (See Dosage and Administration and Warnings and Precautions).

Ovafin (Clomifene Citrate) is indicated only in patients with demonstrated ovulatory dysfunction who meet the conditions described below:

1. Patients who are not pregnant.
2. Patients without ovarian cysts. Ovafin (Clomifene Citrate) should not be used in patients with ovarian enlargement except those with polycystic ovary syndrome. Pelvic examination is necessary prior to the first and each subsequent course of Ovafin (Clomifene Citrate) treatment.
3. 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.
4. Patients with normal liver function.

Dosage and Administration

General Considerations

The workup and treatment of candidates for Ovafin (Clomifene Citrate) therapy should be supervised by physicians experienced in management of gynecologic or endocrine disorders. Patients should be chosen for therapy with Ovafin (Clomifene 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 Ovafin (Clomifene 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 Clomifene 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. The dose should be increased only in those patients who do not ovulate in response to cyclic 50 mg Ovafin (Clomifene Citrate). A low dosage or duration of treatment course is particularly recommended if unusual sensitivity to pituitary gonadotropin is suspected, such as in patients with polycystic ovary syndrome (see Warnings & Precautions; Ovarian Hyperstimulation Syndrome).

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 5th day 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 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 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 Ovafin (Clomifene Citrate) is not recommended and the patient should be reevaluated. 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 reevaluated. Long-term cyclic therapy is not recommended beyond a total of about six cycles (see Warnings & Precautions).

Administration Requirements:

In addition, patients selected for Ovafin (Clomifene Citrate) therapy should be evaluated in regard to the following:

1. Estrogen Levels. Patients should have adequate levels of endogenous estrogen (as estimated from vaginal smears, endometrial biopsy, assay of urinary estrogen, or from bleeding in response to progesterone). Reduced estrogen levels, while less favorable, do not preclude successful therapy.

2. Primary Pituitary or Ovarian Failure. Ovafin (Clomifene Citrate) therapy cannot be expected to substitute for specific treatment of other causes of ovulatory failure.

3. 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 Ovafin (Clomifene Citrate) therapy in this population.

4. Other Impediments to Pregnancy. Impediments to pregnancy can include thyroid disorders, adrenal disorders, hyperprolactinemia, and male factor infertility.

5. Uterine Fibroids. Caution should be exercised when using Ovafin (Clomifene Citrate) in patients with uterine fibroids due to the potential for further enlargement of the fibroids.

Contraindications

Hypersensitivity

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

Pregnancy

Pregnancy Category X

Clomifene use in pregnant women is contraindicated, as Clomifene does not offer benefit in this population.

Liver Disease

Clomifene therapy is contraindicated in patients with liver disease or a history of liver dysfunction (see also Indications and Adverse Reactions).

Abnormal Uterine Bleeding

Clomifene is contraindicated in patients with abnormal uterine bleeding of undetermined origin (see Indications).

Ovarian Cysts

Clomifene is contraindicated in patients with ovarian cysts or enlargement not due to polycystic ovarian syndrome (see Indications and Warnings & Precautions).

Other

Clomifene is contraindicated in patients with uncontrolled thyroid or adrenal dysfunction or in the presence of an organic intracranial lesion such as pituitary tumor (see Indications).

Warnings & Precautions

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 Clomifene. These visual symptoms increase in incidence with increasing total dose or therapy duration. These visual disturbances are usually reversible; however, prolonged visual disturbance may occur after Clomifene discontinuation. The visual disturbances may be irreversible, especially with increased dosage or duration of therapy. Patients should be warned that these visual symptoms may render such activities as driving a car or operating machinery more hazardous than usual, particularly under conditions of variable lighting.

While the etiology 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) may occur in patients receiving Clomifene therapy for ovulation induction. OHSS may progress rapidly (within 24 hours to several days) and become a serious medical disorder. Sometimes, OHSS may occur following cyclic use of Clomifene therapy or when Clomifene is used in combination with gonadotropins. Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, may occur in association with OHSS.

OHSS is a medical event distinct from uncomplicated ovarian enlargement. The clinical signs of this syndrome in severe cases can include gross ovarian enlargement, gastrointestinal symptoms, ascites, dyspnea, 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 edema, intraperitoneal and ovarian hemorrhage, deep venous thrombosis, torsion of the ovary, and acute respiratory distress. The early warning signs of OHSS are abdominal pain and distention, nausea, vomiting, diarrhea, and weight gain. Elevated urinary steroid levels, varying degrees of electrolyte imbalance, hypovolemia, hemoconcentration, and hypoproteinemia may occur. Death due to hypovolemic shock, hemoconcentration, 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 Clomifene therapy, the lowest dose consistent with expected clinical results should be used. Maximal enlargement of the ovary, whether physiologic or abnormal, may not occur until several days after discontinuation of the recommended dose of Clomifene Citrate. Some patients with polycystic ovary syndrome who are unusually sensitive to

gonadotropin may have an exaggerated response to usual doses of Clomifene Citrate. Therefore, patients with polycystic ovary syndrome should be started on the lowest recommended dose and shortest treatment duration for the first course of therapy (see Dosage and Administration).

If enlargement of the ovary occurs, additional Clomifene 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. Ovarian enlargement and cyst formation associated with Clomifene therapy usually regresses spontaneously within a few days or weeks after discontinuing treatment. The potential benefit of subsequent Clomifene therapy in these cases should exceed the risk. Unless surgical indication for laparotomy exists, such cystic enlargement should always be managed conservatively.

General

Careful attention should be given to the selection of candidates for Clomifene therapy. Pelvic examination is necessary prior to Clomifene treatment and before each subsequent course (see Contraindications and Warnings & Precautions).

Interactions

Drug interactions with Clomifene Citrate have not been documented.

Pregnancy & Breast Feeding

Pregnancy Category X (See Contraindications)

Clomifene Citrate use in pregnant women is contraindicated, as Clomifene treatment does not offer benefit in this population. 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 fetus.

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

Effects on ability to drive and use machines

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.

Adverse Reactions

Clomifene, at recommended dosages, is generally well tolerated. Adverse reactions are usually mild and transient and most have disappeared promptly after treatment has been discontinued. Side effects are dose-related being more frequent and more severe when higher doses of Clomifene are administered.

Body as a Whole: Fever, tinnitus, weakness

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

Central Nervous System: Migraine headache, paresthesia, seizure, stroke, syncope

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

Fetal/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

Downs syndrome

Ear abnormalities and deafness

Gastrointestinal tract abnormalities

Cleft lip and palate, imperforate anus, tracheoesophageal fistula, diaphragmatic hernia, omphalocele

Genitalia abnormalities: hypospadias, cloacal exstrophy

Lung tissue malformations

Malformations of the eye and lens (cataract)

Neoplasms

Neuroectodermal tumor, thyroid tumor, hepatoblastoma, lymphocytic leukemia

Nervous system abnormalities

Neural tube defects (anencephaly, meningomyelocele), microcephaly, and hydrocephalus

Renal abnormalities

Renal agenesis and renal dysgenesis

Others

Dwarfism, mental retardation

Gastrointestinal

Pancreatitis

Genitourinary

Endometriosis, ovarian cyst (ovarian enlargement or cysts could, as such, be complicated by adnexal torsion), ovarian hemorrhage, tubal pregnancy, uterine hemorrhage, reduced endometrial thickness

Hepatic

Transaminases increased, hepatitis

Metabolism Disorders

Hypertriglyceridemia, in some cases with pancreatitis

Musculoskeletal

Arthralgia, back pain, myalgia

Neoplasms

Liver (hepatic hemangiosarcoma, liver cell adenoma, hepatocellular carcinoma); breast (fibrocystic disease, breast carcinoma); endometrium (endometrial carcinoma); nervous system (astrocytoma, pituitary tumor, prolactinoma, neurofibromatosis, glioblastoma multiforme, brain abcess); 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)

Psychiatric
Anxiety, irritability, mood changes, psychosis
Visual Disorders
Abnormal accommodation, cataract, eye pain, macular edema, optic neuritis, photopsia, posterior vitreous detachment, retinal hemorrhage, retinal thrombosis, retinal vascular spasm, temporary or prolonged loss of vision, possibly irreversible.
Other
Leukocytosis, thyroid disorder

Overdose
Signs and Symptoms
Toxic effects accompanying acute overdosage of Clomifene Citrate may not occur. Signs and symptoms of overdosage as a result of the use of more than the recommended dose during Clomifene Citrate therapy include nausea, vomiting, vasomotor flushes, visual blurring, spots or flashes, scotomata, ovarian enlargement with pelvic or abdominal pain. (See Contraindications: Ovarian Cyst)
Treatment
In the event of overdose, appropriate supportive measures should be employed in addition to gastrointestinal decontamination.

PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: ovulation stimulants, synthetic. ATC code: G03BG02
Mechanism of Action
Clomifene is a drug of considerable pharmacologic potency. With careful selection and proper management of the patient, Clomifene Citrate has been demonstrated to be a useful therapy for the anovulatory patient desiring pregnancy.
Clomifene is capable of interacting with estrogen - receptor - containing tissues, including the hypothalamus, pituitary, ovary, endometrium, vagina, and cervix. It may compete with estrogen for estrogen-receptor-binding sites and may delay replenishment of intracellular estrogen receptors. Clomifene 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 Clomifene 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 estradiol. Following ovulation, plasma progesterone and estradiol rise and fall as they would in a normal ovulatory cycle. Clomifene has no apparent progestational, androgenic, or antiandrogenic effects and does not appear to interfere with pituitary-adrenal or pituitary-thyroid function. Although there is no evidence of a "carryover effect" of Clomifene, spontaneous ovulatory menses have been noted in some patients after Clomifene therapy.
Pharmacokinetics
Orally administered ^{14}C labelled Clomifene Citrate is readily absorbed when administered to humans. Cumulative excretion of the ^{14}C label by way of urine and faeces averages 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 is 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.

PHARMACEUTICAL INFORMATION
Shelf life
2 years

ہدایات:
Special Precautions for Storage
- Store below 30°C. ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
- Protect from light and moisture. دوا کو روشنی اور نمی سے بچائیں۔
- Keep out of the reach of children. بچوں کی پہنچ سے دور رکھیں۔

To be sold on the prescription of a registered medical practitioner only. صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔

Nature and contents of container
Ovafin (Clomifene Citrate) 50 mg tablets are available in a blister pack of 10's (1 x 10's).

MANUFACTURED BY
OBS Pakistan (Pvt.) Ltd.
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Karachi-75700, Pakistan.

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