Clomifene citrate
Pregina®

50 mg Tablet
Ovulation Inducing Agent

FORMULATION

Each tablet contains:
Clomifene citrate .... 50 mg

PHARMACOLOGIC CATEGORY

Ovulation-inducing Medicine

PRODUCT DESCRIPTION

Clomifene citrate 50 mg is a white, uncoated tablet.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Clomifene citrate is a nonsteroidal agent which may induce ovulation in appropriately selected anovulatory women. It has both estrogenic and anti-estrogenic properties but its precise mechanism of action in inducing ovulation has not been determined.

Clomifene citrate appears to stimulate the release of the pituitary gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), either from direct stimulation of the hypothalamic-pituitary axis or from a decreased inhibitory influence of estrogens on the hypothalamic-pituitary axis by competing with the endogenous estrogens of the uterus, pituitary or hypothalamus. This results in development and maturation of the ovarian follicle, ovulation and subsequent development and function of the corpus luteum.

Clomifene citrate may also directly affect the biosynthesis of ovarian hormones. Clomifene has no progestational, androgenic or antiandrogenic effects and does not appear to interfere with pituitary-adrenal or pituitary-thyroid function.

Pharmacokinetics

Clomifene is readily absorbed from the gastrointestinal tract after oral administration. Blood concentrations of the drug are low and exhibit interpatient variation in studies using radiolabeled clomifene citrate. The volume of distribution and plasma protein binding of clomifene citrate is unknown. The E-isomer is reported to be less well absorbed and more rapidly eliminated than the Z-isomer.

Clomifene citrate is metabolized in the liver and slowly excreted via the bile. The biological half-life is reported to be 5 days although traces are found in the feces for up to 6 weeks. Mean urinary excretion is approximately 8% and fecal excretion is about 42%.

Limited studies suggest that the drug is excreted slowly from a sequestered enterohepatic recirculation pool or may be stored in body fat and subsequently released slowly.

INDICATION

Clomifene citrate is indicated for induction of ovulation in patients with persistent ovulatory dysfunction who desire pregnancy. The work-up and treatment of candidates for clomifene therapy should be supervised by physicians experienced in the management of gynecologic or endocrine disorders. Patients should be chosen for therapy with clomifene only after careful diagnostic evaluation. The work-up 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.

1. Exclusion of pregnancy: Treatment should be withheld until diagnosis of pregnancy has been ruled out.
2. Assessment of abnormal excessive bleeding: Patients with this condition should be evaluated prior to therapy. It is important to ensure that neoplastic lesions are not overlooked.
3. Exclusion of presence or history of liver dysfunction: Assess liver function prior to treatment.
4. Exclusion of presence of ovarian cyst: Do not use clomifene citrate in patients with ovarian enlargement except those with polycystic ovary syndrome (PCOS). Perform pelvic examination before the first and each subsequent treatment cycle.
5. Confirmed ovulatory dysfunction: Establish the diagnosis of ovulatory dysfunction by standard techniques such as basal body temperature curves, serial vaginal smears, cervical mucus, endometrial biopsy, and pregnanediol determination.
6. Exclusion of primary pituitary or ovarian failure: Successful therapy with clomifene requires intact pituitary and ovaries. Ovulatory dysfunction in the presence of abnormally high levels of pituitary gonadotropins indicates ovarian failure and does not respond to clomifene.
7. Assessment of estrogen levels: Adequate levels of endogenous estrogen provide a favorable prognosis for treatment with clomifene. Physiologic indicators of normal endogenous estrogen include vaginal smears, cervical mucus, endometrial biopsy, assay of urinary estrogen, or from bleeding in response to progesterone. Reduced estrogen level, although less favorable, does not preclude successful therapy.
8. Exclusion of mechanical impediments to conception: Exclude or adequately treat mechanical impediments to conception (e.g., tubal obstruction) before taking clomifene.
9. Exclusion of medical impediments to pregnancy: Clomifene is not a substitute for appropriate therapy of other disturbances leading to ovulatory dysfunction (e.g., diabetes, diseases of the thyroid and adrenals). Specific treatment should be undertaken and subfertility therapy reconsidered only after the underlying disorder has been adequately treated.
10. Exclusion of male factor infertility: Determine the husband's fertility potential using semen analysis and other indicated examination. The efficacy of clomifene for male infertility has not been established. Testicular tumors and gynecomastia have been reported in men using clomifene citrate. However, the cause and effect relationship between reports of testicular tumors and the administration of clomifene is unknown.

Clomifene has also been used in conjunction with gonadotropins and in *in vitro* fertilization programmes.

Clomifene has also been used in the treatment of male fertility due to oligospermia to stimulate gonadotropin release and enhance spermatogenesis.

DOSAGE AND ADMINISTRATION

General Considerations:

The workup and treatment of candidates for clomifene citrate therapy should be supervised by physicians experienced in the management of gynecologic or endocrine disorders. Clomifene should only be given to appropriately chosen anovulatory patients. The therapeutic objective should be balanced with potential risks. These should be discussed with the patient and others who are involved in the achievement of a pregnancy. The plan of therapy should be outlined in advance.

Data suggest that clomifene treatment of 100 mg/day for 5 days is more effective compared with 50 mg/day for 5 days. However, an increased incidence of ovarian hyperstimulation and other adverse effects may be expected. It is recommended that clomifene be usually started with the lowest effective dose and increased only in those patients who do not respond to the first course of treatment. Special care in dosage is particularly recommended if unusual sensitivity to pituitary gonadotropin is suspected, such as in patients with PCOS.

Recommended Dosage:

First Course: 50 mg once a day for five (5) days.
Treatment may be started at any time in the patient who has had no recent uterine bleeding. Start clomifene therapy about the 5th day of the menstrual cycle if progestin-induced bleeding is planned or if spontaneous uterine bleeding occurs prior to therapy. When ovulation occurs at this dose, there is no advantage to increasing the dose in subsequent treatment cycles.

If ovulation appears not to have occurred after the first course of therapy, a second course of 100 mg once a day (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. **Increasing the dose or duration of therapy beyond 100 mg per day for 5 days should never be undertaken.**

The majority of patients who respond do so during the first course of therapy; three (3) courses should constitute an adequate therapeutic trial. If ovulatory menses have not occurred, the diagnosis should be re-evaluated. Treatment beyond this is not recommended in the patient who does not exhibit evidence of ovulation.

In most patients, ovulation will take place 6 to 12 days after completion of therapy. Coitus should be timed to coincide with the expected time of ovulation. Appropriate tests to determine ovulation may be useful during this time.

Long-term cyclic therapy (more than a total of 6 cycles, including 3 ovulatory cycles) with clomifene is not recommended. The relative safety of long-term cyclic administration of clomifene citrate has not been established.

CONTRAINDICATIONS

- Known hypersensitivity to clomifene citrate or to any ingredient in the product
- Pregnancy
- Active liver disease or history of liver dysfunction
- Hormone-dependent tumors or abnormal uterine bleeding of undetermined origin
- Pituitary or ovarian tumors
- Ovarian cysts (other than in association with polycystic ovarian syndrome) and pre-existing endometriosis

WARNINGS AND PRECAUTIONS

Ovarian Hyperstimulation Syndrome (OHSS)

Clomifene citrate alone or in combination with gonadotropins has been reported to cause OHSS. Early warning signs of OHSS include 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. In severe cases, OHSS can induce gross ovarian enlargement, gastrointestinal symptoms, ascites, dyspnea, oliguria, and pleural effusion. OHSS has been associated with transient liver function test abnormalities suggestive of hepatic dysfunction which may be accompanied by morphologic changes on liver biopsy.

Severe forms of OHSS have been reported rarely with the use of clomifene (either alone or in combination with gonadotropins). Pericardial effusion, anasarca, hydrothorax, acute abdomen, renal failure, pulmonary edema, hypotension, intraperitoneal and ovarian hemorrhage, deep venous thrombosis, torsion of the ovary, and acute respiratory distress occurred in these patients. Death due to hypovolemic shock, hemoconcentration or thromboembolism has occurred. If conception results, rapid progression to the severe form of the syndrome may occur.

The lowest dose consistent with expected clinical results should be used to minimize the hazard associated with occasional abdominal ovarian enlargement, associated with clomifene citrate therapy. Maximal enlargement of the ovary, whether physiologic or abnormal, may not occur until several days after discontinuation of the drug. Some patients with PCOS who are unusually sensitive to gonadotropins may experience an exaggerated response to usual doses of clomifene. Patients with PCOS should be started on the lowest recommended dose and shortest treatment duration for the first course of therapy.

Patients should be advised of the possibility of ovarian cyst formation during therapy and should be instructed to return for repeat pelvic examination between 2 to 3 weeks after starting each course of treatment. Patients should inform their attending physician of any abdominal or pelvic pain, weight gain, discomfort or distention after taking clomifene.

Patients who complain of pain in the pelvic or abdominal area should be examined to rule out ovarian cyst formation or other cause. Due to fragility of enlarged ovaries in severe cases, abdominal and pelvic examination should be performed carefully.

Unless the ovaries have returned to its pretreatment size, additional dose of clomifene should not be given in patients. The dose or duration of the next course should be reduced. Clomifene-induced ovarian enlargement and cyst formation regress spontaneously within a few days or weeks after discontinuation of treatment. Cystic enlargement should always be managed conservatively unless surgical indication exists.

Visual Symptoms

Blurring and/or other visual symptoms such as spots or flashes (scintillating scotomata), diplopia, phosphenes, or photophobia may occur occasionally during therapy. These symptoms appear to be related to the dose and duration of treatment and generally disappear within a few days or weeks after discontinuation.

Patients should be warned that visual symptoms may make activities such as driving or operating machinery more hazardous than usual under conditions of variable lighting. These visual symptoms are usually reversible; however, cases of prolonged visual disturbances may be irreversible especially with increased dosage and duration of therapy. It is recommended to discontinue treatment and a complete ophthalmologic evaluation be performed if a patient has any visual symptoms.

Diagnosis Prior to Clomifene Therapy

The incidence of anovulatory disorders and the tendency to develop endometrial carcinoma increases with age. Prior to clomifene therapy in such patients, dilatation and curettage should always be done for diagnosis. Full diagnostic measures are mandatory if abnormal bleeding is present.

Ovarian Cancer

Fertility drugs have been rarely associated with ovarian cancer with infertility itself being a primary risk factor. Since epidemiological data suggest that prolonged therapy with clomifene citrate may increase this risk, the recommended duration of treatment should not be exceeded.

Uterine Fibroids

Patients with uterine fibroids should use clomifene with caution because of the risk of further enlargement of the fibroids.

Hepatic Impairment

Clomifene is not recommended in these patients (see Contraindications) and therefore clinical evaluation of liver function should always precede therapy.

Pre-existing Mental Depression or Thrombophlebitis

Use clomifene with caution in patients with pre-existing mental depression or thrombophlebitis to avoid the risk of exacerbation of the disease.

Teratogenic/Non-teratogenic Effects: In clinical studies, the overall incidence of birth anomalies resulting from clomifene ingestion during pregnancy was within range of that reported for the general population.

Pregnancy Wastage: A pregnancy (single and multiple) wastage or fetal loss rate of 21.4% (abortion rate of 19%), ectopic pregnancies 1.18%, hydatidiform mole 0.17%, fetal papyraceous 0.04%, and pregnancies with one or more still births 1.01% have been observed in patients of all diagnoses during clinical investigation of clomifene citrate.

Multiple Pregnancy: Treatment with clomifene citrate increases the chance of multiple pregnancy (including triplets, quadruplets and quintuplets). The incidence of multiple pregnancy was 7.9% in clinical studies. Among these pregnancies, 6.9% were twin, 0.5% triplet, 0.3% quadruplet, and 0.13% quintuplet. The ratio of monozygotic to dizygotic twins was 1:5 of the twin pregnancies. Before starting treatment, the patient and her spouse should be advised of the frequency and potential hazards of multiple pregnancy.

Combination therapy with clomifene citrate and chorionic gonadotropin has resulted in simultaneous bilateral tubal pregnancy, an extremely rare form of twin pregnancy.

Ectopic Pregnancy: An increased risk of ectopic pregnancy (including tubal and ovarian sites) has been observed in women who conceive after clomifene therapy.

INTERACTIONS WITH OTHER MEDICAMENTS

None known.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: *Pregnancy Category X*

Clomifene citrate should not be administered during pregnancy. Although no causative evidence of a deleterious effect of clomifene on the human fetus has been established, birth anomalies (e.g., Down's syndrome, exstrophy, club foot, tibial torsion, blocked tear duct, hemangioma, neural tube defects) have been reported. These observations in clinical studies have occurred at an incidence within the range reported for the general population.

In order to avoid the unintentional administration of clomifene in early pregnancy, the basal body temperature should be monitored throughout all treatment cycles and therapy withheld if there is a suspected pregnancy. A sensitive pregnancy test should be performed in the absence of menses; the possibility of an ovarian cyst and/or pregnancy should be excluded. Only those with negative results may be given the course of clomifene citrate.

Lactation: It is not known whether clomifene citrate is excreted in human milk. In some patients, clomifene citrate may supress lactation.

Infants and Children: Clomifene citrate is not intended for use in children.

Elderly: Clomifene is not intended for use in the elderly.

UNDESIRABLE EFFECTS

The incidence and severity of adverse events due to clomifene citrate therapy are usually related to the dose and duration of use.

Birth Defects: Congenital heart lesions, Down's syndrome, neural tube defects, club foot, congenital gut lesions, hypospadias, microcephaly, harelip and cleft palate, congenital hip, hemangioma, undescended testes, polydactyly, 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 multiple somatic defect

Body as a Whole: Fever, tinnitus, weakness, fatigue, increased appetite

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

CNS Effects: Increased nervous tension, insomnia, depression, vertigo, convulsions, dizziness or lightheadedness/vertigo, headache, migraine, paresthesia, stroke, syncope, and seizures; anxiety, irritability, mood changes, and psychosis have also been reported

Dermatologic: Rash, urticaria or allergic dermatitis, acne, allergic reaction, erythema, erythema multiforme, erythema nodosum, hypertrichosis, reversible hair loss, and alopecia

Gastrointestinal Effects: Abdominal-pelvic discomfort, (distention, bloating, pain, or soreness), nausea and/or vomiting, acute abdomen, constipation, and diarrhea

Genitourinary Effects: Abnormal ovarian enlargement, rare instances of massive ovarian enlargement, ovarian hyperstimulation syndrome, cyclic ovarian pain (mittelschmerz), and cyst formation (usually luteal); new cases of endometriosis and exacerbation of pre-existing endometriosis have also been reported

Multiple pregnancies (but rarely more than twins), including simultaneous intrauterine and extrauterine pregnancies, ovarian hemorrhage, tubal pregnancy, ectopic or heterotopic pregnancies, and uterine hemorrhage have also been reported.

Hepatic Effects: Increased levels of transaminases, jaundice, hepatitis, and infectious hepatitis

Musculoskeletal Effects: Arthralgia, back pain, myalgia

Special Senses: Dose-related visual symptoms described as "blurring" or spots or flashes (scintillating scotomata) usually appear due to intensification and prolongation of after-images, ophthalmologically definable scotomata, photophobia, diplopia, phosphenes, and reduced visual acuity. Cataracts and optic neuritis have been reported rarely. Light-sensitivity, light floaters waves, etc., and other visual complaints (not otherwise specified) have also been reported.

Tumors/Neoplasms: Ovarian cancer; liver cancer (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 abscess), trophoblastic (hydatidiform mole, choriocarcinoma), miscellaneous (melanoma, myeloma, perianal cysts, renal cell carcinoma, Hodgkinís lymphoma, tongue carcinoma, bladder carcinoma), and neoplasms of offspring (neuroectodermal tumor, thyroid tumor, hepatoblastoma, lymphocytic leukemia)

Isolated reports of endocrine-related or dependent tumors/neoplasms or their aggravation

Vasomotor Symptoms: Hot flushes resembling menopausal symptoms, breast discomfort, breast soreness, breast tenderness, heavier menses/menorrhagia, intermenstrual spotting, vaginal dryness, abnormal uterine bleeding

Other Effects: Leukocytosis increased, urinary frequency or volume, weight gain, weight loss, ascites, moderate and reversible hair loss, (prolonged continuous therapy) and thyroid disorder

Laboratory Studies: Administration of clomifene resulted in retention of sulfobromophthalein (BSP) in patients in whom BSP is measured. Retention was usually minimal unless associated with prolonged continuous administration or with apparently unrelated liver disease.

Clomifene has not been shown to cause significant abnormality in hematologic or renal tests, in protein bound iodine or in serum cholesterol levels.

OVERDOSAGE & MANAGEMENT

There is no experience with overdosage. There is no known antidote but gastric lavage and other appropriate supportive measures should be performed.

ADVERSE DRUG REACTION REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

STORAGE CONDITIONS

Store at temperatures below 30ºC.
Protect from heat, light, and excess humidity.
Keep the product out of reach and sight of children.
Store in original packaging.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispending without prescription.

AVAILABILITY

PVC blister pack of 10's; Box of 10 tablets.

Manufactured by:
RENATA LIMITED
Section VII Milk Vita Road
Mirpur, Dhaka, Bangladesh
Imported and Distributed by:
UNILAB, Inc.
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

Reg. IPOPHIL

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