Fermid Tablet

Clomifene citrate BP 50 mg

COMPOSITION

Each tablet contains 50 mg Clomifene citrate BP.

DESCRIPTION

Clomifene citrate is an orally administered, nonsteroidal, ovulatory stimulant.

CLINICAL PHARMACOLOGY

Action

Clomifene citrate 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 citrate is capable of interacting 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 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 Clomifene 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 estradiol. Following ovulation, plasma progesterone and estradiol rise and fall as they would in a normal ovulatory cycle. Available data suggest that both the estrogenic and antiestrogenic properties of Clomifene citrate may participate in the initiation of ovulation. The two Clomifene isomers have been found to have mixed estrogenic and antiestrogenic effects, which may vary from one species to another. Some data suggest that zuClomifene has greater estrogenic activity than Clomifene. Clomifene 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 "carry over effect of Clomifene citrate, spontaneous ovulatory menses have been noted in some patients after Clomifene citrate therapy.

PHARMACOKINETICS

Based on early studies with 14C-labeled Clomifene citrate, the drug was shown to be readily absorbed orally in humans and excreted principally in the feces. Cumulative urinary and fecal excretion of the 14C averaged about 50% of the oral dose and 37% of an intravenous dose after 5 days. Mean urinary excretion was approximately 8% with fecal excretion of about 42%. Some 14C label was still present in the feces 6 weeks after administration.

INDICATIONS AND USAGE

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 Clomifene citrate therapy. Those patients most likely to achieve success with Clomifene therapy include patients with polycystic ovary 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 Clomifene citrate therapy 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). Clomifene citrate tablets BP 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. Clomifene citrate should not be used in patients with ovarian enlargement except in those with polycystic ovary syndrome. Pelvic examination is necessary prior to the first and each subsequent course of 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. In addition, patients selected for 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: 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 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 Clomifene citrate in patients with uterine fibroids due to the potential for further enlargement of the fibroids. There are no adequate and well-controlled studies that demonstrate the effectiveness of Clomifene citrate in the treatment of male infertility. In addition, testicular tumors and gynecomastia have been reported in males using Clomifene. The cause and effect relationship between reports of testicular tumors and the administration of Clomifene citrate is not known. Although the medical literature suggests various methods, there is no universally accepted standard regimen for combined therapy (i.e., Clomifene citrate in conjunction with other ovulation-inducing drugs). Similarly, there is no standard Clomifene citrate regimen for ovulation induction in in vitro fertilization programs to produce ova for fertilization and reintroduction. Therefore, Clomifene is not recommended for these uses.

CONTRAINDICATIONS

Hypersensitivity

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

Pregnancy

Clomifene tablet should not be administered during pregnancy. Clomifene citrate may cause fetal harm in animals. Although no causative evidence of a deleterious effect of Clomifene citrate therapy on the human fetus 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.

Fetal/Neonatal Anomalies and Mortality: The following fetal abnormalities have been reported subsequent to pregnancies following ovulation induction therapy with Clomifene citrate during clinical triais. Each of the following fetal abnormalities were reported at a rate of <1% (experiences are listed in order of decreasing frequency): Congenital heart lesions, Down syndrome, club foot, congenital gut lesions, hypospadias, microcephaly, harelip and cleft palate, congenital hip, hemangioma, undescended testicles, polydactyly, conjoined twins and teratomatous malformation, patent ductus arteriosus, amaurosis, arteriovenous fistula, inguinal hemia, umbilical hernia, syndactyly. pectus excavatum, myopathy, dermoid cyst of scalp, omphalocele, spina bifida occulta, ichthyosis, and persistent lingual frenulum. Neonatal death and fetal 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 Clomifene citrate ingestion during clinical studies was within the range of that reported for the general population.

Liver Disease: Clomifene citrate therapy is contraindicated in patients with liver disease or a history of liver dysfunction.

Abnormal Uterine Bleeding: Clomifene citrate is contraindicated in patients with abnormal uterine bleeding of undetermined origin.

Ovarian Cysts: Clomifene citrate is contraindicated in patients with ovarian cysts or enlargement not due to polycystic ovarian syndrome.

Other: Clomifene citrate is contraindicated in patients with uncontrolled thyroid or adrenal dysfunction or in the presence of an organic intracranial lesion such as pituitary tumor.

WARNINGS

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 citrate. These visual symptoms increase in incidence with increasing total dose or therapy duration and generally within a few days or weeks after Clomifene citrate therapy is discontinued. However, prolonged visual disturbances have been reported after ted after Clomifene citrate therapy has been discontinued and these disturbances may be irreversible. 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.

Ovarian Hyperstimulation Syndrome

The ovarian hyperstimulation syndrome (OHSS) has been reported to occur in patients receiving Clomifene citrate therapy for ovulation induction. In some cases, OHSS occurred following cyclic use of Clomifene citrate therapy or when Clomifene 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 ovarian hyperstimulation syndrome (OHSS).

To minimize the hazard associated with occasional abnormal ovarian enlargement associated with Clomifene citrate 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 dase 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. If enlargement of the ovary occurs, additional Clomifene citrate 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 citrate therapy usually regress spontaneously within a few days or weeks after discontinuing treatment. The potential benefit of subsequent Clomifene 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.

PRECAUTIONS

General

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

DRUG INTERACTIONS

Drug interactions with Clomifene citrate have not been documented.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term toxicity studies in animals have not been performed to evaluate the carcinogenic or mutagenic potential of Clomifene citrate. Oral administration of Clomifene citrate to male rats at doses of 0.3 or 1 mg/kg/day caused decreased fertility, while higher doses caused temporary infertility.

Oral doses of 0.1 mg/kg/day in fernale. rats temporarily interrupted the normal cyclic vaginal smear pattern and prevented conception. Doses of 0.3 mg/kg/day slightly reduced the number of ovulated ova and corpora lutea, while 3 mg/kg/day inhibited ovulation.

Nursing Mothers

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

Ovarian Cancer

Prolonged use of Clomifene citrate tablets BP may increase the risk of a borderline or invasive ovarian tumor.

ADVERSE REACTIONS

Clinical Trial Adverse Events Clomifene 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 Clomifene citrate during clinical studies are:

Incidence of Adverse Events in Clinical Studies (Events Greater than 1%) (n = 8029")

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, Blurred vision, lights, floaters, waves, unspecified visual complaints, photophobia, diplopia, scotomata, phosphenes, Headache. 1.3. Abnormal Uterine Bleeding 1.3 (Intermenstrual spotting. menorrhagia). The following adverse events have been reported in fewer than 1% of patients in clinical trials: Acute abdomen, appetite increase, constipation, dermatitis or rash, appetite depression, diarrhea, dizziness, fatigue, hair loss/dry hair, increased urinary frequency/volume, insomnia, light-headedness, nervous tension, vaginal dryness, vertigo, weight gain/loss.

DRUG ABUSE AND DEPENDENCE

Tolerance, abuse, or dependence with Clomifene citrate has not abuse, been reported.

OVERDOSAGE

Signs and Symptoms

Toxic effects accompanying acute overdosage of Clomifene citrate have not been reported. 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, Treatment of overdosage in the event of overdose, appropriate supportive measures should be employed in addition to gastrointestinal decontamination.

DOSAGE AND ADMINISTRATION

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 e 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 Clomifene citrate. A low dosage or duration of treatment course is particularly recommended if unusual sensitivity to pituitary gonadotropin is expected, such as in patients with polycystic ovary 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 Clomifene citrate 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.

HOW SUPPLIED

Fermid 50mg tablet press through blister strips pack containing 1 x 10 tablets.

STORAGE CONDITION

Store tablets at controlled room temperature (below 30°C) away from children. Protect from heat, light, moisture and store in pack

Manufactured by:
Gaco Pharmaceuticals
(G. A. Company Ltd.)
Dhaka, Bangladesh