AURORA REMEDIES

CLOMIPHENE CITRATE

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Clomiphene Citrate is an oral medication, indicated for the treatment of ovulatory dysfunction in women desiring pregnancy. Impediments to achieving pregnancy must be excluded or adequately treated before beginning CLOMIPHENE CITRATE therapy. Those patients most likely to achieve success with clomiphene 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.

Chemical: Clomiphene Citrate
CAS Name: 2-[4-(2-chloro-1,2-diphenylethenyl)phenoxy]-~{N},~{N}-diethylethanamine;2-hydroxypropane-1,2,3-tricarboxylic acid
Molecular Formula: C32H36ClNO8
Molecular Weight: 405.96.

Prescription Medicine

CLINICAL PHARMACOLOGY

Clomiphene is a drug of considerable pharmacologic potency. With careful selection and proper management of the patient, clomiphene has been demonstrated to be a useful therapy for the anovulatory patient desiring pregnancy.
Clomiphene citrate 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. 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 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 clomiphene may participate in the initiation of ovulation. The two clomiphene isomers have been found to have mixed estrogenic and antiestrogenic effects, which may vary from one species to another. Some data suggest that zuclomiphene has greater estrogenic activity than enclomiphene.
Clomiphene citrate 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 clomiphene, spontaneous ovulatory menses have been noted in some patients after clomiphene therapy.

INDICATIONS AND USAGE

Clomiphene 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. Clomiphene 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 clomiphene 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.

CONTRAINDICATIONS

Hypersensitivity
Clomiphene is contraindicated in patients with a known hypersensitivity or allergy to clomiphene citrate or to any of its ingredients.
Pregnancy
Clomiphene use in pregnant women is contraindicated, as clomiphene 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. However, animal reproductive toxicology studies showed increased embryo-fetal loss and structural malformations in offspring. 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.
Liver Disease
Clomiphene therapy is contraindicated in patients with liver disease or a history of liver dysfunction.
Abnormal Uterine Bleeding
Clomiphene is contraindicated in patients with abnormal uterine bleeding of undetermined origin.
Ovarian Cysts
Clomiphene is contraindicated in patients with ovarian cysts or enlargement not due to polycystic ovarian syndrome.
Other
Clomiphene is contraindicated in patients with uncontrolled thyroid or adrenal dysfunction or in the presence of an organic intracranial lesion such as pituitary tumor.

PRECAUTIONS

General
Careful attention should be given to the selection of candidates for clomiphene therapy. Pelvic examination is necessary prior to clomiphene treatment and before each subsequent course.
Carcinogenesis, Mutagenesis, Impairment Of Fertility
Long-term toxicity studies in animals have not been performed to evaluate the carcinogenic or mutagenic potential of clomiphene citrate.
Oral administration of clomiphene 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 female 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.
Pregnancy
Fetal Risk Summary
Clomiphene use in pregnant women is contraindicated, as clomiphene treatment does not offer benefit in this population. Available human data do not suggest an increased risk for congenital anomalies above the background population risk. However, animal reproductive toxicology studies showed increased embryo-fetal loss and structural malformations in offspring. 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.

ADVERSE REACTIONS

The following adverse reactions have been identified during post approval use of Clomiphene. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
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

Genitalia
- Abnormalities: hypospadias, cloacal exstrophy
- Lung tissue malformations
- Malformations of the eye and lens (cataract)
- 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.

DOSAGE AND ADMINISTRATION

General Considerations
The workup and treatment of candidates for clomiphene citrate therapy should be supervised by physicians experienced in management of gynecologic or endocrine disorders. Patients should be chosen for therapy with clomiphemne 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 therapy. 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. The dose should be increased only in those patients who do not ovulate in response to cyclic 50 mg clomiphene. 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.
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 clomiphene 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.

STORAGE

Store at room temperature between 59-86 degrees Fahrenheit (15-30 degrees Celsius), away from light and moisture. Do not store in the bathroom. Keep all medicines away from children and pets.Do not flush medications down the toilet or pour them into a drain unless instructed to do so. Properly discard this product when it is expired or no longer needed. Consult your pharmacist or local waste disposal company for more details about how to safely discard your product.

PRESENTATION:

50mg tablets in blister packs of 10 tablets – 5 blisters per box (50 tablets).

AURORA REMEDIES, SINGAPORE
www.aurora-remedies.com