Clomiphene 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 PHARMACOLOGY

Action

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.

Pharmacokinetics

Based on early studies with 14C-labeled clomiphene 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.

Subsequent single-dose studies in normal volunteers showed that zuclomiphene (cis) has a longer half-life than enclomiphene (trans).

Detectable levels of zuclomiphene persisted for longer than a month in these subjects. This may be suggestive of stereo-specific enterohepatic recycling or sequestering of the zuclomiphene.

Thus, it is possible that some active drug may remain in the body during early pregnancy in women who conceive in the menstrual cycle during clomiphene therapy.

CLINICAL STUDIES

During clinical investigations, 7578 patients received clomiphene citrate, some of whom had impediments to ovulation other than ovulatory dysfunction (see INDICATIONS AND USAGE). In those clinical trials, successful therapy characterized by pregnancy occurred in approximately 30% of these patients. There were a total of 2635 pregnancies reported during the clinical trial period. Of those pregnancies, information on outcome was only available for 2369 of the cases. Table 1 summarizes the outcome of these cases. Of the reported pregnancies, the incidence of multiple pregnancies was 7.8%: 5.0% twin, 0.5% triplet, 0.3% quadruplet, and 0.1% quintuplet. Of the 165 twin pregnancies for which sufficient information was available, the ratio of monzygotic to dizygotic twins was about 1:5.

Several studies 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, hemangia, undescended testicles, polydactyly, conjoined twins and tetra- maternal malfomation, patent ductus arteriosus, amursus, artherosclerotic fistula, inguinal hernia, umbilical hernia, syndactyly, pectus excavatum, myopathy, dermoid cyst of scalp, omphalocele, spina bifida, cleft palate, and persistent pyloric stenosis. Neonatal death and fetal death/birth in infants with birth defects have also been reported at a rate of <1%. The overall incidence of reported congenital anomalies from pregnancies associated with maternal clomiphene citrate ingestion during clinical studies was within the range of that reported for the general population.

In addition, reports of congenital anomalies have been received during postmarketing surveillance of clomiphene citrate (see ADVERSE REACTIONS).

INDICATIONS AND USAGE

Clomiphene is indicated for the treatment of ovulatory dysfunction in women desiring pregnancy.

Impediments to achieving pregnancy must be excluded or adequately treated before beginning clomiphene therapy. Those patients most likely to achieve success with clomiphene therapy include women with ovulatory dysfunction who meet the conditions described below:

1. Patients who are not pregnant.
2. Patients without ovular 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 with normal 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 clomiphene 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 progestosterone). Reduced estrogen levels, while less favorable, do not preclude successful therapy.
2. Primary Pituitary or Ovarian Failure. Clomiphene 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 clomiphene therapy in this population.
4. Other Impediments to Pregnancy. Impediments to pregnancy can include thyroid disorders, pituitary disorders, hyperprolactinemia, and male factor infertility.

5. Uterine Fibroids. Caution should be exercised when using clomiphene in patients with uterine fibroids due to the potential for further enlargement of the fibroids.

There are no adequate or well-controlled studies that demonstrate the effectiveness of clomiphene in the treatment of male infertility. In addition, testicular tumors and gynecomastia have been reported in males using clomiphene. The cause and effect relationship between reports of testicular tumors and the administration of clomiphene is not known.

Although the medical literature suggests various methods, there is no universally accepted standard regimen for combined therapy (ie, clomiphene in conjunction with other ovulation-inducing drugs). Similarly, there is no standard clomiphene regimen for ovulation induction in in vitro fertilization programs to produce ova for fertilization and reintroduction. Therefore, clomiphene is not recommended for these uses.

CONTRAINDICATIONS

Hypersensitivity

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

Pregnancy

Pregnancy Category X

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 embryofetal 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. (See Precautions: Pregnancy.)

Liver Disease

Clomiphene therapy is contraindicated in patients with liver disease or a history of liver dysfunction (see also INDICATIONS AND USAGE and ADVERSE REACTIONS).

Abnormal Uterine Bleeding

Clomiphene is contraindicated in patients with abnormal uterine bleeding of undetermined origin (see INDICATIONS AND USAGE).

Ovarian Cysts

Clomiphene is contraindicated in patients with ovarian cyst or enlargement not due to polycystic ovarian syndrome (see INDICATIONS AND USAGE and WARNINGS).

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 (see INDICATIONS AND USAGE).

WARNINGS

Visual Symptoms

Patients should be advised that blurred or other visual symptoms such as spots or flashes (scintillating scotomata) may occasionally occur during therapy with clomiphene. These visual symptoms increase in incidence with increasing total dose or therapy duration. These visual disturbances are usually reversible, however, cases of prolonged visual disturbance have been reported with some occurring after clomiphene 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.

These visual symptoms appear to be due to intensification and prolongation of afterimages. Symptoms often first appear or are accentuated with exposure to a brightly lit environment. While measured visual acuity usually has not been affected, a study patient taking 200 mg CLOMID daily developed visual blurring on the 7th day of treatment, which progressed to severe diminution of visual acuity by the 10th day. No other abnormality was found, and the visual acuity returned to normal on the 3rd day after treatment was stopped.

Ophthalmologically definable scotomata and retinal cell function (electroretinographic) changes have also been reported. A patient treated during clinical studies developed phosphometastases and scotomata during prolonged CLOMID administration, which disappeared by the 32nd day after stopping therapy. Postmarketing surveillance of adverse events has also revealed other visual signs and symptoms during CLOMID therapy (see ADVERSE REACTIONS).

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) has been reported to occur in patients receiving clomiphene citrate therapy for ovulation induction. OHSS may progress rapidly (within 24 hours to several days) and become a serious medical disorder. In some cases, OHSS occurred following cyclic use of clomiphene citrate therapy or when clomiphene 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 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, dyspepsia, oliguria, and pleural effusion. In addition, the following symptoms have been reported in association with this syndrome: peripheral edema, abdominal pain, ascites, anasarca, hypovolemia, hypotension, renal failure, pulmonary edema, intraperitoneal and ovarian hemorrhage, deep venous thrombosis, and torsion of the ovary. 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, hemorrhagic shock, and hypocalcemia may occur. Death due to hypovolemic shock, hemococoncentration, or thrombocytopenia 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 CLOMID 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 CLOMID. 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 CLOMID therapy should not be given until the ovaries have returned to pretreatment size, and the dosage or duration of the next cycle should be reduced. Ovarian enlargement and cyst formation associated with CLOMID therapy usually regresses spontaneously within a few days or weeks after discontinuing treatment. The potential benefit of subsequent CLOMID 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 CLOMID therapy. Pelvic examination is necessary prior to CLOMID treatment and before each subsequent course (see CONTRAINDICATIONS and WARNINGS).

Information for Patients

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

- Visual Symptoms

Advise that blurring or other visual symptoms occasionally may occur during or shortly after CLOMID therapy. It should be made clear to the patient that, in some instances, visual disturbances may be prolonged, and possibly irreversible, especially with increased dosage or duration of therapy. Warn 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 patient should be informed to the physician whenever any unusual visual symptoms occur. If the patient has any visual symptoms, treatment should be discontinued and complete ophthalmologic evaluation performed.

Abdominal/Pelvic Pain or Distortion

Ovarian enlargement may occur during or shortly after therapy with CLOMID. To minimize the risks associated with ovarian enlargement, the patient should be instructed to inform the physician of any abdominal or pelvic pain, weight gain, discomfort, or distention after taking CLOMID (see WARNINGS).

Metabolism Disorders

Cases of hyperglycemia have been reported. Preexisting or family history of hyperglycemia and use of higher than recommended dose and/or longer duration of treatment with CLOMID are associated with a risk of hypertriglyceridemia. Periodic monitoring of plasma triglycerides is recommended in patients with preexisting or family history of hyperglycemia (see ADVERSE REACTIONS). Please refer to the DOSAGE AND ADMINISTRATION section for recommended dosage and treatment duration.

Multiple Pregnancy

Inform the patient that there is an increased chance of multiple pregnancy, including bilateral tubal pregnancy and coexisting tubal and intrauterine pregnancy, when conception occurs in relation to CLOMID therapy. The potential complications and hazards of multiple pregnancy should be explained.

Spontaneous Abortion and Congenital Anomalies

Inform the patient that the available data suggest no increase in the rates of spontaneous abortion (miscarriage) or congenital anomalies with maternal CLOMID use compared to rates in the general population.

During clinical investigation, the experience from patients with known pregnancy outcome (Table 1) shows a spontaneous abortion rate of 20.4% and stillbirth rate of 1.0%. (See CLINICAL STUDIES). Among the birth anomalies spontaneously reported as individual cases since commercial availability of Clomid, the proportion of neural tube defects has been high among pregnancies associated with ovulation induced by Clomid, but this has not been supported by data from population-based studies.

Drug Interactions

Drug interactions with CLOMID 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 clomiphene citrate.

Oral administration of CLOMID 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

Pregnancy Category X

(See CONTRAINDICATIONS.) CLOMID use in pregnant women is contraindicated, as CLOMID treatment does not offer benefit in this population.

Available human data do not suggest an increased risk for congenital anomalies above the background occurrence risk. However, animal reproductive toxicity studies showed increased embryofetal-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.

Clinical Considerations

To avoid inadvertent CLOMID administration during early pregnancy, appropriate tests should be utilized during each treatment cycle to determine whether ovulation and/or pregnancy occurs. Patients should be evaluated carefully to exclude ovarian enlargement or ovarian cyst formation between each treatment cycle. The next course of CLOMID therapy should be delayed until these conditions have been excluded.

Human data

The available human data from epidemiologic studies do not show any apparent cause and effect relationship between clomiphene citrate periconceptual exposure and an increased risk of overall birth defects, or any specific anomaly. However, due to the small number of cases of congenital anomalies occurring in clomiphene citrate treated women, these epidemiologic studies were only able to rule out large differences in risk. The studies did not consider factors associated with female subfertility and various confounders. In addition, available data do not support an increased rate of spontaneous abortion among subfertile women treated with clomiphene citrate for ovulation induction.

Animal data

Oral administration of clomiphene citrate to pregnant rats during organogenesis at doses of 1 to 2 mg/kg/day resulted in hydramnion and weak, edematous fetuses with wavy ribs and other temporary bone changes. Doses of 8 mg/kg/day or more also caused increased resorptions and dead fetuses, dystocia, and delayed parturition, and 40 mg/kg/day resulted in increased maternal mortality. Single doses of 50 mg/kg caused fetal cataracts, while 200 mg/kg caused cleft palate. Following injection of clomiphene citrate 2 mg/kg to mice and rats during pregnancy, the offspring exhibited metabolic changes of the reproductive tract. Newborn mice and rats injected in the first few days of life also developed metabolic changes in uterine and vaginal mucosa, as well as premature vaginal opening and anovulatory ovaries. These findings are similar to the abnormal reproductive behavior and sterility described with other estrogens and antiestrogens.

In rabbits, some temporary bone alterations were seen in fetuses from dams given oral doses of 20 or 40 mg/kg/day during pregnancy, but not following 8 mg/kg/day. No permanent malformations were observed in those studies. Also, mouses monkeys given oral doses of 1.5 to 4.5 mg/kg/day for various periods during pregnancy did not have any abnormal offspring.

Nursing Mothers

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

Ovarian Cancer

Prolonged use of clomiphene citrate tablets USP may increase the risk of a borderline or invasive ovarian tumor (see ADVERSE REACTIONS).

ADVERSE REACTIONS

Clinical Trial Adverse Events

CLOMID, 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 clomiphene citrate during clinical studies are shown in Table 2.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian Enlargement</td>
<td>13.6</td>
</tr>
<tr>
<td>Vasomotor Flashes</td>
<td>10.4</td>
</tr>
<tr>
<td>Abdominal-Pelvic Discomfort/Distention/Blotting</td>
<td>5.5</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>2.2</td>
</tr>
<tr>
<td>Breast Discomfort</td>
<td>2.1</td>
</tr>
<tr>
<td>Visual Symptoms</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Table 2. Incidence of Adverse Events in Clinical Studies (Events Greater than 1%) (n = 8029)
The acute oral LD₅₀ for gastrointestinal decontamination.

Treatment

Dialysis

humans is not known.

Genitourinary: Endometriosis, ovarian cyst (ovarian enlargement or cysts could, as such, be associated with pelvic or abdominal pain. (See CONTRAINDICATIONS: Ovarian Cyst.)

therapy include nausea, vomiting, vasomotor flushes, visual blurring, spots or flashes, scotomata, and other symptoms of overdosage as a result of the use of more than the recommended dose during CLOMID therapy. 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 CLOMID 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 menopause 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 PRECAUTIONS).

HOW SUPPLIED

NDC 0068-0226-30: 50 mg tablets in cartons of 30

Tablet is round, white, scored, and debossed CLOMID 50.

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, alopecia, 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
Genital 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 abscess); ovary (luteoma of pregnancy, dermoid cyst of the ovary, ovarian carcinoma); trophoblastic (hydatidiform mole, chorionic carcinoma); miscellaneous (melanoma, myeloma, pheochromocytoma, 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, phoria, posterior vitreous detachment, retinal hemorrhage, retinal thrombosis, retinal vascular spasm, temporary or prolonged loss of vision, possibly irreversible

Other: Leukocytosis, thyroid disorder

DRUG ABUSE AND DEPENDENCE

Tolerance, abuse, or dependence with CLOMID has not been reported.

OVERDOSEAGE

Signs and Symptoms

Toxic effects accompanying acute overdosage of CLOMID have not been reported. Signs and symptoms of overdosage as a result of the use of more than the recommended dose during CLOMID therapy include nausea, vomiting, vasomotor flushes, visual blurring, spots or flashes, scotomata, ovarian enlargement with pelvic or abdominal pain. (See CONTRAINDICATIONS: Ovarian Cyst.)

Oral LD₅₀

The acute oral LD₅₀ of CLOMID is 1700 mg/kg in mice and 5750 mg/kg in rats. The toxic dose in humans is not known.

Dialysis

It is not known if CLOMID is dialyzable.

Treatment

In the event of overdose, appropriate supportive measures should be employed in addition to gastrointestinal decontamination.

Table 2. Incidence of Adverse Events in Clinical Studies (Events Greater than 1%) (n = 8629) (continued)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blurred vision, lights, floaters, waves, unspecified visual complaints, photophobia, diplopia, scotomata, phosphenes</td>
<td>1.3</td>
</tr>
<tr>
<td>Headache</td>
<td>1.3</td>
</tr>
<tr>
<td>Abnormal Uterine Bleeding</td>
<td></td>
</tr>
<tr>
<td>Intermenstrual spotting, menorrhagia</td>
<td></td>
</tr>
</tbody>
</table>

Includes 498 patients whose reports may have been duplicated in the event totals and could not be distinguished as such. Also, excludes 47 patients who did not report symptom data.

The following adverse events have been reported in fewer than 1% of patients in clinical trials: Acute abdomen, appetite increase, constipation, dermatitis or rash, depression, diarrea, dizziness, fatigue, hair loss/dry hair, increased urinary frequency, volume, insomnia, light-headedness, nervous tension, vaginal dryness, vertigo, weight gain/loss.

Patients on prolonged CLOMID therapy may show elevated serum levels of desmosterol. This is most likely to be due to a difference in urine levels of cholesteryl. However, the serum sterols in patients receiving the recommended dose of CLOMID are not significantly altered. Ovarian cancer has been infrequently reported in patients who have received fertility drugs. Infertility is a primary risk factor for ovarian cancer; however, epidemiological data suggest that prolonged use of clomiphene may increase the risk of a borderline or invasive ovarian tumor.

Postmarketing Adverse Events

The following adverse reactions have been identified during post approval use of Clomid. 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, alopecia, 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
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Psychiatric: Anxiety, irritability, mood changes, psychosis

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DRUG ABUSE AND DEPENDENCE

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OVERDOSEAGE

Signs and Symptoms

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