

## PRODUCT MONOGRAPH

Pr **CLOMID**<sup>®</sup>

(clomiphene citrate USP)

50 mg Tablets

Ovulatory Agent

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Date of Revision:  
August 9, 2013

Submission Control No.: 165671

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(clomiphene citrate USP)

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Ovulatory agent.

### ACTION AND CLINICAL PHARMACOLOGY

CLOMID (clomiphene citrate) is an orally-administered, non-steroidal agent which may induce ovulation in anovulatory women in appropriately selected cases.<sup>1-16</sup> The ovulatory response to cyclic CLOMID therapy appears to be mediated through increased output of pituitary gonadotropins, which in turn stimulate the maturation and endocrine activity of the ovarian follicle and the subsequent development and function of the corpus luteum. The role of the pituitary is indicated by increased plasma levels of gonadotropins and by the response of the ovary, as manifested by increased plasma level of estradiol. Antagonism of competitive inhibition of endogenous estrogen may play a role in the action of CLOMID on the hypothalamus.

**CLOMID is a drug of considerable pharmacologic potency. Its administration should be preceded by careful evaluation and selection of the patient, and must be accompanied by close attention to the timing of the dose. With conservative selection and management of the patient, CLOMID has been demonstrated to be a useful therapy for the anovulatory patient.**

Based on studies with 14C-labeled clomiphene, the drug is readily absorbed orally in humans, and is excreted principally in the feces. Cumulative excretion of the 14C-label averaged 51% of the oral dose after 5 days in 6 subjects, with mean urinary excretion of 8% and mean fecal excretion of 42%; less than 1% per day was excreted in fecal and urine samples collected from 31 to 53 days after 14C-labelled clomiphene administration. Since C-14 appeared in the feces 6 weeks after administration, available data suggested that the remaining drug/metabolites were being slowly excreted from a sequestered enterohepatic recirculation pool.<sup>17</sup> After intravenous administration, 37% was excreted in 5 days.

### INDICATIONS AND CLINICAL USE

**CLOMID (clomiphene citrate) is indicated for induction of ovulation in patients with persistent ovulatory dysfunction who desire pregnancy. The work-up and treatment of candidates for CLOMID therapy should be supervised by physicians experienced in management of gynecologic or endocrine disorders. Patients should be chosen for therapy with CLOMID 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.**

CLOMID is indicated only in patients who meet the criteria or have been assessed as described below:

- (1) Exclusion of pregnancy:  
If any doubt exists as to the presence of early pregnancy, CLOMID therapy should be withheld until a diagnosis of pregnancy has been excluded.
- (2) Assessment of abnormal or excessive bleeding:  
Patients with abnormal or excessive bleeding should have particularly careful evaluation prior to CLOMID therapy. It is most important to ensure that neoplastic lesions are not overlooked (see also CONTRAINDICATIONS). Uterine fibroids may increase in size as a result of CLOMID administration.
- (3) Exclusion of presence or history of liver dysfunction:  
Clinical evaluation of liver function should always precede CLOMID therapy. (see also CONTRAINDICATIONS).
- (4) Exclusion of presence of ovarian cyst:  
CLOMID 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 CLOMID treatment in order to rule out the presence of an ovarian cyst (see also CONTRAINDICATIONS).
- (5) Confirmed ovulatory dysfunction:  
The diagnosis of ovulatory dysfunction should be established by using appropriate techniques such as basal body temperature curves, cervical mucus modifications, endometrial biopsy, and progesterone plasma level.
- (6) Exclusion of primary pituitary or ovarian failure:  
Appropriate diagnostic measures should be undertaken to exclude primary pituitary failure or primary ovarian failure. Intact pituitary and ovaries are required for successful therapy. Ovulatory dysfunction in the presence of abnormally high levels of pituitary gonadotropins is indicative of ovarian failure, and patients in this category cannot be expected to respond to CLOMID.
- (7) Assessment of estrogen levels:  
Adequacy of endogenous estrogen, as estimated by vaginal smears, cervical mucus, endometrial biopsy, or plasma level of estradiol furnishes a measure of ovarian function and indirectly of pituitary function. Bleeding after progesterone administration (progesterone alone, not combined with estrogen) furnishes evidence of endogenous estrogen activity. A good level of endogenous estrogen provides a favourable prognosis for treatment with CLOMID.

A reduced estrogen level, although less favourable, does not always preclude successful therapy.

- (8) Exclusion of mechanical impediments to conception:  
Mechanical impediments to conception, such as tubal obstruction or abnormality of the uterine cavity, should be excluded or adequately treated, before undertaking CLOMID therapy.
- (9) Exclusion of medical impediments to pregnancy:  
When disorders such as diabetes, adrenal disease, thyroid disease or hyperprolactinemia possibly associated or not with pituitary adenoma or other organic intracranial lesion are identified during the investigation, specific treatment should be undertaken and subfertility therapy reconsidered only after the underlying disorder has been adequately treated. CLOMID cannot be expected to substitute for specific therapy of these conditions.
- (10) Exclusion of medical illnesses that could be aggravated by pregnancy.
- (11) Exclusion of male factor infertility:  
The male partner's potential fertility should be ascertained by semen analysis and other indicated examination. There are no adequate or well-controlled studies that demonstrate the effectiveness of CLOMID in the treatment of male infertility. In addition, testicular tumors and gynecomastia have been reported in males using CLOMID. The cause and effect relationship between reports of testicular tumors and the administration of CLOMID is not known.

## CONTRAINDICATIONS

### Pregnancy:

CLOMID (clomiphene citrate) should not be administered during pregnancy. Although no causative evidence of a deleterious effect of CLOMID therapy on the human fetus has been established, such evidence in regard to the rat and the rabbit has been presented (see PRECAUTIONS and TOXICOLOGY - Reproduction Studies). **To avoid inadvertent CLOMID administration during early pregnancy, careful pelvic examination must be done prior to each course of therapy, the basal body temperature must be recorded throughout all treatment cycles, and the patient should be carefully observed to determine whether ovulation occurs.** If the basal body temperature following CLOMID is biphasic and is not followed by menses, the patient should be examined carefully for the presence of an ovarian cyst and should have a pregnancy test. The next course of therapy should be delayed until the possibility of pregnancy has been excluded.

### Liver disease:

CLOMID therapy is contraindicated in patients with liver disease or a history of liver dysfunction.

Hormone-dependent tumors or Abnormal uterine bleeding:

CLOMID is contraindicated in patients with hormone-dependent tumors and in patients with abnormal uterine bleeding of undetermined origin. CLOMID is not indicated for the management of menstrual disorders.

Ovarian cyst:

CLOMID should not be given in the presence of an ovarian cyst, except polycystic ovary, since further enlargement of the cyst may occur. Patients should be evaluated for the presence of ovarian cyst prior to each course of treatment.

Hypersensitivity:

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

## **WARNINGS**

Ovarian Hyperstimulation Syndrome During CLOMID (clomiphene citrate) Therapy:

Ovarian Hyperstimulation Syndrome (OHSS) has been reported in patients receiving CLOMID therapy alone or in combination with gonadotropins.

OHSS is a medical event distinct from uncomplicated ovarian enlargement. Warning signs of OHSS are abdominal pain and distension, nausea, vomiting, diarrhea, and weight gain. Elevated estradiol plasma level, varying degrees of electrolyte imbalance, hypovolemia, hemoconcentration, and hypoproteinemia may occur. 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. The clinical signs of this syndrome in severe cases can include gross ovarian enlargement, gastrointestinal symptoms, ascites, dyspnea, oliguria, and pleural effusion.

Rare cases of severe forms of OHSS have been reported in patients receiving CLOMID therapy alone or in combination with gonadotropins where the following symptoms have occurred: 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. Death due to hypovolemic shock, hemoconcentration or thromboembolism has occurred. If conception results, rapid progression to the severe form of the syndrome may occur.

In order to minimize the hazard associated with the occasional abnormal ovarian enlargement associated with CLOMID (see ADVERSE REACTIONS), the lowest dose consistent with expectation of good 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. Some patients with polycystic ovary syndrome who are unusually sensitive to gonadotropin may have an exaggerated response to usual doses 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).

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

The patient who complains of abdominal or pelvic pain after receiving CLOMID should be examined because of the possible presence of an ovarian cyst or other cause. Due to fragility of enlarged ovaries in severe cases, abdominal and pelvic examination should be performed with care. Ultrasound examination of the pelvic cavity should be considered for appropriate follow-up of these patients.

If abnormal 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 course should be reduced. Ovarian enlargement and cyst formation associated with CLOMID therapy regress spontaneously within a few days or weeks after discontinuing treatment, unless pregnancy occurs. Once pregnancy has been ruled out, if ovarian cysts do not regress spontaneously, a thorough evaluation should be performed to exclude the presence of ovarian neoplasia. **Unless surgical indication for laparotomy exists, such cystic enlargement should always be managed conservatively.**

#### Visual symptoms:

Patients should be advised that blurring or other visual symptoms such as spots or flashes (scintillating scotomata) may occasionally occur during therapy or shortly after therapy with CLOMID. 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. These visual disturbances are usually reversible; however, cases of prolonged visual disturbance have been reported even after CLOMID discontinuation. The visual disturbances may be irreversible, especially with increased dosage or duration of therapy. The significance of these visual symptoms is not yet understood (see ADVERSE REACTIONS). If the patient has any visual symptoms, treatment should be discontinued and complete ophthalmologic evaluation carried out.

## **PRECAUTIONS**

#### Diagnosis Prior to CLOMID (clomiphene citrate) Therapy:

Careful attention should be given to diagnosis in candidates for CLOMID therapy. Complete pelvic examination including cervical cytology is mandatory prior to treatment, and pelvic examination should be repeated before each subsequent course.

Patients with prolonged period of anovulation have a greater risk of endometrial abnormalities associated with anovulatory disorders. If abnormal bleeding is present, full diagnostic measures

are mandatory (see also CONTRAINDICATIONS and WARNINGS). Appropriate use of the ultrasound evaluation and endometrial biopsy should be considered.

#### Uterine Fibroids:

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

#### Pregnancy:

(See also CONTRAINDICATIONS and ADVERSE REACTIONS – Birth Defects sections)

- **Teratogenic/Non-teratogenic Effects:**  
The overall incidence of reported birth anomalies from pregnancies associated with maternal CLOMID ingestion during clinical studies was within the range of that reported for the general population.
- **Pregnancy Wastage:**  
The experience from patients of all diagnoses during clinical investigation of CLOMID shows a pregnancy (single and multiple) wastage or fetal loss rate of 21.4% (abortion rate of 19.0%), ectopic pregnancies 1.18%, hydatidiform mole 0.17%, and pregnancies with one or more stillbirths 1.01%.
- **Multiple pregnancy:**  
The incidence of multiple pregnancy (including triplets, quadruplets and quintuplets) has been increased up to tenfold when conception takes place during a cycle in which CLOMID therapy is given. During the clinical investigation studies, the incidence of multiple pregnancy was 7.9% (186 of 2369 CLOMID associated pregnancies on which outcome was reported). Among these 2369 pregnancies, 165 (6.9%) were twin, 11 (0.5%) triplet, 7 (0.3%) quadruplet, and 3 (0.13%) quintuplet. Of the 165 twin pregnancies for which sufficient information was available, the ratio of monozygotic to dizygotic twins was 1:5. The patient and her male partner should be advised of the frequency and potential hazards of multiple pregnancy before starting treatment.
- **Ectopic Pregnancy:**  
There is an increased chance of ectopic pregnancy (including tubal and ovarian sites) in women who conceive following CLOMID therapy.

#### Lactation:

It is not known whether CLOMID is excreted in human milk. CLOMID may reduce lactation.

#### Carcinogenicity:

Prolonged use of CLOMID may increase the risk of developing a borderline or invasive ovarian tumor.

#### Mutagenicity:

Mutagenic potential of CLOMID has not been evaluated.

### Hypertriglyceridemia:

Cases of hypertriglyceridemia (with or without pancreatitis) have been reported (see ADVERSE REACTIONS - Metabolism Disorders section) in the postmarketing experience with CLOMID. Preexisting or family history of hyperlipidemia and use of higher than recommended dose and/or longer duration of treatment with CLOMID are associated with risk of hypertriglyceridemia. Periodic monitoring of plasma triglycerides may be indicated in these patients.<sup>23-29</sup>

## **ADVERSE REACTIONS**

### Clinical Trials

#### Overview:

At recommended dosage, side effects are not prominent and infrequently interfere with treatment. Side effects tend to be dose related, occurring more frequently at the higher doses and longer duration of treatment courses used in some earlier studies. The more common side effects include hot flashes, abdominal-pelvic discomfort (distention, bloating, pain, or soreness), ovarian enlargement, and visual blurring. The vasomotor symptoms resembling menopausal “hot flashes” are not usually severe and disappear promptly after treatment is discontinued. Abdominal symptoms may be most often related to ovulatory (mittelschmerz) or premenstrual phenomena, or to ovarian enlargement.

Other less frequently reported symptoms during CLOMID (clomiphene citrate) therapy have included nausea or vomiting, appetite increase, constipation, diarrhea, increased nervous tension, depression, fatigue, dizziness or lightheadedness, insomnia, headache, breast soreness, abnormal uterine bleeding, heavier menses, intermenstrual spotting, vaginal dryness, urticaria or allergic dermatitis, vertigo, weight gain, and increased urinary frequency or volume. Moderate, reversible hair loss has been reported in a few patients, primarily on prolonged continuous therapy.

#### Birth defects:

From 2339 completed pregnancies associated with CLOMID administration, 58 birth defects have been reported. They have been reported in 4 conceptions in the abortion/stillbirth category, 14 of 353 infants from multiple pregnancies, and 39 of 1676 infants from single pregnancies. Three live-born infants failed to survive.

Reported defects were congenital heart lesions (8 infants), Down's syndrome (5 infants), club foot (4 infants), congenital gut lesions (4 infants), hypospadias (3 infants), microcephaly (2 infants), harelip and cleft palate (2 infants), congenital hip (2 infants), hemangioma (2 infants), undescended testes (2 infants), polydactyly (both of twins), 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 7 infants with multiple somatic defects.



Eight of the entire group of 58 infants were born to 7 of 153 mothers who received a course of CLOMID during the first 6 weeks after conception.

An interval of 4, 4, and 10 months respectively elapsed between the last CLOMID therapy and conception in 3 mothers. In a 4th mother conception occurred during a subsequent ovulation induced by gonadotropin therapy.

#### Gastrointestinal System:

Sulfobromophthalein (BSP) retention of greater than 5% has been reported in 32 of 141 patients in whom it was measured, including 5 of 43 patients who received approximately the dose of CLOMID now recommended. Retention was usually minimal unless associated with prolonged continuous CLOMID administration or with apparently unrelated liver disease. In some patients, pre-existing BSP retention decreased even though CLOMID therapy was continued. Other liver function tests were usually normal. In a later study in which patients were given 6 consecutive monthly courses of CLOMID (100 mg daily for 3 days) or matching placebo, BSP tests were done on 94 patients. Values in excess of 5% retention were recorded in 11 patients, 6 of whom had received drug and 5 placebo. One patient developed jaundice on the nineteenth day of treatment (50 mg/day); liver biopsy revealed bile stasis without evidence of hepatitis.<sup>11</sup> A male prison subject who received 200 mg daily for 77 days developed the clinical picture of infectious hepatitis; his cellmate was discovered to have had infectious hepatitis four months earlier.

#### Genitourinary System:

At recommended dosage, abnormal ovarian enlargement (see also WARNINGS) is infrequent, although the usual cyclic variation in ovarian size may be exaggerated. Similarly, cyclic ovarian pain (mittelschmerz) may be accentuated. Adnexal torsion may be a complication of ovarian enlargement. With higher or prolonged dosage, more frequent ovarian enlargement and cyst formation (usually luteal) may occur, and the luteal phase of the cycle may be prolonged. Rare instances of massive ovarian enlargement are on record. Southam and Janovski<sup>18</sup> described such an instance in a patient with polycystic ovary syndrome whose CLOMID therapy consisted of 100 mg daily for 14 days. Abnormal ovarian enlargement usually regresses spontaneously, and while laparotomy was performed on several such patients, investigators believe most of these patients should have been treated conservatively.

Multiple pregnancies, (see also PRECAUTIONS), including simultaneous intrauterine and extrauterine pregnancies, ovarian hemorrhage, tubal pregnancy, uterine hemorrhage have been reported.

#### Laboratory:

CLOMID has not been reported to cause significant abnormality in the hematologic or renal systems, in protein bound iodine, or in serum cholesterol. Analysis by gas liquid chromatography (GLC) of serum sterols from patients on prolonged, continuous administration of CLOMID yields a peak compatible with an elevated level of desmosterol. This peak is indicative of an interference with cholesterol synthesis. However, the serum sterol GLC pattern from patients receiving recommended doses of CLOMID is not significantly altered.

### Special Senses:

Visual symptoms (see also WARNINGS for further recommendations) described usually as “blurring” or spots or flashes (scintillating scotomata) increase in incidence with increasing total dose. These symptoms appear to be due to intensification and prolongation of after-images. Symptoms often first appear or are accentuated with exposure to a more brightly lit environment. Ophthalmologically definable scotoma, lights, floaters, waves, unspecified visual complaints, photophobia, diplopia, phosphenes, and reduced visual acuity have been reported. There are rare reports of cataracts and optic neuritis.

These visual disturbances are usually reversible; however, cases of prolonged visual disturbance have been reported even after CLOMID discontinuation. The visual disturbances may be irreversible, especially with increased dosage or duration of therapy.

While measured visual acuity has not generally been affected, one patient taking 200 mg daily developed visual blurring on the seventh day of treatment, which progressed to severe diminution of visual acuity by the tenth day. No other abnormality was found and the visual acuity returned to normal on the third day after treatment was stopped. Another patient treated during clinical studies developed scotomata during prolonged CLOMID administration, which disappeared on placebo.<sup>19</sup> Monolateral exophthalmos associated with laboratory evidence of hyperthyroidism was observed in one patient concomitant with completion of the third course of CLOMID.

In a 34-year-old patient who had taken 3 courses of CLOMID, slit-lamp microscopic examination showed a mild amount of posterior cortical subcapsular opacity in each eye. Ophthalmoscopic examination revealed normal findings. The ocular diagnosis was posterior cortical senile cataracts.

### Tumors/Neoplasms:

Ovarian cancer has been reported in a very small number of infertile women who have been treated with fertility drugs. A causal relationship between treatment with fertility drugs and ovarian cancer has not been established.

### Post-Marketing Surveillance

Other than the adverse events reported above, the following adverse events were reported in post-marketing surveillance data.

### Birth Defects:

The following fetal abnormalities have also been reported: delayed development; abnormal bone development including skeletal malformations of the spine, skull, face, nasal passages, jaw, hand, limb (ectromelia including amelia, hemimelia, and phocomelia), foot and joints; tissue malformations including imperforate anus, tracheoesophageal fistula, diaphragmatic hernia, renal agenesis and dysgenesis, and malformations of the eye and lens (cataract), ear, lung, heart (ventricular septal defect, coarctation of the aorta and tetralogy of Fallot), and genitalia; as well as dwarfism, deafness, mental retardation, chromosomal disorders, and neural tube defects (including anencephaly).

Body as a Whole:

Fever and weakness have also been reported.

Cardiovascular:

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

Central Nervous System:

Migraine headache, paresthesia, stroke and syncope have been reported. Seizures have been observed rarely with CLOMID therapy.

Dermatologic:

Rash, urticaria, acne, allergic reaction, erythema, erythema multiforme, erythema nodosum, hypertrichosis, pruritus.

Gastrointestinal disorders

- Pancreatitis, with or without hypertriglyceridemia (see PRECAUTIONS, Hypertriglyceridemia)

Genitourinary System:

- There are reports of new cases of endometriosis and exacerbation of pre-existing endometriosis during CLOMID therapy.
- Reduced endometrial thickness

Hepatic:

Transaminases increased, hepatitis.

Metabolism Disorders

Hypertriglyceridemia, in some cases with pancreatitis has been observed in patients with preexisting or a family history of hypertriglyceridemia and/or with dose and duration of treatment exceeding the label recommendations.<sup>23-29</sup>

Musculoskeletal:

Arthralgia, back pain, myalgia.

Other:

Leukocytosis and thyroid disorder have also been reported.

Psychiatric:

Anxiety, irritability, mood changes, and psychosis have also been reported.

### Special Senses:

Abnormal accommodation, eye pain, macular edema, photopsia, posterior vitreous detachment, retinal hemorrhage, retinal thrombosis, retinal vascular spasm, temporary loss of vision and tinnitus.

### Tumors/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); trophoblastic (hydatidiform mole, choriocarcinoma); miscellaneous (melanoma, myeloma, perianal cysts, renal cell carcinoma, Hodgkin's lymphoma, tongue carcinoma, bladder carcinoma); and neoplasms of offspring (neuroectodermal tumor, thyroid tumor, hepatoblastoma, lymphocytic leukemia).

Isolated reports have been received on the occurrence of endocrine-related or dependent tumors/neoplasms or their aggravation.

**Drug Abuse and Dependence:** Tolerance, abuse, or dependence with CLOMID has not been reported.

## **SYMPTOMS AND TREATMENT OF OVERDOSE**

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

## **DOSAGE AND ADMINISTRATION**

### General considerations:

The work-up and treatment of candidates for CLOMID (clomiphene citrate) therapy should be supervised by physicians experienced in management of gynecologic or endocrine disorders. Patients should be chosen for therapy with CLOMID only after careful diagnostic evaluation (see INDICATIONS AND CLINICAL USE). The plan of therapy should be outlined in advance. Impediments to achieving the goal of therapy must be excluded or adequately treated before beginning CLOMID. Many patients will respond to 50 mg daily for 5 days (see Recommended Dosage). In the determination of a recommended starting dose schedule, efficacy must be balanced against potential side effects. For example, the data available so far suggest that ovulation and pregnancy are slightly more attainable on 100 mg/day for 5 days than on 50 mg/day for 5 days. As the dosage is increased, however, ovarian overstimulation and other side effects may be expected to increase. Furthermore, although the data do not yet establish a relationship between dosage and multiple births, it would seem reasonable on pharmacologic grounds that such a relationship does exist.

For these reasons, it would seem prudent to begin the treatment of the usual patient with a lower dose, 50 mg daily for 5 days, and to increase the dose only in those patients who do not respond

to the first course (see Recommended Dosage). Special care in dosage is particularly recommended if unusual sensitivity to pituitary gonadotropin is suspected, such as in patients with polycystic ovary syndrome.

Recommended dosage:

The recommended dose for the first course of CLOMID is 50 mg (1 tablet) daily for 5 days. Therapy may be started at any time in the patient who has had no recent uterine bleeding. 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 fifth day of the cycle. When ovulation occurs at this dosage, there is no advantage to increasing the dose in subsequent cycles of treatment.

If ovulation appears not to have occurred 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. **Increasing the dosage or duration of therapy beyond 100 mg/day for 5 days should never be undertaken.**

The majority of patients who are going to respond will respond to the first course of therapy, and 3 courses should constitute an adequate therapeutic trial. If ovulatory menses have not yet occurred, the diagnosis should be re-evaluated. Treatment beyond this is not recommended in the patient who does not exhibit evidence of ovulation.

Pregnancy:

The importance of properly timed coitus cannot be over-emphasized. In most patients, ovulation appears to occur from 5 to 12 days after completion of therapy. Appropriate tests to determine ovulation may be useful during this time. For regularity of cyclic ovulatory response it is also important that each course of CLOMID be started on or about the fifth cycle day, once ovulation has been established. In common with other therapeutic modalities, CLOMID therapy follows the rule of diminishing returns, such that likelihood of conception diminishes with each succeeding course of therapy. If pregnancy has not been achieved after 3 ovulatory responses to CLOMID, further treatment is not recommended. Patients should be advised of the possibility of multiple pregnancy and its potential hazards if conception occurs during a cycle in which CLOMID is given.

Long-term cyclic therapy not recommended:

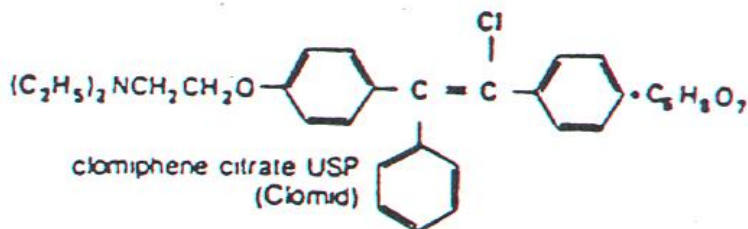
Since the relative safety of long-term cyclic therapy has not yet been conclusively demonstrated, and since the majority of patients will ovulate following 3 courses, long-term cyclic therapy is not recommended i.e., beyond a total of about 6 cycles (including 3 ovulatory cycles).

## PHARMACEUTICAL INFORMATION

### Drug Substance:

CLOMID (clomiphene citrate) is designated chemically as 2-[p-(2-chloro-1,2-diphenylvinyl)phenoxy] triethylamine dihydrogen citrate, and structurally as:

### Structural Formula:



## AVAILABILITY

CLOMID (clomiphene citrate) is available as 50 mg white rounded, flat face bevelled edges, compressed tablets, scored on one side. "CLOMID" debossed above score and "50" debossed below score. Other side is plain. CLOMID comes in packages of 50 tablets.

One 50 mg tablet of CLOMID contains the following non-medicinal ingredients; cornstarch, lactose monohydrate, magnesium stearate, pregelatinized starch and sucrose.

## PHARMACOLOGY<sup>17, 20, 21</sup>

### Animal Pharmacology:

Clomiphene was found to inhibit endogenous pituitary gonadotropic activity in rats based on organ weight indices, but did not block superovulation produced in immature female rats by pregnant mare's serum and chorionic gonadotropin. It also produced a reversible anti-fertility effect in both male and female rats. In immature female mice, clomiphene acted both as a weak estrogen, judged by its uterotrophic effect, and as anti-estrogen because of its antagonism to the uterotrophic effect of estradiol monobenzoate. Clomiphene had no progestational, androgenic, or anti-androgenic effects and appeared not to interfere with pituitary-adrenal or pituitary-thyroid function. In rats and dogs, a dose-dependent decrease in plasma cholesterol and total sterols, and an increase in desmosterol were observed after higher doses.

Studies with C-14 labelled clomiphene in rats indicate that it is readily absorbed after oral administration and is excreted principally in the feces. The body half-life of C-14 derived from administered clomiphene was 24 hours in the rat (I.P.) and 48 hours in the monkey (I.V.). Rats with biliary fistulas excreted the C-14 label in the bile, and enterohepatic recirculation was demonstrated. In monkeys after 6.3 days, when 83 to 90% of the dose had been eliminated, the

liver, gallbladder, and bile had the highest concentration of C-14 remaining in the animals, followed by adrenal, eye (exclusive of lens, which had very low levels), colon, and pancreas. Low levels of C-14 were observed in pituitary and testis of both rats and monkeys, whereas the ovary had levels close to the median value of tissues examined. High levels of C-14 were found in the ocular tissue after intravenous administration in rats, dogs, and monkeys. A relatively high concentration persisted for over 6 days in the monkey and over 40 days in the dog.

#### Human Pharmacology:

Following therapy with clomiphene, presumptive signs of ovulation resemble those associated with the normal menstrual cycle. It should be noted, however, that during drug administration and for several days thereafter, the effects of endogenous estrogen on the vaginal mucosa and cervical mucus are inhibited. Suggested criteria for ovulation following clomiphene may include the ovulatory peak of estrogen excretion, a biphasic basal body temperature curve, progesterone plasma level at postovulatory or higher levels, and luteal phase endometrial histologic findings characteristic of the time of biopsy in relation to subsequent menses. In most patients, ovulation appears to occur from 6 to 12 days after completion of therapy in recommended dosage.

During clinical studies, an ovulatory response occurred in 5412 of 7558 patients with ovulatory dysfunction who received CLOMID. Successful therapy characterized by pregnancy occurred in 2004 of these patients.<sup>17</sup>

Some patients had more than one pregnancy associated with CLOMID therapy, the outcomes of which are included in the table of pregnancy outcomes below. It should be noted that some of the 7558 patients were single, and some additional patients either did not desire pregnancy at the time of treatment or had impediments to achievement of pregnancy other than ovulatory dysfunction.

<b>PREGNANCIES FOLLOWING CLOMID</b>		
<b>OUTCOME*</b>	<b>Patients With Ovulatory Dysfunction</b>	<b>Total Patients All Diagnoses†</b>
Total Pregnancies	2259	2615
Undelivered	239	276
Delivered	2020	2339
Abortions/Stillbirths	424	500
Live Births		
Single Pregnancies	1455	1676
Survival	1424	1644
Multiple Pregnancies	141	163
Survival	254/301	293/353
Infants with Birth Defects	51	58

**\* The above data are derived from investigational case reports received by the Medical Research Department of Merrell Pharmaceuticals Inc., as of December 16, 1968.**

**† Includes 356 pregnancies that resulted during studies involving patients with diagnoses other than ovulatory dysfunction.**



## TOXICOLOGY<sup>22</sup>

### Acute Toxicity:

In rats, the acute LD<sub>50</sub> was 5750 mg/kg on oral administration and 530 mg/kg I.P. The acute LD<sub>50</sub> in mice was 1700 mg/kg orally, 390 mg/kg I.P., and 86 mg/kg I.V. Convulsions occurred in dogs after infusion of 40 to 62 mg/kg and the animals died of respiratory failure at 112 to 121 mg/kg.

### Chronic Toxicity:

In chronic toxicity studies, clomiphene was administered at various dose levels to rats and dogs for as long as 53 weeks. Some decrease in growth rate and food consumption was observed at all dose levels in rats but not in dogs. No significant hematologic changes were observed, and in the dog serum transaminase, alkaline phosphatase, bilirubin, glucose, blood urea nitrogen levels, and urinalysis were within normal limits. Changes in the reproductive system compatible with inhibition of gonadotropin were observed in both species. Thinning of fur occurred in rats receiving 5 to 40 mg/kg/day for 53 weeks, with incidence related to dose and duration of therapy.

**Subcapsular cataracts occurred in 4 of 29 rats** (but not in dogs) receiving 40 mg/kg/day, which were sacrificed at 53 weeks; in one of these animals, opacities had first appeared at 31 weeks. No cataracts were observed in rats receiving 15 mg/kg and 5 mg/kg for 53 weeks. At the end of 53 weeks, one dog exhibited an eye derangement in the form of a granular, dot-like opacity.

### Reproduction Studies:

After oral administration of clomiphene to pregnant rats during the interval of organogenesis in doses of 1.6 to 200 mg/kg/day, malformations were observed in the pups from one of five litters in the group receiving 8 mg/kg/day. Higher oral doses (40-200 mg/kg/day) inhibited fetal development and only one litter (normal) was born. Subcutaneous administration of clomiphene to pregnant rats on one day (12th) during the period of organogenesis resulted in a dose-dependent increase in the incidence of malformations in doses of 1.0 to 1000 mg/kg. In rabbits, deformed fetuses were seen following oral doses of 20 and 40 mg/kg/day from the eighth through the fifteenth day of a 32-day gestation. None was seen after the oral dose of 8 mg/kg/day.

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# IMPORTANT: PLEASE READ

## PART III: CONSUMER INFORMATION

### <sup>Pr</sup>**CLOMID**<sup>®</sup> clomiphene citrate USP

This leaflet is part III of a three-part “Product Monograph” published when **CLOMID** was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **CLOMID**. Contact your doctor or pharmacist if you have any questions about the drug.

#### ABOUT THIS MEDICATION

##### What the medication is used for:

CLOMID is an ovulation stimulant used for some types of infertility, in women who desire pregnancy but who are not ovulating properly.

##### What it does:

CLOMID belongs to a group of medications called ovulation stimulants. CLOMID works by stimulating the release of eggs from the ovary (ovulation) to increase the chances of conception.

##### When it should not be used:

You should not take CLOMID if you have any of the following conditions:

- You are allergic (hypersensitive) to clomiphene or any of the other ingredients of CLOMID (listed below).
- You have or ever had liver disease
- You have unusual menstrual bleeding where the cause is not known
- You have a type of cancer that is made worse by hormones
- You have a cyst on your ovary
- You are pregnant. You should have a test to make sure you are not pregnant before you take CLOMID

##### What the medicinal ingredient is:

clomiphene citrate

##### What the non-medicinal ingredients are:

Corn starch, lactose monohydrate, magnesium stearate, pregelatinized starch and sucrose.

##### What dosage forms it comes in:

CLOMID tablets are available as a 50 mg white and round tablet scored on one side with debossed “CLOMID” above score and debossed “50” below score. The other side is plain.

#### WARNINGS AND PRECAUTIONS

BEFORE you use CLOMID talk to your doctor or pharmacist if:

- You have “fibroids” in your womb
- You have “polycystic” ovaries
- Your ovaries are swollen
- You have hypertriglyceridemia (an excess of fats in the

blood) or a family history of hypertriglyceridemia.

- You are pregnant or plan to become pregnant
- You are breastfeeding or plan to breastfeed

Your doctor should check for any other causes of fertility problems before starting treatment with CLOMID.

**The chances of multiple pregnancies are higher when you use CLOMID.** You should be aware of the potential complications of multiple pregnancies before taking CLOMID.

Do not drive or use any tools or machines if you have a blurry vision from treatment with CLOMID.

#### INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken any other medications. This includes medications you buy without a prescription, including herbal medicines. This is because CLOMID can affect the way some other medicines work. Also some medicines can affect the way CLOMID works.

#### PROPER USE OF THIS MEDICATION

Always take CLOMID exactly as your doctor has told you. You should check with your doctor.

##### Taking this medication

- Take this medication by mouth
- Swallow the tablets whole with a drink of water.
- Do not take more than two tablets in one day
- Do not take the tablets for more than five days at a time
- If you feel the medication is not working, do not change the dose yourself, but ask your doctor

Usual dose: (for adult women only), treatment should begin with a low dose, 50 mg daily (1 tablet) for 5 days; dose changes will be made by your doctor. The first dose should be taken on the 5<sup>th</sup> day of your ovulatory cycle and the subsequent doses at about the same time of day for a total of 5 days. The tablet should be swallowed with a glass of water.

##### Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

##### Missed Dose:

If you forget a dose, talk to your doctor as you may need to change your treatment cycle. Do not take a double dose to make up for a forgotten tablet.

#### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, CLOMID can cause side effects, although not everybody gets them.

## IMPORTANT: PLEASE READ

The more common side effects include hot flashes, abdominal-pelvic discomfort (distention, bloating, pain, or soreness), ovarian enlargement, and visual blurring. The symptoms resembling menopausal “hot flashes” are not usually severe and disappear promptly after treatment is discontinued. Abdominal symptoms may be most often related to ovulatory or premenstrual phenomena, or to swollen ovaries.

Other less frequently reported symptoms during CLOMID (clomiphene citrate) therapy have included nausea or vomiting, appetite increase, constipation, diarrhea, increased nervous tension, depression, fatigue, dizziness or lightheadedness, insomnia, headache, breast soreness, abnormal uterine bleeding, heavier menses, intermenstrual spotting, vaginal dryness, urticaria or allergic dermatitis, vertigo, weight gain, and increased urinary frequency or volume. Moderate, reversible hair loss has been reported in a few patients, primarily on prolonged continuous therapy. Birth defects have been reported.

### **Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days:**

- Increased pain with periods, heavy periods or bleeding between periods
- Pain in the lower part of the stomach. This could be a sign of endometriosis or worsening of endometriosis, ovarian cancer or enlarged ovaries
- Pain in the upper middle or upper left part of the abdomen. This could be a sign of hypertriglyceridemia (excess of fats in the blood)-induced pancreatitis (inflammation of the pancreas).
- Cloudy lenses in the eye (cataracts)
- Feeling tired or difficulty in sleeping (insomnia), depression or change in moods or behaviour
- Skin rash or itching
- Flushing of the skin
- Swelling of the face, around the eyes, lips or tongue
- Painful breasts
- Heart palpitations (sensation of rapid, pounding, or irregular heartbeat)

There have been rare reports of ovarian cancer with fertility drugs. Some studies suggest that prolonged use of clomiphene may increase this risk. Therefore the recommended duration of treatment should not be exceeded.

Talk to your doctor or pharmacist if any of the side effects gets serious or lasts longer than a few days or if you notice any side effects not listed in this leaflet.

### **SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Allergic reactions, such as rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue			✓
Blurring of vision or spots or flashes in front of the eyes.			✓
Stroke with symptoms such as numbness, weakness or paralysis on one side of your body, slurred speech, sudden blurred vision, confusion or unsteadiness.			✓
Over-stimulation of the ovary. This can lead to pain in the pelvis, stomach or calf, swelling or feeling bloated, passing less urine, difficulty in breathing or an increase in weight.			✓
Liver problems that may cause the eyes or skin to go yellow (jaundice)			✓
Sudden and severe headaches			✓
Mental illness such as “psychosis”			✓
Symptoms of pancreatitis may include: Upper abdominal pain that radiates into the back; swollen and tender abdomen, nausea and vomiting, fever, increased heart rate			✓

*This is not a complete list of side effects. For any unexpected effects while taking CLOMID, contact your doctor or pharmacist.*

### **HOW TO STORE IT**

Keep out of the reach and sight of children.

Store in original container between 15 to 30°C.

## IMPORTANT: PLEASE READ

### **REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701E  
Ottawa, Ontario  
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

### **MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found at:  
[www.sanofi.ca](http://www.sanofi.ca) or by contacting the sponsor, sanofi-aventis Canada Inc. at: 1-800-265-7927

This leaflet was prepared by sanofi-aventis Canada Inc.

Last revised: