

## **OVACLOMIN**

**Tablets**

### **Composition**

Each tablet contains Clomiphene citrate 50 mg.

### **Action**

Clomiphene citrate, an orally administered, non-steroidal agent, may induce ovulation in selected anovulatory women.

Clomiphene citrate is a drug of considerable pharmacological potency. Careful evaluation and selection of the patient and close attention to the timing of the dose is mandatory prior to treatment with clomiphene citrate. Conservative selection and management of the patient contribute to successful therapy of anovulation.

Clomiphene citrate induces ovulation in most selected anovulatory patients.

The various criteria for ovulation include an ovulation peak of oestrogen excretion followed by a biphasic basal body temperature curve; urinary excretion of pregnanediol at post-ovulatory levels and, endometrial histologic findings characteristic of the luteal phase.

Clomiphene citrate therapy appears to mediate ovulation through increased output of pituitary gonadotropins. These stimulate the maturation and endocrine activity of the ovarian follicle that is followed by the development and function of the corpus luteum. Increased urinary excretion of gonadotropins and oestrogen suggest involvement of the pituitary.

In males, when Clomiphene citrate is administered in appropriate amounts, spermatogenesis is stimulated by an increase in the gonadotropins and testicular steroids. Augmentation of sperm output is thus due to stimulation of spermatogonia by increased testosterone.

### **Pharmacokinetics**

Clomiphene citrate is absorbed from the gastro-intestinal tract. It is metabolised in the liver and slowly excreted via the bile. Unchanged drug and metabolites are excreted in the faeces. The biological half-life is reported to be 5 days although traces are found in the faeces for up to 6 weeks. Enterohepatic recirculation takes place.

### **Indications**

#### **Females**

Ovaclomin is indicated for the treatment of ovulatory failure in women desiring pregnancy, whose partners are fertile and potent. Impediments to this goal must be excluded or adequately treated before initiating therapy.

Administration of Ovaclomin is indicated only in patients with demonstrated ovulatory dysfunction, and in whom the following conditions apply:

- Normal liver function
- Physiological indications of normal endogenous estrogen (as estimated from vaginal smears, endometrial biopsy, assay of urinary estrogen or bleeding in response to progesterone).

Reduced estrogen levels, while less favourable, do not prevent successful therapy.

Ovaclomin therapy is not effective in patients with primary pituitary or ovarian failure. It cannot substitute for appropriate therapy of other disturbances leading to ovulatory dysfunction, e.g. diseases of the thyroid or adrenals.

#### **Males**

To improve fertility in idiopathic oligospermia and varicocele-associated oligospermia.

As a useful adjunct to varicocelectomy, and as first line therapy for sperm counts under 10 million/ml, when surgical therapy has not been successful.

Reported to be effective in men with long-standing infertility that has been refractory to previous treatments, such as exogenous injections of human chorionic gonadotropin and varicocelectomy.

Patients with pregerminal hypofertility respond to treatment with improved ejaculate and an increased rate of conception, and considered eligible candidates for long-term, low dose treatment with Ovaclomin.

Note that Ovaclomin has not been found effective in patients with primary hypofertility, germinal hypofertility and post-germinal hypofertility.

### **Contraindications**

- Pregnancy .
- Abnormal uterine bleeding.
- Male and female patients with liver disease or a history of liver dysfunction.
- Infertile males or females who have either pituitary tumours or pituitary failure with hypogonadotropic hypogonadism.

### **Warnings**

It is important that neoplastic lesions be detected before Clomiphene citrate therapy is instituted.

Although no direct effect of Clomiphene citrate therapy on the human fetus has been seen, Clomiphene citrate should not be administered in cases of suspected pregnancy, as effects on the fetus have been reported in animals. To prevent inadvertent Clomiphene citrate administration during early pregnancy, the basal body temperature should be recorded throughout all treatment cycles, and therapy should be discontinued if pregnancy is suspected. If the basal body temperature following Clomiphene citrate is biphasic and not followed by menses, the possibility of an ovarian cyst and/ or pregnancy should be excluded. The next course of therapy should be delayed until the correct diagnosis has been determined.

Patients should be warned that blurring and/or other visual symptoms might occur occasionally with Clomiphene citrate therapy. These may make activities such as driving or operating machinery more hazardous than usual, particularly under conditions of poor lighting. While their significance is not yet understood, patients experiencing any visual symptoms should discontinue treatment and undergo a complete ophthalmological evaluation.

### **Adverse Reactions**

Side effects are not prominent at the recommended dosage of Clomiphene citrate, and only infrequently interfere with treatment. Side effects tend to occur more frequently at the higher doses, and during the extended treatment courses, used in some early studies. The more common side effects include vasomotor flushes, abdominal discomfort, abnormal uterine bleeding, ovarian enlargement, breast tenderness and visual symptoms. The vasomotor symptoms resemble menopausal hot flushes, and are not usually severe. They promptly disappear after treatment is discontinued. Abdominal discomfort may resemble ovulatory (mittelschmerz) or premenstrual phenomena, or that due to ovarian enlargement. In addition, nausea and vomiting, nervousness and insomnia, headache, dizziness and light-headedness, increased urination, depression and fatigue, urticaria and allergic dermatitis, weight gain and reversible hair loss have been reported.

### **Ovarian Enlargement**

When Clomiphene citrate is administered at the recommended dosage, abnormal ovarian enlargement is infrequent, although the usual cyclic variation in ovarian size may be exaggerated. Similarly, mid-cycle ovarian pain (mittelschmerz) may be accentuated. With prolonged or higher dosage, ovarian enlargement and cyst formation (usually luteal) may occur more often, and the luteal phase of the cycle may be prolonged.

Patients with polycystic ovary disease may be unusually sensitive to Clomiphene therapy. Rare occurrences of massive ovarian enlargement have been reported, for example, in a patient with

polycystic ovary syndrome in whom Clomiphene citrate therapy consisted of 100 mg daily, for 14 days. Since abnormal ovarian enlargement usually regresses spontaneously, most of these patients should be treated conservatively.

### **Visual Disturbances**

The incidence of visual symptoms usually described as "blurring", spots or flashes (scintillating scotomata) correlate with increases in the total dose. The symptoms disappear within a few days or weeks after Clomiphene citrate is discontinued. This may be due to intensification and/or prolongation of after-images. Symptoms often appear first, or are accentuated, upon exposure to a more brightly lit environment. While measured visual acuity has not generally been affected, in one patient taking 200 mg daily, visual blurring developed on day 7 of treatment, progressing to severe diminution of visual acuity by day 10. No other abnormality was coincident, and the visual acuity was normal by day 3 after discontinuation of treatment.

Ophthalmologically definable scotomata and electroretinographic retinal function changes have also been reported.

### **Precautions**

#### **Diagnosis Prior to Clomiphene Citrate Therapy**

Careful evaluation and diagnosis prior to Clomiphene citrate therapy should be made with regard to female candidates for Clomiphene citrate therapy. A complete pelvic examination should be performed prior to treatment, and repeated before each subsequent course.

Clomiphene citrate should not be administered to patients with an ovarian cyst, as further ovarian enlargement may result.

Since the incidence of endometrial carcinoma and ovulatory disorders increases with age, endometrial biopsy should always exclude the former as causative in such patients. If abnormal uterine bleeding is present, full diagnostic measures are necessary.

#### **Ovarian Overstimulation during Treatment with Clomiphene Citrate**

To minimize the hazards associated with occasional abnormal ovarian enlargement during Clomiphene citrate therapy, the lowest dose producing good results should be chosen. Some patients with polycystic ovary syndrome are unusually sensitive to gonadotropin, and may have an exaggerated response to usual doses of Clomiphene citrate. Maximal enlargement of the ovary, whether abnormal or physiological, does not occur until several days after discontinuation of Clomiphene citrate.

Patients complaining of pelvic pains after receiving Clomiphene citrate should be examined carefully. If enlargement of the ovary occurs, Clomiphene citrate therapy should be withheld until the ovaries have returned to pre-treatment size, and the dosage or duration of the next course should be reduced. The ovarian enlargement and cyst formation following Clomiphene citrate therapy regress spontaneously within a few days or weeks after discontinuing treatment. Therefore, unless a strong indication for laparotomy exists, such cystic enlargement should always be managed conservatively.

#### **Multiple Pregnancies**

In the reviewed publications, the incidence of multiple pregnancies was increased during those cycles in which Clomiphene citrate was administered.

Among the 1,803 pregnancies for which the outcome was reported, 90% were single and 10%, twins. Less than 1% of the reported deliveries resulted in triplets or more.

Of these multiple pregnancies, 96-99% resulted in the birth of live infants. Patients and their male partners should be advised of the frequency and potential hazards of multiple pregnancies before starting treatment.

#### **Diagnostic Interference**

Greater than 5% retention of sulfobromophthalein (BSP) has been reported in approximately 10-20% of patients in whom it was measured. Retention was usually minimal, but was elevated during prolonged Clomiphene citrate administration or with apparently unrelated liver disease. In some patients, pre-existing BSP retention decreased, even though Clomiphene citrate therapy was continued. Other liver function tests were usually normal.

Clomiphene citrate has not been reported to cause significant abnormality in hematological or renal tests, in protein-bound iodine, or in serum cholesterol levels.

### **Dosage and Administration**

Physicians experienced in managing gynaecological or endocrine disorders should supervise the workup and treatment of candidate female and male patients for Clomiphene citrate therapy. Patients should be selected for Clomiphene citrate therapy 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 initiation of Clomiphene citrate therapy.

#### **Females**

The recommended dosage for the first course of Ovaclomin is 50 mg (1 tablet) daily for 5 days. Therapy may be started at any time if the patient has had no recent uterine bleeding. If progestin-induced bleeding is intended, 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 in dose in subsequent cycles of treatment.

If ovulation does not appear 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 may be started. This course may begin as early as 30 days after the previous one. Increasing the dosage or duration of therapy beyond 150 mg/day for 5 days should not be undertaken.

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

#### *Pregnancy*

Properly timed coitus is very important for good results. For regularity of cyclic ovulatory response, it is also important that each course of clomiphene citrate be started on or about the fifth day of the cycle, once ovulation has been established. As with other therapeutic modalities, Serophene 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 Ovaclomin, further treatment is not generally recommended.

#### **Males**

Different treatment schedules have been successfully used:

25 mg, daily for 25 consecutive days with 5 days rest, for not less than 6 months, or until the female partner becomes pregnant.

100 mg, 3 times a week on the same alternate days (Monday, Wednesday, Friday), for a minimum of 3 months and a maximum of 15 months.

If the patient shows a semen response but his partner does not become pregnant within 15 months, the drug should be discontinued for a minimum of 3 months and another course started thereafter.

### **Presentation**

Box of 10 tablets.