

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Clomifene 50mg Tablets

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contain 50mg of Clomifene Citrate

Excipient with known effect

Lactose 0.220 g

For the full list of excipients, see section 6.1

### **3 PHARMACEUTICAL FORM**

Tablet

White, round tablets with HG C50 on one side and a breakline on the other side.

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Clomifene 50mg Tablets are indicated for the treatment of ovulatory failure in women desiring pregnancy. Clomifene 50mg Tablets is indicated only for patients in whom ovulatory dysfunction is demonstrated. Other causes of infertility must be excluded or adequately treated before giving Clomifene 50mg Tablets.

#### **4.2 Posology and method of administration**

Posology

Adults Only:

The recommended dose for the first course of Clomifene 50mg Tablets is 50mg (one tablet) daily for five 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 before therapy, the regimen of 50mg 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 100mg daily (two 50mg 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.

Increase of the dosage or duration of therapy beyond 100mg/day for 5 days should not be undertaken.

The majority of patients who are going to respond will respond to the first course of therapy, and three 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.

*Long-term cyclic therapy:*

Not recommended.

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

#### Special Populations

Special care with lower dosage or duration of treatment is particularly recommended if unusual sensitivity to pituitary gonadotrophin is suspected, such as in patients with polycystic ovary syndrome (See Section 5.1).

#### Method of administration

Oral

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

*Pregnancy:* See 4.6

*Liver disease:* Clomifene 50mg Tablets therapy is contraindicated in patients with liver disease or a history of liver dysfunction.

*Hormone-Dependent Tumours or Abnormal uterine bleeding:* Clomifene 50mg Tablets is contraindicated in patients with hormone-dependent tumours or in patients with abnormal uterine bleeding of undetermined origin.

*Ovarian cyst:* Clomifene 50mg Tablets 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.

Visual disorders: Clomifene 50mg Tablets should not be given if history of significant, medically confirmed, vision disorders related to the use of Clomifene 50mg Tablets (prior or ongoing treatment) is known.

#### **4.4 Special warnings and precautions for use**

##### **Warnings:**

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Causes of infertility other than ovarian dysfunction should be excluded before the start of treatment.

##### General:

Good levels of endogenous oestrogen (as estimated from vaginal smears, endometrial biopsy, assay of urinary oestrogen, or endometrial bleeding in response to progesterone) provide a favourable prognosis for ovulatory response induced by Clomifene 50mg Tablets. A low level of oestrogen, although clinically less favourable, does not preclude successful outcome of therapy. Clomifene 50mg Tablets therapy is ineffective in patients with primary pituitary or primary ovarian failure. Clomifene 50mg Tablets therapy cannot be expected to substitute for specific treatment of other causes of ovulatory failure, such as thyroid or adrenal disorders. For hyperprolactinaemia there is other preferred specific treatment. Clomifene 50mg Tablets is not first line treatment for low weight related amenorrhoea, with infertility, and has no value if a high FSH blood level is observed following an early menopause.

##### Ovarian Hyperstimulation Syndrome:

Ovarian Hyperstimulation Syndrome (OHSS) has been reported in patients receiving Clomifene 50mg Tablets therapy for ovulation induction. In some cases, OHSS occurred following the cyclic use of Clomifene 50mg Tablets therapy or when Clomifene 50mg Tablets was used in combination with gonadotropins. The following symptoms have been reported in association with this syndrome during Clomifene 50mg Tablets therapy: pericardial effusion, anasarca, hydrothorax, acute abdomen, renal failure, pulmonary oedema, ovarian haemorrhage, deep venous thrombosis, torsion of the ovary and acute respiratory distress. If conception results, rapid progression to the severe form of the syndrome may occur.

To minimise the hazard of the abnormal ovarian enlargement associated with Clomifene 50mg Tablets therapy, the lowest dose consistent with expectation of good results should be used. The patient should be instructed to inform the physician of any abdominal or pelvic pain, weight gain, discomfort or

distension after taking Clomifene 50mg Tablets. Maximal enlargement of the ovary may not occur until several days after discontinuation of the course of Clomifene 50mg Tablets. Some patients with polycystic ovary syndrome who are unusually sensitive to gonadotropin may have an exaggerated response to usual doses of Clomifene 50mg Tablets.

The patient who complains of abdominal or pelvic pain, discomfort, or distension after taking Clomifene 50mg Tablets 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 very cautiously. If abnormal enlargement occurs Clomifene 50mg Tablets should not be given until the ovaries have returned to pre-treatment size. Ovarian enlargement and cyst formation associated with Clomifene 50mg Tablets therapy usually regress spontaneously within a few days or weeks after discontinuing treatment. Most of these patients should be managed conservatively. The dosage and/or duration of the next course of treatment should be reduced.

#### Visual Symptoms:

Patients should be advised that blurring or other visual symptoms such as spots or flashes (scintillating scotomata), partial or complete loss of vision may occasionally occur during or shortly after therapy with Clomifene 50mg Tablets. These visual disturbances are usually reversible; however, cases of prolonged or irreversible visual disturbance have been reported including after Clomifene 50mg Tablet discontinuation. The visual disturbances may be irreversible especially with increased dosage or duration of therapy. The significance of these visual symptoms is not understood. If the patient has any visual symptoms, treatment should be discontinued and ophthalmologic evaluation performed.

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.

#### **Precautions:**

##### Hypertriglyceridemia

Cases of hypertriglyceridemia have been reported (see section 4.8 Undesirable effects) in the post-marketing experience with Clomifene 50mg Tablets. Pre-existing or family history of hyperlipidemia and use of higher than recommended dose and/or longer duration of treatment with Clomifene 50mg Tablets are associated with risk of hypertriglyceridemia. Periodic monitoring of plasma triglycerides may be indicated in these patients.

##### Multiple Pregnancy:

There is an increased chance of multiple pregnancy when conception occurs in relationship to Clomifene 50mg Tablets therapy. The potential complications and hazards of multiple pregnancy should be discussed with the patient.

During the clinical investigation studies, the incidence of multiple pregnancy was 7.9% (186 of 2369 clomifene associated pregnancies on which outcome was reported). Among these 2369 pregnancies, 165 (6.9%) 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 twins was 1:5.

Ectopic Pregnancy:

There is an increased chance of ectopic pregnancy (including tubal and ovarian sites) in women who conceive following Clomifene 50mg Tablets therapy. Multiple pregnancies, including simultaneous intrauterine and extrauterine pregnancies, have been reported.

Uterine Fibroids:

Caution should be exercised when using Clomifene 50mg Tablets in patients with uterine fibroids due to potential for further enlargement of the fibroids.

Pregnancy Wastage and Birth Anomalies:

The overall incidence of reported birth anomalies from pregnancies associated with maternal Clomifene ingestion (before or after conception) during the investigational studies was within the range of that reported in the published references for the general population. Among the birth anomalies spontaneously reported in the published literature as individual cases, the proportion of neural tube defects has been high among pregnancies associated with ovulation induced by Clomifene, but this has not been supported by data from population based studies.

The physician should explain so that the patient understands the assumed risk of any pregnancy whether the ovulation was induced with the aid of Clomifene or occurred naturally.

The patient should be informed of the greater pregnancy risks associated with certain characteristics or conditions of any pregnant woman: e.g. age of female and male partner, history of spontaneous abortions, Rh genotype, abnormal menstrual history, infertility history (regardless of cause), organic heart disease, diabetes, exposure to infectious agents such as rubella, familial history of birth anomaly, and other risk factors that may be pertinent to the patient for whom Clomifene is being considered. Based upon the evaluation of the patient, genetic counselling may be indicated.

Population based reports have been published on possible elevation of risk of Down's Syndrome in ovulation induction cases and of increase in trisomy defects among spontaneously aborted fetuses from subfertile women receiving ovulation inducing drugs (no women with Clomifene 50mg Tablets alone and without additional inducing drug). However, as yet, the reported observations are too few to confirm or not confirm the presence of an increased risk that would justify amniocentesis other than for the usual indications because of age and family history.

The experience from patients of all diagnosis during clinical investigation of Clomifene shows a pregnancy (single and multiple) wastage or foetal loss rate

of 21.4% (abortion rate of 19.0%), ectopic pregnancies, 1.18%, hydatidiform mole, 0.17%, foetus papyraceous, 0.04% and of pregnancies with one or more stillbirths, 1.01%.

Clomifene therapy after conception was reported for 158 of the 2369 delivered and reported pregnancies in the clinical investigations. Of these 158 pregnancies 8 infants (born of 7 pregnancies) were reported to have birth defects.

There was no difference in reported incidence of birth defects whether Clomifene was given before the 19th day after conception or between the 20th and 35th day after conception. This incidence is within the anticipated range of general population.

#### Ovarian Cancer:

There have been rare reports of ovarian cancer with fertility drugs; infertility itself is a primary risk factor. Epidemiological data suggest that prolonged use of Clomifene 50mg Tablets may increase this risk. Therefore the recommended duration of treatment should not be exceeded (see section 4.2).

#### **4.5 Interaction with other medicinal products and other forms of interaction**

None known.

#### **4.6 Fertility, pregnancy and lactation**

Clomifene 50mg Tablets are not indicated during pregnancy.

Although there is no evidence that clomifene has a harmful effect on the human foetus, there is evidence that clomifene has a deleterious effect on rat and rabbit foetuses when given in high doses to the pregnant animal. To avoid inadvertent clomifene administration during early pregnancy, appropriate tests should be utilised during each treatment cycle to determine whether ovulation occurs. The patient should have a pregnancy test before the next course of clomifene therapy.

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

#### **4.7 Effects on ability to drive and use machines**

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. (See Section 4.4. 'Warnings').

#### **4.8 Undesirable effects**

Symptoms/Signs/Conditions: Adverse effects appeared to be dose—related, occurring more frequently at the higher dose and with the longer courses of treatment used in investigational studies. At recommended dosage, adverse effects are not prominent and infrequently interfere with treatment.

During the investigational studies, the more commonly reported adverse effects included ovarian enlargement (13.6%), vasomotor flushes (10.4%), abdominal-pelvic discomfort (distention, bloating) (5.5%), nausea and vomiting (2.2%), breast discomfort (2.1%), visual symptoms (1.5%), headache (1.3%) and intermenstrual spotting or menorrhagia (1.3%).

Ovarian enlargement: At recommended dosage, abnormal ovarian enlargement is infrequent although the usual cyclic variation in ovarian size may be exaggerated. Similarly, cyclic ovarian pain (mittelschmerz) may be accentuated. With higher or prolonged dosage, more frequent ovarian enlargement and cyst formation may occur, and the luteal phase of the cycle may be prolonged.

Rare instances of massive ovarian enlargement are recorded. Such an instance has been described in a patient with polycystic ovary syndrome whose clomifene therapy consisted of 100mg daily for 14 days. Abnormal ovarian enlargement usually regresses spontaneously; most of the patients with this condition should be treated conservatively.

#### Immune system disorders

Not known: Hypersensitivity reactions including anaphylaxis and angioedema (see section 4.4).

Eye/Visual Symptoms: Symptoms 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. After-images as such have also been reported. Symptoms often first appear or are accentuated with exposure to bright-light environment. Ophthalmologically definable scotomata, phosphenes and reduced visual acuity have been reported.

There are rare reports of cataracts and optic neuritis.

Post marketing adverse events reported are accommodation disorder, blindness, blindness transient, diplopia, eye pain, macular oedema, vitreous detachment and retinal disorders.

These visual disturbances are usually reversible. However, cases of prolonged or irreversible visual disturbances have been reported, including after Clomifene 50mg Tablets have been discontinued. The visual disturbances may be irreversible, especially with increased dosage or duration of therapy.

Genitourinary: There are reports of new cases of endometriosis and exacerbation of pre-existing endometriosis during Clomifene 50mg Tablets therapy.

Multiple pregnancies, including simultaneous intrauterine and extrauterine pregnancies, have been reported. There is an increased chance of ectopic pregnancy in women who conceive following Clomifene 50mg Tablets therapy. Reduced endometrial thickness (frequency not known)

Tumours/neoplasms: Isolated reports have been received on the occurrence of endocrine-related or dependent neoplasms or their aggravation. Ovarian cancer: see section 4.4.

Central nervous system: Convulsions have been reported; patients with a history of seizures may be predisposed, transient paraesthesia (frequency not known), dizziness (frequency not known). In investigational patients, CNS symptoms/signs, conditions of dizziness, light-headedness/vertigo (0.9%), nervous tension/insomnia (0.8%) and fatigue/depression (0.7%) were reported. After prescription availability, there were isolated additional reports of these conditions and also reports of other conditions such as syncope/fainting, cerebrovascular accident, cerebral thrombosis, psychotic reactions including paranoid psychosis, neurologic impairment, disorientation and speech disturbance.

Psychiatric Disorders: Anxiety (frequency not known), depression (frequency not known), mood disturbances (including mood altered, mood swings and irritability) (frequency not known), nervousness (frequency not known), insomnia (frequency not known).

Skin and Subcutaneous Tissue Disorders: Dermatitis and rash were reported by investigational patients. Conditions such as rash and urticaria were the most common ones reported after prescription availability but also reported were conditions such as allergic reaction, erythema multiforme, ecchymosis and angioneurotic oedema. Hair thinning (alopecia) has been reported very rarely.

Liver function: Bromsulphalein (BSP) retention of greater than 5% was reported in 32 of 141 patients in whom it was measured, including 5 of 43 patients who took approximately the dose of Clomifene 50mg Tablets now recommended. Retention was usually minimal unless associated with prolonged continuous Clomifene 50mg Tablets administration or with apparently unrelated liver disease. Other liver function tests were usually normal. In a later study in which patients were given 6 consecutive monthly courses of Clomifene 50mg Tablets (50 or 100mg 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 taken drug and 5 placebo.

In a separate report, one patient taking 50mg of Clomifene 50mg Tablets daily developed jaundice on the 19th day of treatment; liver biopsy revealed bile stasis without evidence of hepatitis.

Metabolism Disorders: Hypertriglyceridemia (frequency: not known), in some cases with pancreatitis, has been observed in patients with pre-existing or a family history of hypertriglyceridemia and/or with dose and duration of treatment exceeding the label recommendations.

Cardiac disorders: Tachycardia, (frequency not known) palpitations (frequency not known).

Hepatobiliary disorders: Increased Transaminases

Gastrointestinal disorders: Pancreatitis (frequency not known)

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard).

## **4.9 Overdose**

Toxic effects of acute overdosage of Clomifene 50mg Tablets have not been reported but the number of overdose cases recorded is small. In the event of overdose, appropriate supportive measures should be employed.

# **5 PHARMACOLOGICAL PROPERTIES**

## **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: ovulation stimulants, synthetic  
ATC code: G03BG02

#### Mechanism of action:

The ovulatory response to cyclic Clomifene 50mg Tablets therapy is mediated through increased output of pituitary gonadotrophins by binding to oestrogen receptors in the hypothalamus, which in turn stimulates the maturation and endocrine activity of the ovarian follicle.

Pharmacodynamic effects:

Clomifene 50mg Tablets is a triarylethylene compound (related to chlorotrianisene and triparanol). It is a non-steroidal agent which stimulates ovulation in a high percentage of appropriately selected anovulatory women.

## **5.2 Pharmacokinetic properties**

Orally administered <sup>14</sup>C labelled Clomifene citrate was readily absorbed when administered to humans. Cumulative excretion of the <sup>14</sup>C label by way of urine and faeces averaged about 50% of the oral dose after 5 days in 6 subjects, with mean urinary excretion of 7.8% and mean faecal excretion of 42.4%. A mean rate of excretion of 0.73% per day of the <sup>14</sup>C dose after 31 days to 35 days and 0.45% per day of the <sup>14</sup>C dose after 42 days to 45 days was seen in faecal and urine samples collected from 6 subjects for 14 to 53 days after Clomifene citrate <sup>14</sup>C administration. The remaining drug/metabolites may be slowly excreted from a sequestered enterohepatic recirculation pool.

## **5.3 Preclinical safety data**

Carcinogenicity

Prolonged use of Clomifene 50mg Tablets may increase the risk of developing ovarian cancer.

Long term toxicity studies in animals have not been performed to evaluate the carcinogenic potential of Clomifene 50mg Tablets.

Mutagenicity

Mutagenic potential of Clomifene 50mg Tablets has not been evaluated.

# **6 PHARMACEUTICAL PARTICULARS**

## **6.1 List of excipients**

Magnesium stearate

Maize starch

Lactose

## **6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

5 years

**6.4 Special precautions for storage**

Do not store above 25°C.

Store in original packaging.

**6.5 Nature and contents of container**

Blister packs of 10 tablets manufactured from 250 micron white opaque PVC and 20 micron hard temper aluminium foil.

Pack Sizes: 10, 20, 30, 100 tablets (1,2,3 or 10 strips) in an outer carton.

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Wockhardt UK Ltd

Ash Road North

Wrexham LL13 9UF

United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 29831/0037

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

21/04/1992 / 03/06/2005

## **10 DATE OF REVISION OF THE TEXT**

24/06/2024