SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clomid 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clomifene Citrate 50 mg

3 PHARMACEUTICAL FORM

Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clomid (Clomifene Citrate BP) is indicated for the treatment of ovulatory failure in women desiring pregnancy. Clomid is indicated only for patients in whom ovulatory dysfunction is demonstrated. Other causes of infertility must be excluded or adequately treated before giving Clomid.

4.2 Posology and method of administration

Posology

Adults
The recommended dose for the first course of Clomid (Clomifene Citrate BP) 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 before 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. Increase of the dosage or duration of therapy beyond 100 mg/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 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.

Long-term cyclic therapy.
Not recommended.
Efficacy and safety of clomifene for more than 6 treatment cycles have not been demonstrated.

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

Pregnancy: See section 4.6.

Liver disease: Clomid (Clomifene Citrate BP) therapy is contraindicated in patients with liver disease or a history of liver dysfunction.

Hormone-Dependent Tumours or Abnormal uterine bleeding: Clomid is contraindicated in patients with hormone-dependent tumours or in patients with abnormal uterine bleeding of undetermined origin.

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.

4.4 Special warnings and precautions for use

Warnings:

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 Clomid. A low level of oestrogen, although clinically less favourable, does not preclude successful outcome of therapy. Clomid therapy is ineffective in patients with primary pituitary or primary ovarian failure. Clomid 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. Clomid 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 Clomid therapy for ovulation induction. In some cases, OHSS occurred following the cyclic use of Clomid therapy or when Clomid was used in combination with gonadotropins. The following symptoms have been reported in association with this syndrome during Clomid 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 Clomid 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 Clomid. Maximal enlargement of the ovary may not occur until several days after discontinuation of the course of Clomid. Some patients with polycystic ovary syndrome who are unusually sensitive to gonadotropin may have an exaggerated response to usual doses of Clomid.

The patient who complains of abdominal or pelvic pain, discomfort, or distension after taking 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 very cautiously. If abnormal enlargement occurs Clomid should not be given until the ovaries have returned to pre-treatment size. Ovarian enlargement and cyst formation associated with Clomid 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 Clomid. These visual disturbances are usually reversible; however, cases of prolonged or irreversible visual disturbances have been reported including 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 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.

Hypersensitivity reactions
Hypersensitivity reactions including anaphylaxis and angioedema have been reported with Clomid use. In case of allergic reactions, treatment with Clomid must be discontinued and appropriate symptomatic treatment initiated (see section 4.8).

Precautions:

Cases of hypertriglyceridemia have been reported (see section 4.8) in the post-marketing experience with Clomid. Pre-existing 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.

Multiple Pregnancy:
There is an increased chance of multiple pregnancy when conception occurs in relationship to Clomid 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 Clomid 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 Clomid therapy. Multiple pregnancies, including simultaneous intrauterine and extrauterine pregnancies, have been reported.

Uterine Fibroids:
Caution should be exercised when using Clomid 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 Clomid 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 Clomid, 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 Clomid 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 Clomid 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 sub-fertile women receiving ovulation inducing drugs (no women with Clomid 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 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%, fetus papyraceous, 0.04% and of pregnancies with one or more stillbirths, 1.01%.

Clomid 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 Clomid 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.

4.5 Interaction with other medicinal products and other forms of interaction

None stated.

4.6 Fertility, pregnancy and lactation

Clomid is not indicated during pregnancy. Although there is no evidence that Clomid has a harmful effect on the human fetus, there is evidence that Clomid has a deleterious effect on rat and rabbit fetuses when given in high doses to the pregnant animal. To avoid inadvertent Clomid 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 Clomid 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).

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 Clomid therapy consisted of 100 mg 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 Clomid 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 Clomid 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 Clomid 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 (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, 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 Clomid now recommended. Retention was usually minimal unless associated with prolonged continuous Clomid 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 Clomid (50 mg or 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 taken drug and 5 placebos.

In a separate report, one patient taking 50 mg of Clomid 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Toxic effects of acute overdosage of Clomid 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: G03GB02

Mechanism of action:
The ovulatory response to cyclic Clomid 50 mg Tablets therapy is mediated through increased output of pituitary gonadotrophins, which in turn stimulates the maturation and endocrine activity of the ovarian follicle.

Pharmacodynamic effects:
Clomid 50 mg 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 ^{14}C labelled Clomifene citrate was readily absorbed when administered to humans. Cumulative excretion of the ^{14}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 ^{14}C dose after 31 – 35 days and 0.45% per day of the ^{14}C dose after 42 – 45 days was seen in faecal and urine samples collected from 6 subjects for 14 – 53 days after Clomifene citrate ^{14}C administration.

The remaining drug/metabolites may be slowly excreted from a sequestered enterohepatic recirculation pool.

5.3 Preclinical safety data

Long-term carcinogenicity studies have not been performed to evaluate the carcinogenic potential of Clomid.

Clomifene citrate did not induce gene mutations in bacteria (Ames test) or chromosome aberrations in cultured human peripheral blood lymphocytes. Clomifene citrate at oral doses up to 2000 mg/kg/day did not induce genotoxic effects in rats. At the highest dose tested of 2000 mg/kg/day in rats, the ratios of exposure ranged from 2 – 232 for Z-clomifene and E-clomifene respectively, taking into account limited PK data available in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Lactose
Soluble starch
Maize starch
Magnesium stearate
Iron oxide yellow E172
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in original container, do not store above 25°C.

6.5 Nature and contents of container

Blister pack:
Base: 250-micron PVC
Foil: 20 micron hard-tempered aluminium
(in cardboard cartons)

Pack sizes: 5, 30 and 100 tablets.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Fidia Pharma UK Ltd
170 Edmund Street, Ground Floor
Birmingham, B3 2HB, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 56485/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28/02/1966
Date of latest renewal: 07/11/2002

10 DATE OF REVISION OF THE TEXT

30/09/2025

LEGAL CLASSIFICATION

POM