Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clomid 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Clomifene Citrate 50 mg.

Excipients: Each tablet contains 67.5mg sucrose and 67.5mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Beige, round, flat, bevelled tablet. A scored bisect line on one side and the other engraved M within two circles.
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indications

Clomid (Clomifene Citrate) is indicated for the treatment of ovulatory failure in women desiring pregnancy.

Good levels of endogenous oestrogen provide a favourable prognosis for ovulatory response induced by Clomid. Clomid therapy is ineffective in patients with primary pituitary or primary ovarian failure.

4.2 Posology and method of administration

Route of Administration:
Oral

Adults Only:

The recommended dose for the first course of Clomid (Clomifene Citrate) is 50mg (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 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 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-emphasised (i.e. at about the time of ovulation). 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. Clomid therapy follows the rule of diminishing returns, such that likelihood of conception diminishes with each succeeding course of therapy. Before starting treatment, patients and their male partners should be advised of the possibility of multiple pregnancy and its potential hazards if conception occurs in relation to Clomid therapy.

Long-term cyclic therapy:

Not recommended.
Efficacy and safety of clomifene for more than 6 treatment cycles have not been demonstrated.

4.3 Contraindications

Pregnancy: Clomid is not indicated during pregnancy. Although there is no evidence that Clomid has a harmful effect on the human foetus, there is evidence that Clomid has a deleterious effect on rat and rabbit foetuses when given in high doses to the pregnant animal.

Clomid should not be administered during pregnancy. 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.

Liver disease: Clomid (Clomifene Citrate) therapy is contraindicated in patients with active liver disease, a history of liver dysfunction or a family or personal history of disorders of bilirubin metabolism.

Ovarian dysgenesis: Clomid is contraindicated in patients with ovarian dysgenesis, menopause or any state in which a response could not be expected.

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.

Visual disorder: Clomid is contraindicated in patients with a history of significant medically confirmed visual disorder related to Clomid use (previous or current treatment course).(See section 4.4.)

4.4 Special warnings and precautions for use

Warnings:

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

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. Rare cases of severe forms of OHSS have been reported where the following symptoms have occurred: 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 visual disorders such as accommodation disorders, blurred vision, spots or flashes (scintillating scotomata), may occasionally occur during or shortly after therapy with Clomid. These visual disorders are usually reversible; however, cases of prolonged or irreversible visual disorder sometimes associated with a partial or complete visual impairment (blindness) have been reported including after Clomid discontinuation.

These visual disorders occur especially with increased dosage or duration of therapy (See section 4.7 and 4.8).

The patient should be instructed to stop the treatment immediately whenever any unusual visual symptoms occur and inform the physician. In such cases a a complete ophthalmological examination is required and the treatment should be permanently discontinued if no other cause of visual disorder has been determined.

Hypersensitivity reactions

Hypersensitivity reactions including anaphylaxis and angioedema have been reported with the use of Clomid 50mg Tablets. In case of allergic reactions, treatment with Clomid 50mg Tablets must be discontinued and appropriate symptomatic treatment initiated (see Section 4.8).

Precautions:

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

Treatment with Clomid should only be undertaken by a specialist having available the appropriate facilities for close supervision of clinical and laboratory responses. The patient's physical state and the aetiological diagnosis should be carefully investigated prior to this therapy. Any pre-existent endocrine defect or other cause of infertility in patients or partner should be examined and treated prior to this therapy.

Multiple Pregnancy: There is an increased chance of multiple pregnancy when conception occurs in relationship to Clomid therapy. 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. Ectopic pregnancy associated with Clomid involves a multiple pregnancy with coexisting extrauterine and intrauterine gestations.

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

Pregnancy loss 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 foetuses from subfertile 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) loss 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%.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

None stated.

4.6 Fertility, pregnancy and lactation

Clomid should not be administered during pregnancy. See contraindications
(*See section 4.3, Contraindications*).

Lactation: It is not known whether clomiphene citrate is excreted in human milk. Clomiphene may reduce lactation.

4.7 Effects on ability to drive and use machines

Clomid has moderate influence on the ability to drive and use machines. Patients should be warned that a feeling of blurred vision or other visual symptoms may occasionally occur during treatment with Clomid or immediately after stopping it. These 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

The following CIOMS frequency rating is used, when applicable: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000); not known (cannot be estimated from the available data).

	Very common	Common	Uncommon	Rare	Not known
Eye disorders		Visual symptoms: blurring, scintillating scotomata (spots or flashes) after images		Cataracts Optic neuritis	Scotomata, Phosphenes, Reduced visual acuity, Diplopia, Eye pain, Accommodation disorders, Optic ischaemic neuropathy, Retinal detachment Central retinal vein occlusion Vitreous detachment,
Cardiac disorders					Tachycardia, Palpitations
Pregnancy, puerperium and perinatal					Multiple pregnancies, Simultaneous intrauterine and extra uterine pregnancies, Ectopic pregnancy

conditions					
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)					Endocrine related or dependent tumors/neoplasms (see section 4.4)
Nervous system disorders		Headache,	Dizziness, Light-headedness/ vertigo, Nervous tension /insomnia, Fatigue	Seizures	Syncope/fainting, Cerebrovascular accident, Cerebral thrombosis Neurologic impairment, Disorientation and speech disturbance, Transient paraesthesia,
Psychiatric disorders			Depression		Paranoid psychosis
Vascular disorders	Flushing				
Hepatobiliary disorders					Impaired hepatocellular function: abnormal bromosulphalein test (see below) , Jaundice
Gastrointestinal disorders		Nausea, Vomiting, Distension, Bloating			Pancreatitis
Skin and subcutaneous tissue disorders					Urticaria, Dermatitis/rash, Alopecia, Erythema multiforme, Ecchymosis, Angioneurotic oedema
Reproductive system and breast disorders	Ovarian enlargement	Breast discomfort, Inter-menstrual spotting or menorrhagia			Endometriosis, Exacerbation of pre-existing endometriosis reduced endometrial thickness, Massive ovarian enlargement
Metabolism and nutrition disorders					Hypertriglyceridemia
Immune System Disorders					Allergic reaction Hypersensitivity reactions including anaphylaxis and angioedema (see Section 4.4).

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.

Reproductive system and breast disorders:
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 100mg daily for 14 days. Abnormal ovarian enlargement usually regresses spontaneously; most of the patients with this condition should be treated conservatively.

Eye disorders: 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.

During post marketing, the above mentioned adverse drug reactions (ADRs) were reported in some cases with reversible or irreversible, partial or total, visual impairment (blindness), especially with increased dosage or duration of therapy (See sections 4.3, 4.4 and 4.9).

Hepatobiliary disorders:

Increased transaminases have been reported.

The Bromsulphalein test (BSP) is a test of liver function based on the removal of a known quantity of Brom-sulphalein from the blood in a measured period of time. Normal values are less than 5% retention at the end of 45 minutes with an intravenous dose of 5 mg/kg body weight. It is a useful test of hepatocellular disease and detoxifying ability but is not applicable in the presence of extra-hepatic or intrahepatic obstructive jaundice.

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 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 Clomid daily developed jaundice on the 19th day of treatment; liver biopsy revealed bile stasis without evidence of hepatitis.

Metabolism Disorders: Hypertriglyceridemia , 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.

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 HPRA Pharmacovigilance.
Website: www.hpra.ie

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

Clomid 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 days to 35 days and 0.45% per day of the ^{14}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 ^{14}C administration. The remaining drug/metabolites may be slowly excreted from a sequestered enterohepatic recirculation pool.

When Clomid is administered over prolonged periods it may interfere with cholesterol synthesis. Patients on prolonged therapy may show elevated blood levels of desmosterol.

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 to 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 monohydrate
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

Do not store above 25^{o}C. Store in the original container in order to protect from light.

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 tablets, 30 tablets and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special precautions required.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 December 1982

Date of last renewal: 01 December 2007

10 DATE OF REVISION OF THE TEXT

August 2023