AUSTRALIAN PRODUCT INFORMATION – CLOMID (CLOMIFENE CITRATE) TABLETS

1 NAME OF THE MEDICINE

Clomifene citrate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Clomid tablet contains the active ingredient 50 mg clomifene citrate.

Excipients with known effect: contains lactose and sugars. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Tablet, 50 mg (beige, scored on one side and M into two concentric circles engraved on the other side).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Clomid is indicated for the treatment of ovulatory failure in carefully selected infertile women who wish to become pregnant.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose for the first course of Clomid is 50 mg (one tablet) daily for five days. When ovulation occurs at this dosage there is no advantage in increasing the dose in subsequent cycles of treatment. If ovulation occurs at this dosage but is not followed by pregnancy, subsequent courses for a total maximum of six cycles of Clomid treatment may be administered.

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 five days should be given. Increase of the dosage or duration of therapy beyond 100 mg daily for five days should not be undertaken. If ovulatory menses do not occur, this dose may be repeated for two additional cycles but failure to induce ovulation after three consecutive cycles at this dosage should constitute an adequate therapeutic trial. If, however, ovulation does occur at this dosage but is not followed by pregnancy, subsequent courses for a total maximum of 6 cycles of Clomid treatment may be administered.

Therapy may be started at any time in a patient who has had no recent uterine bleeding but if progestin-induced bleeding is planned, or if spontaneous uterine bleeding occurs prior to

therapy, the course of Clomid 50mg daily for five days should be started on or about the fifth day of the cycle.

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

4.3 CONTRAINDICATIONS

Liver disease

Clomid is contraindicated in patients with known 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.

Pregnancy

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.

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 disorders

Clomid should not be given if history of significant, medically confirmed, vision disorders related to the use of Clomid (prior or ongoing treatment) is known.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Careful evaluation and selection of patients and close attention to dosage instructions, contraindications and side effects are mandatory. Since Clomid is indicated only in patients with ovarian dysfunction, other possible causes of infertility should be excluded or treated before giving Clomid.

A pelvic examination should be made before each course of Clomid is given.

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

Ovarian hyperstimulation syndrome (OHSS)

Ovarian hyperstimulation syndrome (OHSS) has been reported in patients receiving Clomid therapy alone or in combination with gonadotrophins. 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 abnormal ovarian enlargement associated with Clomid therapy, patients should be given the smallest dose possible of Clomid consistent with an expectation of good results. It should be borne in mind that maximal ovarian enlargement may not occur until several days after the treatment cycle is completed. Some patients with polycystic ovary syndrome who are unusually sensitive to gonadotrophin may have an exaggerated response to the usual doses of Clomid.

The patient should be instructed to inform the physician of any abdominal or pelvic pain, weight gain, discomfort or distension after taking Clomid.

Patients who complain of abdominal or pelvic pain, discomfort or distension after receiving Clomid should be examined for the presence of an ovarian cyst or other cause. Due to the fragility of enlarged ovaries in severe cases, abdominal and pelvic examination should be performed very cautiously. If abnormal enlargement of the ovary occurs, additional courses of Clomid should not be given until the ovaries have returned to pre-treatment size, and then a shorter course or smaller dose should be administered. Ovarian enlargement and cyst formation that is associated with Clomid therapy usually regresses spontaneously within a few days or weeks after discontinuing treatment. Unless surgical indication for laparotomy exists, such cystic enlargement should be managed conservatively. The dosage and/or duration of the next course of treatment should be reduced.

Risk of Ovarian Cancer

Available data indicate that the use of clomifene citrate may increase the risk of ovarian cancer, especially in nulligravid women (see Section 4.8 Adverse effects (undesirable effects)).

Patients should be evaluated for the presence of ovarian neoplasia before the start of treatment (see Section 4.3 Contraindications).

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 Clomid therapy. 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 symptoms is not yet understood. If they do occur Clomid should be discontinued and a complete ophthalmological evaluation should be made. No further courses of Clomid should be administered.

Patients should be warned that visual symptoms may render such activities as driving a car or operating machinery hazardous, particularly under conditions of variable lighting. The patient should be instructed to inform the physician whenever any unusual visual symptoms occur.

Hypersensitivity reactions

Hypersensitivity reaction 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 Adverse effects (Undesirable effects)).

Uterine fibroids

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

Hypertriglyceridemia

Cases of hypertriglyceridemia have been reported (see Section 4.8 Adverse effects (Undesirable effects)) in the postmarketing 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.

Carcinogenicity/mutagenicity

Epidemiological case control studies reported an increased relative risk for both ovarian cancer and ovarian tumours of low malignant potential in infertile women who used fertility drugs compared to women without a history of infertility. However, because infertility is a primary risk factor for ovarian cancer, and because of other limitations such as small sample sizes, it cannot be determined from these studies whether the use of fertility drugs increases the risk of ovarian cancer beyond the effect of infertility. Therefore, prolonged use of Clomid may increase the risk of developing a borderline or invasive ovarian tumour.

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

The mutagenic potential of Clomid has not been evaluated.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions with other drugs have not been documented.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

4.6.1.1 Multiple pregnancy

The incidence of multiple pregnancy is increased when conception takes place during a cycle in which Clomid is given. The potential complications and hazards of multiple pregnancy should be discussed with the patient.

In a large series of closely monitored patients who became pregnant after receiving Clomid, there were 6.9% (165) twins, 0.5% (11) triplets, 0.3% (7) quadruplets, and 0.13% (3) quintuplets. Of the 165 twin pregnancies for which sufficient information was available, the ratio of monozygotic to dizygotic twins was 1:5.

Of these multiple pregnancies, 357 live infants were born of 165 multiple births. After excluding 60 neonatal deaths, 297 survived, including 27 of 61 live infants from triplet, quadruplet, and quintuplet pregnancies. In addition, one sextuplet pregnancy has been reported in a patient treated with Clomid. Patients (and their husbands) should be advised of the possibility and potential complications and hazards of multiple pregnancy associated with Clomid therapy.

4.6.1.2 Ectopic pregnancy

There is an increased chance of ectopic pregnancy (including tubal and ovarian sites) in women who conceive following Clomid therapy.

Use in pregnancy

Category B3.

See Section 4.3 Contraindications, Pregnancy. Clomid was found to damage rat and rabbit foetuses when given in high doses to the pregnant animal. Clomid should not be used during pregnancy.

4.6.1.3 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%), 1.18% ectopic pregnancies, 0.17% hydatidiform mole, 0.04% foetus papyraceous and 1.01% of pregnancies with one or more stillbirths.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be warned that visual symptoms, dizziness, seizures or fatigue (see Section 4.8 Adverse Effects (Undesirable Effects)), may render such activities as driving a car or operating machinery more hazardous than usual, particularly under conditions of variable lighting. The patient should be instructed to inform the physician whenever any unusual visual symptoms occur.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Side effects are dose-related being more frequent and more severe when higher doses of Clomid are administered.

During clinical trials, the more common side effects included ovarian enlargement (13.6%), vasomotor flushes (10.4%), abdominal-pelvic discomfort (distension, bloating, pain or soreness) (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%).

Vasomotor symptoms resembling menopausal hot flushes are not usually severe and disappear soon after treatment is discontinued. Abdominal symptoms are most often related to ovulatory (Mittelschmerz) or pre-menstrual phenomena, or to ovarian enlargement. At recommended dosage, the normal variation in ovarian size may be exaggerated. Rare instances of massive ovarian enlargement and rupture of a lutein cyst with haemoperitoneum have been reported.

Neoplasm, benign, malignant and unspecified (including cysts and polyps): Ovarian malignancies (frequency not known).

Visual 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 a more brightly lit environment.

Immune system disorders, anaphylaxis, angioedema have been reported, frequency not known (see Section 4.4 Special warnings and precautions for use).

Ophthalmologically definable scotomata, phosphenes, reduced visual acuity and retinal cell function (electroretinographic) changes have also been reported. There have been 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 discontinuation. The visual disturbances may be irreversible, especially with increased dosage or duration of therapy.

Other less frequently reported symptoms included increased nervous tension, depression, fatigue, dizziness or light headedness, insomnia, heavier menses, weight gain, skin and subcutaneous tissue disorders, urticaria and allergic dermatitis/rash, increased urinary frequency, alopecia or moderate reversible hair loss, the frequency of erythema multiforme is not known.

Anxiety, nervousness and mood disturbances including altered mood, mood swings and irritability have been reported.

There have been reports of new cases of endometriosis and exacerbation of pre-existing endometriosis during Clomid therapy.

Isolated reports have been received of the occurrence of endocrine-related or dependent tumours/neoplasms or the aggravation of such growths.

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.

Seizures have been rarely reported. Transient paraesthesia has been reported.

Tachycardia, palpitations and pancreatitis have been reported.

Multiple pregnancies, including simultaneous intrauterine and extrauterine pregnancies, have been reported.

There is an increased chance of ectopic pregnancy (including tubal and ovarian sites) in women who conceive following Clomid therapy.

Reduced endometrial thickness has been reported.

Defects at birth have been reported in 58 infants from 2,369 delivered pregnancies in mothers treated with Clomid. Four of the infants were in the abortion/stillbirth category, 14 were from multiple pregnancies, and the remaining were single births. The defects have included Down's syndrome (5 infants), congenital heart lesions (8 infants), microcephaly (2 infants), harelip and cleft palate (2 infants), hypospadias (3 infants), undescended testes (2 infants), club foot (4 infants), gastrointestinal malformations (4 infants), congenital hip (2 infants) and polydactyly (both of twins).

Eight of the total of 58 infants were born to 7 of 158 mothers who received (inadvertently) a course of Clomid during the first 6 weeks after conception.

Clomid when given continuously for prolonged periods, may interfere with cholesterol synthesis. Serum from patients treated in this way appears to have elevated desmosterol levels. In patients taking recommended doses of Clomid, serum sterol patterns are not significantly altered.

Bromosulphophthalein (BSP) retention of greater than 5% has been reported in 32 of 141 patients in whom it was measured. Increased transaminases have been reported. Other liver function tests were usually normal. 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. One patient developed jaundice on the 14th day of Clomid therapy; liver biopsy revealed bile stasis without evidence of hepatitis. Clomid has not been reported to cause significant abnormality in the haematopoietic or renal system, the protein bound iodine or in serum cholesterol.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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 an overdose, appropriate supportive measures should be employed.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Ovulation stimulants, ATC code: G03BG02

Commonly associated diagnoses include polycystic ovary syndrome, lactation amenorrhoea syndrome, psychogenic amenorrhoea, certain cases of secondary amenorrhoea of undetermined aetiology, and post-oral contraceptive amenorrhoea. In such patients, approximately 70% will ovulate and (provided that there is no other cause of infertility in them or in their partners) about 30% will become pregnant. It is worthwhile to note that the data from which these percentages were derived included patients who were single and some who either did not desire pregnancy at the time of treatment or had impediments to achievement of pregnancy other than ovulatory dysfunction.

Good levels of endogenous oestrogen (estimated from vaginal smears, endometrial biopsy, assay or urinary oestrogen, or from bleeding in response to progesterone) are a favourable prognosis for treatment with Clomid, but reduced oestrogen levels do not always rule out the possibility of successful therapy.

Some anovulatory patients that appear to respond to Clomid but either do not actually ovulate or whose luteal phases are so short that the opportunity to conceive is limited may benefit by

having, following Clomid courses, injections of human chorionic gonadotrophin (HCG) at about the expected time of ovulation.

Clomid therapy is ineffective in patients in whom primary pituitary or ovarian failure precludes the possibility of stimulating normal function.

Mechanism of action

The ovulatory response to cyclic Clomid therapy appears to be mediated through increased output of pituitary gonadotrophins, which in turn stimulates 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 urinary excretion of gonadotrophins and the response of the ovary, as manifested by increased urinary oestrogen excretion.

Ovulation most often occurs from 6-12 days after a course of Clomid. With this in mind, coitus should be timed to coincide with the expected time of ovulation.

Although there is no evidence of a "carry over effect" of Clomid, spontaneous ovulatory menses have been noted after Clomid therapy in some patients.

Infertile patients with the polycystic ovary syndrome who have not responded to wedge resection of the ovary may respond to Clomid.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Orally administered 14C labelled clomifene citrate was readily absorbed when administered to humans.

Excretion

Cumulative excretion of the 14C label in 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%. Less than 1% per day was excreted in faecal and urine samples collected from 31 to 53 days after clomifene citrate 14C administration. Some clomifene and/or its metabolites (here measured as 14C) may therefore remain in the body during early pregnancy in women who conceive in the menstrual cycle of Clomid treatment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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.

The mutagenic potential of Clomid has not been evaluated. See Section 4.4 Special warnings and precautions for use.

Carcinogenicity

Epidemiological case control studies reported an increased relative risk for both ovarian cancer and ovarian tumours of low malignant potential in infertile women who used fertility drugs compared to women without a history of infertility. However, because infertility is a primary risk factor for ovarian cancer, and because of other limitations such as small sample sizes, it cannot be determined from these studies whether the use of fertility drugs increases the risk of ovarian cancer beyond the effect of infertility.

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

See Section 4.4 Special warnings and precautions for use.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sucrose, lactose monohydrate, pregelatinised maize starch, maize starch and magnesium stearate, iron oxide yellow.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 degrees Celsius.

6.5 NATURE AND CONTENTS OF CONTAINER

Clomid is available in PVC/Al blister packs of 5 or 10♦ tablets.

♦ Marketed pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Clomifene citrate is a white to pale yellow powder.

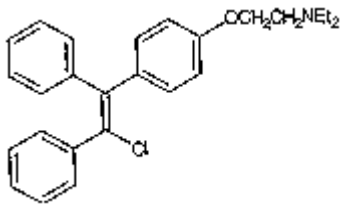
Chemical structure

Clomid contains clomifene citrate, a triarylethylene compound (related to chlorotrianisene and triparanol).

2-[4–(2–chloro–1,2–diphenylethenyl)phenoxyl]–N,N–diethylethanamine 2–hydroxy–1,2,3-propanetricarboxylate (1:1) or 2–[p–(2–chloro–1,2–diphenylvinyl) phenoxy] triethylamine citrate (1:1).

The empirical formula is $C_{26}H_{28}ClNO,C_6H_8O_7$ (MW = 598.09).

The structural formula appears below:



CAS number

50-41-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine (Schedule 4)

8 SPONSOR

Vitalion Pty Ltd
393 Bronte Road,
Bronte,
NSW 2024
Australia
Phone: 1800 954 410

9 DATE OF FIRST APPROVAL

8 July 1991

10 DATE OF REVISION

26 February 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Change in Sponsor details