1. Name of the medicinal product

CLOMIFENE TABLETS BP 50 MG

2. Qualitative and quantitative composition

SR. NO.	NAME OF THE INGREDIENTS	PHARMACOPEIAL SPECIFICATION	LABLE CLAIM	OVERAGES %	QTY. / TABLET	PURPOSE
ACTIVE INGREDIENTS						
1.	Clomifene citrate*	BP	50 mg	5.00%	52.500 mg	API
INACTIVE INGREDIENTS						
2.	Beta Cyclodextrin	BP	-	0.00 %	6.000 mg	Solubility enhancer
3.	Maize Starch	BP	-	0.00 %	112.500 mg	Diluent
4.	Anhydrous lactose	BP	-	0.00 %	77.000 mg	Diluent
5.	Croscarmellose sodium	BP	-	0.00 %	6.000 mg	Disintegrant
6.	Povidone	BP	-	0.00 %	10.500 mg	Binder
7.	Isopropyl Alcohol**	BP		0.00 %	0.200 ml	Solvent
8.	Colloidal silicon dioxide	USP	-	0.00 %	3.000 mg	Glidant
9.	Sodium lauryl Sulphate	BP	-	0.00 %	4.000 mg	Surfactant
10.	Croscarmellose sodium	BP	-	0.00 %	9.000 mg	Disintegrant
11.	Purified talc	BP		0.00 %	6.000 mg	Glidant
12.	Magnesium stearate	BP	-	0.00 %	3.000 mg	Lubricant
13.	Tartrazine Yellow	INHOUSE	-	0.00 %	0.500 mg	Colour

* 5.00% overages are added to the label claim due to narrow assay limit of finish product
** Evaporates during manufacturing & does not remain in final product

3. Pharmaceutical form

Oral Tablets

4. Clinical particulars

4.1 Therapeutic indications

Clomifene Tablets is indicated for the treatment of ovulatory failure in women desiring pregnancy. Clomifene 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 Tablets.

4.2 Posology and method of administration

Posology

Adults

The recommended dose for the first course of Clomifene Tablets (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.

Method of Administration: Oral.

4.3 Contraindications

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

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

Ovarian cyst: Clomifene 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.

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 Clomifene Tablets. A low level of oestrogen, although clinically less favourable, does not preclude successful outcome of therapy. Clomifene Tablets therapy is ineffective in patients with primary pituitary or primary ovarian failure. Clomifene 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 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 Tablets therapy for ovulation induction. In some cases, OHSS occurred following the cyclic use of Clomifene Tablets therapy or when Clomifene Tablets was used in

combination with gonadotropins. The following symptoms have been reported in association with this syndrome during Clomifene 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 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 Tablets. Maximal enlargement of the ovary may not occur until several days after discontinuation of the course of Clomifene Tablets. Some patients with polycystic ovary syndrome who are unusually sensitive to gonadotropin may have an exaggerated response to usual doses of Clomifene Tablets.

The patient who complains of abdominal or pelvic pain, discomfort, or distension after taking Clomifene 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 Tablets should not be given until the ovaries have returned to pre-treatment size. Ovarian enlargement and cyst formation associated with Clomifene 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) may occasionally occur during or shortly after therapy with Clomifene Tablets. These visual disturbances are usually reversible; however, cases of prolonged visual disturbance have been reported including after Clomifene Tablets 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 Clomifene Tablets use. In case of allergic reactions, treatment with Clomifene Tablets must be discontinued and appropriate symptomatic treatment initiated.

Precautions:

Cases of hypertriglyceridemia have been reported in the post-marketing experience with Clomifene Tablets. Pre-existing or family history of hyperlipidemia and use of higher than recommended dose and/or longer duration of treatment with Clomifene 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 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 Tablets 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 Tablets therapy. Multiple pregnancies, including simultaneous intrauterine and extrauterine pregnancies, have been reported.

Uterine Fibroids: Caution should be exercised when using Clomifene 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 Tablets 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 Tablets, 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 Tablets 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 Tablets 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 Clomifene 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 Tablets 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%.

Clomifene Tablets 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 Tablets was given before the 19^{th} day after conception or between the 20^{th} and 35^{th} 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 Pregnancy lactation and Fertility

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

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 Tablets 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 .
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.
These visual disturbances are usually reversible. However, cases of prolonged visual disturbance have been reported, including after Clomifene 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 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 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.
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 Clomifene Tablets now recommended. Retention was usually minimal unless associated with prolonged continuous Clomifene 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 Tablets (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 Clomifene 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)

4.9 Overdose

Toxic effects of acute overdosage of Clomifene 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 Pharmacodynamics properties

Pharmacotherapeutic group: ovulation stimulants, synthetic, **ATC code:** G03GB02.
Mechanism of action: The ovulatory response to cyclic Clomifene Tablets therapy is mediated through increased output of pituitary gonadotrophins, which in turn stimulates the maturation and endocrine activity of the ovarian follicle.

5.2 Pharmacokinetic properties

Orally administered 14C labelled Clomifene citrate was readily absorbed when administered to humans. Cumulative excretion of the 14C label by way of urine and feces averaged about 50% of the oral dose after 5 days in 6 subjects, with mean urinary excretion of 7.8% and mean fecal excretion of 42.4%.
A mean rate of excretion of 0.73% per day of the 14C dose after 31 – 35 days and 0.45% per day of the 14C dose after 42 – 45 days was seen in fecal and urine samples collected from 6 subjects for 14 – 53 days after Clomifene citrate 14C 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 Clomifene Tablets.
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

- Beta Cyclodextrin
- Maize Starch
- Anhydrous lactose
- Croscarmellose sodium
- Povidone
- Isopropyl Alcohol
- Colloidal silicon dioxide
- Sodium lauryl Sulphate
- Croscarmellose sodium
- Purified talc
- Magnesium stearate
- Tartrazine Yellow

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in dry place below 30^0 C. Protect from light.

6.5 Nature and contents of container

1 X 10 Tablets Alu-PVC Blister pack, packed in printed and laminated carton.

6.6 Special precautions for disposal and other handling

Not Applicable

7. Marketing authorization holder

West Coast Pharmaceutical Works LTD, Ahmedabad

8. Marketing authorization number(s)

Not Applicable

9. Date of first authorization/renewal of the authorization

Not Applicable

10. Date of revision of the text

February, 2021