PROFESSIONAL INFORMATION

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

CLOMIDEP Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains clomipramine hydrochloride BP 25 mg.

Preservative: Sodium methylparaben 0,028 % m/m.

Contains sugar: Lactose monohydrate 68,0 mg/tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

A blue coloured, circular film-coated tablet having a break line on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

- Treatment of depressive episodes, recurrent depressive disorders or major depression.
- Cataplexy accompanying narcolepsy.
- Obsessive-compulsive syndromes.

Children and adolescents:

Obsessive-compulsive syndromes in children 5 years of age and older.

4.2 Posology and method of administration

Posology

Medical supervision is essential.

Before initiating treatment with CLOMIDEP, any pre-existing hypokalaemia should be treated (see section 4.4)

The dosage should be determined individually and adapted to the patient's condition.

The lowest dose possible, in order to achieve an optimal therapeutic effect should be used and the dosage should be built up gradually to ensure maximum tolerability. Caution should be exercised in elderly and adolescent patients.

As a precaution against possible QTc prolongation and serotonergic toxicity, adherence to the recommended doses of CLOMIDEP is advised and any increase in dose should be made with caution if medicines that prolong QTc interval or other serotonergic agents are co-administered (see section 4.4 & section 4.5).

Adults:

Depression and obsessive-compulsive disorders:

Treatment should be initiated with 1 tablet of 25 mg 2 to 3 times daily.

The daily dosage should be raised stepwise, e.g. 25 mg every few days, (depending on how the medication is tolerated) to 2 to 4 tablets of 25 mg during the first week of treatment.

Higher doses may be needed in some patients, particularly those suffering from obsessional disorders.

A maximum dose of 250 mg should not be exceeded.

Once a distinct improvement has occurred, adjust the daily dosage to a maintenance level averaging two to four 25 mg tablets.

CLOMIDEP may be given in divided doses throughout the day or may be administered in a single dose at bedtime by administration of the 25 mg tablets. The dosage should be built up gradually for the single bedtime dose, in order to ensure maximum tolerability.

Cataplexy accompanying narcolepsy:

CLOMIDEP should be given orally in a daily dose of 25 to 75 mg.

Special populations

Elderly population

Initiate treatment with 1 tablet of 10 mg daily. Gradually raise the dosage to an optimum level of 30 to 50 mg daily, which should be reached after about 10 days and then adhered to until the end of treatment.

Paediatric population

Children (5 years of age and older) and adolescents:

Obsessive-compulsive syndromes:

The starting dose is 25 mg daily and should be gradually increased (also given in divided doses) during the first two weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller.

Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller.

Method of administration

Oral.

CLOMIDEP can be administered with or without food.

4.3 Contraindications

- Hypersensitivity to clomipramine, known hypersensitivity to tricyclic antidepressants belonging to the dibenzazepine group, or to any of the excipients listed in sections 6.1.
- Combination therapy with other antidepressants.
- Recent myocardial infarction
- Congenital long QT syndrome.
- Hypokalaemia.
- Concomitant treatment with CLOMIDEP and MAO-inhibitors is contraindicated. CLOMIDEP should not be administered for a period of at least 14 days after the discontinuation of treatment with MAO-inhibitors due to the potential for severe interactions; severe hypertensive reactions, hyperpyretic crisis, convulsions and fatalities have been reported.
- The same caution should also be observed when administering a MAO-inhibitor after previous treatment with CLOMIDEP (see section 4.5).

- Contraindicated in breastfeeding, see section 4.6

4.4 Special warnings and precautions for use

This medicine should at all times be kept out of reach of children, as relatively small overdoses may be fatal to them.

Caution should be exercised when prescribing tricyclic antidepressants in patients with:

- Cardiovascular insufficiency, atrioventricular block (grades I to III) and dysrhythmias.
- Narrow-angle glaucoma.
- Disorders of micturition due to an impeded flow of urine (e.g. in diseases of the prostate).
- A low convulsion threshold (e.g. due to brain damage of varying aetiology, epilepsy, alcoholism).
- Severe hepatic or renal disease.
- Tumours of the adrenal medulla (e.g. phaeochromocytoma, neuroblastoma) in whom the medicine may provoke hypotensive crisis.
- Simultaneous treatment of patients with CLOMIDEP and electroconvulsive therapy should only be resorted to under careful supervision.
- **Anaphylactic shock:** Isolated cases of anaphylactic shock have been reported.

Risk of suicide:

Risk of suicide is inherent to severe depression and may persist until significant remission occurs. Patients with depressive disorders, both adult and paediatric, may experience worsening of depression and/or suicidality or other psychiatric symptoms, whether or not they are taking antidepressant medication. Antidepressants increased the risk of suicidal thinking and behaviour (suicidality) in short-term studies in children and adolescents with depressive disorders and other psychiatric disorders.

All patients being treated with CLOMIDEP for any indication should be observed closely for clinical worsening, suicidality and other psychiatric symptoms (see section 4.8), especially during the initial phase of therapy or at times of dose changes.

Modifying the therapeutic regimen, including possibly discontinuing the medication, should be considered in these patients, especially if these changes are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of both paediatric and adult patients being treated with antidepressants for both

psychiatric and non-psychiatric indications, should be alerted about the need to monitor patients for the emergence of other psychiatric symptoms (see section 4.8), as well as the emergence of suicidality, and to report such symptoms immediately to health care providers.

Prescriptions for CLOMIDEP should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

In children and adolescents, there is not sufficient evidence of safety and efficacy of CLOMIDEP in the treatment of depressive states of varying aetiology and symptomatology and cataplexy accompanying narcolepsy.

The use of CLOMIDEP in children and adolescents (0-17 years of age) in these indications is therefore not recommended.

Other psychiatric effects:

Activation of psychosis has occasionally been observed in patients with schizophrenia receiving CLOMIDEP.

Caution should be observed with patients suffering from a bipolar disorder, as hypomania or mania can be precipitated in such patients. Withdraw CLOMIDEP immediately if the depression turns into a manic phase.

In predisposed and elderly patients, CLOMIDEP may, particularly at night, provoke pharmacogenic (delirious) psychoses, which may disappear without treatment within a few days of withdrawing the medicine.

Cardiac and vascular disorders:

Tricyclic antidepressants such as CLOMIDEP should be employed with caution in patients with cardiovascular disorders, especially those who have a history of conduction disorders and elderly patients. Monitoring of cardiovascular function and ECG is advised in such cases.

There is a risk of QTc prolongation and torsades de pointes, particularly at supra-therapeutic doses or supra-therapeutic plasma concentrations of clomipramine, as occur in the case of co-medication with selective serotonin reuptake inhibitors (SSRIs) or serotonin and noradrenergic reuptake inhibitors (SNaRIs). Therefore, concomitant administration of medicines that can cause accumulation of clomipramine should be avoided. Equally, concomitant administration of medicines that can prolong the QTc interval should be avoided (see sections 4.2 and 4.5).

It is established that hypokalaemia is a risk-factor of QTc prolongation and torsades de pointes. Therefore, hypokalaemia should be treated before initiating treatment with CLOMIDEP (see sections 4.2 and 4.5).

Before initiating treatment it is advisable to check the patient’s blood pressure because hypotensives and

individuals with a labile circulation may react to the medicine with a fall in blood pressure. This can be controlled by reducing the dosage.

Serotonin syndrome:

Due to the risk of serotonergic toxicity, it is advisable to adhere to recommended doses. Serotonin Syndrome, with symptoms such as hyperpyrexia, myoclonus, agitation, seizures, delirium and coma, can possibly occur when CLOMIDEP is administered with serotonergic co-medications such as SSRIs, SNaRIs, tricyclic antidepressants or lithium (see sections 4.2 and 4.5). For fluoxetine a washout period of two to three weeks is advised before and after treatment with fluoxetine.

Convulsions:

CLOMIDEP should be used with caution in patients with epilepsy or in patients prone to convulsions or seizures; and also in other predisposing factors such as brain damage, concomitant use of neuroleptics, withdrawal from alcohol or medicines with anticonvulsive properties (e.g. benzodiazepines). The occurrence of seizures is dose related; therefore the recommended total daily dose of CLOMIDEP should not be exceeded.

Anticholinergic effects:

Narrow-angle glaucoma may be aggravated.

Particular caution is indicated when employing CLOMIDEP in the presence of disorders of micturition due to an impeded flow of urine (e.g. in diseases of the prostate), since in patients suffering from prostatism, urinary retention may be precipitated.

Decreased lacrimation and accumulation of mucoid secretion due to the anticholinergic properties of tricyclic antidepressants may cause damage to the corneal epithelium in patients with contact lenses. The use of artificial tears is recommended in these patients.

The simultaneous administration of anticholinergic agents may be dangerous (see section 4.5).

Specific treatment populations:

Caution is indicated in patients with hyperthyroidism or in the case of concomitant treatment with thyroid preparations since aggravation of unwanted cardiac effects may occur owing to the anticholinergic action.

In patients with liver disease, periodic monitoring of hepatic enzyme levels is recommended.

CLOMIDEP may cause paralytic ileus especially in the elderly and in bedridden patients and those patients suffering from chronic constipation.

Prolonged treatment with CLOMIDEP can lead to an increased incidence of dental caries. Regular dental check-ups are therefore advisable during long-term treatment.

Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available.

White blood cell count:

Occurrences of agranulocytosis have been connected with the use of CLOMIDEP. It is therefore also advisable to perform blood counts during treatment with CLOMIDEP, especially if the patient develops fever, an influenzal infection or sore throat.

Anaesthesia:

Before general or local anaesthesia, the anaesthetist should be told that the patient has been receiving CLOMIDEP.

Treatment discontinuation:

Abrupt withdrawal should be avoided because of possible adverse reactions. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see section 4.8, for a description of the risks of discontinuation of CLOMIDEP).

The risks of central nervous system depression are greater when administered together with other central nervous system depressants (e.g. alcohol and barbiturates) and should therefore not usually be administered simultaneously. Since CLOMIDEP may diminish alcohol tolerance, patients should be advised to abstain from alcohol while under treatment.

Owing to its antagonistic effect on dopamine, CLOMIDEP may increase prolactin secretion.

Blood sugar concentrations may be altered in diabetic patients.

Excipients

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

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions:

Adrenergic neurone blockers:

CLOMIDEP may diminish or abolish the antihypertensive effects of guanethidine, betanidine, reserpine, clonidine and alpha-methyldopa. Patients requiring co-medication for hypertension should therefore be given antihypertensives of a different type (e.g. vasodilators or beta-blockers).

Anticholinergic agents:

CLOMIDEP may potentiate the effects of anticholinergic agents (e.g. phenothiazine, antiparkinsonian agents, antihistamines, atropine, biperiden).

CNS depressants:

The risks of central nervous system depression are greater when CLOMIDEP is administered together with other central nervous system depressants (e.g. alcohol and barbiturates) and should therefore not usually be administered simultaneously.

Diuretics:

Co-medication of CLOMIDEP with diuretics may lead to hypokalaemia, which in turn increases the risk of QTc prolongation and torsades de pointes. Hypokalaemia should therefore be treated prior to administration of CLOMIDEP (see sections 4.2 and 4.4).

MAO-Inhibitors:

Do not give CLOMIDEP for at least 2 weeks after discontinuation of treatment with MAO-inhibitors (there is a risk of severe symptoms such as hypertensive crisis, hyperpyrexia and those consistent with Serotonin Syndrome e.g. myoclonus, agitation, seizures, delirium and coma).

The same applies when giving a MAO-inhibitor after previous treatment with CLOMIDEP. In both instances CLOMIDEP or the MAO-inhibitor should initially be given in small, gradually increasing doses and its effects monitored (see section 4.3).

Selective serotonin re -uptake inhibitors (SSRI):

Concomitant administration of CLOMIDEP with selective serotonin re-uptake inhibitors (e.g. fluoxetine and fluvoxamine) may lead to additive effects on the serotonergic system (see *Serotonergic Agents).*

Serotonergic medicines:

Serotonin Syndrome can possibly occur when clomipramine is administered with serotonergic co-medications such as selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenergic reuptake inhibitors (SNaRIs),

tricyclic antidepressants or lithium (see sections 4.2 and 4.4). For fluoxetine, a washout period of two to three weeks is advised before and after treatment with fluoxetine.

Sympathomimetic medicines:

CLOMIDEP may potentiate the cardiovascular effects of norepinephrine or epinephrine and the use of local anaesthetics and nose drops containing these vasoconstrictors should be avoided as hypertensive reactions may occur.

Pharmacokinetic interactions:

CLOMIDEP (clomipramine) is predominantly eliminated through metabolism. The primary route of metabolism is demethylation to form the active metabolite, /V-desmethylclomipramine, followed by hydroxylation and further conjugation of both /V-desmethylclomipramine and the parent medicine. Several cytochrome P450s are involved in the demethylation, mainly CYP3A4, CYP2C19 and CYP1A2.

Elimination of both active components is by hydroxylation and this is catalyzed by CYP2D6.

Concomitant administration of CYP2D6 inhibitors may lead to an increase in concentration of both active components, up to 3-fold in patients with a debrisoquine/sparteine extensive metaboliser phenotype, converting them to a poor-metaboliser phenotype. Concomitant administration of CYP1A2, CYP2C19 and CYP3A4 inhibitors are expected to increase clomipramine concentrations and decrease /V-desmethylclomipramine, thus not necessarily affecting the overall pharmacology.

MAO inhibitors, which are also potent CYP2D6 inhibitors in vivo, such as moclobemide, are contraindicated for coadministration with clomipramine (such as CLOMIDEP, see section 4.3).

Antidysrhythmic medicines (such as quinidine and propafenone), which are potent inhibitors of CYP2D6, should not be used in combination with tricyclic antidepressants such as CLOMIDEP.

SSRIs which are inhibitors of CYP2D6, such as fluoxetine, paroxetine, orsertraline, and of others including CYP1A2 and CYP2C19 (e.g. fluvoxamine), may also increase plasma concentrations of clomipramine (such as CLOMIDEP), with corresponding adverse effects. Steady- state serum levels of clomipramine increased ~ 4-fold by co- administration of fluvoxamine (/V-desmethylclomipramine decreased~ 2-fold) (see sections 4.2 and 4.3).

Comedication of neuroleptics (e.g. phenothiazines) may result in increased plasma levels of tricyclic antidepressants (such as CLOMIDEP), a lowered convulsion threshold, and seizures. Combination with thioridazine may produce severe cardiac dysrhythmias.

Coadministration with histamine$_2$ (H_2)-receptor antagonist, cimetidine (an inhibitor of several P450 enzymes, including CYP2D6 and CYP3A4), may increase plasma concentrations of clomipramine whose dosage should therefore be reduced.

No interaction between chronic oral contraceptive use (15 or 30 micrograms ethinyl oestradiol daily) and CLOMIDEP (25 mg daily) has been documented.

Oestrogens are not known to be inhibitors of CYP2D6, the major enzyme involved in clomipramine clearance and, therefore, no interaction is expected.

Although, in a few cases with high dose oestrogen (50 micrograms daily) and the tricyclic antidepressant imipramine, increased side effects and therapeutic response were noted, it is unclear as to the relevance of these cases to CLOMIDEP (clomipramine) and lower dose oestrogen regimens. Monitoring therapeutic response of tricyclic antidepressants at high dose oestrogen regimens (50 micrograms daily) is recommended and dose adjustments may be necessary.

Methylphenidate (e.g. Ritalin) may also increase concentrations of tricyclic antidepressants by potentially inhibiting their metabolism, and a dose reduction of the tricyclic antidepressant such as CLOMIDEP may be necessary.

Some tricyclic antidepressants such as CLOMIDEP may potentiate the anticoagulant effect of coumarin medicines, such as warfarin, and this may be through inhibition of their metabolism (CYP2C9). There is no evidence for the ability of clomipramine to inhibit the metabolism of anticoagulants, such as warfarin, however, careful monitoring of plasma prothrombin has been advised for this class of medicines.

Concomitant administration of medicines known to induce cytochrome P450 enzymes, particularly CYP3A4, CYP2C19, and/or CYP1A2 may accelerate the metabolism and decrease the efficacy of CLOMIDEP.

CYP3A and CYP2C inducers, such as rifampicin or anticonvulsants (e.g. barbiturates, carbamazepine, phenobarbital and phenytoin), may decrease CLOMIDEP (clomipramine) concentrations.

Known inducers of CYP1A2 (e.g. nicotine/components in cigarette smoke), decrease plasma concentrations of tricyclic medicines.

In cigarette smokers, CLOMIDEP (clomipramine) steady-state plasma concentrations were decreased 2 -fold compared to non-smokers (no change in /V-desmethylclomipramine).

CLOMIDEP (clomipramine) is also an in vitro (K_i < = 2.2 microM) and in vivo inhibitor of CYP2D6 activity (sparteine oxidation) and therefore, may cause increased concentrations of co-administered compounds that are

primarily cleared by CYP2D6 in extensive metabolisers.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety in pregnancy has not been established.

There have been reports of withdrawal symptoms in babies born to mothers who received CLOMIDEP shortly before delivery.

Lactation:

Since the active substance passes into the breast milk, nursing mothers receiving CLOMIDEP should not breastfeed their infants.

4.7 Effects on ability to drive and operate machines

At the time of initiation of therapy, patients should be advised not to drive a motor vehicle, climb dangerous heights or operate machinery for at least several days. In these situations, impaired decision making could lead to accidents.

4.8 Undesirable effects

Tabulated list of adverse reactions

MedDRA System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	*Less frequent*	Leukopenia, agranulocytosis, thrombocytopenia, eosinophilia and purpura.
Immune system disorders	*Less frequent*	Allergic alveolitis (pneumonitis) with or without eosinophilia, systemic anaphylactic / anaphylactoid reactions including hypotension.
Endocrine disorders	*Less frequent*	SIADH (inappropriate antidiuretic hormone secretion syndrome).

Metabolism and nutrition disorders	*Frequent*	Weight gain; increased appetite, anorexia
Psychiatric disorders	*Frequent*	Drowsiness, transient fatigue, restlessness, confusion, disorientation, hallucinations (particularly in geriatric patients and patients suffering from Parkinson's disease), anxiety states, agitation, sleep disturbances, mania, hypomania, aggressiveness, impaired memory, depersonalisation, depression aggravated, impaired concentration, insomnia, nightmares, yawning.
	Less frequent	Activation of psychotic symptoms.
Nervous system disorders	*Frequent*	Dizziness, tremor, headache, myoclonus, delirium, speech disorders, paraesthesia.
	Less frequent	Ataxia, convulsions, EEG changes, hyperpyrexia, neuroleptic malignant syndrome, peripheral neuropathy.
Eye disorders	*Frequent*	Disorders of visual accommodation and blurred vision, mydriasis.
	Less frequent	Glaucoma.
Ear and labyrinth disorders	*Frequent*	Tinnitus.

Cardiac disorders	*Frequent*	Sinus tachycardia, palpitations, postural hypotension, clinically insignificant ECG changes (e.g. ST and T changes), in patients of normal cardiac status.
	Less frequent	Dysrhythmias, increased blood pressure; conduction disorders (e.g. widening of QRS complex, prolonged QT interval, PQ changes, bundle-branch block, torsade de pointes, particularly in patients with hypokalaemia).
Vascular disorders	*Frequent*	Hot flushes; sweating.
Gastrointestinal disorders	*Less frequent*	Nausea; vomiting, abdominal disorders, diarrhoea, taste disturbances, stomatitis, dry mouth.
Hepato-biliary disorders	*Frequent*	Elevated transaminases.
	Less frequent	Hepatitis with or without jaundice.
Skin and subcutaneous tissue disorders	*Frequent*	Allergic skin reactions (skin rash, urticaria), photosensitisation, pruritus
	Less frequent	Oedema (local or generalised), hair loss.
Musculoskeletal and connective tissue disorders	*Frequent*	Muscle weakness, muscle hypertonia.
Renal and urinary disorders	*Less frequent*	Urinary retention.
Reproductive system and breast disorders	*Frequent*	Disturbances of libido and potency, breast enlargement, galactorrhoea.
General disorders and administration site conditions	*Frequent*	The following symptoms commonly occur after abrupt withdrawal or

		reduction of the dose: Nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness and anxiety (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Signs and symptoms:

Overdosage and poisoning may be characterised by central nervous system depression or excitation, severe anticholinergic effects (which set in about a half to two hours after ingestion) and cardiotoxicity. The following symptoms and signs are characteristic of acute overdosage:

Central nervous system:

Drowsiness, stupor, coma, ataxia, restlessness, agitation, enhanced reflexes, muscular rigidity and choreoathetoid movements, convulsions. In addition, symptoms consistent with Serotonin Syndrome (e.g. hyperpyrexia, myoclonus, delirium and coma) may be observed.

Cardiovascular system:

Hypotension, tachycardia, arrhythmias, QTc prolongation and dysrhythmias including torsades de pointes, conduction disorders, shock, heart failure, in very rare cases cardiac arrest.

Respiratory depression, cyanosis, vomiting, fever, mydriasis, sweating and oliguria or anuria may also occur.

Treatment:

There is no specific antidote.

Since physostigmine increases the risk of seizures occurring, it should not be used.

Attempts should be made to eliminate the medicine by inducing vomiting if the patient is alert and/or irrigating the stomach. The patient should be transferred to hospital and vital functions safeguarded.

Activated charcoal should be administered.

Treatment is symptomatic and supportive.

Vital functions (including the ECG) should be monitored for not less than 5 days.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 1.2 Psychoanaleptics (antidepressants)

Clomipramine has actions at several sites. These include alpha$_1$-adrenolytic, anticholinergic, antihistaminic and antiserotonergic activities.

The therapeutic activity of clomipramine is believed to be based on its ability to inhibit neuronal re-uptake of serotonin, primarily, and also norepinephrine.

5.2 Pharmacokinetic properties

Absorption: The active substance is completely absorbed by the oral and intramuscular routes.

Plasma concentration: May range between 20 to 175 ng/ml after oral administration of a daily dosage of 75 mg. There are large inter- individual differences in clomipramine's distribution and clearance.

Steady-state concentrations of the active metabolite desmethylclomipramine are 40 to 85 % higher than those of clomipramine.

Owing to lower clearance of clomipramine, doses should be adjusted in elderly patients. The concentration in the CSF is equivalent to approximately 2 % of the plasma concentration.

Protein binding: 97,6 %.

Plasma half-life for the beta-phase of elimination: approximately 21 hours.

Distribution volume: approximately 12 litres/kg body mass.

Biotransformation:

The primary route of clomipramine metabolism is demethylation to form the active metabolite, /V-desmethylclomipramine.

/V-desmethylclomipramine can be formed by several P 450 enzymes, primary CYP3A4, CYP2C19 and CYP1A2.

Clomipramine and /V- desmethylclomipramine are hydroxylated to form 8-hydroxyclomipramine or 8-hydroxy-/V-

desmethylclomipramine. The activity of the 8-hydroxy metabolites are not defined in vivo. Clomipramine is also hydroxylated at the 2-position and /V-desmethylclomipramine can be further demethylated to form didesmethylclomipramine. The 2- and 8-hydroxy metabolites are excreted primarily as glucuronides in the urine. Elimination of the active components, clomipramine and /V-desmethylclomipramine by formation of 2- and 8-hydroxy clomipramine is catalysed by CYP2D6.

Excretion:

Two-thirds in the form of water- soluble conjugates in the urine, and approximately one -third in the faeces. The quantity of unchanged clomipramine and of active metabolites excreted in the urine amounts to less than 1 % of the dose administered.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Brilliant blue lake

Colloidal anhydrous silica

Lactose monohydrate

Magnesium stearate

Maize starch

Microcrystalline cellulose

Purified talc

Sodium methyl paraben

Sodium starch glycolate

Film-coat

Acetone

Amino methacrylic acid copolymer (Eudragit E 100)

Brilliant blue lake

Isopropyl alcohol

Macrogol 6 000

Magnesium stearate

Purified talc

Sodium lauryl sulphate

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 25 °C in a cool, dry place, protected from light.

6.5 Nature and contents of container

Aluminium-aluminium strip pack

CLOMIDEP tablets are available in an aluminium-aluminium strip pack. Five such strips of 10 tablets each are packed in an outer carton.

PVC cold form blister pack

CLOMIDEP tablets are available in a PVC cold form blister pack. Five of such blisters of 10 tablets each are packed in an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

a Sun Pharma Company

14 Lautre Road, Stormill Ext 1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER

35/1.2/0253

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 October 2003

10. DATE OF REVISION OF THE TEXT

13 May 2022