APPROVED 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

PROFESSIONELE INLIGTING

SKEDULERINGSTATUS: S5

1. NAAM VAN DIE MEDISYNE

CLOMIDEP Filmbedekte tablette

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

Elke filmbedekte tablet bevat 25 mg klomipramienhidrochloried BP.

Preserveermiddel: Natriummetielparabeen 0,028 % *m/m*.

Bevat suiker: 68,0 mg laktosemonohidraat per tablet.

Vir die volledige lys van hulpstowwe, sien afdeling 6.1.

3. FARMASEUTIESE VORM

Filmbedekte tablette.

'n Blou, ronde, filmbedekte tablet met 'n breeklyn aan die een kant.

4. KLINIESE BESONDERHEDE

4.1 Terapeutiese indikasies

Volwassenes:

- Behandeling van depressiewe episodes, herhaalde depressiewe versteurings of major depressie.
- Katapleksie gepaardgaande met narkolepsie.
- Obsessief-kompulsiewe sindrome.

Kinders en adolessente:

Obsessief-kompulsiewe sindrome by kinders van 5 jaar en ouer.

4.2 Posologie en metode van toediening

Posologie

Mediese toesig is noodsaaklik.

Enige voorafbestaande hipokalemie moet behandel word voordat treapie met CLOMIDEP begin word (sien afdeling 4.4).

Die dosis moet vir elke individu bepaal word en volgens die pasiënt se toestand aangepas word.

Die laagste moontlike dosis moet gebruik word om die optimale terapeutiese effek te behaal en die dosering moet geleidelik verhoog word om maksimum verdraagsaamheid te verseker. Omsigtigheid is nodig by bejaarde en adolessente pasiënte.

As ’n voorsorgmaatreël teen moontlike QTc-verlenging en serotonergiese toksisiteit, word aangeraai dat gehou word by die aanbevole dosisse vir CLOMIDEP en enige verhoging van die dosis moet versigtig gedoen word indien medisynes wat die QTc-interval verleng of ander serotonergiese middels gepaardgaande toegedien word (sien afdeling 4.4 & afdeling 4.5).

Volwassenes:

Depressie en obsessief-kompulsiewe versteurings:

Behandeling moet begin word met 1 tablet van 25 mg 2 tot 3 keer daagliks.

Die daaglikse dosering moet stapsgewyse verhoog word, bv. 25 mg elke paar dae (afhangende van hoe die medikasie verdra word) tot by 2 tot 4 tablette van 25 mg gedurende die eerste week van behandeling.

Sommige pasiënte mag hoër dosisse nodig hê, veral dié wat aan obsessionele versteurings ly.

’n Maksimumdosis van 250 mg moenie oorskry word nie.

Sodra ’n duidelike verbetering voorgekom het, pas die daaglikse dosering aan tot ’n instandhoudingsvlak van gemiddeld twee tot vier 25 mg tablette.

Deur toediening van die 25 mg tablette kan CLOMIDEP in verdeelde dosisse regdeur die dag gegee word, of dit kan as ’n enkele dosis teen slapenstyd gegee word. Die dosering moet geleidelik verhoog word vir die enkele dosis teen slapenstyd, om maksimum verdraagsaamheid te verseker.

Katapleksie gepaardgaande met narkolepsie:

CLOMIDEP moet oraal toegedien word teen ’n daaglikse dosis van 25 tot 75 mg.

Spesiale populasies

Bejaarde populasie

Begin behandeling met 1 tablet van 10 mg daagliks. Verhoog die dosering geleidelik na ’n optimum vlak van 30 tot 50 mg daagliks, wat na omtrent 10 dae bereik behoort te word en dan tot die einde van behandeling volgehou moet word.

Pediatriese populasie

Kinders (5 jaar en ouer) en adolessente:

Obsessief-kompulsiewe sindrome:

Die aanvangsdosis is 25 mg daagliks en behoort geleidelik verhoog te word (ook in verdeelde dosisse gegee) tydens die eerste paar weke, soos wat dit deur die pasiënt verdra word, tot ’n daaglikse maksimum van 3 mg/kg of 100 mg, watter een ook al die laagste is.

Daarna kan die dosering oor die volgende paar weke geleidelik verhoog word tot ’n daaglikse maksimum van 3 mg/kg of 200 mg, watter een ook al die laagste is.

Metode van toediening

Oraal.

CLOMIDEP kan met of sonder voedsel toegedien word.

4.3 Kontra-indikasies

- Hipersensitiwiteit vir klomipramien, bekende hipersensitiwiteit vir trisikliese antidepressante wat aan die dibensasepien-groep behoort, of vir enige van die hulpstowwe gelys by afdeling 6.1.
- Kombinasieterapie met ander antidepressante.
- Onlangse miokardiale infarksie.
- Kongenitale lang QT-sindroom.
- Hipokalemie.
- Gepaardgaande behandeling met CLOMIDEP en MAO-inhibitors word teenaangedui. CLOMIDEP moet vir ’n tydperk van ten minste 14 dae na staking van behandeling met MAO-inhibitors nie toegedien word nie, weens die potensiaal vir hewige interaksies; hewige hipertensiewe reaksies, hiperpiretiese krisis, konvulsies en noodlottige gevalle is gerapporteer.
- Dieselfde omsigtigheid is nodig wanneer ’n MAO-inhibitor na vorige behandeling met CLOMIDEP toegedien word (sien afdeling 4.5).

- Teenaangedui tydens borsvoeding, sien afdeling 4.6.

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

Hierdie medisyne moet te alle tye buite bereik van kinders gehou word, aangesien relatief klein oordosisse vir hulle dodelik mag wees.

Versigtigheid is nodig wanneer trisikliese antidepressante voorgeskryf word aan pasiënte met:

- Kardiovaskulêre ontoereikendheid, atrioventrikulêre blok (grade I tot III) en disritmieë.
- Nouhoekgloukoom.
- Versteurings van mikturisie weens belemmerde urienvloei (bv. by siektes van die prostaat).
- 'n Lae drempel vir konvulsies (bv. weens breinskade met verskillende etiologie, epilepsie, alkoholisme).
- Erge lewer- of niersiekte.
- Tumore van die adrenale medulla (bv. feochromositoom, neuroblastoom), waar die medisyne hipotensiewe krisis kan uitlok.
- Gelyktydige behandeling van pasiënte met CLOMIDEP en elektrokonvulsiewe terapie moet slegs onder streng toesig toegepas word.
- **Anafilaktiese skok:** Daar is geïsoleerde gevalle van anafilaktiese skok gerapporteer.

Risiko van selfdood:

Risiko van selfdood is inherent aan erge depressie en kan volhou totdat beduidende remissie voorkom. Pasiënte met depressiewe steurings, beide volwasse en pediatries, mag verergering van depressie en/of selfdoodneigings of ander psigiatriese simptome ondervind, of hulle antidepressant-medikasie neem of nie. Antidepressante het die risiko van selfdoodgedagtes en -gedrag (selfdoodneigings) verhoog in korttermynstudies by kinders en adolessente met depressiewe versteurings en ander psigiatriese versteurings. Alle pasiënte wat vir enige indikasie met CLOMIDEP behandel word, moet noukeurig waargeneem word vir kliniese agteruitgang, selfdoodneigings en ander psigiatriese simptome (sien afdeling 4.8), veral tydens die aanvanklike fase van terapie of wanneer die dosis verander word.

Aanpassing van die terapeutiese regimen, insluitende moontlike staking van die medikasie, behoort by hierdie pasiënte oorweeg te word, veral indien hierdie simptome hewig is, vinnige aanvang het, of nie deel was van die simptome waarmee die pasiënt gepresenteer het nie.

Families en versorgers van beide pediatriese en volwasse pasiënte wat met antidepressante behandel word vir

sowel psigiatriese as nie-psigiatriese indikasies, moet gewaarsku word rakende die noodsaaklikheid om pasiënte vir die verskyning van ander psigiatriese simptome (sien afdeling 4.8) te monitor, sowel as die verskyning van selfdoodneigings, en om sulke simptome onmiddellik aan gesondheidsorgverskaffers te rapporteer.

Die kleinste hoeveelheid CLOMIDEP-tablette moet in ooreenstemming met goeie pasiëntbestuur voorgeskryf word, ten einde die risiko van oordosering te verlaag.

By kinders en adolessente, is daar nie genoegsame bewys van die veiligheid en doelmatigheid van CLOMIDEP in die behandeling van depressiewe toestande van wisselende etiologie en simptomatologie, en katapleksie met gepaardgaande narkolepsie nie.

Die gebruik van CLOMIDEP by kinders en adolessente (0 – 17 jaar oud) word gevolglik nie vir hierdie indikasies aanbeveel nie.

Ander psigiatriese effekte:

Per geleentheid is waargeneem dat psigose geaktiveer word by pasiënte met skisofrenie wat CLOMIDEP ontvang.

Omsigtigheid is nodig by pasiënte wat aan bipolêre steuring ly, aangesien hipomanie of manie by sulke pasiënte geaktiveer kan word. Onttrek CLOMIDEP onmiddellik indien die depressie oorgaan in ’n maniese fase.

By pasiënte wat geneig is daartoe en by bejaarde pasiënte, kan CLOMIDEP, veral snags, farmakogeniese (ylhoofdige) psigoses uitlok, wat sonder behandeling binne ’n paar dae nadat die medisyne onttrek is kan verdwyn.

Kardiale en vaskulêre versteurings:

Trisikliese antidepressante soos CLOMIDEP moet versigtig gebruik word by pasiënte met kardiovaskulêre versteurings, veral dié met ’n geskiedenis van geleidingsversteurings en bejaarde pasiënte. Monitering van kardiovaskulêre funksie en EKG word in sulke gevalle aanbeveel.

Daar is ’n risiko van QTc-verlenging en torsades de pointes, veral teen supra-terapeutiese dosisse of supra-terapeutiese plasmakonsentrasies van klomipramien, soos wat voorkom in die geval van gepaardgaande toediening van selektiewe serotonienheropname-inhibitors (SSRI’s) of serotonien- en noradrenergiese heropname-inhibitors (SNaRI’s). Gelyktydige toediening van medisynes wat akkumulasie van klomipramien kan veroorsaak, moet dus vermy word. Eweneens moet gepaardgaande toediening van medisynes wat die QTc-

interval kan verleng, vermy word (sien afdelings 4.2 en 4.5).

Dit is vasgestel dat hipokalemie ’n risikofaktor vir QTc-verlenging en torsades de pointes is. Hipokalemie moet dus behandel word voordat behandeling met CLOMIDEP begin word (sien afdelings 4.2 en 4.5).

Dit is raadsaam om die pasiënt se bloeddruk na te gaan voordat behandeling begin word, want hipotensiewe persone en individue met ’n onstabiele bloedsomloop mag op die medisyne reageer met ’n val in bloeddruk. Dit kan beheer word deur die dosis te verlaag.

Serotoniensindroom:

Dit is raadsaam om te hou by die aanbevole dosisse weens die risiko van serotonergiese toksisiteit. Serotoniensindroom, met simptome soos hiperpireksie, mioklonus, agitasie, toevalle, delirium en koma, kan moontlik voorkom wanneer CLOMIDEP toegedien word met serotonergiese ko-medikasies soos SSRI’s, SNaRI’s, trisikliese antidepressante of litium (sien afdelings 4.2 en 4.5). Vir fluoksetien word ’n uitwasperiode van twee tot drie weke aangeraai voor en na behandeling met fluoksetien.

Konvulsies:

CLOMIDEP moet met omsigtigheid gebruik word by pasiënte met epilepsie of by pasiënte wat geneig is tot konvulsies of toevalle; en ook waar daar ander predisponerende faktore is, soos breinskade, gelyktydige gebruik van neuroleptiese middels, alkoholonttrekking of onttrekking van medisynes met antikonvulsiewe eienskappe (bv. bensodiasepiene). Die voorkoms van toevalle hou verband met die dosis; die aanbevole totale daaglikse dosis van CLOMIDEP moet gevolglik nie oorskry word nie.

Anticholinergiese effekte:

Noukoekgloukoom kan vererger word.

Besondere sorg is nodig wanneer CLOMIDEP gebruik word waar daar versteurings van mikturisie weens belemmerde urienvloei teenwoordigheid is (bv. by siektes van die prostaat), aangesien urienretensie gepresipiteer kan word by pasiënte wat aan prostatisme ly.

Verminderde traanafskeiding en opeenhoping van mukusagtige afskeiding weens die anticholinergiese eienskappe van trisikliese antidepressante kan skade aan die korneale epiteel by pasiënte met kontaklense veroorsaak. Gebruik van kunsmatige trane word by hierdie pasiënte aanbeveel.

Die gelyktydige toediening van anticholinergiese middels kan gevaarlik wees (sien afdeling 4.5).

Spesifieke behandelingspopulasies:

Omsigtigheid word aangedui by pasiënte met hipertiroïdisme of in die geval van gepaardgaande behandeling met tiroïedmiddels, aangesien verergering van ongewenste kardiale effekte weens die anticholinergiese werking kan voorkom.

By pasiënte met lewersiekte, word periodieke monitering van lewerensiemvlakke aanbeveel.

CLOMIDEP kan paralitiese ileus veroorsaak, veral by bejaarde en bedlêende pasiënte en by pasiënte wat aan chroniese hardlywigheid ly.

Langdurige behandeling met CLOMIDEP kan tot ’n verhoogde voorkoms van tandbederf lei. Gereelde tandheelkundige ondersoeke is dus raadsaam tydens langtermynbehandeling.

Langtermyn-veiligheidsdata rakende groei, maturasie en kognitiewe en gedragsontwikkeling is nie beskikbaar vir kinders en adolessente nie.

Witbloedseltelling:

Daar is ’n verband tussen die voorkoms van agranulositose en die gebruik van CLOMIDEP gevind. Gevolglik is dit ook raadsaam om bloedtellings tydens CLOMIDEP na te gaan, veral indien die pasiënt koors, ’n griepagtige infeksie of seer keel ontwikkel.

Anestesie:

Die narkotiseur moet voor algemene of plaaslike anestesie ingelig word dat die pasiënt CLOMIDEP gebruik het.

Staking van behandeling:

Skielike onttrekking behoort weens moontlike ongunstige reaksies vermy te word. Indien die besluit geneem is om behandeling te staak, behoort medikasie afgeskaal te word, so vinnig as wat haalbaar is, maar met inagneming dat meteense staking met sekere simptome gepaard kan gaan (sien afdeling 4.8 vir ’n beskrywing van die risiko’s van staking van CLOMIDEP).

Die risiko’s van sentralesenuweestelselonderdrukking is groter wanneer dit saam met ander sentralesenuweestelselonderdrukkers (bv. alkohol en barbiturate) toegedien word en dit behoort dus as ’n reël nie gelyktydig toegedien te word nie. Aangesien CLOMIDEP alkoholtoleransie kan verminder, moet pasiënte aangeraai word om nie alkohol te gebruik terwyl hulle onder behandeling is nie.

CLOMIDEP kan afskeiding van prolaktien verhoog weens die antagonistiese effek wat dit op dopamien het.

Bloedsuikerkonsentrasies kan by diabetiese pasiënte gewysig word.

Hulpstowwe

Pasiënte met seldsame oorerflike probleme van galaktose-intoleransie, totale laktasegebrek of glukose-galaktosewanabsorpsie behoort nie hierdie medisyne te neem nie.

4.5 Interaksie met ander medisynes en ander vorms van interaksie

Farmakodinamiese interaksies:

Adrenergiese neuronblokkers:

CLOMIDEP kan die antihipertensiewe effekte van guanetidien, betanidien, reserpien, klonidien en alfa-metieldopa verminder of heeltemal afskaf. Pasiënte wat terselfdertyd medikasie vir hipertensie benodig, moet dus ’n ander soort antihipertensiewe middels ontvang (bv. vasodilators of betablokkers).

Anticholinergiese middels:

CLOMIDEP kan die uitwerking van anticholinergiese middels (bv. fenotiasien, middels teen parkinsonisme, antihistamiene, atropien, biperideen) versterk.

SSS-onderdrukkers:

Die risiko’s van sentralesenuweestelselonderdrukking is groter wanneer CLOMIDEP saam met ander sentralesenuweestelselonderdrukkers (bv. alkohol en barbiturate) toegedien word en dit behoort dus as ’n reël nie gelyktydig toegedien te word nie.

Diuretika:

Gepaardgaande toediening van CLOMIDEP met diuretika mag lei tot hipokalemie, wat op sy beurt die risiko van QTc-verlenging en torsades de pointes verhoog. Hipokalemie behoort gevolglik behandel te word voordat begin word met toediening van CLOMIDEP (sien afdelings 4.2 en 4.4).

MAO-inhibitors:

CLOMIDEP moet vir ten minste 2 weke na staking van behandeling met MAO-inhibitors nie gegee word nie (daar is ’n risiko van strawwe simptome, soos hipertensiewe krisis, hiperpireksie en dié in ooreenstemming met serotoniensindroom, bv. mioklonus, agitasie, toevalle, delirium en koma).

Dieselfde geld wanneer ’n MAO-inhibitor gegee word na vorige behandeling met CLOMIDEP. In beide gevalle moet CLOMIDEP of die MAO-inhibitor aanvanklik in klein dosisse, wat geleidelik verhoog word, gegee word en die effekte daarvan moet gemonitor word (sien afdeling 4.3).

Selektiewe serotonienheropname-inhibitors (SSRI’s):

Gepaardgaande toediening van CLOMIDEP met selektiewe serotonienheropname-inhibitors (bv. fluoksetien en fluvoksamien) kan tot additiewe effekte op die serotonergiese stelsel lei (sien *Serotonergiese medisynes).*

Serotonergiese medisynes:

Serotoniensindroom kan moontlik voorkom wanneer klomipramien gelyktydig toegedien word saam met serotonergiese medikasies, soos selektiewe serotonienheropname-inhibitors (SSRI’s), serotonien- en noradrenergiese heropname-inhibitors (SNaRI’s), trisikliese antidepressante of litium (sien afdelings 4.2 en 4.4). Vir fluoksetien word ’n uitwasperiode van twee tot drie weke aangeraai voor en na behandeling met fluoksetien.

Simpatomimetiese medisynes:

CLOMIDEP kan die kardiovaskulêre effekte van norepinefrien of epinefrien versterk en die gebruik van plaaslike anestetika en neusdruppels wat hierdie vasokonstriktors bevat moet vermy word, aangesien hipertensiewe reaksies mag voorkom.

Farmakokinetiese interaksies:

CLOMIDEP (klomipramien) word hoofsaaklik via metabolisme geëlimineer. Die primêre roete van metabolisme is demetilering om die aktiewe metaboliet, *N*-desmetielklomipramien, te vorm, gevolg deur hidroksilasie en verdere konjugasie van beide *N*-desmetielklomipramien en die moedermedisyne. Verskeie sitochroom P450-isosieme is betrokke by die demetilering, hoofsaaklik CYP3A4, CYP2C19 en CYP1A2.

Beide aktiewe komponente word deur hidroksilasie geëlimineer en dit word deur CYP2D6 gekataliseer. Gepaardgaande toediening van CYP2D6-inhibitors mag tot ’n styging in die konsentrasie van beide aktiewe komponente lei, tot soveel as 3-voudig by pasiënte met ’n debrisokien/sparteïen ekstensiewe metaboliseerder-fenotipe, wat dit omskakel na ’n swak-metaboliseerder-fenotipe. Daar word verwag dat gepaardgaande toediening van CYP1A2-, CYP2C19- en CYP3A4-inhibitors klomipramienkonsentrasies sal

verhoog en *N*-desmetielklomipramien sal verlaag, en sodoende nie noodwendig die algehele farmakologie sal affekteer nie.

MAO-inhibitors, wat ook kragtige CYP2D6-inhibitors in vivo is, soos moklobemied, word teenaangedui vir gepaardgaande toediening met klomipramien (soos in CLOMIDEP, sien afdeling 4.3).

Antidisritmiese medisynes (soos kinidien en propafenoon), wat kragtige inhibitors van CYP2D6 is, behoort nie in kombinasie met trisikliese antidepressante, soos CLOMIDEP, gebruik te word nie.

SSRI's wat inhibitors van CYP2D6 is, soos fluoksetien, paroksetien of sertralien, en van andere, insluitende CYP1A2 en CYP2C19 (bv. fluvoksamien), kan ook die plasmakonsentrasies van klomipramien (soos CLOMIDEP) verhoog, met ooreenstemmende newe-effekte. Serumvlakke van klomipramien by ewewigstoestand het ~ 4-voudig verhoog deur gepaardgaande toediening van fluvoksamien (*N*-desmetielklomipramien het ~ 2-voudig verlaag) (sien afdelings 4.2 en 4.3).

Gepaardgaande toediening van neuroleptiese middels (bv. fenotiasiene) kan verhoogde plasmavlakke van trisikliese antidepressante (soos CLOMIDEP), 'n verlaagde toevaldrempel, en toevalle veroorsaak. Kombinasie met tioridasien kan erge kardiale disritmieë veroorsaak.

Gepaardgaande toediening met 'n histamien$_2$ (H_2)-reseptorantagonis, simetidien ('n inhibitor van verskeie P450-ensieme, insluitende CYP2D6 en CYP3A4), kan plasmakonsentrasies van klomipramien verhoog, en die dosis daarvan moet dus verlaag word.

Daar is geen interaksie tussen chroniese orale kontraseptiewe (15 of 30 mikrogram etinielestradiol daagliks) en CLOMIDEP (25 mg daagliks) gedokumenteer nie.

Sover bekend is estrogene nie inhibitors van CYP2D6, die belangrikste ensiem betrokke by opruiming van klomipramien, nie, en gevolglik word geen wisselwerking verwag nie.

In 'n paar gevalle waar hoë-dosis estrogeen (50 mikrogram daagliks) en die trisikliese antidepressant imipramien gebruik is, is daar egter verhoogde newe-effekte en terapeutiese respons waargeneem, maar dit is onduidelik wat die belang van hierdie gevalle is vir CLOMIDEP (klomipramien) en laer-dosis estrogeen regimens. Dit word aanbeveel dat die terapeutiese respons van trisikliese antidepressante by hoë-dosis estrogeen regimens (50 mikrogram daagliks) gemonitor word en dit mag nodig wees om die dosis aan te pas.

Metielfenidaat (bv. Ritalin) kan ook die konsentrasies van trisikliese antidepressante verhoog deur potensiële onderdrukking van die metabolisme daarvan, en dit mag nodig wees om die dosis van die trisikliese antidepressant, soos CLOMIDEP, te verlaag.

Party trisikliese antidepressante, soos CLOMIDEP, kan die antikoagulant-effek van kumarien-medisynes, soos warfarien, versterk en dit kan deur onderdrukking van die metabolisme daarvan wees (CYP2C9). Daar is geen bewyse vir die vermoë van klomipramien om die metabolisme van antikoagulante, soos warfarien, te onderdruk nie, noukeurige monitering van plasmaprotrombien word egter vir hierdie klas van medisynes aangeraai.

Gepaardgaande toediening van medisynes wat bekend is dat dit sitochroom P450-ensieme induseer, in besonder CYP3A4, CYP2C19 en/of CYP1A2, kan die metabolisme van CLOMIDEP versnel en die doelmatigheid daarvan verlaag.

CYP3A- en CYP2C-induseerders, soos rifampisien of antikonvulsante (bv. barbiturate, karbamasepien, fenobarbitaal en fenitoïen), kan die konsentrasie van CLOMIDEP (klomipramien) verlaag.

Bekende induseerders van CYP1A2 (bv. nikotien/komponente in sigaretrook) verlaag die plasmakonsentrasies van trisikliese medisynes.

By sigaretrokers is die plasmakonsentrasies van CLOMIDEP (klomipramien) by ewewigstoestand 2-voudig verlaag in vergelyking met nierokers (geen verandering in *N*-desmetielklomipramien nie).

CLOMIDEP (klomipramien) is ook 'n in vitro (K_i < = 2,2 mikroM) en in vivo inhibitor van CYP2D6-aktiwiteit (sparteïen-oksidasie) en kan gevolglik verhoogde konsentrasies veroorsaak van verbindings wat gepaardgaande toegedien word wat hoofsaaklik deur CYP2D6 opgeruim word by ekstensiewe metaboliseerders.

4.6 Vrugbaarheid, swangerskap en borsvoeding

Swangerskap:

Dit is nie bepaal of dit veilig is om tydens swangerskap te gebruik nie.

Daar was verslae van onttrekkingsimptome by babas wie se moeders kort voor verlossing CLOMIDEP ontvang het.

Borsvoeding:

Aangesien die aktiewe bestanddeel uitgeskei word in borsmelk, moet moeders wat CLOMIDEP ontvang nie hulle babas borsvoed nie.

4.7 Uitwerking op die vermoë om te bestuur en masjiene te gebruik

Wanneer terapie begin word, moet pasiënte aangeraai word om vir ten minste ’n paar dae nie ’n motorvoertuig te bestuur, gevaarlike hoogtes te bestyg of masjinerie te hanteer nie. Belemmerde besluitneming kan onder hierdie omstandighede tot ongelukke lei.

4.8 Ongewenste effekte

Getabuleerde lys van ongunstige reaksies

MedDRA Stelsel-orgaan-klas	**Frekwensie**	**Ongunstige reaksies**
Bloed- en limfstelselversteurings	*Minder dikwels*	Leukopenie, agranulositose, trombositopenie, eosinofilie en purpura.
Immuunstelselversteurings	*Minder dikwels*	Allergiese alveolitis (pneumonitis) met of sonder eosinofilie, sistemiese anafilaktiese / anafilaktoïede reaksies insluitende hipotensie.
Endokrienversteurings	*Minder dikwels*	SIADH (ontoepaslike antidiuretiese hormoonsekresiesindroom).
Metabolisme- en voedingsversteurings	*Dikwels*	Gewigstoename; verhoogde aptyt, anoreksie.
Psigiatriese versteurings	*Dikwels*	Lomerigheid, kortstondige moegheid, rusteloosheid, verwardheid, disoriëntasie, hallusinasies (veral by geriatriese pasiënte en pasiënte wat aan Parkinson se siekte ly), angstigheid, agitasie, slaapversteurings, manie, hipomanie, aggressiwiteit, belemmerde geheue, depersonalisasie, verergerde depressie, belemmerde konsentrasie, slaaploosheid, nagmerries, gaap.
	Minder dikwels	Aktivering van psigotiese simptome.
Senuweestelselversteurings	*Dikwels*	Duiseligheid, tremor, hoofpyn, mioklonus, delirium, spraakversteurings,

		parestesie.
	Minder dikwels	Ataksie, konvulsies, EEG-veranderings, hiperpireksie, neuroleptiese maligne sindroom, perifere neuropatie.
Oogversteurings	*Dikwels*	Visuele akkommodasieversteurings en dowwe visie, midriase.
	Minder dikwels	Gloukoom.
Oor- en labirintversteurings	*Dikwels*	Tinnitus.
Kardiale versteurings	*Dikwels*	Sinustagikardie, palpitasies, posturale hipotensie, klinies onbeduidende EKG-veranderings (bv. ST- en T-veranderings) by pasiënte met normale kardiale status.
	Minder dikwels	Disritmieë, verhoogde bloeddruk; geleidingsversteurings (bv. verwyding van die QRS-kompleks, verlengde QT-interval, PQ-veranderings, bondeltakblok, torsade de pointes, veral by pasiënte met hipokalemie).
Vaskulêre versteurings	*Dikwels*	Warm gloede; sweting.
Gastroïntestinale versteurings	*Minder dikwels*	Naarheid; braking, abdominale versteurings, diarree, smaakversteurings, stomatitis, droë mond.
Hepatobiliêre versteurings	*Dikwels*	Verhoogde transaminases.
	Minder dikwels	Hepatitis met of sonder geelsug.

Vel- en subkutaneweefselversteurings	*Dikwels*	Allergiese velreaksies (veluitslag, urtikarie), fotosensitisering, pruritus.
	Minder dikwels	Edeem (plaaslik of veralgemeen), haarverlies.
Muskuloskeletale en bindweefselversteurings	*Dikwels*	Spierswakheid, spierhipertonie.
Nier- en urienwegversteurings	*Minder dikwels*	Urinêre retensie.
Voortplantingstelsel- en borsversteurings	*Dikwels*	Versteurings van libido en potensie, borsvergroting, galaktorree.
Algemene versteurings en toestande by die plek van toediening	*Dikwels*	Die volgende simptome kom dikwels voor na skielike onttrekking of verlaging van die dosis: Naarheid, braking, abdominale pyn, diarree, slaaploosheid, hoofpyn, senuweeagtigheid en angstigheid (sien afdeling 4.4).

Rapportering van vermoedelike newe-effekte

Dit is belangrik om vermoedelike newe-effekte wat gesien word nadat die medisyne geregistreer is, te rapporteer. Dit help met volgehoue monitering van die voordeel/risiko-balans van die medisyne. Gesondheidsorgverskaffers moet asseblief enige vermoedelike newe-effekte aan SAHPRA rapporteer via die vorm om ongunstige geneesmiddelreaksies te rapporteer, wat aanlyn by SAHPRA se publikasies beskikbaar is: https://www.sahpra.org.za/Publications/Index/8.

4.9 Oordosering

Tekens en simptome:

Oordosering en vergiftiging kan deur sentralesenuweestelselonderdrukking of -eksitasie, erge anticholinergiese effekte (wat ongeveer ’n halfuur tot twee uur na inname begin) en kardiotoksisiteit gekenmerk word. Die volgende simptome en tekens is kenmerkend van akute oordosering:

Sentrale senuweestelsel:

Lomerigheid, stupor, koma, ataksie, rusteloosheid, agitasie, ooraktiewe reflekse, spierrigiditeit en choreo-atetoïede bewegings, konvulsies. Daarby mag simptome in ooreenstemming met serotoniensindroom (bv. hiperpireksie, mioklonus, delirium en koma) waargeneem word.

Kardiovaskulêre stelsel:

Hipotensie, tagikardie, aritmie, QTc-verlenging en disritmie insluitende torsades de pointes, geleidingsversteurings, skok, hartversaking, in uiters seldsame gevalle hartstilstand.

Respiratoriese onderdrukking, sianose, braking, koors, midriase, sweting en oligurie of anurie mag ook voorkom.

Behandeling:

Daar is geen spesifieke teenmiddel nie.

Fisostigmien verhoog die risiko dat toevalle kan voorkom en moet gevolglik nie gebruik word nie.

Pogings moet aangewend word om die medisyne te elimineer deur braking te induseer indien die pasiënt wakker is, en/of maagspoeling. Die pasiënt moet oorgeplaas word na die hospitaal en vitale funksies moet onderhou word.

Geaktiveerde houtskool behoort toegedien te word.

Behandeling is simptomatiese en ondersteunend.

Vitale funksies (insluitende die EKG) moet vir ten minste 5 dae gemonitor word.

5. FARMAKOLOGIESE EIENSKAPPE

5.1 Farmakodinamiese eienskappe

A 1.2 Psigoanaleptika (antidepressante)

Klomipramien werk by verskeie setels. Dit sluit in alfa$_1$-adrenolitiese, anticholinergiese, antihistaminiese en antiserotonergiese aktiwiteite.

Dit word geglo dat terapeutiese aktiwiteit van klomipramien gegrond is op die vermoë daarvan om neuronale heropname van hoofsaaklik serotonien, en ook norepinefrien, te onderdruk.

5.2 Farmakokinetiese eienskappe

Absorpsie: Die aktiewe bestanddeel word volkome via die orale en intramuskulêre roetes geabsorbeer.

Plasmakonsentrasie: Kan wissel tussen 20 tot 175 ng/ml na orale toediening van ’n daaglikse dosis van 75 mg. Daar is groot verskille in die verspreiding en opruiming van klomipramien tussen individue.

Gelykvlakkonsentrasies van die aktiewe metaboliet desmetielklomipramien is 40 tot 85 % hoër as dié van klomipramien.

Dosisse behoort aangepas te word by bejaarde pasiënte weens die verminderde opruiming van klomipramien.

Die konsentrasie in die SSV is gelykstaande aan ongeveer 2 % van die plasmakonsentrasie.

Proteïenbinding: 97,6 %.

Plasmahalfleeftyd vir die beta-fase van eliminasie: ongeveer 21 uur.

Volume van verspreiding: ongeveer 12 liter/kg liggaamsmassa.

Biotransformasie:

Die primêre roete van klomipramienmetabolisme is demetilering om die aktiewe metaboliet, *N*-desmetielklomipramien, te vorm.

N-desmetielklomipramien kan deur verskeie P450-ensieme gevorm word, hoofsaaklik CYP3A4, CYP2C19 en CYP1A2.

Klomipramien en *N*-desmetielklomipramien word gehidroksileer om 8-hidroksiklomipramien of 8-hidroksi-*N*-desmetielklomipramien te vorm. Die aktiwiteit van die 8-hidroksi-metaboliete word nie in vivo gedefinieer nie.

Klomipramien word ook gehidroksileer by die 2-posisie en *N*-desmetielklomipramien kan verder gedemetileer word om didesmetielklomipramien te vorm. Die 2- en 8-hidroksi-metaboliete word hoofsaaklik as glukuroniede in die urine uitgeskei. Eliminasie van die aktiewe komponente, klomipramien en *N*-desmetielklomipramien, deur vorming van 2- en 8-hidroksi-klomipramien, word deur CYP2D6 gekataliseer.

Uitskeiding:

Twee-derdes in die vorm van wateroplosbare konjugate in die urine, en ongeveeg een-derde in die feses. Die hoeveelheid onveranderde klomipramien en aktiewe metaboliete wat in die urine uitgeskei word, beloop minder as 1 % van die toegediende dosis.

6. FARMASEUTIESE BESONDERHEDE

6.1 Lys van hulpstowwe

Tabletkern

Brilliant Blue-lak

Kolloïdale anhidriese silika

Laktosemonohidraat

Magnesiumstearaat

Mieliestysel

Mikrokristallyne sellulose

Gesuiwerde talkum

Natriummetielparabeen

Natriumstyselglikolaat

Filmlagie

Asetoon

Amino-metakrielsuur-kopolimeer (Eudragit E 100)

Brilliant Blue-lak

Isopropielalkohol

Makrogol 6 000

Magnesiumstearaat

Gesuiwerde talkum

Natriumlourielsulfaat

Titaandioksied

6.2 Onverenigbaarhede

Nie van toepassing nie.

6.3 Rakleeftyd

48 maande.

6.4 Spesiale voorsorgmaatreëls vir bewaring

Bewaar by of benede 25 °C op ’n koel, droë plek, beskerm teen lig.

6.5 Aard en inhoud van die houer

Aluminium-aluminiumstulpstrook

CLOMIDEP-tablette is beskikbaar in ’n aluminium-aluminiumstulpstrook. Vyf stulpstroke met 10 tablette elk word in ’n buitekarton verpak.

AL/PVC koudgevormde stulpverpakking

CLOMIDEP tablette is beskikbaar in ‘n PVC koudgevormde stulpverpakking. Vyf sulke stulpstroke van 10 tablette elk word in 'n buitekarton verpak.

Nie alle verpakkingstipes mag gelyktydig bemark word nie.

6.6 Spesiale voorsorgmaatreëls vir wegdoening

Geen spesiale vereistes nie.

7. HOUER VAN DIE REGISTRASIESERTIFIKAAT

Ranbaxy Pharmaceuticals (Edms.) Bpk.

’n Sun Pharma-maatskappy

Lautreweg 14, Stormill Uitbr. 1

Roodepoort 1724

Suid-Afrika

8. REGISTRASIENOMMER

35/1.2/0253

9. DATUM VAN EERSTE MAGTIGING/HERNUWING VAN DIE MAGTIGING

24 Oktober 2003

10. DATUM VAN HERSIENING VAN DIE TEKS

13 Mei 2022