PROFESSIONAL INFORMATION

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

CLOMIDEP 25 mg Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains preservative: sodium methylparaben 0,028 % *m/m*.

Contains sugar: lactose monohydrate 68,0 mg per 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 mg 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 mg 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, any degree of heart block or other cardiac dysrhythmias.
- 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 (such as moclobemide) due to the potential for severe interactions~~;~~ hyperactivity, hypertensive reactions, hyperpyrexia, spasticity, convulsions, coma 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).
- Narrow-angle glaucoma.
- Retention of urine.
- Mania.

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.

Abrupt discontinuation of therapy with CLOMIDEP should be avoided because of possible withdrawal symptoms. Therefore, dosage should be stopped gradually after regular use for long duration and the patient should be monitored carefully when clomipramine therapy is discontinued.

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:

Many patients with panic disorders experience intensified anxiety symptoms at the start of the treatment with CLOMIDEP. This paradoxical initial increase in anxiety is most pronounced during the first few days of treatment and generally subsides within two weeks.

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.

Hypomanic or manic episodes have also been reported during a depressive phase in patients with cyclic affective disorders receiving treatment with a tricyclic antidepressant. In such cases it may be necessary to reduce the dosage of CLOMIDEP or to withdraw it and administer an antipsychotic agent. After such episodes have subsided, low dose therapy with clomipramine
may be resumed if required.

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.

As improvement in depression may not occur for the first two to four weeks of treatment, patients should be closely monitored during this period.

Elderly patients are particularly liable to experience adverse effects, especially agitation, confusion, and postural hypotension.

Before initiating treatment, it is advisable to check the patient's blood pressure because hypotensive medicines 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.

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.

Concomitant treatment with CLOMIDEP and electroconvulsive therapy should only be resorted to under careful supervision.

Anticholinergic effects:

Because of its anticholinergic properties, CLOMIDEP should be used with caution in patients with a history of increased intra-ocular pressure, narrow-angle glaucoma, urinary retention or with symptoms of bladder neck obstruction, e.g., diseases of the prostate, such as prostatic hypertrophy.

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 medicines may be dangerous (see section 4.5).

Specific treatment populations:

Caution is called for when giving CLOMIDEP to patients with severe hepatic disease and tumours of the adrenal medulla (e.g., phaeochromocytoma, neuroblastoma), in whom the medicine may provoke

hypertensive crises.

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.

It is advisable to monitor cardiac and hepatic function during long-term therapy with CLOMIDEP In patients with hepatic and renal disease, periodic monitoring of hepatic enzyme levels and renal function is recommended.

An increase in dental caries has been reported during long-term treatment with CLOMIDEP. Regular dental check-ups are therefore advisable during long-term treatment.

Caution is called for in patients with chronic constipation. CLOMIDEP may cause paralytic ileus particularly in the elderly and in bedridden patients.

In elderly patients, tricyclic antidepressants may provoke pharmacogenic (delirious) psychoses, particularly at night. These disappear within a few days of withdrawing the medicine.

Monitoring of cardiac function and the ECG is indicated in elderly patients.

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.

Anticoagulants / Non-steroidal anti-inflammatory medicines:

Skin and mucous membrane bleeding has been reported with clomipramine. CLOMIDEP should be used with caution among patients that simultaneously use medicines that increase the risk of bleeding, for example anticoagulants, salicylic acid derivatives and non-steroidal anti-inflammatory medicines (NSAIDs). Care should be taken in patients with an increased tendency to bleed.

Anaesthesia:

Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of dysrhythmias and hypotension. Before general or local anaesthesia, the anaesthetist should be told that the patient has been receiving CLOMIDEP.

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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).

Central nervous system depression:

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.

Increased prolactin secretion:

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

Excipients: Lactose

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

Blood sugar concentrations may be altered in diabetic patients.

4.5 Interaction with other medicines and other forms of interaction

Interactions resulting in a contraindication

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).

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).

Interactions resulting in a concomitant use not recommended

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).

Antiarrhythmics:

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.

Selective serotonin re -uptake inhibitors (SSRI):

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 (*N*-desmethylclomipramine decreased~ 2-fold) (see sections 4.2 and 4.~~3~~4).

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.

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).*

Interactions resulting in increased effect of clomipramine

CLOMIDEP (clomipramine) is predominantly eliminated through metabolism. The primary route of metabolism is demethylation to form the active metabolite, *N*-desmethylclomipramine, followed by hydroxylation and further conjugation of both *N*-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.

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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 *N*-desmethylclomipramine, thus not necessarily affecting the overall pharmacology.

Oral antifungal, terbinafine:

Co-administration of clomipramine with terbinafine, a strong inhibitor of CYP2D6, may result in increased exposure and accumulation of clomipramine and its N-demethylated metabolite. Therefore, dose adjustments of CLOMIDEP may be necessary when co-administered with terbinafine.

Cimetidine:

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.

Oral contraceptives:

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.

Antipsychotics:

Co-medication 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.

Methylphenidate:

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.

Valproate:

Concomitant administration of valproate with CLOMIDEP may cause inhibition of CYP2C and/or UGT enzymes, resulting in increased serum levels of clomipramine and desmethylclomipramine.

Grapefruit, grapefruit juice, or cranberry juice:

Concomitant administration of CLOMIDEP with grapefruit, grapefruit juice, or cranberry juice may increase the plasma concentrations of clomipramine**.**

Interactions resulting in decreased effect of clomipramine

Rifampicin:

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.

Anticonvulsants:

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

Cigarette smoking:

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 *N*-desmethylclomipramine).

Colestipol and cholestyramine:

Concomitant administration of ion exchange resins such as cholestyramine or colestipol may reduce the plasma levels of clomipramine. Staggering the dosage of CLOMIDEP and resins, such that the medicine is administered at least 2 h before or 4 – 6 h after the administration of resins, is recommended.

St. John's wort:

Concomitant administration of CLOMIDEP with St. John's wort during the treatment may decrease the plasma concentrations of clomipramine.

Interactions affecting other medicines

Anticholinergic agents:

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

Antiadrenergic agents:

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).

It would be advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

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.

Sympathomimetic medicines:

CLOMIDEP may potentiate the cardiovascular effects of norepinephrine, noradrenaline, adrenaline, epinephrine, isoprenaline, phenylephrine and phenylpropanolamine and the use of local anaesthetics and nose drops containing these vasoconstrictors should be avoided as hypertensive reactions may occur.

Anticoagulants:

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.

Inhibition of CYP2D6 activity:

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.

Medicines that can cause increase plasma clomipramine levels or which in themselves prolong the QTc interval:

The risk of QTc prolongation and torsades de pointes is likely to be increased if CLOMIDEP is co-administered with other medicines that can cause QTc prolongation. Therefore, concomitant use of such medicines with CLOMIDEP is not recommended (see section 4.4). Examples include certain antiarrhythmics, such as those of Class IA (such as quinidine, disopyramide and procainamide) and Class III (such as amiodarone and sotalol), tricyclic antidepressants (such as amitriptyline), certain tetracyclic antidepressants (such as maprotiline), certain antipsychotic medications (such as phenothiazines and pimozide), certain antihistamines (such as terfenadine); lithium, quinine and pentamidine. This list is not exhaustive. The risk of QTc prolongation and torsades de pointes is likely to be increased if CLOMIDEP is co-administered with medicines that can cause increased plasma clomipramine levels. Clomipramine is metabolised by cytochrome P450 2D6 and the plasma concentration of clomipramine may therefore be increased by medicines that are either substrates and/or inhibitors of this P450 isoform. Therefore, concurrent use of these medicines with CLOMIDEP is not recommended (see section 4.4). Examples of medicines which are substrates or inhibitors of cytochrome P450 2D6 include antiarrhythmics, certain antidepressants including SSRIs, tricyclic antidepressants and moclobemide; certain antipsychotics; β-blockers; protease inhibitors, opiates, ecstasy (MDMA), cimetidine and terbinafine. This list is not exhaustive.

Calcium channel blockers:

Diltiazem and verapamil may increase the plasma concentration of imipramine, and possibly other tricyclic antidepressants.

Non-steroidal anti-inflammatory medicines:

The potential pharmacodynamic interactions with medicines that increase the risk of bleeding, for example, salicylic acid derivatives, non-steroidal anti-inflammatory / antirheumatic medicines (NSAIDs) should be considered because of the increased risk of bleeding with concomitant CLOMIDEP.

Cytotoxic:

Altretamine: risk of severe postural hypotension.

Analgesics

Possible increased side effects with nefopam; possible increased risk of convulsions with tramadol; possible increased sedation with opioid analgesics; increased risk of ventricular dysrhythmias with levacetylmethadol.

Dopaminergics:

Concomitant use of tricyclic antidepressants and entacapone should be avoided; central nervous system toxicity has been reported with selegiline.

Muscle relaxants:

Tricyclic antidepressants may enhance the muscle relaxant effect of baclofen.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential:

There are no data supporting any special recommendations in women of child-bearing potential.

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.

There is a limited amount of data from the use of clomipramine in pregnant women that indicates a potential to harm the foetus or cause congenital malformation.

Neonates whose mothers had taken CLOMIDEP up until delivery have developed dyspnoea, lethargy, colic, irritability, hypotension or hypertension, tremor or spasms, during the first few hours or days.

Studies in animals have shown reproductive toxicity (see section 5.3). CLOMIDEP is not recommended during pregnancy and in women of child-bearing potential not using contraception.

Breastfeeding:

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

Fertility:

Clomipramine hydrochloride did not appear to have any significant effects on fertility and general reproductive performance.

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.

Patients receiving CLOMIDEP should be warned that blurred vision, drowsiness and other nervous system and psychiatric related disorders such as somnolence, disturbance in attention, confusion, disorientation, aggravation or depression, delirium etc. (see section 4.8) have been observed. In the presence of such effects, patients should not drive, operate machinery or do anything else which may require alertness or quick actions. Patients should also be warned that alcohol or other medicines potentiate these effects (see section 4.5).

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.
Immune system disorders	*Less frequent*	Systemic anaphylactic / anaphylactoid reactions including hypotension.
Endocrine disorders	*Less frequent*	SIADH (inappropriate antidiuretic hormone secretion syndrome).
Metabolism and nutrition disorders	*Frequent*	Increased appetite, decreased 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, depersonalisation, depression aggravated,

		insomnia, nightmares, delirium.
	Less frequent	Activation of psychotic symptoms.
	Frequency unknown	Suicidal ideation, suicidal behaviours.
Nervous system disorders	*Frequent*	Dizziness, tremor, headache, myoclonus, speech disorders, paraesthesia. somnolence, hypertonia, dysgeusia, memory impairment, disturbance in attention.
	Less frequent	Ataxia, convulsions, EEG changes, hyperpyrexia, neuroleptic malignant syndrome, peripheral neuropathy.
	Frequency unknown	Serotonin syndrome, extrapyramidal disorder (including akathisia and tardive dyskinesia).
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.
Respiratory, thoracic, and mediastinal disorders:	*Frequent*	Yawning.
	Less frequent	Allergic alveolitis (pneumonitis) with or without eosinophilia.

Gastrointestinal disorders	*Frequent*	Nausea, dry mouth constipation.
	Less frequent	vomiting, abdominal disorders, diarrhoea, taste disturbances, stomatitis.
Hepato-biliary disorders	*Less frequent*	Hepatitis with or without jaundice.
Skin and subcutaneous tissue disorders	*Frequent*	Allergic skin reactions (skin rash, urticaria), photosensitisation, pruritus, Hyperhidrosis.
	Less frequent	Oedema (local or generalised), hair loss. Ecchymosis, purpura.
Musculoskeletal and connective tissue disorders	*Frequent*	Muscle weakness.
	Frequency unknown	Rhabdomyolysis (as a complication of neuroleptic malignant syndrome).[3]
Renal and urinary disorders	*Frequent*	Urinary retention, Micturition disorder.
Reproductive system and breast disorders	*Frequent*	Disturbances of libido and potency, breast

		enlargement, galactorrhoea, women occasionally experience orgasmic impotence.
	Less frequent	Vaginal bleeding.
	Frequency unknown	Ejaculation failure, ejaculation delayed.
General disorders and administration site conditions	*Frequent*	Fatigue.
Investigations	*Frequent*	Weight increased, blood sugar changes. Elevated transaminases.
	Less frequent	Electroencephalogram abnormal.
	Frequency unknown	Blood prolactin increased.

[1]In post-marketing experience very rarely malignant neuroleptic syndrome has been reported although a causal relationship has not been confirmed.

[2]Cases of suicidal ideation and suicidal behaviours have been reported during clomipramine therapy or early after treatment discontinuation (see section 4.4).

[3]These adverse events were reported in patients treated with clomipramine based on post-marketing reports.

Withdrawal symptoms:

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).

Class effects:

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and tricyclic antidepressants. The mechanism leading to this risk is unknown.

Elderly population:

Elderly patients are particularly sensitive to anticholinergic, neurological, psychiatric, or cardiovascular effects. Their ability to metabolise and eliminate medicines may be reduced, leading to a risk of elevated plasma concentrations at therapeutic doses. Therapy should be initiated at lower than standard doses in the elderly.

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-Med Safety APP (Medsafety X SAHPRA) and eReporting platform {who-umc.org) found on SAHPRA website.
Suspected adverse reactions can also be reported directly to the Holder of registration via email:pharmacovigilance.africasme@sunpharma.com or tel:+27(0) 126432000

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. Treatment is symptomatic and supportive.

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

Anyone suspected of receiving an overdose of CLOMIDEP, particularly children, should be hospitalised and kept under close surveillance for at least 72 hours.

Attempts should be made to eliminate the medicine by inducing vomiting if the patient is alert and/or irrigating the stomach.

If the patient has impaired consciousness, secure the airway with a cuffed endotracheal tube before beginning lavage, and do not induce vomiting. These measures are recommended for up to 12 hours or even longer after the overdose, since the anticholinergic effect of the medicine may delay gastric emptying. Administration of activated charcoal may help to reduce medicine absorption.

The patient should be transferred to hospital and vital functions safeguarded.

Activated charcoal should be administered.

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

Treatment of symptoms is based on modern methods of intensive care, with continuous monitoring of cardiac function, blood gases, and electrolytes, and if necessary, emergency measures such as:

For respiratory failure:

- intubation and artificial respiration.

For cardiovascular symptoms:

- in severe hypotension the patient should be placed in an appropriate position and be given a plasma expander, dopamine, or dobutamine by intravenous drip.
- cardiac dysrhythmias must be treated according to the requirements of the case.
- implantation of a cardiac pacemaker should be considered.
- low potassium values and acidosis should be corrected.

In all patients with ECG abnormalities, cardiac function should - even after the ECG tracings have reverted to normal - be kept under close observation for at least another 48 hours because relapses may occur.

Treatment of torsades de pointes:

If torsades de pointes should occur during treatment with CLOMIDEP, the medicine should be discontinued and hypoxia, electrolyte abnormalities and acid base disturbances should be corrected. Persistent torsades de pointes may be treated with magnesium sulphate if necessary. Alternatively, if these measures fail, the arrhythmia may be abolished by increasing the underlying heart rate. This can be achieved by atrial and ventricular pacing or by isoprenaline (isproterenol) infusion. Torsades de pointes is usually not helped by antiarrhythmic medicines and those which prolong the QTc interval (e.g., amiodarone, quinidine) may make it worse.

Since it has been reported that physostigmine may cause severe bradycardia, asystole and seizures, its use is not recommended in cases of overdosage with CLOMIDEP.

Haemodialysis or peritoneal dialysis are ineffective because of the low plasma concentrations of clomipramine.

For convulsions:

Diazepam should be given intravenously or other anticonvulsants such as phenobarbitone or paraldehyde (these substances may exacerbate existing respiratory failure, hypotension, or coma).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 1.2 Psychoanaleptics (antidepressants), ATC code: N06AA04

Mechanism of action

The therapeutic activity of clomipramine is believed to be based on its ability to inhibit the neuronal re-uptake of noradrenalin (NA) and serotonin (5-HT) released in the synaptic cleft, with inhibition of 5-HT reuptake being the more important of these activities.

Clomipramine also has a wide pharmacological spectrum of action, which includes alpha1- adrenolytic, anticholinergic, antihistaminic and antiserotonergic (5-HT-receptor blocking) properties.

5.2 Pharmacokinetic properties

Absorption:

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

The systemic bioavailability of unchanged clomipramine is reduced by 50 % by "first-pass" metabolism to desmethylclomipramine (an active metabolite). The bioavailability of clomipramine is not markedly

affected by the ingestion of food, but the onset of absorption, and therefore the time to peak, may be delayed. Coated tablets and sustained release tablets are bioequivalent with respect to amount absorbed.

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.

Clomipramine slows gastrointestinal transit time, absorption can, however, be delayed, particularly in overdosage.

Distribution:

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.

It is reported to have a low and variable bioavailability following oral administration (48,2 % of that after intravenous administration) and this has been related to extensive first-pass hepatic metabolism. Following single oral doses of 50 mg and 100 mg in healthy volunteers peak plasma concentrations of clomipramine of 28,8 ± 11,2 ng/mL range 16,5 to 53 ng/mL (at 3 to 5 hours post-dose) and 70 – 140 ng/mL (at 1 to 2,5 hours post-dose) respectively are reported. Peak plasma concentrations of desmethylclomipramine of 5,0 ± 1,4 ng/ml (range 2,9 to 7,8 ng/mL) have been reported to occur between 5 to 12 hours after a single oral dose of 50 mg.

After chronic administration in depressed patients, steady state plasma concentrations of clomipramine have been noted to vary 20 to 30 fold. Vandel et al reported that following repeated doses of 75 mg a

day for 1 month, steady state plasma concentrations of clomipramine and desmethylclomipramine were 124,5 ± 94 ng/mL and 144,8 ± 113 ng/mL respectively.

Biotransformation:

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

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

Clomipramine and *N*- desmethylclomipramine are hydroxylated to form 8-hydroxyclomipramine or 8-hydroxy-*N*-desmethylclomipramine. The activity of the 8-hydroxy metabolites are not defined in vivo. Clomipramine is also hydroxylated at the 2-position and *N*-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 *N*-desmethylclomipramine by formation of 2- and 8-hydroxy clomipramine is catalysed by CYP2D6.

Elimination:

Oral clomipramine is eliminated from the blood with a mean half-life of 21 hours (range 12 – 36 h), and desmethylclomipramine with a half-life of 36 hours.

About two-thirds of a single dose of clomipramine is excreted in the form of water-soluble conjugates in the urine, and approximately one-third in the faeces. The quantity of unchanged clomipramine and desmethylclomipramine excreted in the urine amounts to about 2 % and 0,5 % of the administered dose respectively.

Elderly:

In the elderly, plasma clomipramine concentrations may be higher for a given dose than would be expected in younger patients, because of reduced metabolic clearance.

Hepatic and renal impairment:

The effects of hepatic and renal impairment on the pharmacokinetics of clomipramine have not been determined.

Section 5.3

Not available.

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.

AL/PVC cold form blister pack:

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

Not all pack types may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

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