SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clomipramine 10 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 10 mg clomipramine hydrochloride.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.
Size 4 gelatin capsule, brown cap and yellow body. Printed '1806'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clomipramine capsules are indicated for the symptoms of depressive illness, especially where sedation is required, and obsessive and phobic states.

Clomipramine capsules are also indicated for cataplexy associated with narcolepsy.

Children and Adolescents

In children and adolescents, there is not sufficient evidence of safety and efficacy of clomipramine in the treatment of depressive states, phobias and cataplexy associated with narcolepsy. The use of clomipramine in children and adolescents (0-17 years of age) in these indications is therefore not recommended (see section 4.4 Special Warnings and Precautions for use).

4.2 Posology and method of administration

Before initiating treatment with clomipramine, hypokalemia should be treated (see 4.4. Special Warnings and Precautions for use).

As a precaution against possible QTc prolongation and serotonergic toxicity, adherence to the recommended doses of clomipramine is advised and any

increase in dose should be made with caution if other serotonergic agents are co-administered (see sections 4.4 Special Warnings and Precautions for use and 4.5 Interaction with other Medicinal Products and other forms of Interaction).

Depression

Adults

Initially 10 mg daily, increasing gradually to 30 - 150 mg daily if required, in divided doses throughout the day, or as a single dose at bedtime. In most patients the adequate maintenance dose is 30 - 50 mg daily, although some patients may require higher doses, particularly those suffering from obsessional or phobic disorders. In severe cases the dosage may be increased up to 250 mg per day. Once a distinct improvement has set in, the daily dosage may be adjusted to a maintenance level averaging either 2-4 capsules of 25mg or 1 tablet of 75mg.

Elderly

Initially 10 mg daily, which may be increased with caution under close supervision to 30 - 75 mg daily which should be reached after about 10 days and then maintained until the end of treatment.

Children

Children and Adolescents (0-17 years of age): Not recommended (see section 4.4 Special Warnings and Precautions for use).

Obsessional and phobic states
Obsessional/phobic states: The maintenance dosage of clomipramine is generally higher than that used in depression. It is recommended that the dose be built up to 100-150mg clomipramine daily, according to the severity of the condition. This should be attained gradually over a period of 2 weeks starting with 1 x 25mg clomipramine daily. In elderly patients and those sensitive to tricyclic antidepressants a starting dose of 1 x 10mg clomipramine daily is recommended.

Adjunctive treatment of cataplexy associated with narcolepsy(Oral treatment)

10 - 75 mg daily. It is recommended that an initial dose of 10 mg daily is given and then gradually increased until a satisfactory response is obtained. Control of cataplexy should occur within 24 hours of reaching the optimal dose.

Treatment discontinuation
Abrupt withdrawal should be avoided because of possible adverse reactions. If the decision is 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 4.4 Special Warnings and

Precautions for use and section 4.8 Undesirable effects, for a description of the risks of discontinuation of clomipramine).

Route of Administration
oral

4.3 Contraindications

Clomipramine is contra-indicated in patients with known hypersensitivity to clomipramine, any of the excipients, or cross-sensitivity tricyclic antidepressants of the dibenzazepine group, severe liver disease, recent myocardial infarction, cardiac failure or any degree of heart block or cardiac arrhythmias, narrow angle glaucoma, urine retention and mania.

Clomipramine should not be administered concurrently with monoamine oxidase inhibitors, or within 3 weeks before or after treatment with a MAO inhibitor (see section 4.5 Interactions with other Medicinal Products and other forms of Interaction). (see section 4.5). The concomitant treatment with selective, reversible MAO-A inhibitors such as moclobemide, is also contraindicated.

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which clomipramine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Use in Children and Adolescents (0-17 years of age)

Clomipramine should not be used in the treatment of depressive states, phobias and cataplexy associated with narcolepsy in children and adolescents under the age of 18 years (see section 4.1 Therapeutic indications).

Antidepressants increase the risk of suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominately aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long term safety data in children and adolescents concerning growth, maturation and cognitive behavioural development are lacking.

Families and care givers 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 Undesirable effects), as well as the emergence of suicidality, and to report such symptoms immediately to health care providers.

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

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.

Other Psychiatric Effects

Many patients with panic disorders may experience a paradoxical increase in anxiety particularly at the start of treatment but this usually subsides within the first 2 weeks.

Activation of psychosis has occasionally been observed in schizophrenic patients receiving tricyclic antidepressants.

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 clomipramine 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, tricyclic antidepressants may provoke pharmacogenic (delirious) psychoses, particularly at night. These disappear within a few days of withdrawing the drug.

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

The elderly are particularly liable to experience adverse effects, especially confusion, agitation and postural hypotension.

Before initiating treatment it is advisable to check the patient's blood pressure, because individuals with hypotension or a labile circulation may react to the drug with a fall in blood pressure.

Cardiac and Vascular Disorders

Clomipramine should be administered with particular precaution in patients with cardiovascular disorders, especially those with cardiovascular insufficiency, conduction disorders, (e.g. atrioventricular block grades I to III), arrhythmias. Monitoring of cardiac function and the ECG is indicated in such patients, as well as in elderly patients.

There may be a risk of QTc prolongation and Torsade 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). Therefore, concomitant administration of drugs that can cause accumulation of clomipramine should be avoided. Equally, concomitant administration of drugs that can prolong the QTc interval should be avoided. (see section 4.5 Interactions with other Medicinal Products and other forms of Interaction). It is established that hypokalemia is a risk-factor of QTc prolongation and Torsade de Pointes. Therefore, hypokalemia should be treated before initiating treatment with clomipramine (see section 4.5. Interactions with other Medicinal Products and other forms of Interaction.)

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 clomipramine is administered with serotonergic co-medications such as SSRIs SNaRIs, tricyclic antidepressants, buprenorphine or lithium. Therefore, concomitant administration of drugs that can cause accumulation of

clomipramine should be avoided (see sections 4.2 Posology and Method of Administration and 4.5 Interactions with other Medicinal Products and other forms of Interaction). For fluoxetine a washout period of two to three weeks is advised before and after treatment with fluoxetine.

Concomitant administration of clomipramine and buprenorphine may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5). If concomitant treatment with buprenorphine containing medicinal products is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Convulsions

Tricyclic antidepressants are known to lower the convulsion threshold and clomipramine should therefore be used with extreme caution in patient with epilepsy and other predisposing factors, e.g. brain damage of varying aetiology, concomitant use of neuroleptics, withdrawal from alcohol or drugs with anticonvulsive properties (e.g. benzodiazepines). It appears that the occurrence of seizures is dose dependent, therefore the recommended total daily dose of clomipramine should not be exceeded.

Concomitant administration of clomipramine and electroconvulsive therapy should only be resorted to under careful supervision.

Anticholinergic Effects

Because of its anticholinergic properties, caution should be exercised when using clomipramine in patients with a history of increased intra-ocular pressure, urinary retention (e.g. diseases of the prostate) , or narrow angle glaucoma.

Decreased lacrimation and accumulation of mucoid secretions due to the anticholinergic properties of tricyclic antidepressants may cause damage to the corneal epithelium in patients with contact lenses.

Specific Treatment Populations

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

Caution is indicated in patients with hyperthyroidism or during concomitant treatment with thyroid preparations since aggravation of unwanted cardiac effects may occur.

During long term therapy, it is advisable to monitor cardiac and hepatic function. In patients with liver disease, periodic monitoring of hepatic enzyme levels is recommended.

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

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

White Blood Cell Count

Although changes in the white blood cell count have been reported with Clomipramine only in isolated cases, periodic blood cell counts and monitoring for symptoms such as fever and sore throat are called for,or other symptoms of non-specific infection, particularly during the first few months of therapy. They are also recommended during prolonged therapy.

Anaesthesia

The risk of arrhythmias and hypotension may be increased if the patient undergoes anaesthesia, therefore before general or local anaesthesia, the anaesthetist should be aware that the patient has been receiving clomipramine and of the possible interactions (see section 4.5 Interactions with other Medicinal Products and other forms of Interaction).

Anxiety, feelings of unrest and hyperexcitation may occur in agitated patients and patients with accompanying schizophrenic symptoms.

Treatment Discontinuation

Abrupt withdrawal should be avoided because of possible adverse reactions). If the decision is 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 Undesirable effects, for a description of the risks of discontinuation of clomipramine).

Patients with cataplexy may experience worsening cataplexy symptoms including status cataplecticus upon abrupt withdrawal.

Excipient(s)

Lactose

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

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

MAO inhibitors
Do not give clomipramine for at least 3 weeks after discontinuation of treatment with MAO inhibitors (there is a risk of severe symptoms consistent with Serotonin Syndrome such as hypertensive crisis, hyperpyrexia, myoclonus, agitation, seizures, delirium and coma). The same applies when giving a MAO inhibitor after previous treatment with clomipramine. In both instances the treatment should initially be given in small gradually increasing doses and its effects monitored.There is evidence to suggest that clomipramine may be given as little as 24 hours after a reversible MAO-A inhibitor such as moclobemide, but the 3 week wash-out period must be observed if the MAO-A inhibitor is used after clomipramine.

Serotonergic Agents

Serotonin Syndrome can possibly occur when clomipramine is administered with other serotonergic comedications such as selective serotonin reuptake inhibitors (SSRI's), serotonin and noradrenergic reuptake inhibitors (SNaRI's), tricyclic antidepressants, buprenorphine and lithium (see sections 4.2 Posology and Method of Administration and 4.4 Special Warnings and Precautions for use). Fluoxetine and fluvoxamine may also increase plasma concentrations of clomipramine. For fluoxetine a washout period of two to three weeks is advised before and after treatment with fluoxetine.

Clomipramine should be used cautiously when co-administered with buprenorphine as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

CNS depressants
Tricyclic antidepressants may potentiate the effect of alcohol, central depressant drugs (e.g. barbiturates, benzodiazepines, general anaesthetics).
Neuroleptics
Comedication may result in increased plasma levels of tricyclic antidepressants, a lowered convulsion threshold, and seizures. Concomitant administration with thioridazine may produce severe cardiac arrhythmias.

Anticoagulants
Tricyclic antidepressants may potentiate the anticoagulant effect of coumarins by inhibiting their metabolism by the liver. Plasma prothrombin time should be carefully monitored.

Anticholinergic agents

Tricyclic antidepressants may potentiate the effects of these drugs (e.g. phenothiazine, antiparkinsonian agents, antihistamines, atropine, biperiden) on the eye, central nervous system, bowel and bladder.

Adrenergic neurone blockers

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

Sympathomimetic drugs

Clomipramine may potentiate the cardiovascular effects of sympathomimetic agents such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine (e.g. as contained in local and general anaesthetics preparation containing sympathomimetics and nasal decongestants)

Quinidine

Tricyclic antidepressants should not be employed in combination with anti-arrhythmic agents of the quinidine type.

Liver-enzyme inducers

Drugs which activate the hepatic mono-oxygenase enzyme system (e.g. barbiturates, carbamazepine, phenytoin, nicotine and oral contraceptives) may accelerate the metabolism and lower the plasma concentrations of clomipramine, resulting in decreased efficacy. Plasma levels of phenytoin and carbamazepine may increase, with corresponding adverse effects. It may be necessary to adjust the dosage of these drugs.

Diuretics

Diuretics may lead to hypokalemia, which increases the risk of QTc prolongation and Torsade de Pointes, Hypokalaemia should therefore be treated prior to administration of clomipramine. (see sections 4.2 Posology and Method of Administration and 4.4 Special Warnings and Precautions for Use).

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

The risk of QTc prolongation and Torsade de Pointes is likely to be increased if clomipramine is coadministered with other drugs that can cause QTc prolongation. Therefore concomitant use of such agents with clomipramine is not recommended. (see sections 4.4 Special Warnings and Precautions for use). Examples include certain anti-arrhythmics, such as those of Class 1A (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 Torsade de Pointes is likely to be increased if clomipramine is co-administered with drugs 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 drugs that are either substrates and/or inhibitors of this P450 isoform. Therefore, concurrent use of these drugs with clomipramine is not recommended (see section 4.4 Special Warnings and Precautions for use). Examples of drugs which are substrates or inhibitors of cytochrome P450 2D6 include anti-arrhythmics, 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.

Cimetidine, methylphenidate and oestrogens
These drugs may also increase plasma concentrations of tricyclic antidepressants, whose dosage should therefore be reduced.

Oral antifungal, terbinafine

Coadministration 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 clomipramine may be necessary when coadministered with terbinafine.

4.6 Pregnancy and lactation

Pregnancy
There is inadequate evidence of safety of clomipramine in human pregnancy. Do not use unless there are compelling reasons, especially during the first and last trimesters. Animal work has not shown clomipramine to be free from hazard.
Neonates of mothers being treated with tricyclic antidepressants until delivery, have developed hypotension or hypertension, tremor or spasms, dyspnoea, lethargy, colic, and irritability during the first few hours or days.
Clomipramine should - if this is at all justifiable - be withdrawn at least 7 weeks before the calculated date of confinement.
Data from Swedish health registries with 1,029 women exposed to clomipramine in the first trimester do not suggest an increased risk of overall congenital anomalies in the offspring.
However, the risk for any cardiac defect was increased (risk of 2/100 compared to 1/100 in the general population). The strongest association was found for ventricular or atrial septal defects.

Breastfeeding

Clomipramine is excreted in breast milk in small quantities. Therefore, nursing mothers should be advised to withdraw the medication or cease breast-feeding.

4.7. Effects on ability to drive and use machines

Patients receiving clomipramine should be warned that blurred vision, drowsiness and other CNS symptoms (see section 4.8) may occur, in which case they should not drive, operate machinery or do anything else which may require alertness or quick actions. Patients should also be warned that consumption of alcohol or other drugs may potentiate these effects (see section 4.5).

4.8 Undesirable effects

Unwanted effects are usually mild and transient, disappearing under continued treatment or with a reduction in the dosage. They do not always correlate with plasma levels or dose. It is often difficult to distinguish certain undesirable effects from symptoms of depression such as fatigue, sleep disturbances, agitation, anxiety, constipation, and dry mouth.
If severe neurological or psychiatric reactions occur, clomipramine should be withdrawn.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10) common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), unknown (frequency cannot be estimated from available data).

Blood and lymphatic system disorders

Very rare: leucopenia, agranulocytosis, thrombocytopenia, eosinophilia.

Cardiac disorders
Common: orthostatic hypotension, sinus tachycardia, palpitations and clinically irrelevant ECG changes (e.g. T and ST changes) in patients of normal cardiac status.

Uncommon: arrhythmias, increased blood pressure.

Very rare: conduction disorders (e.g. widening of QRS complex, prolonged QTc interval, PQ changes, bundle-branch block, Torsade de Pointes, particularly in patients with hypokalemia).

Not known: cardiomyopathy, cardiac failure

Ear and labyrinth disorders

Common: tinnitus.
Endocrine disorders
Very rare: SIADH (inappropriate antidiuretic hormone secretion syndrome).
Eye disorders
Very common: accommodation disorder, vision blurred

Common: mydriasis
Very rare: glaucoma

Gastrointestinal disorders
Very common: nausea, dry mouth, constipation
Common: vomiting, abdominal disorders, diarrhoea

General disorders and administration site conditions
Very common: fatigue
Very rare: oedema (local or generalised), alopecia, hyperpyrexia.

Hepatobiliary disorders

Very rare**:** hepatitis with or without jaundice.

Immune system disorders

Very rare: systemic anaphylactic/anaphylactoid reactions including hypotension.

Investigations
Very common: weight increased
Common: transaminases increase
Very rare: electroencephalogram abnormal
Unknown: blood prolactin increased[3]

Metabolism and nutrition disorders
Very common: increased appetite
Common: decreased appetite

Musculoskeletal and connective tissue disorders
Common: muscular weakness
Unknown: rhabdomyolysis (as a complication of neuroleptic malignant syndrome)[3]

Nervous system disorders
Very common: dizziness, tremor, headache, myoclonus, somnolence

Common: speech disorder, paraesthesias, muscle hypertonia, dysgeusia, memory impairment, disturbance in attention

Uncommon: convulsions, ataxia

Very rare: EEG changes, neuroleptic malignant syndrome[1]

Unknown: serotonin syndrome, extrapyramidal symptoms (including akathisia and tardive dyskinesia)[3]

Psychiatric disorders:

Very common: restlessness, drowsiness, transient fatigue.

Common: confusion, ,disorientation, hallucinations (particularly in geriatric patients and patients suffering from Parkinson's disease), anxiety states, agitation, sleep disturbances, mania, hypomania, aggressiveness, depersonalisation, insomnia, nightmares, aggravated depression, impaired concentration, delirium

Uncommon: activation of psychotic symptoms.

Unknown: suicidal ideation, suicidal behaviours[1]. Cases of suicidal ideation and suicidal behaviours have been reported during clomipramine therapy or early after treatment discontinuation (see section 4.4).

Renal and urinary disorders
Very common: micturition disorder
Common: urinary retention

Reproductive system and breast disorders
Very common**: l**ibido disorder, erectile dysfunction

Common: galactorrhoea, breast enlargement.

Respiratory, thoracic, and mediastinal disorders
Common: yawning
Very rare: alveolitis allergic (pneumonitis) with or without eosinophilia

Skin and subcutaneous tissue disorders
Very common: hyperhidrosis
Common**:** dermatitis allergic (skin rash, urticaria), photosensitivity reaction, pruritus
Very rare **: p**urpura.

Vascular disorder

Common: hot flush

[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 4.4 Special Warnings and Precautions for use).

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 TCAs. 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 drugs may be reduced, leading to a risk of elevated plasma concentrations at therapeutic doses.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The signs and symptoms of overdose with clomipramine are similar to those reported with other tricyclic antidepressants. Cardiac abnormalities and neurological disturbances are the main complications. In children accidental ingestion of any amount should be regarded as serious and potentially fatal.

Signs and symptoms:

Symptoms generally appear within 4 hours of ingestion and reach maximum severity after 24 hours. Owing to delayed absorption (anticholinergic effect), long half-life, and enterohepatic recycling of the drug, the patient may be at risk for up to 4-6 days.

The following signs and symptoms may be seen:

Central nervous system

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

Cardiovascular system: hypotension, tachycardia, arrhythmias, conduction disorders, shock, heart failure and in very rare instances cardiac arrest.

In addition, vomiting, fever, mydriasis, respiratory depression, cyanosis, sweating, and oliguria, or anuria may occur.

Treatment:

There is no specific antidote, and treatment is essentially symptomatic and supportive. Anyone suspected of receiving an overdose of clomipramine, particularly children, should be hospitalised and kept under close surveillance for at least 72 hours.

Perform gastric lavage or induce vomiting as soon as possible if the patient is alert. 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 drug may delay gastric emptying. Administration of activated charcoal may help to reduce drug absorption.

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

- anticonvulsive therapy,
- artificial respiration,
- insertion of a temporary cardiac pacemaker,
- plasma expander, dopamine or dobutamine administered by intravenous drip,
- resuscitation.

Treatment of Torsade de Pointes.

If Torsade de Pointes should occur during treatment with clomipramine, the drug should be discontinued and hypoxia, electrolyte abnormalities and acid base disturbances should be corrected. Persistent Torsade de Pointes may be treated with magnesium sulphate 2g (20ml of 10% solution) intravenously over 30-120 seconds, repeated twice at intervals of 5-15 minutes 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 to achieve a heart rate of 90-110 beats/minute. Torsade de Pointes is usually not helped by antiarrhythmic drugs 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 clomipramine. Haemodialysis or peritoneal dialysis are ineffective because of the lower plasma concentrations of clomipramine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tricyclic antidepressant. Noradrenaline and preferential serotonin-reuptake inhibitor (non selective monoamine reuptake inhibitors), ATC code: N06A A04.

Mechanism of action

The therapeutic activity of clomipramine is believed to be based on its ability to inhibit the neuronal re-uptake of noradrenaline (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 following oral administration and intramuscular injection.

The systemic bioavailability of unchanged clomipramine is reduced by 50% by "first-pass" metabolism to desmethylclomipramine (an active metabolism). 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. During oral administration of constant daily doses of clomipramine the steady state plasma concentrations of clomipramine and desmethylclomipramine (active metabolite) and the ratio between these concentrations show a high variability between patients, e.g. 75 mg clomipramine daily produced steady state concentrations of clomipramine ranging from about 20-175 ng/ml. Levels of desmethylclomopramine follow a similar pattern but are 40-85% higher.

Distribution:
Clomipramine is 97.6% bound to plasma proteins. The apparent volume of distribution is about 12-17 1/kg bodyweight. Concentrations in cerebrospinal fluid are about 2% of the plasma concentration. Clomipramine passes into breast-milk in concentrations similar to those found in plasma.

Biotransformation:
The major route of transformation of clomipramine is demethylation to desmethylclomipramine. In addition, clomipramine and desmethylclomipramine are hydroxylated to 8-hydroxy-clomipramine and 8-hydroxy-desmethylclomipramine but little is known about their activity in vivo. The hydroxylation of clomipramine and desmethylclomipramine is under genetic control similar to that of debrisoquine. In poor metabolisers of debrisoquine this may lead to high concentrations of desmethylclomipramine, concentrations of clomipramine are less significantly influenced.

Elimination:

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

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

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

5.3. Preclinical safety data

Preclinical data has not been included because the safety profile of clomipramine has been established after many years of clinical use. Please refer to section 4.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contains:
Lactose monohydrate
Maize starch
Povidone (E1201)
Sodium starch glycolate (E576)
Sodium laurilsulfate
Magnesium stearate (E572).

Capsule shell contains:
Gelatine
Yellow iron oxide (E172)
Red iron oxide (E172)
Black iron oxide (E172)
Titanium dioxide (E171).

Printing ink contains:

Shellac
Black iron oxide (E172)
Propylene Glycol (E1520).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5. Nature and contents of container

PVDC coated PVC film with hard temper aluminium foil (blister pack) in packs of 28, 30, 56, 60 and 100 tablets.

HDPE or polypropylene containers with caps in packs of 28, 30, 56, 60, 100, 250, 500, or 1000 tablets.

Not all pack sizes may be marketed.

6.6. Instruction for use/handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited
Ridings Point, Whistler Drive,
Castleford, WF10 5HX, United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00289/0217

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/10/2004

10 DATE OF REVISION OF THE TEXT

19/02/2026