1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Clorek-25
(Clomipramine Hcl Tablet 25 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Clomipramine Hydrochloride	USP	25mg
Excipients		q.s.

Colour: Quinoline Yellow

3. PHARMACEUTICAL FORM

Filmcoated Tablet

Yellow coloured round shaped biconvex scored on one side film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of depressive states (in adults only) including endogenous, reactive, neurotic, organic, masked and involutional forms of depression, depression associated with schizophrenia and personality disorders, depressive syndromes due to presenility or senility, chronic painful conditions, and chronic somatic diseases, and depressive mood disorders of a reactive, neurotic or psychopathic nature.

Obsessive-compulsive syndromes

Phobias and panic attacks.

Cataplexy accompanying narcolepsy

Chronic painful conditions

4.2 Posology and method of administration

The dosage and method of administration should be adapted to the individual patient's condition. The aim is to achieve an optimum effect while keeping the doses as low as possible and increasing them cautiously, particularly in elderly patients, who generally show a stronger response to clomipramine than patients of intermediate age groups.

Dose

Depression, Obsessive-Compulsive Syndromes, and Phobias

Start treatment with one coated tablet of 25mg 2 -3 times daily. Raise the daily dosage stepwise, e.g. 25mg every few days (depending on how the medication is tolerated) to 4 to 6 tablets of 25mg during the first week of treatment. In severe cases this dosage can be increased up to a maximum of 250mg daily. Once there is a distinct improvement, adjust the daily dosage to a maintenance level of about 2 to 4 coated tablets of 25mg.

Panic Attacks, Agoraphobia

Start with one tablet of 10mg daily, possibly in combination with a benzodiazepine. Depending on how the medication is tolerated, raise the dosage until the desired response is obtained, while gradually withdrawing the benzodiazepine. The daily dosage required varies greatly from patient to patient and lies between 25 and 100mg. If necessary it can be increased to 150mg. It is advisable for treatment not to be discontinued for at least 6 months and for the maintenance dose to be reduced slowly during this time.

Cataplexy Accompanying Narcolepsy

Daily dose of 25 - 75mg.

Chronic Painful Conditions

The dosage must be individualised (10 - 150mg daily), while taking account of concomitant analgesic medication (and of the possibility of reducing use of analgesics).

Elderly Patients

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

Adolescent Depression

Not recommended for use in adolescent patients 13-18 years of age for the treatment of depression, unless under the supervision of a specialist

Method of administration

Maximum Tolerated Daily Dose

Maximum daily dose is 250mg

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

4.3 Contraindications:

Clomipramine is contraindicated for the treatment of depression in patients 12 years of age and under.

Clomipramine is contraindicated for the treatment of nocturnal enuresis.

Hypersensitivity to clomipramine and any of the excipients, or cross-sensitivity to tricyclic antidepressants of the dibenzazepine group.

Clomipramine should not be given in combination, or within 14 days before or after treatment, with a MAO inhibitor (see section 4.5 and 4.8). The concomitant treatment with selective, reversible MAO-A inhibitors, such as moclobemide, is also contraindicated.

Recent myocardial infarction.

4.4 Special warnings and precautions for use:

Clinical Worsening and Suicide Risk

Patients of any age with Major Depressive Disorder may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Patients should be closely monitored, especially at the beginning of therapy or when the dose is changed, until such improvement occurs.

There has been a long-standing concern that some antidepressants may have a role in the emergence of suicidality in some patients. The possible risk of increased suicidality in patients applies to all classes of antidepressant medicines, as available data are not adequate to exclude this risk for any antidepressant. Therefore, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Generally, when stopping an antidepressant, doses should be tapered rather than stopped abruptly.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and paediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric.

Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when

treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Mania and Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that clomipramine is not approved for use in treating bipolar depression.

Information for Patients and Families

Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, and hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to the medicines efficacy and safety when used in the treatment regimen proposed.

Tricyclic antidepressants are known to lower the convulsion threshold and clomipramine should, therefore, be used with extreme caution in patients with epilepsy and other predisposing factors, e.g. brain damage of varying aetiology, concomitant use of neuroleptics, and withdrawal from alcohol or medicines 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.

Cardiovascular disorders

Clomipramine should be administered with particular caution in patients with cardiovascular disorders, especially those with cardiovascular insufficiency, conduction disorders (e.g. atrioventricular block grades I to III), or arrhythmias. Monitoring of cardiac function and the ECG is indicated in such patients, as well as in elderly patients. An ECG should be performed prior to starting treatment, at steady state, after an increase in dose or after starting any potentially interacting medicine.

Tricyclic Antidepressant medicines, including clomipramine, particularly when given in high doses, have been reported to product QTc prolongation, arrhythmias (including torsades de pointers (TdP), sinus tachycardia and prolongation of the conduction time). Myocardial Infarction and stroke have been reported with medicines of this class. (see section 4.8).

Clomipramine should be used with caution in patients with risk factors for QTc prolongation/TdP including congenital long QT syndrome, age >65 years, female sex, structural heart disease/LV dysfunction, medical conditions such as renal or hepatic disease, use of medicines that inhibit the metabolism of clomipramine and the concomitant use of other QTc prolonging medicines (see 4.5). Hypokalaemia and hypomagnesaemia should be corrected prior to treatment.

Consideration should be given to stopping clomipramine treatment or reducing the dose if the QTc interval is >500ms or increases by >60ms.

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

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.

Many patients with panic disorder experience more marked anxiety at the start of the treatment with clomipramine (see Dosage and Administration). This paradoxical initial increase in anxiety is most pronounced during the first few days of treatment and generally subsides within two weeks.

Before starting treatment with clomipramine it is advisable to check blood pressure, because patients with postural hypotension or a labile circulation may experience a fall in blood pressure.

Caution is indicated in patients with hyperthyroidism or patients receiving thyroid preparations, owing to the possibility of cardiac toxicity.

In patients with liver disease, periodic monitoring of hepatic enzyme levels is recommended. 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, particularly during the first few months of therapy and during prolonged treatment. Like related tricyclic antidepressants, clomipramine should be given with electroconvulsive therapy only under careful supervision.

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

Clomipramine has been reported to be associated with fewer deaths following overdose than other tricyclic antidepressants.

Caution is called for in patients with chronic constipation. Tricyclic antidepressants may cause paralytic ileus, particularly in elderly and in bedridden patients.
Before general or local anaesthesia, the anaesthetist should be told that the patient has been receiving clomipramine (see 4.5).

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.

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.
Abrupt withdrawal should be avoided because of possible adverse reactions (see section 4.8 Undesirable Effects).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetics Interactions MAO Inhibitors
Do not give clomipramine for at least 2 weeks after discontinuation of treatment with MAO inhibitors (there is a risk of severe symptoms 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 clomipramine or the MAO inhibitor 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 two-week washout period must be observed if the MAO-A inhibitor is given after clomipramine has been used.

Adrenergic Neurone Blockers
Clomipramine 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 (eg. diuretics, vasodilators, or beta-blockers).

Sympathomimetic Agents

Clomipramine may potentiate the cardiovascular effects of adrenaline, noradrenaline, isoprenaline, ephedrine and phenylephrine (eg. local anaesthetics).

Medicines that can prolong the QT interval

The risk of QTc prolongation and/or ventricular arrhythmias (e.g. torsades de pointes) is increased with concomitant use of other medicines which prolong the QTc interval (e.g. some Antipsychotics and antibiotics). Please check the data sheet of other medicines administered for information on their effects on the QTc interval.

CNS Depressants

Tricyclic antidepressants may potentiate the effects of alcohol and other central depressant substances (e.g. barbiturates, benzodiazepines, or general anaesthetics).

Anticholinergic Agents

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

Quinidine

Tricyclic antidepressants should not be employed in combination with antiarrhythmic agents of the quinidine type.

Selective Serotonin Reuptake Inhibitors (SSRI)

Co-medication may lead to additive effects on the serotonergic system. Fluoxetine and fluvoxamine may also increase plasma concentrations of clomipramine, with corresponding adverse effects.

Liver-Enzyme Inducers

Agents 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 medicines.

Neuroleptics

Co-medication may result in increased plasma levels of tricyclic antidepressants, a lowered convulsion threshold, and seizures. Combination with thioridazine may produce severe cardiac arrhythmias.

Anticoagulants

Tricyclic antidepressants may potentiate the anticoagulant effect of coumarin agents due to their inhibition of hepatic metabolism. Careful monitoring of plasma prothrombin is therefore advised.

Cimetidine, Methylphenidate, Oestrogens

These medicines increase plasma concentrations of tricyclic antidepressants, whose dosage should therefore be reduced.

Pharmacodynamic Interactions

N/A

4.6 Pregnancy and lactation

Pregnancy

Category C

Experience with clomipramine in pregnancy is limited. Since there have been isolated reports of a possible connection between the use of tricyclic antidepressants and adverse effects (developmental disorders) on the foetus, treatment with clomipramine should be avoided during pregnancy, unless the anticipated benefits justify the potential risk to the foetus.

Neonates whose mothers had taken tricyclic antidepressants until delivery showed withdrawal symptoms, such as dyspnoea, lethargy, colic, irritability, hypotension or hypertension, and tremor or spasms, during the first few hours or days. To avoid such

symptoms, clomipramine should if possible be gradually withdrawn at least 7 weeks before the calculated date of confinement.

Breast-feeding

Since the active substance passes into the breast milk, clomipramine should be gradually withdrawn or the infant weaned if the patient is breastfeeding.

Fertility

See section 5.3.

4.7 Effects on ability to drive and use machines

Likely to produce severe adverse effects or presumed to be potentially dangerous on the ability to drive or use machinery.

Patients receiving clomipramine should be warned that blurred vision, drowsiness and other CNS symptoms (see undesirable effects) may occur, in which case they should not drive, operate machinery, or do anything else requiring alertness. Patients should also be warned that alcohol or other medicines 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.

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.

Frequency of Undesirable Effects

Estimates from clinical trials and spontaneous ADR reports, classified as follows:

Classification Frequency (%)

Frequent > 10%

Occasional > 1% to 10%

Rare > 0.001% to 1% Isolated cases < 0.001%

Central Nervous System

Psychic Effects

Frequent: drowsiness, fatigue, restlessness, increased appetite.

Occasional: confusion, disorientation, hallucinations (particularly in elderly patients and patients with Parkinson's disease), anxiety states, agitation, sleep disturbances, mania, hypomania, aggressiveness, impaired memory, de-personalisation, aggravated depression, impaired concentration, insomnia, nightmares, yawning.

Rare: activation of psychotic symptoms.

Neurological Effects

Frequent: dizziness, tremor, headache, myoclonus.

Occasional: delirium, speech disorders, paraesthesias, muscle weakness, muscle hypertonia.

Rare: convulsions, ataxia.

Isolated cases: EEG changes, hyperpyrexia.

Anticholinergic Effects

Frequent: dry mouth, sweating, constipation, disorders of visual accommodation, blurred vision, disturbances of micturition.

Occasional: hot flushes, mydriasis.

Isolated cases: glaucoma.

Cardiovascular System

Occasional: tachycardia, palpitations, hypotension, syncope, myocardial infarction, stroke, and ECG changes (including QTc prolongation, non-specific ST and T wave

changes and conduction disorders such as heart block, bundle branch block and widened QRS complex) in patients of normal cardiac status.

Rare: arrhythmias (including ventricular tachycardia, ventricular fibrillation and Torsades de Pointes), hypertension.

Isolated cases: conduction disorders (e.g. widening of QRS complex, PQ changes, bundle-branch block).

Gastrointestinal Tract

Frequent: nausea.

Occasional: vomiting, abdominal disorders, diarrhoea, anorexia. Isolated cases: gastrointestinal haemorrhage.

Liver

Occasional: elevated transaminases.

Isolated cases: hepatitis with or without jaundice.

Skin

Occasional: allergic skin reactions (skin rash, urticaria), photosensitivity, pruritus.

Isolated cases: oedema (local or generalised), hair loss.

Endocrine System and Metabolism

Frequent: weight gain, disturbances of libido and potency.

Occasional: galactorrhoea, breast enlargement.

Isolated cases: SIADH (inappropriate antidiuretic hormone secretion syndrome).

Hypersensitivity

Isolated cases: allergic alveolitis (pneumonitis) with or without eosinophilia, systemic anaphylactic/anaphylactoid reactions including hypotension.

Blood

Isolated cases: leucopenia, agranulocytosis, thrombocytopenia, eosinophilia, purpura.

Sense Organs

Occasional: taste disturbances, tinnitus.

Others

The following symptoms occasionally occur after abrupt withdrawal or reduction of the dose: nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness, and anxiety.

Post-marketing Experience

See Undesirable effects

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 clomipramine, 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, restlessness, agitation, enhanced reflexes, muscular rigidity and choreoathetoid movements, convulsions.

Cardiovascular System: hypotension, tachycardia, QTc prolongation, arrhythmias (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, 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 is not alert, 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 of cardiac function, blood gases, and electrolytes, and if necessary emergency measures such as anticonvulsive therapy, artificial respiration, and resuscitation. 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 low plasma concentrations of clomipramine.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, Non-selective monoamine reuptake inhibitors, ATC code: N06AA04.

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 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.

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 produces steady state concentrations of clomipramine ranging from about 20 to 175 ng/ml. Levels of desmethylclomipramine follow a similar pattern but are 40-85% higher.

Clomipramine slows gastro-intestinal transit time, absorption can, however, be delayed, particularly in overdosage.

Distribution

Clomipramine and desmethylclomipramine are widely distributed throughout the body and is 97.6% bound to plasma and tissue protein. The apparent volume of distribution is about 12-17 l/kg body weight. Concentrations in cerebrospinal fluid are about 2% of the plasma concentration.

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 major route of transformation of clomipramine is demethylation to desmethylclomipramine. In addition, clomipramine and desmethylclomipramine are hydroxylated to 8-hydroxy-clomipramine and 8-hydroxy-desmethyl-clomipramine 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 12-36 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.

5.3 Preclinical safety data

Repeat-dose toxicity

Phospholipidosis and testicular changes considered to be secondary to the phospholipidosis, commonly associated with tricyclic compounds, have been observed with clomipramine hydrochloride at doses ≥4 fold greater than the

maximum recommended human daily dose (MRHD). The clinical relevance of these findings is unknown.

Reproductive toxicity

Clomipramine hydrochloride demonstrated evidence of embryotoxicity *e.g.* increased embryolethality and growth retardation, in the rat and mouse studies (at doses which are 5 to 10 times the estimated oral MRHD of 5 mg/kg on a mg/kg basis), but not in the rabbit study. The safety margin for increased embryolethality based on the administered dose is 2.5 times the oral MHRD.

No teratogenic effects were detected in mice, rats, and rabbits at doses up to 100, 50, and 60 mg/kg, respectively.

Mutagenicity

Various *in vitro* and *in vivo* mutagenicity tests were performed and did not reveal any mutagenic activity of clomipramine hydrochloride.

Carcinogenicity

The administration of clomipramine hydrochloride to mice and rats for 104 weeks did not show any evidence of carcinogenicity at dose levels representing 16 - 20 times the estimated oral MRHD of 5 mg/kg on a mg/kg basis.

6. Pharmaceutical particulars

6.1 List of excipients

Starch

Di basic calcium phosphate

Iso Propyl Alcohol

Povidone(PVPK-30)

Talc

Magnesium Stearate

Cross Carmellose sodium

Colloidal silicon Dioxide

Titanium Dioxide

Hypromellose (HPMC E15)

Methylene Dichloride

Colour Quinoline Yellow

6.2 Incompatibilities

None

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a dry and dark place at temperatures below 30°C.

6.5 Nature and contents of container

10 x 10 Alu-Pvc blister pack.

6.6 Special precautions for disposal and other handling

No Special Requirements.

7. MARKETING AUTHORISATION HOLDER

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9. MARKETING AUTHORISATION NUMBER(S)

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10. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

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11. DATE OF REVISION OF THE TEXT
