# Clomipramine HCl Tablets 25mg/50mg/75mg

## 1. Name of the medicinal product

Clomipramine HCl 25mg Tablets TajPharma
Clomipramine HCl 50mg Tablets TajPharma
Clomipramine HCl 75mg Tablets TajPharma

## 2. Qualitative and quantitative composition

a) Each film coated tablet contains:

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|---|---|
| Clomipramine Hydrochloride BP | 25mg |
| Excipients | q.s. |
| Colour: Ponceau 4R | |

b) Each film coated tablet contains:

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|---|---|
| Clomipramine Hydrochloride BP | 50mg |
| Excipients | q.s. |
| Colour: Ponceau 4R | |

c) Each film coated tablet contains:

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|---|---|
| Clomipramine Hydrochloride BP | 75mg |
| Excipients | q.s. |
| Colour: Ponceau 4R | |

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Film coated Tablets.

## 4. Clinical particulars

**4.1 Therapeutic indications**

Adults

Clomipramine Tablets are indicated for the treatment of:

- the symptoms of depressive illness especially where sedation is required

- obsessional and phobic states

- adjunctive treatment of 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).

**4.2 Posology and method of administration**

Posology

Before initiating treatment with clomipramine, hypokalaemia should be treated (see section 4.4).

After a response has been obtained, maintenance therapy should be continued at the optimum dose to avoid relapse. Patients with a history of recurrence require maintenance treatment for a longer duration. Duration of maintenance treatment and need for further treatment should be reviewed periodically.

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 drugs that prolong QT interval or other serotonergic agents are co-administered (see sections 4.4 and 4.5).

Abrupt discontinuation of clomipramine therapy 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.

*Adults*

Oral – 75 mg/day initially, increasing gradually to 30-150 mg/day, if required, in divided doses throughout the day or as a single dose at bedtime. Many patients will be adequately maintained on 30-50 mg/day. Higher doses may be needed in some patients, particularly those suffering from obsessional or phobic disorders. In severe cases this dosage can be increased up to a maximum of 250 mg per day. Once a

distinct improvement has set in, the daily dosage may be adjusted to a maintenance level of about 50-100 mg.

*Elderly*

Elderly patients generally show a stronger response to clomipramine than patients of intermediate age groups, clomipramine should be used with caution in elderly patients and doses should be increased cautiously. The initial dose should be 10 mg/day, which may be increased with caution under close supervision to an optimum level of 30-75 mg daily which should be reached after about 10 days and then maintained until the end of treatment.

*Paediatric population*

Not recommended (see section 4.4).

*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 100-150 mg clomipramine daily, according to the severity of the condition. This should be attained gradually over a period of 2 weeks starting with 1 x 25 mg clomipramine daily. In elderly patients and those sensitive to tricyclic antidepressants a starting dose of 1 x 10 mg clomipramine daily is recommended. Again where a higher dosage is required the sustained-release 75 mg formulation may be preferable.

*Adjunctive treatment of cataplexy associated with narcolepsy*

(Oral treatment): 10-75 mg daily. It is suggested that treatment is commenced with 10 mg clomipramine daily and gradually increased until a satisfactory response occurs. Control of cataplexy should be achieved within 24 hours of reaching the optimal dose. Where necessary, therapy may be combined with Tablets up to the maximum dose of 75 mg per day.

*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 sections 4.4 and 4.8 for a description of the risks of discontinuation of clomipramine).

*Renal impairment*

Clomipramine should be given with caution in patients with renal impairment (see sections 4.4 and 5).

*Hepatic impairment*

Clomipramine should be given with caution in patients with hepatic impairment (see sections 4.4 and 5).

Method of administration

For oral use

**4.3 Contraindications**

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or cross-sensitivity to tricyclic antidepressants of the dibenzazepine group

- recent myocardial infarction, any degree of heart block or other cardiac arrhythmias

- severe liver disease

- concurrent administration with monoamine oxidase inhibitors or within 3 weeks of start or cessation of therapy (see section 4.5)

- concomitant treatment with selective, reversible MAO-A inhibitors, such as moclobemide

- narrow-angle glaucoma

- retention of urine

- mania.

**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.

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.

Paediatric population

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).

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), 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 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 (see also treatment discontinuation in section 4.4).

Other psychiatric effects

Many patients with panic disorders experience intensified anxiety symptoms at the start of the treatment with antidepressants. 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 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 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.

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

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.

There may be 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). 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). 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 clomipramine (see section 4.5).

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.

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 or lithium. Therefore, concomitant administration of drugs that can cause accumulation of clomipramine should be avoided (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

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, 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 treatment of clomipramine and electroconvulsive therapy should only be resorted to under careful supervision.

Anticholinergic effects

Because of its anticholinergic properties, clomipramine 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 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 advised in patients with hyperthyroidism or during concomitant treatment with thyroid preparations since aggravation of unwanted cardiac effects may occur.

It is advisable to monitor cardiac and hepatic function during long-term therapy with clomipramine. 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 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 bed-ridden patients.

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

Monitoring of cardiac function and the ECG is indicated in elderly 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, particularly during the first few months of therapy. They are also recommended during prolonged therapy.

Anticoagulants / Non-steroidal anti-inflammatory drugs

Skin and mucous membrane bleeding has been reported with clomipramine. The product 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 drugs (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 arrhythmias and hypotension.

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).

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 for a description of the risks of abrupt discontinuation of clomipramine).

Clomipramine Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactosemalabsorption should not take this medicine.

Clomipramine contains Sunset yellow (E110). May cause allergic reactions.

**4.5 Interaction with other medicinal products and other forms of interaction**

Interactions resulting in a contraindication

*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.

Interactions resulting in a concomitant use not recommended

*Diuretics*

Diuretics may lead to hypokalaemia, which increases the risk of QTc prolongation and torsades de pointes. Hypokalaemia should therefore be treated prior to administration of clomipramine (see sections 4.2 and 4.4).

*Quinidine*

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

*Selective serotonin reuptake inhibitors (SSRIs)*

SSRIs which are inhibitors of CYP2D6, such as fluoxetine, paroxetine, or sertraline, and of others including CYP1A2 and CYP2C19 (*e.g.* fluvoxamine), may also increase plasma concentrations of clomipramine, with corresponding adverse effects. Steady-state serum levels of clomipramine increased ~4-fold by co-administration of fluvoxamine (*N*-desmethylclomipramine decreased ~2-fold). In addition, co-medication with SSRIs may lead to additive effects on the serotonergic system (see serotonergic agents) (see sections 4.2 and 4.4).

*Serotonergic agents*

Serotonin Syndrome can possibly occur when clomipramine is administered with other serotonergic co-medications such as selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenergic reuptake inhibitors (SNaRIs), tricyclic antidepressants and lithium (see sections 4.2 and 4.4). For fluoxetine, a wash-out period of two to three weeks is advised before and after treatment with fluoxetine.

Interactions to be considered

Interactions resulting in increased effect of clomipramine

*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 clomipramine may be necessary when co-administered with terbinafine.

*Cimetidine*

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

*Oral contraceptives*

No interaction between chronic oral contraceptive use (15 or 30 micrograms ethinylestradiol daily) and clomipramine (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 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 antipsychotic (*e.g.* phenothiazines) may result in increased plasma levels of tricyclic antidepressants, a lowered convulsion threshold, and seizures. Combination with thioridazine may produce severe cardiac arrhythmias.

*Methylphenidate*

This drug may also increase plasma concentrations of tricyclic antidepressants, whose dosage should therefore be reduced.

*Valproate*

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

Interactions resulting in decreased effect of clomipramine

*Rifampicin*

Rifampicin (CYP3A and CYP2C inducer), may decrease clomipramine concentrations as concomitant administration of drugs known to induce cytochrome P450 enzymes, particularly CYP3A4, CYP2C19 may accelerate the metabolism and decrease the efficacy of clomipramine.

*Anticonvulsants*

Anticonvulsants (CYP3A and CYP2C inducer) *e.g.* barbiturates, carbamazepine, phenobarbital and phenytoin, may decrease clomipramine concentrations as concomitant administration of drugs known to induce cytochrome P450 enzymes, particularly CYP3A4, CYP2C19 may accelerate the metabolism and decrease the efficacy of clomipramine.

*Cigarette smoking*

Known inducers of CYP1A2 (*e.g.* nicotine/components in cigarette smoke), decrease plasma concentrations of tricyclic drugs. In cigarette smokers, 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 clomipramine and resins, such that the drug 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 clomipramine with St. John's wort during the treatment may decrease the plasma concentrations of clomipramine.

Interactions affecting other drugs

*Anticholinergic agents*

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

*Antiadrenergic agents*

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 (*e.g.* vasodilators, or beta-blockers).

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

*CNS depressants*

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

*Sympathomimetic drugs*

Clomipramine may potentiate the cardiovascular effects of adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine, and phenylpropanolamine (*e.g.* as contained in local and general anaesthetic preparations and nasal decongestants).

*Anticoagulants*

Tricyclic antidepressants may potentiate the anticoagulant effect of coumarin drugs by inhibiting their metabolism by the liver. Careful monitoring of plasma prothrombin is therefore advised.

*Drugs 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 clomipramine is co-administered with other drugs that can cause QTc prolongation. Therefore concomitant use of such agents with clomipramine is not recommended (see section 4.4). Examples include certain antiarrhythmics, 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 torsades 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). Examples of drugs 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 tricyclics.

*Non-steroidal anti-inflammatory drugs*

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

*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 arrhythmias with levacetylmethadol.

*Antipsychotics*

Increased risk of ventricular arrhythmias – avoid concomitant use with pimozide. Antipsychotic agents may increase the plasma concentration of tricyclic agents. No such effects are known to occur in combination with diazepam, but it might be necessary to reduce the dosage of clomipramine if administered concomitantly with alprazolam or disulfiram. There may be

increased antimuscarinic side-effects with phenothiazines, and possibly clozapine.

*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

There is 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 tricyclic antidepressants 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). Clomipramine is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

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

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 use machines**

Patients receiving clomipramine should be warned that blurred vision, drowsiness and other nervous system and psychiatric related disorders such as somnolence, disturbance in attention, confusion, disorientation, aggravation of 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 drugs may potentiate these effects (see section 4.5).

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive

• Do not drive until you know how the medicine affects you

• It is an offence to drive while under the influence of this medicine

• However, you would not be committing an offence (called 'statutory defence') if:

o The medicine has been prescribed to treat a medical or dental problem and

o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

o It was not affecting your ability to drive safely

**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 drug 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 to <1/10); uncommon (≥1/1,000 to < 1/100); rare (≥1/10,000 to < 1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

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|---|---|
| **Blood and lymphatic system disorders** | |
| Very rare | Leucopenia, agranulocytosis, thrombocytopenia, eosinophilia |
| **Immune system disorders** | |
| Very rare | Anaphylactic and anaphylactoid reactions including hypotension |
| **Endocrine disorders** | |
| Very rare | SIADH (inappropriate antidiuretic hormone secretion syndrome) |
| **Metabolism and nutrition disorders** | |
| Very common | Increased appetite |
| Common | Decreased appetite |
| **Psychiatric disorders** | |
| Very common | Restlessness |
| Common | Confusional state, disorientation, hallucinations (particularly in elderly patients and patients with Parkinson's disease), anxiety, agitation, sleep disorder, mania, hypomania, aggression, depersonalisation, aggravation of depression, insomnia, nightmares, delirium |
| Uncommon | Activation of psychotic symptoms |
| Not known | Suicidal ideation, suicidal behaviours[2] |
| **Nervous system disorders** | |
| Very common | Dizziness, tremor, headache, myoclonus, somnolence |
| Common | Speech disorder, paraesthesia, hypertonia, dysgeusia, memory impairment, disturbance in attention |
| Uncommon | Convulsions, ataxia |
| Very rare | Neuroleptic malignant syndrome[1] |
| Not known | Serotonin syndrome, extrapyramidal disorder (including akathisia and tardive dyskinesia)[3] |
| **Eye disorders** | |
| Very common | Accommodation disorder, vision blurred |
| Common | Mydriasis |
| Very rare | Glaucoma |
| **Ear and labyrinth disorders** | |
| Common | Tinnitus |
| **Cardiac disorders** | |
| Common | Sinus tachycardia, palpitation, orthostatic hypotension, clinically irrelevant ECG changes (*e.g.* ST and T changes) in patients of normal cardiac status |
| Uncommon | Arrhythmias, blood pressure increased |
| Very rare | Conduction disorder (*e.g.* widening of QRS complex, prolonged QT interval, PQ changes, bundle-branch block, torsades de pointes, particularly in patients with hypokalaemia) |
| **Vascular disorders** | |
| Common | Hot flush |

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| **Respiratory, thoracic, and mediastinal disorders** | |
| Common | Yawning |
| Very rare | Alveolitis allergic (pneumonitis) with or without eosinophilia |
| **Gastrointestinal disorders** | |
| Very common | Nausea, dry mouth, constipation |
| Common | Vomiting, gastrointestinal disorders, diarrhoea |
| **Hepatobiliary disorders** | |
| Very rare | Hepatitis with or without jaundice |
| **Skin and subcutaneous tissue disorders** | |
| Very common | Hyperhidrosis |
| Common | Dermatitis allergic (skin rash, urticaria), photosensitivity reaction, pruritus |
| Very rare | Ecchymosis, purpura, alopecia |
| **Musculoskeletal and connective tissue disorders** | |
| Common | Muscular weakness |
| Not known | Rhabdomyolysis (as a complication of neuroleptic malignant syndrome)[3] |
| **Renal and urinary disorders** | |
| Very common | Micturition disorder |
| Common | Urinary retention |
| **Reproductive system and breast disorders** | |
| Very common | Libido disorder, erectile dysfunction |
| Common | Galactorrhoea, breast enlargement, women occasionally experience orgasmic impotence |
| Rare | Vaginal bleeding |
| Not known | Ejaculation failure, ejaculation delayed |

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| **General disorders and administration site conditions** | |
| Very common | Fatigue |
| Very rare | Oedema (local or generalised), hyperpyrexia |
| **Investigations** | |
| Very common | Weight increased, blood sugar changes |
| Common | Transaminases increased |
| Very rare | Electroencephalogram abnormal |
| Not known | Blood prolactin increased[3] |

[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 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.

**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, restlessness, agitation, enhanced reflexes, muscular rigidity, athetoid and choreoathetoid movements, convulsions, serotonin syndrome (*e.g.* hypertensive crisis, hyperpyrexia, myoclonus, delirium and coma).

Cardiovascular system

Hypotension, tachycardia, QTc prolongation and arrhythmia 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 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 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 arrhythmias 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 clomipramine, the drug should be discontinued and hypoxia, electrolyte

abnormalities and acid base disturbances should be corrected. Persistent torsades de pointes may be treated with magnesium sulphate 2 g (20 ml 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 per minute. Torsades 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 low plasma concentrations of clomipramine.

For convulsions:

Diazepam should be given iv 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**
Pharmacotherapeutic group: Antidepressants, Non-selective monoamine reuptake inhibitors.

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 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**
Eudragit, Calcium hydrogen phosphate, Silicon dioxide, Calcium stearate, Hypromellose, Red iron oxide, polyoxyl hydrogenated castor oil, talc and titanium dioxide.

**6.2 Incompatibilities**
Not applicable

**6.3 Shelf life**
3 years.

**6.4 Special precautions for storage**
Do not store above 30°C

**6.5 Nature and contents of container**
Aluminium foil/PVC blister packs

Packs of: 7, 14, 28, 30, 50, 90, 100 and 500 Tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**
Not applicable.

**7. Manufactured In India By:**
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