

1 NAME OF THE MEDICINE

Clomipramine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg of clomipramine hydrochloride.

Excipients with known effect: sugars as lactose and trace quantities of sulfites.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Clomipramine hydrochloride 25 mg tablet: white, film coated, biconvex tablets marked “Cl 25” on one side and “G” on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of:

- major depression;
- obsessive-compulsive disorders and phobias in adults; and
- cataplexy associated with narcolepsy.

4.2 DOSE AND METHOD OF ADMINISTRATION

General

The dosage and mode of administration should be determined individually and adapted to the patient's condition. Doses should be kept as low as possible and increased cautiously, particularly when treating elderly patients. These patients generally show a more marked response to PLACIL than patients in intermediate age groups. Note that the plasma concentrations of the drug and active metabolite do not stabilise for 7 to 14 days after commencing treatment and after a dosage change.

The efficacy and tolerability of PLACIL during treatment must be judged by keeping the patient under close surveillance.

Depression, obsessive-compulsive disorders and phobias

Commence treatment with 25 mg (one tablet) two or three times daily. Increase the daily dosage stepwise, e.g. 25 mg every few days (depending on how the medication is tolerated) to 100 to 150 mg (four to six tablets). Once a distinct improvement has set in, adjust the daily dosage to a maintenance level averaging 50 to 100 mg (two to four tablets).

Cataplexy accompanying narcolepsy

PLACIL should be given orally in a daily dose of 25 to 75 mg. Nocturnal medication should only be given in cases where PLACIL does not appear to exacerbate insomnia.

Elderly patients

Elderly patients generally show a more marked response to PLACIL than patients belonging to intermediate age groups. PLACIL should be used with caution in elderly and doses should be increased cautiously. Start treatment with 25 mg (one tablet) daily. Gradually increase the dosage over about ten days to an optimum level of 50 to 75 mg daily. This dose should then be adhered to until the end of treatment.

4.3 CONTRAINDICATIONS

Known hypersensitivity to clomipramine or any of the excipients of the tablets.

Cross sensitivity to tricyclic antidepressants of the dibenzazepine group.

Concomitant use with a monoamine oxidase (MAO) inhibitor, or within 14 days before or after treatment with an irreversible MAO inhibitor (MAOIs), or within 14 days before moclobemide (a reversible MAOI), see Section 4.5 Interactions with other medicines and other forms of interactions regarding moclobemide.

Acute and recovery stages of myocardial infarction.

Congenital long QT syndrome.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Clinical worsening and suicide risk associated with psychiatric disorders

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. 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.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at greater risk of suicidal thoughts or suicidal attempts and should receive careful monitoring during treatment.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the

pooled analysis included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Pooled analysis of short-term studies of antidepressant medications have also shown an increased risk of suicidal thinking and behaviour, known as suicidality, in young adults ages 18 to 24 during initial treatment (generally the first one to two months). Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years; there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children 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 worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non-psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

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

General precautions

Caution is called for when employing tricyclic antidepressants in patients with the following conditions or in the following circumstances:

- **Cardiovascular disorders especially those who have a history of conduction disorders (see below) and in elderly patients.** Cardiovascular insufficiency, atrioventricular block (grades I to III) and arrhythmias. Monitoring of cardiovascular function and ECG is called for in such cases, especially in the elderly. Myocardial infarction, precipitation of congestive cardiac failure, stroke and sudden death have been associated with medicines of this class.
- A history of increased intraocular pressure, narrow angle glaucoma.
- Disorders of micturition due to an impeded flow of urine (e.g. in diseases of the prostate).
- A low convulsion threshold (e.g. due to brain damage of varying aetiology, epilepsy, concomitant use of other drugs such as neuroleptics that may lower seizure threshold, withdrawal from alcohol or drugs with anticonvulsive properties, e.g. benzodiazepines). Clinical trials with clomipramine in the USA have shown a clear relationship between the size of the dose and the occurrence of seizures. The recommended daily dose of PLACIL should therefore not be exceeded.
- Severe hepatic or renal diseases.
- Tumours of the adrenal medulla (e.g. pheochromocytoma, neuroblastoma), in whom the medicine may provoke hypertensive crises.
- Hyperthyroidism or when PLACIL is used concomitantly with thyroid preparations. Due to the anticholinergic action of clomipramine aggravation of unwanted cardiac effects can generally be expected to occur in these patients.

- Chronic constipation, as tricyclic antidepressants may cause paralytic ileus, particularly in elderly and bedridden patients.

QTc prolongation

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) or serotonin and noradrenergic reuptake inhibitors (SNRIs). Therefore, concomitant administration of medicines that can cause accumulation of clomipramine should be avoided (see Section 4.5 Interactions with other medicines and other forms of interactions). Equally, concomitant administration of medicines that can prolong the QTc interval should be avoided. It is established that hypokalaemia is a risk factor for QTc prolongation and torsades de pointes. Therefore, hypokalaemia should be treated before initiating treatment with PLACIL. PLACIL should be used with caution when combined with diuretics (see Section 4.5 Interactions with other medicines and other forms of interactions).

Serotonin syndrome

Due to the increased risk of serotonergic toxicity, it is advisable to adhere to recommended doses of clomipramine. Serotonin syndrome, with symptoms such as hyperpyrexia, myoclonus, agitation, seizures, delirium and coma, can possibly occur when clomipramine is co-administered with serotonergic medications such as SSRIs, SNRIs, tricyclic antidepressants or lithium. For fluoxetine, a washout period of two to three weeks is advised before and after treatment with fluoxetine (see Section 4.5 Interactions with other medicines and other forms of interactions).

Electroconvulsive therapy

Concomitant use of tricyclic antidepressants and electroconvulsive therapy should only be undertaken under careful supervision as there is minimal clinical experience with this combination.

Central nervous system (CNS) effects

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

Owing to their activating effect, tricyclic antidepressants may cause anxiety, feelings of unrest, and hyperexcitation in agitated patients and patients with accompanying schizophrenic symptoms. Activation of psychosis has occasionally been observed in patients with schizophrenia receiving tricyclic antidepressants.

Tricyclic antidepressants may provoke delirious psychoses in predisposed and elderly patients, particularly at night. These disappear without treatment within a few days of withdrawing the medicine.

In patients with bipolar affective disorders, a swing from depression to hypomania or mania is possible. It may be necessary, in such cases, to withdraw PLACIL and administer medicines to control the mania. After such episodes have subsided, low dose therapy with PLACIL may be resumed if required.

Anaesthetics

Before general or local anaesthesia, the anaesthetist should be notified that the patient has been receiving PLACIL (see Section 4.5 Interactions with other medicines and other forms of interactions, Alcohol and other CNS depressants).

Treatment discontinuation

Abrupt withdrawal should be avoided because of possible adverse reactions (see Section 4.8 Adverse Effects (Undesirable effects)). Therefore, dosage should be stopped gradually after regular use for long duration and the patient should be monitored carefully when PLACIL therapy is discontinued.

Patient Monitoring

Before initiating treatment with PLACIL, pre-existing hypokalaemia should be treated.

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

The blood count should be monitored during treatment with PLACIL (especially if the patient develops fever, sore throat or other flu-like symptoms), since isolated cases of agranulocytosis have been associated with the use of tricyclic antidepressants. This is particularly called for during the first few months of therapy and during prolonged treatment.

In patients with known liver disease or a history of liver disease; or known renal impairment, periodic monitoring is recommended (see Section 4.8 Adverse Effects (Undesirable effects)). It is also advisable to monitor hepatic and renal function during long term therapy with tricyclic antidepressants.

Dental effects

Treatment with tricyclic antidepressants can lead to an increased incidence of dental caries.

Effects on the eye

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

Lactose

PLACIL tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency, or glucose-galactose malabsorption should not take PLACIL tablets.

Bipolar disorder and activation of Mania/Hypomania

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

Use in Hepatic Impairment

Caution is called for when employing tricyclic antidepressants in patients with severe hepatic diseases.

In patients with known liver disease or a history of liver disease, periodic monitoring is recommended (see Section 4.8 Adverse Effects (Undesirable effects)). It is also advisable to monitor hepatic function during long term therapy with tricyclic antidepressants.

Use in Renal Impairment

Caution is called for when employing tricyclic antidepressants in patients with severe renal diseases.

In patients with known renal impairment, periodic monitoring is recommended (see Section 4.8 Adverse Effects (Undesirable effects)). It is also advisable to monitor renal function during long term therapy with tricyclic antidepressants.

Use in the Elderly

Caution is called for when employing tricyclic antidepressants in patients with the following conditions or in the following circumstances:

- **Cardiovascular disorders especially those who have a history of conduction disorders (see General precautions above) and in elderly patients.** Cardiovascular insufficiency, atrioventricular block (grades I to III) and arrhythmias. Monitoring of cardiovascular function and ECG is called for in such cases, especially in the elderly. Myocardial infarction, precipitation of congestive cardiac failure, stroke and sudden death have been associated with medicines of this class.
- Chronic constipation, as tricyclic antidepressants may cause paralytic ileus, particularly in elderly and bedridden patients.

Tricyclic antidepressants may provoke delirious psychoses in predisposed and elderly patients, particularly at night. These disappear without treatment within a few days of withdrawing the medicine.

See also Section 4.2 Dose and method of administration, Section 4.8 Adverse effects (Undesirable effects), Geriatric population and Section 5.2 Pharmacokinetic properties, Absorption.

Paediatric Use

The safety and efficacy of PLACIL for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. PLACIL should not be used in this age group for the treatment of depression or other psychiatric disorders. Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available.

Safety note concerning children

Patients should be advised to keep PLACIL out of reach of children.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions resulting in a contraindication

Monoamine oxidase inhibitors (MAOIs)

These agents, which are also potent CYP2D6 inhibitors *in vivo*, such as moclobemide, are contraindicated for co-administration with clomipramine.

If PLACIL is to be used after treatment with a MAOI, it is absolutely essential that an interval of at least 14 days should elapse before starting therapy, otherwise severe interactions may occur (e.g. hyperactivity, hypertensive crisis, hyperpyrexia, spasticity, convulsions, coma or death), including those consistent with serotonin syndrome (see Section 4.4. Special warnings and precautions for use). The same precaution should be taken when administering a MAOI after previous treatment with PLACIL (see Section 4.3 Contraindications). In either instance, medication with PLACIL or with the MAOI should be started cautiously and the dosage raised stepwise until the optimum response is obtained.

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. Patients should be monitored for symptoms suggestive of serotonergic syndrome (serotonin syndrome).

Interactions resulting in a concomitant use not recommended

Antiarrhythmic agents

Tricyclic antidepressants should not be used in combination with antiarrhythmic agents (such as quinidine and propafenone), which are potent inhibitors of CYP2D6.

Diuretics

Co-medication of clomipramine with diuretics may lead to hypokalaemia, which in turn increases the risk of QTc prolongation and torsades de pointes. Therefore, hypokalaemia should be treated prior to administration of PLACIL (see Section 4.4. Special warnings and precautions for use).

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs which are inhibitors of CYP2D6, such as such as fluoxetine, paroxetine, 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 and N-desmethylclomipramine decreased ~2-fold. For fluoxetine, a washout period of two to three weeks is advised before and after treatment with fluoxetine.

Serotonergic agents

Serotonin syndrome can possibly occur when clomipramine is co-administered with serotonergic medications such as SSRIs, SNRIs, tricyclic antidepressants or lithium (see Section 4.4. Special warnings and precautions for use).

Interactions resulting in increased effect of PLACIL

Concomitant administration of CYP2D6 inhibitors may lead to an increase in concentration of both active components, up to ~3-fold in patients with a debrisoquine/sparteine extensive metaboliser phenotype, converting them to a poor-metaboliser phenotype. Concomitant administration of CYP1A2, CYP2C19 and CYP3A4 inhibitors is expected to increase clomipramine concentrations and decrease N-desmethylclomipramine, thus not necessarily affecting the overall pharmacology.

Terbinafine

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

Cimetidine

Cimetidine is an inhibitor of several P450 enzymes, including CYP2D6 and CYP3A4, and raises the plasma concentration of tricyclic antidepressants. Therefore, the dosage of the tricyclic agent should be reduced if the two medicines are administered concurrently.

Oral contraceptives

No interaction between chronic oral contraceptive use (15 or 30 micrograms ethinylestradiol daily) and clomipramine (25 mg daily) has been documented. Estrogens 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 estrogen (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 estrogen regimens. Monitoring therapeutic response of tricyclic antidepressants at high dose estrogen regimens (50 micrograms daily) is recommended and dose adjustments may be necessary.

Antipsychotics

Co-medication of antipsychotics (e.g. phenothiazines) may result in an increase in the plasma concentration of tricyclic antidepressant agents, a lowered convulsion threshold and seizures. Combination with thioridazine may produce severe cardiac arrhythmias.

Methylphenidate

By potentially inhibiting their metabolism, methylphenidate may cause the plasma concentration of tricyclic antidepressants to rise and so intensify their antidepressant effect. A dose reduction of the tricyclic antidepressant may be necessary.

Benzodiazepines

It might be necessary to lower the dosage of the tricyclic antidepressant if administered concomitantly with alprazolam. No such effects are known to occur in combination with diazepam.

Disulfiram

It might be necessary to lower the dosage of the tricyclic antidepressant if administered concomitantly with disulfiram.

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. Caution is therefore required when prescribing PLACIL to patients taking this medicine.

Grapefruit, grapefruit juice, or cranberry juice

Concomitant administration of PLACIL with grapefruit, grapefruit juice, or cranberry juice may increase the plasma concentrations of clomipramine. Caution is therefore required when prescribing PLACIL to patients taking these products.

Interactions resulting in decreased effect of PLACIL

Rifampicin and Anticonvulsants

CYP3A and CYP2C inducers, such as rifampicin or anticonvulsants (e.g. carbamazepine, phenytoin and barbiturates including phenobarbitone), may decrease clomipramine concentrations as concomitant administration of medicines known to induce cytochrome P450 enzymes, particularly CYP3A4, CYP2C19 and CYP1A2, 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. Caution is therefore required when prescribing PLACIL to patients taking these medicines.

St. John's wort

Concomitant administration of St. John's Wort may reduce the plasma levels of clomipramine. Caution is therefore required when prescribing PLACIL to patients taking St. John's Wort.

Interactions affecting other drugs

Anticholinergic agents

When tricyclic antidepressants are given in combination with anticholinergics, including those used to treat Parkinson's disease, antihistamines, atropine, biperiden or neuroleptics such as phenothiazines with an anticholinergic action, hyperexcitation states or delirium may occur, as well as attacks of glaucoma, urinary retention or paralytic ileus.

Antihypertensive agents

Tricyclic antidepressants may reduce or abolish the antihypertensive effect of clonidine, guanethidine, bethanidine, reserpine, debrisoquine and methyldopa. If necessary, antihypertensive agents with a different mode of action (e.g., β -blockers) should be used.

Alcohol and other CNS depressants

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

Sympathomimetic amines

The cardiovascular effects of sympathomimetic agents, such as adrenaline (epinephrine), noradrenaline (norepinephrine) and amphetamine may be potentiated by tricyclic antidepressants. This includes nose drops and local anaesthetics containing sympathomimetics.

Anticoagulants

Some tricyclic antidepressants may potentiate the anticoagulant effect of coumarin medicines such as warfarin, which may be due to inhibition of their hepatic metabolism (CYP2C9). There is no evidence for the ability of clomipramine to inhibit the metabolism of anticoagulants such as warfarin. However, careful monitoring of plasma prothrombin is advised.

Clomipramine is also an in vitro ($K_i = 2.2 \text{ microM}$) and in vivo inhibitor of CYP2D6 activity (sparteine oxidation) and, therefore, may cause increased concentrations of co-administered compounds that are primarily cleared by CYP2D6 in extensive metabolisers.

Anticonvulsants

Concomitant administration of a tricyclic antidepressant with phenytoin or carbamazepine may lead to elevated serum phenytoin or carbamazepine concentrations. If necessary, the doses of the medicines should be adjusted accordingly.

Pharmacokinetic-related interactions

Clomipramine is predominately eliminated through metabolism. The primary route of metabolism is demethylation to form the active metabolite, *N*-desmethylclomipramine, followed by hydroxylation and further conjugation of both *N*-desmethylclomipramine and the parent drug. Several cytochrome P450s are involved in the demethylation, mainly CYP3A4, CYP2C19 and CYP1A2. Elimination of both active components is by hydroxylation and this is catalysed by CYP2D6 (see Section 5.2 Pharmacokinetic properties).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

According to the experimental data available, clomipramine has no mutagenic, carcinogenic or teratogenic effects. However, clomipramine has been shown to be embryotoxic in the mouse and rat at the lowest dose tested (four times the maximum recommended human dose on a bodyweight basis).

Use in Pregnancy

Category C.

Tricyclic antidepressants have not been shown to be associated with an increased incidence of birth defects. However, there is evidence of interference with central monoamine neurotransmission in rats. Care should be taken that there are sound indications for the use of these antidepressants in pregnancy. Experience with clomipramine in pregnancy is limited. There have been isolated reports of a possible connection between the use of clomipramine and adverse effects (developmental disorders) on the foetus, therefore treatment with PLACIL should be avoided during pregnancy, and only considered if the benefits expected justify the potential risk for the foetus.

Withdrawal symptoms in newborn infants have been reported with prolonged maternal use of this class of medicines. Newborn infants whose mothers had taken PLACIL up until delivery showed symptoms such as dyspnoea, cyanosis, lethargy, feeding difficulties, colic, irritability, convulsions, tremor, hypertonia,

hypotonia or spasms, during the first hours or days of life. To guard against such symptoms, PLACIL should be gradually withdrawn if at all possible, at least seven weeks before the calculated date of confinement.

Use in Lactation

As clomipramine passes into human milk, infants should be weaned or the medication gradually withdrawn.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

PLACIL may cause blurred vision, drowsiness and other central nervous system and psychiatric related disorders such as somnolence, disturbance in attention, confusion, disorientation, aggravation of depression, delirium etc (see Section 4.8 Adverse Effects (Undesirable effects)) which may impair the patient's reactions. Patients must therefore be warned against engaging in activities that require quick reactions, such as driving motor vehicles and operating machines. Patients should also be warned that alcohol or other drugs may potentiate these effects (see Section 4.5 Interactions with other medicines and other forms of interactions).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse effects do not always correlate with dose or plasma drug levels.

If severe neurological or psychiatric reactions occur, PLACIL should be withdrawn.

Reporting frequencies are described as follows:

Very common: $\geq 10\%$

Common: ≥ 1 to $<10\%$

Uncommon: ≥ 0.1 to $<1\%$

Rare: $\geq 0.01\%$ to $<0.1\%$

Very rare: $<0.01\%$.

Blood and lymphatic system disorders

Very rare: leucopenia, agranulocytosis, thrombocytopenia, eosinophilia. One case of pancytopenia has been reported.

Cardiac disorders

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

Uncommon: arrhythmias, increased blood pressure.

Very rare: conduction disorders (e.g. widening of QRS complex, prolonged PR and QTc (QT/RR) intervals, bundle branch block, torsades de pointes, particularly in patients with hypokalaemia), cardiomyopathy, congestive cardiac failure, myocardial infarction, stroke and sudden death.

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, anorexia.

Very rare: paralytic ileus.

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, acute hepatitis, hepatic necrosis.

Immune system disorders

Very rare: anaphylactic and anaphylactoid reactions including hypotension.

Investigations

Very common: weight increased.

Common: transaminases increased, alkaline phosphatase increased.

Very rare: electroencephalogram abnormal.

Metabolism and nutrition disorders

Very common: increased appetite.

Common: decreased appetite.

Musculoskeletal and connective tissue disorders

Common: muscular weakness.

Nervous system disorders

Very common: drowsiness, dizziness, tremor, headache, myoclonus, somnolence, increased appetite.

Common: speech disorders, paraesthesia, muscle hypertonia, dysgeusia, memory impairment, disturbance in attention.

Uncommon: convulsions, ataxia.

Very rare: peripheral neuropathy, neuroleptic malignant syndrome.

Psychiatric disorders

Very common: restlessness.

Common: confusional state, disorientation, hallucinations (particularly in elderly patients and patients with Parkinson's disease), anxiety, agitation, sleep disorders, mania, hypomania, aggression, depersonalisation, insomnia, nightmares, aggravation of depression, delirium.

Uncommon: activation of psychotic symptoms.

Renal and urinary disorders

Very common: micturition disorder.

Very rare: urinary retention.

Reproductive system and breast disorders

Very common: libido 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: purpura.

Vascular disorders

Common: hot flush.

Withdrawal symptoms

Common: Although not indicative of addiction, withdrawal symptoms follow abrupt discontinuation of treatment or reduction of dose: nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness, anxiety, dizziness and worsening of psychiatric status.

Bone fractures

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

Geriatric population

Elderly patients are particularly sensitive to anticholinergic, neurological, psychiatric or cardiovascular effects.

Additional adverse drug reactions from post-marketing spontaneous reports

The following additional adverse drug reactions have been identified with PLACIL based on post-marketing spontaneous reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Nervous system disorders

Frequency not known: Serotonin syndrome, extrapyramidal symptoms (including akathisia and tardive dyskinesia).

Musculoskeletal and connective tissue disorders

Frequency not known: Rhabdomyolysis (as a complication of neuroleptic malignant syndrome).

Reproductive system and breast disorders

Frequency not known: Ejaculation failure, Ejaculation delayed.

Investigations

Frequency not known: Blood prolactin increased.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Since children react much more sensitively than adults to acute overdosages of tricyclics, and since fatalities have been reported, every effort should be made to avoid an overdosage, which, if it does occur, should be treated with extreme care (see Section 4.4, Special warnings and precautions for use - Safety note concerning children).

Signs and Symptoms

The first signs and symptoms of poisoning with tricyclic antidepressants generally take the form of severe anticholinergic reactions, which appear about 1/2 to 2 hours after the medicine has been taken. Owing to the delayed absorption (anticholinergic effect), long half-life and enterohepatic recycling of the drug, the patient may be at risk for up to 4 to 6 days.

The severity of poisoning with tricyclic antidepressants may depend on various factors, such as the amount of the drug absorbed, the time elapsing between its ingestion and the start of treatment, and the patient's age.

The following signs and symptoms may be encountered:

- Central nervous system: somnolence, stupor, coma, ataxia, restlessness, agitation, mydriasis, hyperreflexia, muscular rigidity, athetoid and choreoathetosis, convulsions. In addition, symptoms consistent with serotonin syndrome (e.g. hyperpyrexia, myoclonus, delirium and coma) may be observed.
- Cardiovascular system: arrhythmias (including torsades de pointes), tachycardia, QTc prolongation, conduction disorders, hypotension, shock, heart failure; in very rare cases, cardiac arrest.
- Respiratory system: respiratory depression, apnoea, cyanosis.
- Other: vomiting, fever, sweating, and oliguria or anuria may occur.

Treatment

There is no specific antidote and treatment is essentially symptomatic and supportive.

Where the medicine has been taken by mouth, activated charcoal should be administered.

Anyone suspected of receiving an overdose of PLACIL, particularly children, should be hospitalised and kept under close surveillance for at least 72 hours. Severe poisoning with tricyclic medicines requires immediate hospitalisation and continuous cardiovascular monitoring for at least 48 hours.

In all patients with ECG abnormalities, cardiac function should be kept under close observation for at least another 72 hours, even after the ECG tracings have reverted to normal, because relapses may occur.

The following measures should be taken in cases of overdosage:

- In respiratory failure: intubation and artificial respiration.
- In severe hypotension, place the patient in an appropriate position and give a plasma expander.
- Cardiac arrhythmias must be treated according to the requirements of the case.
- Implantation of a cardiac pacemaker should be considered.
- Low serum potassium and acidosis should be corrected.
- In convulsions, diazepam should be given intravenously. Other anticonvulsants may be required.

Dialysis and haemodialysis are of no use.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Clomipramine is a tricyclic antidepressant. It inhibits the neuronal reuptake of noradrenaline (norepinephrine) (NA) and serotonin (5HT) released in the synaptic cleft. The dominant component of this activity is inhibition of 5HT uptake. Clomipramine also has a wide spectrum of pharmacological action, including α_1 -adrenolytic, anticholinergic, antihistaminic and antiserotonergic (5HT-receptor blocking) properties.

Clinical Trials

No data available. See Section 4.4 – Special warnings and precautions for use, Clinical worsening and suicide risk associated with psychiatric disorders for pooled analysis of antidepressant medicine trials.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, the active substance is completely absorbed but due to extensive hepatic first-pass metabolism to the active metabolite, *N*-desmethylclomipramine, less than 50% of a dose reaches the systemic circulation unchanged.

During oral administration of constant daily doses of clomipramine, the steady state plasma concentrations of clomipramine show wide variations between patients.

Administration of the standard dose recommended for treatment of depression, i.e. 25 mg of clomipramine orally three times daily, produced steady state concentrations ranging from 31 to 186 nanogram/mL. This scatter reflects differences in the drug's distribution volume and clearance between individuals. Variations in concentration in any one patient are much less than those between patients.

The steady state concentrations of the active metabolite *N*-desmethylclomipramine follow a similar pattern. On average, they reach 68 to 334 nanogram/mL at a dose of clomipramine 75 mg/day.

The plasma clearance of clomipramine in elderly patients is lower than in patients in intermediate age groups. As a result elderly patients require smaller doses of PLACIL.

Distribution

Clomipramine is highly (97.6%) bound to serum proteins. Its distribution and elimination follow two compartment kinetics, with a beta-phase half-life of 21 hours (range 12 to 36 hours). *N*-desmethylclomipramine, the principle metabolite, has a beta-phase half-life in the range of 13 to 25 hours.

The concentration in the cerebrospinal fluid is equivalent to about 2% of the plasma concentration.

The distribution volume of unchanged clomipramine is approximately 12 L/kg bodyweight.

Metabolism

The primary route of clomipramine metabolism is demethylation to form the active metabolite, *N*-desmethylclomipramine. *N*-desmethylclomipramine can be formed by several P450 enzymes, primarily CYP3A4, CYP2C19 and CYP1A2. Clomipramine and *N*-desmethylclomipramine are hydroxylated to form 8-hydroxyclopmipramine or 8-hydroxy-*N*-desmethylclomipramine. The activity of the 8-hydroxy metabolites are not defined *in vivo*. Clomipramine is also hydroxylated at the 2-position and *N*-desmethylclomipramine can be further demethylated to form didesmethylclomipramine. The 2- and 8- hydroxy metabolites are excreted primarily as glucuronides in the urine. Elimination of the active components, clomipramine and *N*-desmethylclomipramine, by formation of 2- and 8-hydroxy clomipramine is catalysed by CYP2D6.

Excretion

Two-thirds of a single dose of clomipramine is excreted in the urine as the water soluble conjugates of clomipramine or its metabolites. About one-third is excreted in the faeces. Unchanged clomipramine and *N*-desmethylclomipramine in the urine each amount for less than 1% of the dose administered.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

According to the experimental data available, clomipramine has no mutagenic, carcinogenic or teratogenic effects. However, clomipramine has been shown to be embryotoxic in the mouse and rat at the lowest dose tested (four times the maximum recommended human dose on a bodyweight basis).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain the following excipients: lactose monohydrate, maize starch, povidone, sodium starch glycollate, magnesium stearate, purified talc and Instacoat Universal White (A05G15138) (ARTG PI No. 144681).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

Safety note concerning children: Patients should be advised to keep PLACIL out of reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC/Al blister pack. Pack size: 50 tablets.

Australian Register of Therapeutic Goods (ARTG)

AUST R 143879 – PLACIL Clomipramine hydrochloride 25 mg tablet

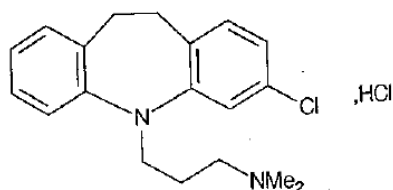
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Clomipramine is the 3-chloro derivative of imipramine. It is a white or slightly yellow crystalline powder, soluble in water, slightly soluble in ethyl alcohol and insoluble in diethyl ether.

Chemical Structure



Chemical name: 3-chloro-5-[3-(dimethylamino)-propyl]-10,11-dihydro-5H-dibenz[b,f]azepine hydrochloride.

Molecular formula: C₁₉H₂₃N₂Cl,HCl

Molecular weight: 351.3

CAS Number

17321-77-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

18/09/2007

10 DATE OF REVISION

08/05/2023

Summary Table of Changes

Section Changed	Summary of New Information
6.1	Update to the excipient name

PLACIL® is a Viatrix company trade mark

PLACIL_pi\May23/00