NEW ZEALAND DATA SHEET

1 APO-CLOMIPRAMINE (25MG FILM-COATED TABLET)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clomipramine Hydrochloride (25mg)

Excipients with known effect

Lactose: APO-Clomipramine contains 9.05mg of lactose per tablet. For the full list of excipients see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

APO-CLOMIPRAMINE 25mg tablets are round, pale yellow, film-coated biconvex tablets, and engraved “25” on one side. Each tablet typically weighs 78mg and contains 25mg Clomipramine hydrochloride.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Major depression
- Obsessive-compulsive syndromes
- Phobias and panic attacks.
- Cataplexy accompanying narcolepsy

4.2 DOSE 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.

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.
- Congenital long QT syndrome

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Clinical Worsening and Suicide Risk

The risk of suicide 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 4,400 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 (aged 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 older than 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 clomipramine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Caution in the following circumstances:

Caution is called for when employing tricyclic antidepressants in patients with:

- Cardiovascular disorders, especially those with cardiovascular insufficiency, conduction disorders (atrioventricular block grades I to III) or arrhythmias. Monitoring of cardiac function and the ECG is required in such patients, especially in the elderly. Myocardial infarction, precipitation of congestive cardiac failure, stroke and sudden death have been reported with drugs 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; and withdrawal from alcohol or drugs with anticonvulsive properties, such as benzodiazepines). The occurrence of seizures seems to be dose dependent. Therefore, the recommended daily dose of clomipramine should not be exceeded.
- Severe hepatic or renal disease.
- Patients with tumours of the adrenal medulla (e.g. phaeochromocytoma, neuroblastoma), in whom the drug may provoke hypertensive crises.
- Hyperthyroidism, or concomitant treatment with thyroid preparations, since aggravation of unwanted cardiac effects can generally be expected to occur owing to the anticholinergic action.
- Chronic constipation, as tricyclic antidepressants may cause paralytic ileus, particularly in elderly and bed-ridden 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 drugs that can cause accumulation of clomipramine should be avoided (see, 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Equally, concomitant administration of drugs 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 clomipramine. Clomipramine should be used with caution when combined with diuretics (see, 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Serotonin Syndrome

Due to the 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, 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 a minimal clinical experience with this combination.

Central Nervous System Effects

Many patients with panic disorder experience intensified anxiety symptoms at the start of the treatment with clomipramine. 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 hyper-excitation in agitated patients and patients with accompanying schizophrenic symptoms. Activation of psychosis has occasionally been observed in patients with schizophrenia receiving tricyclic antidepressants.

In predisposed and elderly patients, particularly at night, tricyclic antidepressants may provoke drug-induced (delirious) psychoses, which disappear without treatment within a few days of withdrawing the drug.

Treatment Discontinuation

Abrupt discontinuation of clomipramine therapy should be avoided because of possible withdrawal symptoms (see, 4.8 UNDESIRABLE EFFECTS. Therefore, dosage should be stopped gradually after regular use for long duration and the patient should be monitored carefully when clomipramine therapy is discontinued.

Patient Monitoring

Before initiating treatment with clomipramine, 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 drug with a fall in blood pressure.

The blood count should be monitored during treatment with clomipramine (especially if the patient develops fever, sore throat, or other symptoms which are associated with influenza infection), 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 hepatic and renal disease or a history of liver disease, periodic monitoring of the hepatic enzyme levels and renal function is recommended (see, 4.8 UNDESIRABLE EFFECTS, Hepatobiliary disorders.

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.

Anaesthesia

Before general or local anaesthesia, the anaesthetist should be notified that the patient has been receiving clomipramine (see, 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Alcohol and Other Central Nervous System Depressants).

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

In patients with hepatic impairment or a history of liver disease, periodic monitoring of the hepatic enzyme levels is recommended.

Use in renal impairment

In patients with renal impairment, periodic monitoring of the renal function is recommended.

Lactose

These tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, severe lactase deficiency, sucrase-isomaltase insufficiency or glucose-galactose malabsorption should not take these tablets.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Use in the elderly

See 4.2 DOSE AND METHOD OF ADMINISTRATION, Elderly Patients.

Paediatric use

The safety and efficacy of clomipramine for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Clomipramine 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.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions resulting in a contraindication

MAO Inhibitors

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

If clomipramine is to be used after treatment with an MAO inhibitor, 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, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Serotonin Syndrome). The same precaution should be taken when administering a MAO inhibitor after previous treatment with clomipramine tablets. In either instance, medication with clomipramine tablets or with the MAO inhibitor should be started cautiously and the dosage raised stepwise until the optimum response is obtained (see, 4.3 CONTRAINDICATIONS).

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 serotoninergic syndrome (serotonin syndrome).

Interactions resulting in a concomitant use not recommended

Antiarrhythmic Agents

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

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 clomipramine (see, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, QTc Prolongation).

Selective Serotonin Re-uptake 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 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 co-medications such as SSRIs, SNRIs, tricyclic antidepressants or lithium (see, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Serotonin Syndrome).

Interactions resulting in increased effect of clomipramine

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.

Oral antifungal, terbinafine

Coadministration with 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 coadministered with terbinafine.

Cimetidine

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

Oral contraceptives

No interaction between chronic oral contraceptive use (15 or 30 µg ethinyl oestradiol 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 µg 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 µg daily) is recommended and dose adjustments may be necessary.

Antipsychotics

Comedication 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 used 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 clomipramine to patients taking this medicine.

Grapefruit, grapefruit juice, or cranberry juice

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

Interactions resulting in decreased effect of clomipramine

Rifampicin and Anticonvulsants

CYP3A and CYP2C inducers, such as rifampicin or anticonvulsants (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. Caution is therefore required when prescribing clomipramine 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 clomipramine 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 patients with Parkinson's disease), atropine, antihistamines, 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

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

Alcohol and Other Central Nervous System Depressants

Tricyclic antidepressants may also increase the effect 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, noradrenaline, and amphetamine), may be potentiated by tricyclic antidepressants. This includes sympathomimetic amines in nose drops or in local anaesthetic preparations.

Anticoagulants

Some tricyclic antidepressants may potentiate the anticoagulant effect of coumarin drugs 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 (Ki = 2.2 μM) 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 drugs 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no adequate and well controlled studies of tricyclic antidepressant medicines in pregnant women. Available information on the risks to the foetus of tricyclic antidepressant medicine use in the first trimester is inconclusive.

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

Adverse reactions do not always correlate with plasma drug levels or dose. If severe neurological or psychiatric reactions occur, clomipramine should be withdrawn.

Reporting frequencies are described as follows:

Very common: ≥ 10%
Common: ≥ 1 to < 10%
Uncommon: ≥ 0.1 to < 1%
Rare: ≥ 0.01 to < 0.1 %
Very rare: < 0.01%

Blood and lymphatic system disorders:

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

Cardiac disorders:

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

Uncommon: arrhythmias, blood pressure increased.

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), testicular swelling, parotid swelling

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 the 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 Anafranil 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 unknown: Serotonin syndrome, extrapyramidal symptoms (including akathisia and tardive dyskinesia).

Musculoskeletal and connective tissue disorders:

Frequency unknown: Rhabdomyolysis (as a complication of neuroleptic malignant syndrome).

Reproductive system and breast disorders:

Frequency not known: Ejaculation failure, Ejaculation delayed

Investigations:

Frequency unknown: Blood prolactin increased.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/

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.

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

Anyone suspected of receiving an overdose of clomipramine, particularly children, should be immediately hospitalised and kept under close surveillance for at least 72 hours. Severe poisoning with tricyclic antidepressants 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 also 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

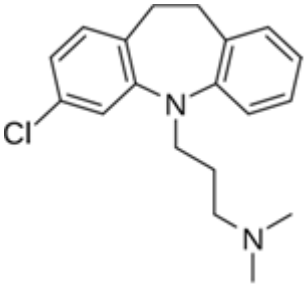
5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antidepressants, Non-selective monoamine reuptake inhibitors,

ATC code: N06AA04

Chemical Structure



Actions

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 re-uptake being the more important of these activities.

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

Clomipramine acts on the depressive syndrome as a whole, including in particular typical features such as psychomotor retardation, depressed mood, and anxiety. The clinical response usually sets in after 2-3 weeks of treatment.

Clomipramine also exerts a specific effect on obsessive-compulsive disorder distinct from its antidepressant effects.

5.2 PHARMACOKINETIC PROPERTIES

Clomipramine is completely absorbed from the gastrointestinal tract. The systemic bioavailability of unchanged clomipramine is reduced to about 50% by hepatic first-pass metabolism due to desmethylclomipramine. The bioavailability of clomipramine is not markedly affected by the ingestion of food. Only the onset of absorption may be slightly delayed and therefore time to peak prolonged.

During oral administration of constant daily doses of clomipramine, the steady-state plasma concentrations of clomipramine show a high variability between patients. The dose of 75mg daily, administered as coated tablets of 25mg t.i.d. produces steady-state plasma concentrations ranging from about 20 to 175 ng/mL.

The steady-state plasma concentrations of the active metabolite, desmethylclomipramine, follow a similar pattern.

However, at a dose of 75mg clomipramine per day, they are 40 - 85% higher than those of clomipramine.

Clomipramine is 97.6% bound to plasma proteins. The apparent distribution volume is about 12 to17 L/kg body weight. Concentrations in cerebrospinal fluid are about 2% of the plasma

concentration. Clomipramine passes into maternal milk in concentrations similar to those in plasma.

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

Clomipramine is eliminated from the blood with a mean half-life of 21h (range: 12-36h), and desmethylclomipramine with a mean half-life of 36h.

About two thirds of a single dose of clomipramine are 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 is about 2% and 0.5% of the dose administered, respectively.

In elderly patients, owing to reduced metabolic clearance, plasma clomipramine concentrations at any given dose are higher than in younger patients. The effects of hepatic and renal impairment on the pharmacokinetics of clomipramine have not been determined. .

5.3 PRECLINICAL SAFETY DATA

Mutagenicity, Carcinogenicity and Reproduction Toxicity Studies

According to the experimental data available, clomipramine has no mutagenic, carcinogenic, or teratogenic effects.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

APO-Clomipramine 25mg tablet contains the following excipients:

- Microcrystalline cellulose
- Lactose Monohydrate
- Magnesium stearate
- Colloidal Silicon Dioxide
- Croscarmellose sodium
- Hydroxypropyl Methylcellulose (Hypromellose)
- Polyethylene Glycol 3350 (Carbowax/ Macrogol 3350)
- Carnauba Wax
- Yellow Ferric Oxide

APO-Clomipramine tablets are gluten free. APO-Clomipramine contain lactose. Yellow Ferric oxide is the colorant.

6.2 INCOMPATIBILITIES

Not applicable. See section 4.5.

6.3 SHELF LIFE

APO-Clomipramine 25mg has a shelf life of 36 months from the date of manufacture.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25°C. Protect from heat and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

APO-CLOMIPRAMINE 25mg: PVC/PVDc or PVC/PE/PVDc blisters containing 50 and 100 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Arrotex Pharmaceuticals (NZ) Limited
C/o Quigg Partners
Level 7, The Bayleys Building
36 Brandon Street
Wellington 6011
New Zealand

9 DATE OF FIRST APPROVAL

06 October 1998

10 DATE OF REVISION OF THE TEXT

13 November 2025

Summary table of changes

Section Changed	Summary of new information
2	Addition of the amount of lactose per tablet. Transfer the lactose warning to section 4.4
4.1	First paragraph reworded to ‘major depression’ and ‘chronic painful conditions’ removed to align with the Australian Anafranil Product Information (PI).
4.3	Included ‘congenital long QT syndrome’
4.4, 4.5, 4.8	Section aligned with Australian Anafranil PI.

Section Changed	Summary of new information
4.9	Treatment section aligned with Australian Anafranil PI
5.1	Correction to Pharmcotherapeutic group and ATC code.
6.1	Removal of reference to the 10mg tablet.
6.4	Storage conditions corrected