PRODUCT INFORMATION LEAFLET

MELIPRAMINE
(Boucher & Muir Pty Ltd)

COMPOSITION
Imipramine hydrochloride.

DESCRIPTION
The chemical name for imipramine hydrochloride is 5-(3-Dimethylamino-propyl)-10,11-dihydro-5H-dibenz[b,f]azepine hydrochloride. Molecular formula C_{19}H_{24}N_{2}.HCl. Molecular weight 316.9. It is a white to yellowish powder. It is freely soluble in water, methanol, and ethanol; soluble in acetone; slightly soluble in ethyl acetate; and practically insoluble in ether and petroleum ether.

Each coated tablet contains 25mg imipramine hydrochloride. It contains as excipients, glycerine, titanium dioxide E171, polyethylene glycol 25000, cosmetic red brown E172, gelatine, magnesium stearate, talc, sucrose and lactose.

PHARMACOLOGY
Pharmacodynamic properties
Pharmacotherapeutic group: antidepressant (tricyclic)
ATC: N06A A02

Mechanism of action
The mechanism of its therapeutic effects is not fully understood. Imipramine, the dibenzoazepine derivative, is a tricyclic antidepressant. Imipramine inhibits the synaptic re-uptake of noradrenalin and serotonin released upon neuronal stimulus, whereby it facilitates noradrenergic and serotoninergic transmission. Imipramine exerts inhibitory effect also on muscarinic and H_{1} histamine-receptors, therefore it exerts anticholinergic and moderate sedative effects. Imipramine also exhibits α-adreno-blocking effects.

The antidepressant effect develops gradually: optimum therapeutic effect can be expected after 2-4 (possibly 6-8) weeks of treatment.

Pharmacokinetic properties
When administered orally, imipramine is well absorbed from the gastrointestinal tract. Concomitant food intake has no effect on the absorption of imipramine. The compound undergoes a high degree of first-pass metabolism in the liver: its main, pharmacologically active metabolite, desipramine, is formed through demethylation.

The plasma levels of imipramine and desipramine show a wide range of individual variation. After a 10-day treatment with 50 mg imipramine t.i.d. taken orally, the steady-state plasma levels of imipramine varied between 33 and 85 ng/ml, and those of desipramine between 43 and 109
ng/ml. Due to decreased metabolism, the plasma levels are usually higher in elderly than in young patients. The apparent volume of distribution of imipramine is 10-20 L/kg.

Both active compounds are bound by plasma proteins to a great extent (imipramine: 60-96%, desipramine: 73-92%).

Imipramine is eliminated by the renal route (about 80 %) and in the faeces (about 20 %) mainly in the form of inactive metabolites. The urinary and faecal excretion of unchanged imipramine and its active metabolite, desipramine, amounts to 5-6 % of the administered dose. After the administration of a single dose, the elimination half-life of imipramine averages about 19 hours, varying between 9 and 28 hours. This half-life may increase significantly in the elderly and in the case of an overdose.

INDICATIONS
- Major depression.
- Nocturnal enuresis (for persons aged 5 years and above and only if organic origin has been excluded).

CONTRA-INDICATIONS
- Known hypersensitivity to any component of the preparation or to other tricyclic antidepressant of the dibenzoazepine group (for a full list of the components of Melipramine, please see under ‘DESCRIPTION’).
- Treatment with MAO-inhibitors - for safety reasons, imipramine treatment must not be started sooner than 2 weeks after the treatment with MAO-inhibitors is stopped (except for moclobemide, the reversible MAO-inhibitor, where a pause of 24 hours is enough). Two-week drug-free period must also be allowed when the patient is switched over from imipramine to a MAO-inhibitor or a reversible MAO-inhibitor such as moclobemide.
- Recent history of myocardial infarction.

PRECAUTIONS
- **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 adolescents patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses 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 an children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. 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 a 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 he 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 Melipramine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

- **Use in Children and Adolescents (<18 years)**
  The safety and efficacy of Melipramine for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Melipramine should not be used in this age group for the treatment of depression or other psychiatric disorders.

- **Abrupt Withdrawal**
  Imipramine treatment should be abandoned gradually for the abrupt cessation of medication may precipitate withdrawal symptoms (nausea, vomiting and abdominal pain, headache, restlessness, anxiety, sleep disorders), particularly in children.

- **Other Precautions**
  - In the case of bipolar disorder, imipramine may provoke mania or hypomania. The preparation should not be used during manic or hypomanic episodes.
  - Like other tricyclic antidepressants, imipramine decreases the convulsion threshold. Therefore patients with a history of any form of epilepsy need close monitoring of their condition and of their anticonvulsant therapy.
  - The risks associated with electroconvulsive therapy may be made worse if a patient is also taking imipramine at the same time. Therefore such a combination of therapies should only be undertaken with extreme caution.
  - As a paradoxical reaction, anxiety may intensify in patients with panic disorder treated with tricyclic antidepressants in the first days of the therapy. The increased anxiety usually decreases gradually within 1 to 2 weeks but it may be treated with a short, limited course of benzodiazepine derivative if necessary.
  - Patients with a history of psychosis may show increased restlessness, anxiety and agitation during treatment with tricyclic antidepressants. Psychosis may be reactivated in such patients.
  - Due to its anticholinergic effect, the use of imipramine requires close medical control in the case of glaucoma or increased intraocular pressure, disorders of the prostate including prostate hypertrophy and chronic or severe constipation for the treatment may augment the severity of these symptoms. The decreased tear production and the accumulation of mucinous discharge may lead to corneal epithelium damage in patients using contact lenses.
  - In the case of patients with ischaemic heart disease, cardiovascular insufficiency, atrioventricular block (grades I-III) and other arrhythmias, close monitoring of cardiovascular function and of the ECG are essential, particularly in the elderly.
  - Supra-therapeutic does of imipramine can lead to isolated cases of QTc prolongation and very rare cases of ventricular tachycardia and sudden unexplained death. This can occur primarily in cases of overdosing but also due to comedication with drugs such as thioridazine, which has a propensity itself to cause QTc interval.
  - In patients with hepatic or renal dysfunction or in patients with diabetes mellitus or impaired glucose tolerance, imipramine should be used cautiously.
  - Treatment of patients with adrenal tumours (pheochromocytoma, or neuroblastoma) requires special caution, for imipramine may provoke a hypertensive crisis.
• Patients with hyperthyroidism or those using thyroid hormone preparations require close monitoring because of the increased risk of adverse cardiac events in these patients.

• Before the patient is administered any form of general, regional or local anaesthesia, the anaesthetist should be informed that the patient has been or is taking imipramine. Prior to elective surgery consideration should be given to discontinuing the imipramine for as long as is clinically feasible.

• Eosinophilia, leukopaenia, agranulocytosis, thrombocytopenia and purpura have been reported in isolated cases of imipramine treatment. Therefore, the blood count should be checked regularly, especially if the patient develops a fever or sore throat.

• An increased incidence of caries has been noted in long-term imipramine therapy. Therefore regular dental checking is recommended.

• Imipramine tablets contain lactose and saccharose. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, severe lactase deficiency, sucrase-isomaltase insufficiency or glucose-galactose malabsorption should not take imipramine tablets.

• Imipramine may cause photosensitive skin reactions. Thus excessive exposure to sunlight should be avoided during therapy.

• In predisposed and/or elderly patients imipramine may cause anticholinergic (delirious) psychosyndrome, which resolves within a few days after the treatment is stopped.

• Treatment with imipramine, particularly in the early stages, may be associated with impairment of the patient’s visual accommodation and ability to concentrate (see ADVERSE REACTIONS). Patients therefore need to be warned that their reaction times may be slowed and that, as a result, they should not drive motor vehicles or operate machinery. Later on, the extent and duration of such restrictions may be modified by the physician on a case-by-case basis. Patients should also be warned that alcohol or other drugs may compound these effects (see INTERACTIONS WITH OTHER DRUGS).

**Patient Monitoring - Before and at regular intervals during the therapy it is recommended to check the following:**

- Blood pressure, both supine and standing (especially in patients with unstable circulation or hypotension).
- Liver function (especially in hepatically compromised patients).
- Renal function in patients with renal impairment.
- Differential blood count (immediately in the case of fever, sore throat and pharyngitis, as they may be the signs of leukopenia and agranulocytosis, otherwise at the beginning of and regularly during the treatment)
- ECG (in elderly patients and particularly those with cardiovascular insufficiency, atroventricular block (grades I-III) and arrhythmias). Myocardial infarction, precipitation of congestive cardiac failure, stroke and sudden death have been reported with drugs of this class.

**USE IN PREGNANCY (Category C)**

Since in certain cases, there have been reports of a possible relationship between tricyclic antidepressant treatment and adverse effects on the foetus, treatment with imipramine cannot be recommended during pregnancy. Treatment during pregnancy should only be contemplated where the expected benefits outweigh the potential risks to the foetus.
Symptoms such as lethargy, dyspnoea, irritability, colic, hypotension or hypertension, tremor or spasms have been reported in infants born to mothers who had taken imipramine up until delivery. It is recommended that imipramine therapy should be gradually withdrawn at least 7 weeks prior to the calculated date of confinement.

**USE IN LACTATION**
Both imipramine and desmethylimipramine are excreted in human milk but nothing is known about the clinical impact of this on an infant. The recommended options at this time would be either to wean the baby or to take the mother gradually off imipramine.

**INTERACTIONS WITH OTHER DRUGS**
- **MAO-inhibitors:** Combination with MAO-inhibitors is contraindicated, and should be avoided, since the two types of drugs act synergistically and the central and peripheral noradrenergic effects may increase to toxic levels (hypertensive crisis, hyperpyrexia, myoclonus, agitation, convulsion, delirium, coma). For safety reasons, imipramine treatment must not be started sooner than 2 weeks after the treatment with MAO-inhibitors is stopped (except after moclobemide, the reversible MAO-inhibitor, where a pause of 24 hours is enough). A two-week imipramine-free period must also be allowed when the patient is switched over from imipramine to a MAO-inhibitor or to a reversible MAO-inhibitor such as moclobemide. The new treatment with either the MAO-inhibitor or with Melipramine should be started with small doses that can be increased gradually with close monitoring of the clinical effects (see CONTRAINDICATIONS).
- **Liver enzyme inhibitors:** if co-administered with imipramine, the inhibitors of cytochrome P-450 2D6 isoenzyme may decrease the metabolism and thus may increase the plasma levels of imipramine. The inhibitors of this type include drugs that are not substrate to CYP2D6 such as cimetidine (but not ranitidine) and methylphenidate but also those that are metabolised by this enzyme (e.g. many other antidepressants, phenothiazines, 1c-type antiarrhythmic agents (propafenon, flecainide). Although with varying potency, all SSRI-type antidepressants are inhibitors of CYP2D6. Accordingly, caution should be exercised when imipramine is combined with these drugs and also when the patient is switched over from an SSRI antidepressant to imipramine (and vice versa) especially in the case of fluoxetine (because of the long elimination half-life of this drug). Tricyclic antidepressants may increase the plasma levels of antipsychotic preparations (competition at the level of hepatic enzymes).
- **Oral contraceptives, oestrogens:** Decreased antidepressant effects and the development of antidepressant toxic effects have been observed sporadically in female patients using oral contraceptive or oestrogen preparations and tricyclic antidepressant concomitantly. Accordingly, co-administration of these drugs requires caution and, if toxic effects occur, then the dose of imipramine should be reduced.
- **Liver enzyme inducers:** Substances or conditions which stimulate the P 450 enzyme system, e.g. chronic alcohol abuse, nicotine, meprobamate, barbiturates, antiepileptic agents such as phenytoin and carbamazepine, enhance the metabolism of imipramine and decrease its plasma levels and anti-depressant effect. In addition phenytoin and tricyclic antidepressants may affect each other’s metabolism with a need for monitoring either for adverse effects or reduced response to either the phenytoin or the antidepressant. Carbamazepine has a variable effect on plasma tricyclic antidepressant concentrations but concomitant imipramine is
reduced. Plasma carbamazepine concentrations are increased. Dose adjustment may be necessary.

- **Anticholinergic drugs** (e.g. phenothiazines, antiparkinsonian agents, antihistamines, atropine, biperidine) increase the anticholinergic effects and side effects (e.g. paralytic ileus, glaucoma, urinary retention, constipation, hyperexcitation states and/or delirium) if they are co-administered with imipramine. Combination with these preparations requires close monitoring of the patients and careful dose adjustment.

- **CNS depressants**: combination of imipramine with CNS depressants (e.g. opiates, benzodiazepines, barbiturates, general anaesthetics and alcohol) markedly augments the effects and side effects of these agents.

- **Antipsychotic drugs** may increase the plasma levels thus the effects and side effects of tricyclic antidepressants. Dose reduction may be necessary. Co-administration with thioridazine may provoke severe arrhythmia.

- **Thyroid hormone preparations** may increase the antidepressant effect of imipramine and also its cardiac side effects, therefore, co-administration requires special caution.

- **Adrenergic neurone blockers**: imipramine may diminish the antihypertensive effects of co-administered adrenergic neurone blockers (guanethidine, betanidine, reserpine, clonidine and α-methyldopa). Patients requiring co-medication for hypertension should therefore be given antiarrhythmics of different types (e.g. diuretics, vasodilators, or β-blockers). However, vasodilators in particular will exacerbate the hypotensive effects of imipramine and their dose should be titrated slowly.

- **Sympathomimetics**: the cardiovascular effects of sympathomimetics (primarily epinephrine, norepinephrine, isoprenaline, ephedrine, phenylephrine) are increased by imipramine. This includes sympathomimetic amines in topical nasal drops or in local anaesthetic preparations.

- **Quinidine**: so as to avoid the risk of conduction disorders and arrhythmia tricyclic antidepressants should not be employed in combination with antiarrhythmic agents of the quinidine type.

- **Oral anticoagulants**: tricyclic antidepressants inhibit the metabolism of oral anticoagulants and increase their elimination half-life. This increases the risk of haemorrhage, therefore, close medical control and monitoring of plasma prothrombin is advised.

- **Hypoglycaemic medication**: Blood sugar levels may change during imipramine treatment. Therefore, closer monitoring of blood sugar levels is recommended, particularly at the beginning and end of treatment and also when the dose is modified.

- **Disulfiram**: Disulfiram and imipramine administered concomitantly may cause an elevation in disulfiram concentration.

**ADVERSE REACTIONS**
The undesirable effects listed below do not necessarily occur in each patient. Some of the side effects are dose-dependent; they would resolve upon dose reduction or spontaneously as the therapy proceeds. Certain side effects are difficult to distinguish from the symptoms of depression (e.g. fatigue, sleep disorders, agitation, anxiety, dryness of the mouth).

Imipramine administration should be suspended if severe neurological or psychiatric reactions occur. 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.
The **frequency of adverse events** is estimated as follows: very common ≥ 10%, common ≥ 1% and < 10%, uncommon ≥ 0.1% and < 1%, rare ≥ 0.01% and < 0.1% and very rare < 0.01%.

**CNS/Psychological effects:** *Common* restlessness, increased anxiety, agitation, sleep disturbances, swings from depression to hypomania or mania, delirium, confusion, disorientation and hallucinations. *Rare:* activation of psychotic symptoms. **Very rare:** aggressiveness.

**Neurological effects:** *Very common:* tremor. *Common:* paraesthesiae, headache, dizziness, somnolence. *Rarely:* epileptic seizures. **Very rare:** EEG changes, myoclonus, extrapyramidal symptoms, ataxia, speech disorders.

**Cardiovascular system:** *Very common:* sinus tachycardia and clinically irrelevant ECG changes (T and ST wave changes) in patients of normal cardiac status, postural hypotension. **Common:** arrhythmias, conduction disorders (widening of QRS complex and PR interval, bundle-branch block), palpitations. **Very rare:** increased blood pressure, cardiac decompensation, peripheral vasospastic reactions, stroke, cardiac failure, QT interval prolongation, ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation, torsades de pointes.

**Anticholinergic effects:** *Very common:* dry mouth, constipation, hot flushes. **Common:** disturbances of micturition, disorders of visual accommodation, blurred vision, decreased lacrimation. **Very rare:** mydriasis, glaucoma, paralytic ileus, urinary retention.

**Gastro-intestinal tract:** **Common:** nausea, vomiting. **Very rare:** stomatitis, tongue lesions, abdominal disorders.

**Hepatic effects:** **Common:** liver function tests abnormal. **Very rare:** hepatitis with or without jaundice, acute hepatitis, hepatic necrosis.

**Skin:** *Very common:* hyperhidrosis. **Common:** allergic skin reactions (skin rash, urticaria, dermatitis). **Very rare:** oedema (local or generalised), photosensitivity, pruritus, petechiae, hair loss, hyperpigmentation.

**Endocrine system and metabolism:** *Very common:* weight gain. **Common:** disturbances of libido and potency, anorexia. **Very rare:** enlarged mammary glands, galactorrhoea, SIADH (syndrome of inappropriate antidiuretic hormone secretion), increase or decrease in blood sugar, weight loss.

**Hypersensitivity:** **Very rare:** allergic alveolitis (pneumonitis) with or without eosinophilia, systemic anaphylactic reactions including hypotension.

**Blood:** **Very rare:** eosinophilia, leukopenia, agranulocytosis, thrombocytopenia and purpura.

**Sensory organs:** **Very rare:** Tinnitus.

**Infections and infestations:** **Very rare:** Dental caries.
**General disorders and administration site conditions:** Common: Fatigue. Very rare: Asthenia, oedema (localised or generalised), pyrexia, sudden death.

**Abrupt withdrawal:** Common: Imipramine treatment should be withdrawn gradually for the abrupt cessation of medication may precipitate withdrawal symptoms (nausea, vomiting and abdominal pain, headache, malaise, restlessness, anxiety, sleep disorders, arrhythmia, extrapyramidal symptoms), particularly in children (see PRECAUTIONS – Abrupt Withdrawal).

**DOSAGE AND ADMINISTRATION**
The daily dosage should be set individually depending on the nature and severity of the symptoms. As with other antidepressants, it takes 2 to 4 weeks (possibly 6 to 8 weeks) of treatment to achieve the required therapeutic effect. The therapy should be started with a low dose that should gradually be increased to find the smallest effective maintenance dose. Dose titration to attain the effective dose requires special caution in the elderly.

**Major Depression**
**Ambulant Patients:**
The usual starting dose is up to 25 mg three times daily, which can be increased gradually to a total daily dose of 150-200 mg by the end of the first week of treatment. The aim is to maintain this dosage until there is evidence of a definite improvement. Once stabilized, the dosage may be carefully reduced, as clinically indicated, to the usual maintenance level of a total daily dose of 50-100 mg.

**Hospitalised Patients**
The starting dose is 25 mg three times daily which can be increased by an extra 25 mg every day up to a total daily dose of 200mg (or to 300 mg in exceptional cases) which should be maintained as above. The usual maintenance dose is 100 mg daily.

**Geriatric Patients:**
This age group generally displays a more marked response to the same dosage of imipramine than younger patients. Therefore treatment should be started with the lowest dose possible, namely 10 mg once daily. This may be slowly increased to a total daily dose of 25-50 mg over a period of at least 10 days and then maintained until the end of treatment.

**Use in Children and Adolescents (<18 years)**
The safety and efficacy of Melipramine for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Melipramine should not be used in this age group for the treatment of depression or other psychiatric disorders (refer to PRECAUTIONS).

**Nocturnal Enuresis**
**Children:**
The medication should be administered only to children aged 5 years and over and only if organic causes have been excluded.
The recommended doses are:

- 5-8 years old: 25 mg daily
- 9-12 years old: 25-50 mg daily
- Above 12 years of age: 25-75 mg daily
The higher recommended doses for each age group are justified only if no satisfactory response is seen after one week of treatment with lower doses of that same range. In children the daily dose should never exceed 2.5 mg/kg body weight.

It is recommended to use the smallest possible dose within each of the above dose ranges. The daily dose is preferably given in a single dose after the evening meal before going to bed. If nocturnal enuresis occurs during the early evening hours, it is recommended to administer the daily dose in two separate doses, one in the later afternoon and one at bedtime. The duration of the treatment should not be longer than 3 months. Depending on the changes in the clinical picture, the maintenance dose can be decreased. At the end of the therapy, Melipramine should be withdrawn gradually.

OVERDOSAGE

The taking of an overdose of a tricyclic antidepressant is a medical emergency, especially in very young children who may have taken unknown quantities. However, even in older people, it is a situation which must be managed with extreme urgency.

Signs and Symptoms:
Severe anticholinergic adverse reactions are the first signs and symptoms of overdosage with tricyclic antidepressants. The following signs and symptoms may appear:
- **Central nervous system**: vertigo, drowsiness, stupor, coma, ataxia, restlessness, agitation, enhanced reflexes, muscular rigidity, athetoid and choreiform movements, convulsions.
- **Cardiovascular System**: Hypotension, tachycardia, arrhythmia, conduction disorders, heart failure; in very rare cases, cardiac arrest.
- **Respiratory system**: respiratory depression, cyanosis, apnoea.
- **Other**: shock, vomiting, fever, sweating, mydriasis and oliguria or anuria.

Isolated cases of QT prolongation, torsades de pointes and death have been reported in overdose.

Treatment:
Anyone suspected of taking an overdose of imipramine, particularly children, should be admitted to hospital and kept under close surveillance for at least 72 hours. There is no specific antidote and treatment is essentially symptomatic and supportive. Activated charcoal may reduce absorption of imipramine if given within one or two hours of ingestion. In patients who are not fully conscious or have an impaired gag reflex, consideration may be given to administering activated charcoal via a naso-gastric tube once the airway is protected.

Continuous monitoring of cardiovascular system, blood gases and electrolytes is required. As symptomatic treatment, anticonvulsant therapy (IV diazepam and others as required), intubation and artificial respiration, insertion of a temporary cardiac pacemaker, plasma expanders and vasopressor agents may all have a role. In exceptional cases, emergency resuscitation may be necessary.

Haemodialysis or peritoneal dialysis is ineffective because of the low plasma concentrations of imipramine.
Since it has been reported that physostigmine may cause severe bradycardia, asystole and seizures, its use is not recommended in cases of overdosage with imipramine.

**Child Safety:**
Imipramine must be kept out of reach and sight of children.

**PACK**
Melipramine tablets 25mg are bi-convex shape, and are shiny, brown, and odourless or almost odourless coated tablets. 50 coated tablets in a bottle.

Store below 25°C, protected from light

**AUSTR 10037**

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All States and A.C.T. – S4.

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