

AUSTRALIAN PRODUCT INFORMATION

Tofranil® Imipramine hydrochloride Tablet

1 NAME OF THE MEDICINE

Imipramine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tofranil 10 tablets contain 10 mg imipramine hydrochloride.

Tofranil 25 tablets contain 25 mg imipramine hydrochloride.

Excipients with known effect: Lactose monohydrate, Sucrose

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

3 PHARMACEUTICAL FORM

Tofranil 10: The tablets are red-brown, triangular-shaped, convex, sugar-coated tablets printed "FT" on one side in white ink.

Tofranil 25: The tablets are reddish-brown, round, biconvex, sugar-coated tablets printed "CZ" on one side in white ink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Major depression.
- Nocturnal enuresis (from the age of 5 years onwards and provided the possibility of organic causes has first been excluded).

4.2 DOSE AND METHOD OF ADMINISTRATION

General

The dosage should be determined individually and adapted to the patient's condition. In principle, every effort must be made to achieve an optimum effect while keeping the dose as low as possible and increasing the dosage cautiously, particularly when treating elderly patients, who generally show a more marked response to Tofranil than patients belonging to intermediate age groups.

During treatment with Tofranil patients must be kept under close surveillance with respect to the efficacy and tolerability of the medication.

Major depression

Treatment in ambulatory patients:

Initiate treatment with 25 mg up to three times daily. Raise the daily dosage stepwise to 150 to 200 mg. This dosage should be reached by the end of the first week and adhered to until a clear-cut improvement has occurred. The subsequent maintenance dose, which must be individually determined by cautiously reducing the dosage, usually amounts to 50 to 100 mg daily.

Treatment in hospitalised patients:

Initiate treatment with 25 mg three times a day. Raise the daily dosage stepwise by 25 mg, until a dose of 200 mg has been reached, and adhere to this dose until the depressive condition has improved. In severe cases the dose may be increased to 100 mg three times a day. Once a distinct improvement has set in, the subsequent daily maintenance dose should be determined according to the patient's individual requirements (generally 100 mg).

Paediatric use:

The safety and efficacy of Tofranil for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Tofranil should not be used in this age group for the treatment of depression or other psychiatric disorders (see Section 4.4 Special warnings and precautions for use).

Use in the elderly:

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

Nocturnal enuresis

Children 5 years and over only:

The initial daily dose is:

5 to 8 years of age: 2 or 3 tablets of 10 mg

9 to 12 years of age: 1 to 2 tablets of 25 mg

Older children: 1 to 3 tablets of 25 mg

The higher doses apply to those cases which do not respond fully to treatment within one week. The tablets should be given in a single dose after the evening meal, although children who wet their beds early in the night should be given part of the dose beforehand (at 4 pm). Once the desired response has been achieved the treatment should be continued (for 1 to 3 months), reducing the dose stepwise to the maintenance dose.

A daily dosage of 2.5 mg/kg should not be exceeded in children. The safety and efficacy of imipramine as temporary adjunctive treatment for nocturnal enuresis in children less than 5 years of age have not been established.

4.3 CONTRAINDICATIONS

- Known hypersensitivity to imipramine or any of the excipients in the tablets.
- Cross-sensitivity to tricyclic antidepressants of the dibenzazepine group.
- Concomitant use with a MAO-inhibitor, or within 14 days before or after treatment with an irreversible MAO inhibitor, or within 14 days before moclobemide, a reversible MAO inhibitor (see Section 4.5 Interactions with other medicines and other forms of interactions).
- Acute and recovery stages of myocardial infarction.
- Subjects under 18 years of age for the treatment of depression or other psychiatric disorders.

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 (selective serotonin reuptake inhibitors (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 nonpsychiatric. Although a casual 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 Tofranil 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 diseases, cardiac disease and in elderly patients, considering the tachycardiac and hypotensive effects of this class of products. Cardiovascular insufficiency, conduction disorders, atrioventricular block (grades I to III), and arrhythmias. Monitoring of cardiovascular 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.
- Isolated cases of QTc prolongation and very rare cases of ventricular tachycardia and sudden unexplained death have occurred at supra-therapeutic doses of Tofranil which have primarily occurred in conjunction with overdose, but also in a few reports of co-medication that itself can lead to a prolonged QTc interval (e.g. thioridazine). Concomitant administration of medicines that can provoke prolonged QT syndrome/Torsades de pointes should be avoided.
- 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 the seizure threshold, and withdrawal from alcohol or drugs with anticonvulsive properties e.g.

benzodiazepines). The occurrence of seizures seems to be dose-dependent. Therefore the recommended total daily dose of Tofranil should not be exceeded. In case of seizures, the treatment should be discontinued.

- 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 in bedridden patients.
- Higher sensitivity to orthostatic hypotension, sedation and possible prostatic hypertrophy in elderly patients.

A daily dose of 2.5 mg/kg of imipramine should not be exceeded in children owing to possible cardiotoxic effects (see Section 4.2 Dose and method of administration).

Concomitant use of Tofranil and electroconvulsive therapy should only be undertaken under careful supervision.

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

Tofranil may cause anxiety, feelings of unrest, and hyperexcitation in agitated patients and psychosis may be activated in schizophrenic patients.

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 an 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.

Hypomanic or manic episodes have also been reported during a depressive phase in patients with bipolar affective disorders receiving treatment with a tricyclic antidepressant. In such cases it is necessary to reduce the dosage or to withdraw Tofranil.

Exacerbation of psychotic states has been observed occasionally in schizophrenic patients receiving tricyclic antidepressants.

In predisposed and elderly patients, particularly at night, Tofranil may provoke pharmacogenic (delirious) psychosis, which disappears without treatment within a few days of withdrawing the drug.

Specific mood improvement often occurs after symptoms such as insomnia or anxiety have improved. This is to be considered prior to making any decision about whether treatment should be continued or adjusting the effective dose.

Treatment discontinuation

Abrupt withdrawal should be avoided because of possible adverse reactions. If the decision has been made to discontinue treatment, medication should be tapered, with recognition that abrupt discontinuation can be associated with certain symptoms [see Section 4.8 Adverse effects (Undesirable effects)].

Patient monitoring

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. Monitoring the plasma concentration may be indicated in patients at risk of overdose (elderly patients, patients with concomitant cardiac, hepatic or renal disease), resistance to treatment and presenting marked adverse effects, or those on multiple medications.

The blood count should be monitored during treatment with Tofranil (especially if the patient develops fever, sore throat, or other symptoms such as are associated with influenzal infections), 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.

Treatment with tricyclic antidepressants can lead to an increased incidence of dental caries. Regular dental check-ups are therefore advisable during long term treatment.

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

Other

Before elective surgery, Tofranil should be discontinued for as long as the clinical situation will allow. Before general or local anaesthesia, the anaesthetist should be aware that the patient has been receiving Tofranil (see Section 4.5 Interactions with other medicines and other forms of interactions).

Serotonin syndrome

Due to the risk of serotonin toxicity, it is advisable to follow the dosage suggested. In cases when imipramine, selective serotonin uptake inhibitors (SSRIs) and noradrenaline reuptake inhibitors are used concomitantly with tricyclic antidepressants or with any other serotonin medicines, serotonin syndrome symptoms may occur with symptoms such as behavioural disorders (confusional state, hypomania, agitation), autonomic nervous system disorders (diarrhoea, chills, hyperpyrexia, sweating, blood pressures alterations, nausea, vomiting) and changes in the neuromuscular functions (myoclonus, hyperreflexia, tremors, difficult movement coordination), delirium and coma.

Paediatric use

The safety and efficacy of Tofranil for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Tofranil should not be used in this age group for the treatment of depression or other psychiatric disorders. There are no long-term safety data available in children and adolescents regarding growth, maturation and cognitive and behavioural development.

Animal toxicology

Acute: Oral LD₅₀ ranges are as follows:

Rat - 355 to 682 mg/kg

Dog - 100 to 215 mg/kg

Depending on the dosage in both species, toxic signs proceeded progressively from depression, irregular respiration and ataxia to convulsions and death.

Lactose monohydrate and sucrose

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

Use in hepatic impairment

Severe hepatic or renal diseases. In case of patients with hepatic impairment, it is appropriate to periodically check hepatic function values. In patients with known liver disease or a history of liver disease, periodic monitoring of hepatic enzyme levels is recommended [see Section 4.8 Adverse effects (Undesirable effects)].

Use in renal impairment

It is also recommended that patients with known renal impairment be monitored.

See Section 4.2 Dose and method of administration

Use in the elderly

See Section 4.2 Dose and method of administration and Section 4.4 Special warnings and precautions for use.

Paediatric use

See Section 4.2 Dose and method of administration and Section 4.4 Special warnings and precautions for use.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

MAO-inhibitors: If Tofranil is to be used after treatment with a 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). The same precaution should be taken when administering a MAO inhibitor after previous treatment with Tofranil. In either instance, medication with Tofranil or with the MAO inhibitor should be started cautiously and the dosage slowly raised stepwise until the optimum response is obtained (see Section 4.3 Contraindications).

There is evidence to suggest that Tofranil 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 Tofranil has been used. Patients should be monitored for symptoms suggestive of serotonergic syndrome (serotonin syndrome).

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 should be used, if necessary (e.g. diuretics, vasodilators or beta-blockers).

Sympathomimetic amines: The cardiovascular effects of sympathomimetic agents, such as adrenaline (epinephrine), noradrenaline (norepinephrine), isoprenaline, ephedrine,

phenylephrine and amphetamine may be potentiated by tricyclic antidepressants. This includes sympathomimetic amines in nose drops or in local anaesthetic preparations.

Alcohol and other central nervous system depressants: Tricyclic antidepressants may also increase the effect of alcohol and central depressant drugs (e.g. barbiturates, benzodiazepines, hypnotics, sedatives, anxiolytics or general anaesthetics).

Anticholinergic agents: When tricyclic antidepressants are given in combination with anticholinergics including those used to treat Parkinson's disease, 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.

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

Selective serotonin reuptake inhibitors: Co-medication may lead to additive effects on the serotonergic system. SSRIs such as fluoxetine and paroxetine are strong inhibitors of CYP2D6. Fluvoxamine is a strong inhibitor of CYP1A2. Therefore, the use of imipramine with these SSRIs may increase plasma concentrations of imipramine with corresponding adverse effects, mainly on the cardiovascular system. An adjustment of the dosage of imipramine may be necessary.

Liver enzyme-inducers: Substances which activate the hepatic mono-oxygenase enzyme system (e.g. barbiturates, phenytoin, carbamazepine, nicotine, oral contraceptives) may accelerate the metabolism of imipramine and lower the plasma concentration of tricyclic antidepressants and so reduce their effect. In addition, 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. Drugs like phenothiazines, haloperidol and cimetidine may delay elimination of imipramine increasing its plasma concentration. Imipramine binding with plasma protein may be reduced by drugs like phenytoin due to the competition.

Neuroleptic agents: Neuroleptic agents (e.g. phenothiazines) may increase the plasma concentration of imipramine, a lowered convulsion threshold and seizures. Combination with thioridazine may produce severe cardiac arrhythmias.

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 may be necessary to lower the dosage of imipramine if administered concomitantly with disulfiram.

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

Cimetidine: Since cimetidine raises the plasma concentration of imipramine, the dosage of imipramine should be reduced if the two drugs are administered concurrently; by contrast, ranitidine does not alter the kinetics of imipramine.

Methylphenidate: Methylphenidate may raise the plasma concentration of tricyclics and so intensify their antidepressant effect.

Oestrogens: If administered concomitantly with oestrogens, the dose of imipramine should be reduced, since steroid hormones inhibit the metabolism of imipramine and at the same time cause increased adverse effects.

Oral antifungals: The concomitant administration of imipramine and terbinafine, a potent inhibitor of CYP2D6, may cause an increased exposure and accumulation of imipramine and desipramine. Therefore, dose adjustments may be necessary when imipramine is coadministered with terbinafine.

Drugs inducing prolonged QT: Prolonged QTc and induction of tachycardia and Torsades de pointes may result from the combined administration of imipramine with medicines prolonging QTc (e.g. thioridazine, cisapride, cotrimoxazole). Coadministration of imipramine with these medicines should be avoided.

Calcium channel blockers: Verapamil and diltiazem may increase plasma levels of imipramine.

Beta-blockers: Labetalol and propranolol increase plasma concentrations of imipramine.

Thyroid preparations: Potential worsening of the cardiac undesirable effect

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy (Category C)

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

Experience with Tofranil in pregnancy is limited. Since there have been isolated reports of a possible connection between the use of Tofranil and adverse effects on the fetus, treatment with Tofranil should be avoided during pregnancy, and only considered if the benefits expected justify the potential risk for the fetus.

Epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of antidepressants in pregnancy and the use of antidepressants in pregnancy may be associated with an increase in pre-term delivery.

Babies whose mothers had taken Tofranil up until delivery showed symptoms, such as dyspnoea, lethargy, colic, irritability, hypotension or hypertension, tremor or spasms, during the first month of life. To avoid such symptoms, Tofranil should, if possible, be gradually withdrawn at least 7 weeks before the calculated date of confinement.

Use in lactation

Imipramine and desmethylimipramine pass into human milk in small quantities. Since nothing is known about the clinical relevance of this finding to the infant, babies should be weaned or the medication gradually withdrawn.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tofranil may cause fatigue, blurred vision, somnolence and other central nervous symptoms [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 reactions do not always correlate with plasma drug levels or dose. If severe neurological or psychiatric reactions occur, Tofranil should be withdrawn. Elderly patients are particularly susceptible to anticholinergic, neurological, psychiatric, and cardiovascular effects.

Reporting frequencies are described as follows:

Very common: $\geq 10\%$

Common: $\geq 1 - < 10\%$

Uncommon: $\geq 0.1 - < 1\%$

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

Very rare: $< 0.01\%$

Blood and lymphatic system disorders

Very rare: Bone marrow depression including leucopenia, agranulocytosis, eosinophilia, thrombocytopenia, lymphadenitis

Immune system disorder

Very rare: Anaphylactic reaction

Endocrine disorders

Very rare: Inappropriate antidiuretic hormone secretion

Metabolism and nutrition disorders

Very common: Weight increased

Common: Anorexia

Very rare: Weight decreased

Psychiatric disorders

Common: Restlessness, euphoria, confusion, delirium, hallucinations, anxiety, agitation, mania, hypomania, libido disorder, sleep disorder, disorientation

Rare: Psychotic disorder

Very rare: Aggression

Not known: Suicide ideation and suicidal behaviours

Nervous system disorders

- Very common: Tremor
- Common: Dizziness, headache, sedation, somnolence, paraesthesias
- Rare: Convulsions
- Very rare: Myoclonus, extrapyramidal disorder, ataxia, speech disorders, progressive stroke
- Not known: Dysgeusia

Eye disorders

- Common: Blurred vision, disorders of visual accommodation, lacrimation decreased
- Very rare: Mydriasis, glaucoma

Ear and labyrinth disorders

- Very rare: Tinnitus

Cardiac disorders

- Very common: Sinus tachycardia
- Common: Arrhythmias, palpitations, conduction disorders (e.g. widening of QRS complex, bundle branch block, PR changes)
- Very rare: Cardiac failure, QT interval prolongation, ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation, Torsades de pointes

Vascular disorders

- Very common: Hot flushes, orthostatic hypotension
- Very rare: Vasospasm, blood pressure increase, stroke

Respiratory, thoracic and mediastinal disorders

- Very rare: Alveolitis allergic (with or without eosinophilia)

Gastrointestinal disorders

- Very common: Dry mouth, constipation
- Common: Nausea, vomiting, diarrhoea
- Very rare: Ileus paralytic, stomatitis, abdominal disorders, tongue ulceration, dental caries

Hepatobiliary disorders

- Very rare: Hepatitis (with or without jaundice), acute hepatitis, hepatic necrosis

Skin and subcutaneous tissue disorders

- Very common: Hyperhidrosis
- Common: Dermatitis allergic contact (skin rash), urticaria
- Very rare: Pruritus, purpura, petechiae, photosensitivity reactions, alopecia, skin hyperpigmentation

Renal and urinary disorders

Common: Micturition disorder

Very rare: Urinary retention

Reproductive system and breast disorders

Very rare: Hypertrophy breast, galactorrhoea

General disorders and administration site conditions

Common: Fatigue

Very rare: Asthenia, oedema (localised or generalised), pyrexia, sudden death

Investigations

Very common: Electrocardiogram abnormalities (e.g. ST and T wave changes)

Common: Liver function test abnormal

Very rare: Blood glucose increased, blood glucose decreased, electroencephalogram abnormal, blood pressure increased

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, chills, sweating, musculoskeletal pain, insomnia, headache, nervousness, irritability, malaise and anxiety. It is advisable to reduce imipramine dose gradually when the treatment is no more necessary (see Section 4.4 Special warnings and precautions for use).

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.

With the class of tricyclic antidepressants the following adverse reactions have been observed: dyskinesia and, serotonin syndrome.

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

The signs and symptoms of overdose with Tofranil are similar to those reported with other tricyclic antidepressants. Cardiac abnormalities and neurological disturbances are the main alterations. In children, accidental ingestion of any amount should be regarded as serious and potentially fatal.

Signs and symptoms

The first signs and symptoms of poisoning with tricyclic antidepressants generally appear rapidly and take the form of severe anticholinergic reactions, which set in about 1/2 to 2 hours after the drug has been taken.

The severity of poisoning with tricyclic antidepressants depends 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: drowsiness, stupor, coma, ataxia, restlessness, agitation, mydriasis, enhanced reflexes, muscular rigidity with athetoid and choreiform movements, convulsions, consciousness, clouding and serotonin syndrome.
- Cardiovascular: arrhythmia, tachycardia, conduction disorders, hypotension, shock, heart failure; in very rare cases, cardiac arrest.
- Respiratory system: respiratory depression, cyanosis, apnoea.
- Other: vomiting, dry mouth, constipation, fever, sweating, and oliguria or anuria may occur.

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

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. Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Anyone suspected of receiving an overdose of Tofranil, particularly children, should be hospitalised and kept under close surveillance for at least 72 hours. Severe poisoning with tricyclic drugs 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 well after the ECG tracings have reverted to normal, because relapses may occur.

The following measures should be taken in cases of overdose:

- 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 in cases of bradycardia, heart block not responding to alkalisation or treatment with isoprenaline.
- Low potassium values and acidosis should be corrected.
- In convulsions: diazepam should be given i.v. 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

Imipramine is a tricyclic antidepressant with a multivalent spectrum of pharmacological action, which includes alpha-adrenolytic, anti-histaminic, anticholinergic, and 5-HT-receptor blocking properties. However, the therapeutic activity of imipramine is believed to be based mainly on its ability to inhibit the neuronal re-uptake of noradrenaline (norepinephrine) (NA) and serotonin (5-HT).

Imipramine belongs to the category of so-called "mixed" re-uptake blockers, i.e. it has been shown to inhibit the re-uptake of NA and 5-HT to approximately the same extent in the rat brain.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Imipramine is well absorbed following oral administration. During its first passage through the liver, orally administered imipramine becomes partly converted to desmethyylimipramine, which also exhibits antidepressant activity.

During oral administration of 50 mg 3 times daily for 10 days, the mean steady-state plasma concentrations of imipramine and desmethyylimipramine (on day 7 in four healthy male volunteers) were 33 to 85 ng/mL and 43 to 109 ng/mL respectively. Owing to lower clearance from the plasma, resulting in greater systemic availability, elderly patients require lower doses of imipramine than patients in intermediate age groups.

Distribution

Protein binding: Mean 86%

Distribution volume: Mean 21 L/kg

Plasma half-life: Mean approximately 20 hours

Excretion

Approximately 80% is excreted in the urine and 20% in the faeces, chiefly in the form of inactive metabolites.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The overall evaluation may be summarised as follows:

Oral: Independent studies in three species (rat, mouse and rabbit) revealed that when Tofranil is administered orally in doses up to approximately two and a half times the maximum human dose in the first two species and up to 25 times the maximum human dose in the third species, the drug is essentially free from teratogenic potential. In the three species studied only one instance of fetal abnormality occurred (in the rabbit) and in that study there was likewise an abnormality in the control group. However, evidence does exist from the rat studies that some systemic and embryotoxic potential is demonstrable. This is manifested by reduced litter size, a slight increase in the stillborn rate and a reduction in the mean birth weight.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tofranil contains colloidal anhydrous silica, glycerol, lactose monohydrate, magnesium stearate, maize starch, stearic acid, purified talc, hypromellose, povidone, copovidone, titanium dioxide, microcrystalline cellulose, macrogol 8000, sucrose, iron oxide red, printing ink Opacode White S-1-18086, carnauba wax (Tofranil 25 mg tablets only).

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 30°C and protected from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Tofranil 10: packaged in PVC/PE/PVDC/Al blister packs of 50 tablets.

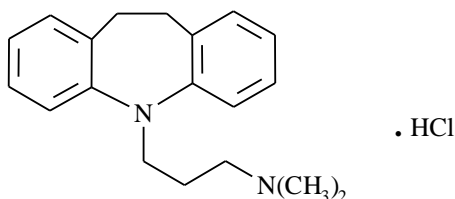
Tofranil 25: packaged in PVC/PE/PVDC/Al blister packs of 50 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Molecular formula: $C_{19}H_{24}N_2 \cdot HCl$

Molecular weight: 316.9

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

Imipramine hydrochloride 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.

CAS number

113-52-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

Amdipharm Mercury (Australia) Pty Ltd
Level 9, 76 Berry Street
North Sydney NSW 2060

Ph: 1800 627 680

9 DATE OF FIRST APPROVAL

Tofranil 10: 02 August 1991

Tofranil 25: 16 September 1997

10 DATE OF REVISION

07 February 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections	Updated to the revised Australian Product Information format