

## Data sheet

---

### 1 TOFRANIL (10 mg and 25 mg Coated Tablet)

---

TOFRANIL 10 mg and 25mg coated tablets

---

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

---

Each tablet contains 10 mg of imipramine hydrochloride

Each tablet contains 25 mg of imipramine hydrochloride

For the full list of excipients, see section 6.1.

---

### 3 PHARMACEUTICAL FORM

---

Tofranil 10 mg tablets are biconvex, reddish brown, sugar coated, triangular tablets printed in white with FT on one side.

Tofranil 25 mg tablets are biconvex, reddish brown, sugar coated, round tablets printed in white with CZ on one side.

---

### 4 CLINICAL PARTICULARS

---

#### 4.1 Therapeutic indications

All forms of depression, including endogenous, organic and psychogenic forms, and depression associated with personality disorders or chronic alcoholism.

#### 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 doses as low as possible and increasing them cautiously, particularly in elderly patients or adolescents, who generally show a stronger response to Tofranil than patients of the intermediate age group.

**Tofranil**  
**Imipramine hydrochloride 10 mg and 25 mg coated tablets**

*Adults*

***Depression and depressive syndromes***

Outpatients: Start treatment with 25 mg 1-3 times daily. Raise the daily dosage gradually to 150-200 mg. This dosage should be reached by the end of the first week and maintained to this dose until a clear improvement is seen. The maintenance dose, which must be individually determined by cautiously reducing the dosage, is usually 50-100 mg daily.

Hospitalised patients: Start treatment with 25 mg 3 times daily. Raise the dosage by 25 mg daily until a dose of 200 mg has been reached, and keep to this dose until the patient's condition has improved. In severe cases the dose may be increased to 100 mg 3 times daily. Once a clear improvement has set in, the maintenance dose should be determined according to the patient's individual requirements (generally 100 mg daily).

*Special populations*

***Elderly***

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

**Paediatric Population**

***Children and adolescents***

There is insufficient evidence of safety and efficacy of Tofranil in the treatment of all forms of depression, including endogenous, organic and psychogenic forms, and depression associated with personality disorders or chronic alcoholism. The use of Tofranil in children and adolescents (0-17 years of age) is therefore not recommended.

**Method of administration**

For oral administration.

**4.3 Contraindications**

Imipramine is contraindicated during the acute recovery phase following myocardial infarction.

Hypersensitivity to imipramine and any of the excipients listed in section 6.1, or cross-sensitivity to tricyclic antidepressants of the dibenzazepine group.

Tofranil should not be given in combination, or within 14 days before or after treatment, with a MAO inhibitor (see Interaction with other medicinal products and other forms of interaction). Concomitant treatment with selective, reversible MAO-A inhibitors, such as moclobemide, is also contraindicated.

## **Tofranil**

### **Imipramine hydrochloride 10 mg and 25 mg coated tablets**

Recent myocardial infarction, heart failure, conduction disorders and history of conduction disorders.

Prostatic hyperplasia, pyloric stenosis and other stenoses of the gastrointestinal and genitourinary systems, liver diseases and confirmed or suspected pregnancy and breast-feeding.

Tofranil is contraindicated for the treatment of depression in patients 18 years of age and under.

Tofranil is contraindicated for the treatment of nocturnal enuresis.

#### **4.4 Special warnings and precautions for use**

##### ***Clinical Worsening and Suicide Risk:***

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.

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 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.

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.

## **Tofranil**

### **Imipramine hydrochloride 10 mg and 25 mg coated tablets**

#### ***Mania and Bipolar Disorder***

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that Tofranil is not approved for use in treating bipolar depression.

#### ***Information for Patients and Families***

Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to the medicines efficacy and safety when used in the treatment regimen proposed.

#### ***Other psychiatric effects***

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

Activation of psychosis has occasionally been observed in schizophrenic patients receiving tricyclic antidepressants.

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 may be necessary to reduce the dosage of Tofranil or to withdraw it and administer an antipsychotic agent. After such episodes have subsided, low dose therapy with Tofranil may be resumed if required.

In predisposed and elderly patients, tricyclic antidepressants may provoke pharmacogenic (delirious) psychoses, particularly at night, and the use of drugs with an anticholinergic effect can also contribute to these disorders. These disappear within a few days of withdrawing the drug.

#### ***Cardiac and vascular disorders***

Particular caution is called for in patients with cardiovascular disorders, especially those with cardiovascular insufficiency, conduction disorders, (e.g. atrioventricular block

## **Tofranil**

### **Imipramine hydrochloride 10 mg and 25 mg coated tablets**

grades I to III), or arrhythmias. Monitoring of cardiac function and the ECG is indicated in such patients, as well as in elderly patients. An ECG should be performed prior to starting treatment, at steady state, after an increase in dose or after starting any potentially interacting medicine.

Isolated cases of QTc prolongation and very rare cases of ventricular tachycardia, Torsades de pointes 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 comedication that itself can lead to a prolonged QTc interval (e.g. thioridazine).

Imipramine should be used with caution in patients with risk factors for QTc prolongation/Torsades de Pointes including congenital long QT syndrome, age > 65 years, female sex, structural heart disease/LV dysfunction, medical conditions such as renal or hepatic disease, use of medicines that inhibit the metabolism of nortriptyline, and the concomitant use of other QTc prolonging medicines (see section 4.5 ). Hypokalaemia and hypomagnesaemia should be corrected prior to treatment.

Consideration should be given to stopping imipramine treatment or reducing the dose if the QTc interval is > 500ms or increase by > 60ms.

Before starting treatment with Tofranil it is advisable to check blood pressure, because patients with postural hypotension or a labile circulation may experience a fall in blood pressure.

Particular attention should be paid to children with congenital cardiac malformation to avoid occurrence of rhythm disorders.

### ***Serotonin syndrome***

Due to serotonergic toxicity risk, it is recommended that the suggested doses are followed and if other serotonergic agents are applied simultaneously, dose increases be made with caution. In situations where imipramine selective serotonin re-uptake inhibitors (SSRI), serotonin and non-adrenaline re-uptake inhibitors are used simultaneously with tricyclic antidepressants or other serotonergic medications like lithium, serotonin syndrome with symptoms like hyperpyrexia, myoclonus, agitation, seizures, delirium and coma may occur.

### ***Convulsions***

Tricyclic antidepressants are known to lower the convulsion threshold, and Tofranil should, therefore be used with extreme caution in patients with epilepsy and other predisposing factors, e.g. brain damage of varying aetiology, concomitant use of neuroleptics, withdrawal from alcohol or drugs with anticonvulsive properties (e.g. benzodiazepines). The occurrence of seizures seems to be dose-dependent. The recommended total daily dose of Tofranil should therefore not be exceeded. If convulsive attacks occur the treatment must be discontinued.

## **Tofranil**

### **Imipramine hydrochloride 10 mg and 25 mg coated tablets**

Like related tricyclic antidepressants, Tofranil should be given with electroconvulsive therapy only under careful supervision.

#### ***Anticholinergic effects***

Because of its anticholinergic properties, Tofranil should be used with caution in patients with a history of increased intraocular pressure, narrow-angle glaucoma, or urinary retention (e.g. diseases of the prostate).

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

#### ***Specific treatment populations***

Caution is called for when giving tricyclic antidepressants to patients with severe hepatic or renal disease and tumours of the adrenal medulla (e.g. pheochromocytoma, neuroblastoma), in whom they may provoke hypertensive crises.

Caution is indicated in patients with hyperthyroidism or patients receiving thyroid preparations, owing to the possibility of unwanted cardiac effects.

Periodic monitoring of hepatic enzyme levels is recommended in patients with liver disease.

Caution is called for in patients with chronic constipation. Tricyclic antidepressants may cause paralytic ileus, particularly in elderly and in bedridden patients.

An increase in dental caries has been reported during long-term treatment with tricyclic antidepressants. Regular dental check-ups are therefore advisable during long-term treatment.

Caution must be exercised in elderly patients presenting greater sensitivity to orthostatic hypotension, sedation and possible prostatic hypertrophy.

#### ***White blood cell count***

Although changes in the white blood cell count have been reported with Tofranil only in isolated cases, periodic blood cell counts and monitoring for symptoms such as fever and sore throat are called for, particularly during the first few months of therapy and during prolonged treatment.

Since the use of tricyclic antidepressants may in rare cases be accompanied by agranulocytosis, it is advisable to perform blood counts, particularly in case of fever, sore throat and other symptoms associated with an influenza type of infection.

#### ***Anaesthesia***

Before general or local anaesthesia, the anaesthetist should be aware that the patient has been receiving Tofranil (see section 4.5).

## **Tofranil**

### **Imipramine hydrochloride 10 mg and 25 mg coated tablets**

#### ***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, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms headaches, malaise, vertigo, nausea, anxiety, sleep disorders (see section 4.8).

#### ***Lactose and sucrose***

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

#### ***Paediatric population***

Tricyclic antidepressants should not be used for the treatment of children or adolescents under 18 years old. Studies conducted on depression in children belonging to this age group have not demonstrated the efficacy of this class of drugs. Studies with other antidepressants have highlighted the risk of suicide, self-harm and hostility associated with these drugs. This risk may also occur with tricyclic antidepressants.

If, in the event of clinical necessity, the decision to treat a child or adolescent with imipramine is nevertheless taken, the patient must undergo close monitoring to ensure any occurrence of suicidal symptoms is detected.

Furthermore, tricyclic antidepressants are associated with a risk of adverse cardiovascular events in all three age groups. It must be borne in mind that long-term safety data regarding growth, maturation and cognitive and behavioural development in adolescents and children are not available.

## **4.5 Interaction with other medicines and other forms of interaction**

#### ***Medicines that can prolong the QTc Interval***

The risk of QTc prolongation and/or ventricular arrhythmias (e.g. Torsades de pointes) is increased with concomitant use of other medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics). Please check the data sheet of other medicines administered for information on their effects on the QTc interval

#### ***MAO inhibitors***

Do not give Tofranil for at least 2 weeks after discontinuation of treatment with MAO inhibitors (there is a risk of severe symptoms such as hypertensive crisis, hyperpyrexia, myoclonus, agitation, seizures, delirium, and coma). The same applies when giving a MAO inhibitor after previous treatment with Tofranil. In both instances Tofranil or the MAO inhibitor should initially be given in small, gradually increasing doses and its effects monitored (see section 4.3).

There is evidence to suggest that tricyclic antidepressants 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 a tricyclic antidepressant has been used.

## **Tofranil**

### **Imipramine hydrochloride 10 mg and 25 mg coated tablets**

#### ***Selective serotonin reuptake inhibitors (SSRIs)***

Co-medication may lead to additive effects on the serotonergic system. SSRI's like fluoxetine, paroxetine, sertraline or citalopram are potent CYP2D6 inhibitors. Fluvoxamine is a potent CYP1A2 inhibitor and a mid-level CYP2D6 inhibitor. Therefore the use of SSRI's together with imipramine may cause exposure to increased plasma concentration of imipramine, with corresponding adverse effects. Therefore a dose adjustment may be necessary for imipramine.

#### ***Other serotonergic agents***

Simultaneous applications may cause additive effects in the serotonergic system. In situations where imipramine and SNRI's are used simultaneously with tricyclic antidepressants or other serotonergic medications like lithium, serotonin syndrome may occur.

#### ***CNS depressants***

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

#### ***Neuroleptics***

Co-medication may result in increased plasma levels of tricyclic antidepressants, a lowered convulsion threshold, and seizures. Combination with thioridazine may produce severe cardiac arrhythmias.

#### ***Oral antifungal, Terbinafine***

Simultaneous administration of imipramine with terbinafine, which is a potent CYP2D6 inhibitor may cause increase in imipramine and desipramine exposure and accumulation. Therefore when administered with terbinafine, imipramine may need a dose adjustment.

#### ***Adrenergic neurone blockers***

Tofranil may diminish or abolish the antihypertensive effects of guanethidine, betanidine, reserpine, clonidine, and alpha-methyldopa. Patients requiring co-medication for hypertension should therefore be given antihypertensives of a different type e.g. diuretics, vasodilators, or beta-blockers.

#### ***Anticoagulants***

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

#### ***Anticholinergic agents***

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



## **Tofranil**

### **Imipramine hydrochloride 10 mg and 25 mg coated tablets**

#### ***Sympathomimetic drugs***

Tofranil may potentiate the cardiovascular effects of adrenaline, noradrenaline, isoprenaline, ephedrine, and phenylephrine e.g. local anaesthetics. Association of imipramine with L-dopa facilitates the onset of hypotension and cardiac arrhythmias. The patient should also avoid using nasal decongestants and products used for treating asthma and pollinosis, which contain sympathomimetic substances.

#### ***Quinidine***

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

#### ***Liver-enzyme inducers***

Drugs which activate the hepatic mono-oxygenase enzyme system e.g. barbiturates, carbamazepine, phenytoin, nicotine, and oral contraceptives may accelerate the metabolism and lower plasma concentrations of imipramine, resulting in decreased efficacy. Plasma levels of phenytoin and carbamazepine may increase, with corresponding adverse effects. It may be necessary to adjust the dosage of these drugs. Phenothiazines, haloperidol and cimetidine can delay its excretion, increasing its blood concentration. The binding of imipramine with plasma proteins can be reduced through competition with phenytoin, phenylbutazone, acetylsalicylic acid, scopolamine and phenothiazine.

#### ***Cimetidine, methylphenidate***

These drugs may increase plasma concentrations of tricyclic antidepressants, whose dosage should therefore be reduced.

#### ***Oestrogens***

There is evidence that oestrogens can sometimes paradoxically reduce the effects of Tofranil yet at the same time cause Tofranil toxicity.

#### ***Calcium channel blockers***

Verapamil and diltiazem can increase the plasma imipramine levels as a result of interference with the metabolism of imipramine.

#### ***Beta-blockers***

Labetalol and propranolol increase the plasma concentration of imipramine.

#### ***Paediatric population***

Interaction studies have only been performed in adults.

## **4.6 Fertility, pregnancy and lactation**

### **Pregnancy**

#### **Category C**

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 Tofranil should be avoided during pregnancy, unless the anticipated

## **Tofranil**

### **Imipramine hydrochloride 10 mg and 25 mg coated tablets**

benefits justify the potential risk to the foetus, taking into account the risks of untreated depression.

Epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of tricyclic antidepressants in pregnancy.

Neonates should be observed if maternal use of imipramine has continued into the later stages of pregnancy, particularly into the third trimester.

Neonates whose mothers had taken tricyclic antidepressants until delivery showed drug 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, Tofranil should if possible be gradually withdrawn at least 7 weeks before the calculated date of confinement.

Epidemiological data suggests that the use of tricyclic antidepressants in pregnancy may be associated with an increase in pre-term delivery.

### **Breastfeeding**

Imipramine and its metabolite desmethyylimipramine pass into the breast milk in small quantities, Tofranil should be gradually withdrawn or the mother be advised to cease breast-feeding.

### **Fertility**

The studies done on animals about the effects on pregnancy and/or embryonic/ foetal development and/or development during and after birth are insufficient. There is no known potential risk for humans. It should not be used unless necessary. Women of childbearing potential should use effective contraceptive methods during treatment.

## **4.7 Effects on ability to drive and use machines**

Patients receiving Tofranil should be warned that blurred vision, somnolence and other CNS symptoms (see section 4.8) 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 drugs may potentiate these effects.

## **4.8 Undesirable effects**

### ***a. Summary of the safety profile***

Unwanted effects are usually mild and transient, disappearing under continued treatment or with a reduction in the dosage. They do not always correlate with plasma drug levels or dose. It is often difficult to distinguish certain adverse effects from symptoms of depression such as fatigue, sleep disturbances, agitation, anxiety, constipation, and dry mouth.

If severe neurological or psychic reactions occur, Tofranil should be withdrawn. Elderly patients are particularly susceptible to anticholinergic, neurological, psychic and

## **Tofranil**

### **Imipramine hydrochloride 10 mg and 25 mg coated tablets**

cardiovascular effects. Their ability to metabolise and eliminate drugs may be reduced, leading to a risk of elevated plasma concentrations at therapeutic doses.

#### **b. Tabulated summary of adverse reactions**

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (frequency cannot be estimated from the available data).

#### **Blood and lymphatic system disorders**

Very rare: Leukopenia, agranulocytosis, eosinophilia, thrombocytopenia

#### **Immune system disorders**

Very rare: Anaphylactic reaction

#### **Endocrine disorders**

Very rare: Inappropriate antidiuretic hormone secretion

#### **Psychiatric disorders**

Common: Restlessness, confusional state, delirium, hallucinations, anxiety, agitation, mania, hypomania, libido disorder, sleep disorder, disorientation, anorexia nervosa

Rare: Psychotic disorder

Very rare: Aggression

Not known: Suicidal behaviour, suicidal ideation

Cases of suicidal thoughts and behaviour have been reported during imipramine therapy or shortly after discontinuation of treatment (See section 4.4)

#### **Nervous system disorders**

Very common: Tremor

Common: Dizziness, headache, sedation, somnolence, paraesthesia

Rare: Convulsions local

Very rare: Myoclonus, extrapyramidal disorder, ataxia, speech disorder, dysarthria, dyskinesia, serotonin syndrome (in combined treatment), stroke in evolution, syncope.

Not known: Dysgeusia

#### **Eye disorders**

Common: Blurred vision, disorders of visual accommodation, lacrimation decreased

Very rare: Mydriasis, glaucoma

#### **Ear and labyrinth disorders**

Common: Vertigo

Very rare: Tinnitus

#### **Cardiac disorders**

Very common: Sinus tachycardia, electrocardiogram abnormalities (e.g. ST and T wave changes)

Common: Arrhythmias, palpitations, conduction disorders (e.g. widening of QRS complex, bundle branch block, PQ changes)

**Tofranil****Imipramine hydrochloride 10 mg and 25 mg coated tablets**

Very rare: Cardiac failure, QT interval prolongation, ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation, torsades de pointes, myocardial infarction.

**Vascular disorders**

Very common: Hot flushes, orthostatic hypotension

Very rare: Vasospasm,

**Respiratory, thoracic and mediastinal disorders**

Very rare: Alveolitis allergic (with or without eosinophilia)

**Gastrointestinal disorders**

Very common: Dry mouth, constipation

Common: Nausea, vomiting

Very rare: Ileus paralytic, stomatitis, abdominal disorders, tongue ulceration, dental caries

**Hepatobiliary disorders**

Very rare: Hepatitis (with or without jaundice)

**Skin and subcutaneous tissue disorders**

Very common: Hyperhidrosis

Common: Dermatitis allergic, rash, urticaria

Very rare: Pruritis, purpura, photosensitivity reactions, alopecia, skin hyperpigmentation, petechiae

**Renal and urinary disorders**

Common: Micturition disorder

Very rare: Urinary retention

**Reproductive system and breast disorders**

Very rare: Gynaecomastia, galactorrhoea

**General disorders and administration site conditions**

Common: Fatigue

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

**Investigations**

Very common: Weight increased

Common: Liver function test abnormal

Very Rare: Blood glucose increased, blood glucose decreased, weight decreased, electroencephalogram abnormal and blood pressure increased

**Injury, poisoning and procedural complications**

Common: Broken bones [Epidemiological studies, conducted mainly on patients who were aged 50 years and older, show an increase in the risk of bone fracture in patients receiving selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCA). The mechanism responsible for this risk is unknown].

**c. Description of selected adverse reactions**

## **Tofranil**

### **Imipramine hydrochloride 10 mg and 25 mg coated tablets**

#### *Withdrawal symptoms*

The following symptoms occasionally occur after abrupt withdrawal or reduction of the dose: nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness, and anxiety.

It is therefore recommended to gradually reduce the imipramine doses when treatment is no longer necessary (see Warnings and Precautions). Cases of impotence have also been observed. Some very rare cases of cardiomyopathy have been reported.

Effects linked to the actual nature of the depressive illness:

- Raised psychomotor inhibition, with the risk of suicide
- Mood changes with the occurrence of manic episodes
- Reoccurrence of delirium in psychotic patients
- Paroxysmic manifestations of anguish.

#### ***d. Paediatric population***

Not recommended in children and adolescents (0-17 years of age).

#### Reporting of suspected adverse reactions

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 <https://nzphvc.otago.ac.nz/reporting/>

## **4.9 Overdose**

The signs and symptoms of Tofranil overdose are similar to those observed with other tricyclic antidepressants. The main complications are cardiac and neurological in nature. In children, accidental intake of any dose must be considered as a serious and potentially fatal event.

#### *Symptoms*

Symptoms generally appear within 4 hours of ingestion and reach maximum severity after 24 hours. Owing to delayed absorption (increased anticholinergic effect due to overdose), long half-life, and enterohepatic recycling of the drug, the patient may be at risk for up to 4-6 days.

The following signs and symptoms may be seen:

Central nervous system: somnolence, drowsiness, stupor, coma, ataxia, restlessness, agitation, enhanced reflexes, muscular rigidity, choreoathetoid movements, convulsions, numbness and serotonin syndrome.

Cardiovascular system: hypotension, tachycardia, QTc prolongation, arrhythmias (including Torsades de pointes), conduction disorders, shock, heart failure; in very rare cases cardiac arrest.

Others: respiratory depression, cyanosis, vomiting, fever, mydriasis, sweating, and oliguria or anuria may also occur.

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

**Tofranil**  
**Imipramine hydrochloride 10 mg and 25 mg coated tablets**

*Treatment*

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

Anyone suspected of receiving an overdose of Tofranil, particularly children, should be hospitalised and kept under close surveillance for at least 72 hours.

Perform gastric lavage or induce vomiting as soon as possible if the patient is fully conscious. If the patient has impaired consciousness, secure the airway with a cuffed endotracheal tube before beginning lavage, and do not induce vomiting. These measures are recommended for up to 12 hours or even longer after the overdose, since the anticholinergic effect of the drug may delay gastric emptying. Administration of activated charcoal may help to reduce drug absorption.

Treatment of symptoms is based on modern methods of intensive care, with continuous monitoring of cardiac function, blood gases, and electrolytes, and if necessary emergency measures such as anticonvulsive therapy, artificial respiration, insertion of a temporary cardiac pacemaker, plasma expander, dopamine or dobutamine administered by intravenous drip, and resuscitation. Since it has been reported that physostigmine may cause severe bradycardia, asystole, and seizures, its use is not recommended in cases of overdosage with Tofranil. Haemodialysis or peritoneal dialysis are ineffective because of the low plasma concentrations of Tofranil.

In case of overdose, immediately contact the New Zealand Poisons Information Centre for advice on 0800 764 766.

---

## **5 PHARMACOLOGICAL PROPERTIES**

---

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Tricyclic antidepressant

ATC code: N06A A02

#### Mechanism of action

Imipramine is a tricyclic antidepressant. It has several pharmacological properties, including alpha-adrenolytic, antihistaminic, anticholinergic, and 5-HT-receptor blocking properties. However, the main therapeutic activity is believed to be inhibition of the neuronal reuptake of noradrenaline (NA) and serotonin (5-HT) (non-selective monoamine reuptake inhibitor).

Imipramine is a so-called "mixed" re-uptake blocker, i.e. it inhibits the re-uptake of NA and 5-HT to about the same extent.

### **5.2 Pharmacokinetic properties**

## **Tofranil**

### **Imipramine hydrochloride 10 mg and 25 mg coated tablets**

#### **Absorption**

Imipramine hydrochloride is absorbed rapidly and almost completely from the gastrointestinal tract. Food has no effect on its absorption and bioavailability. During its first passage through the liver, orally administered imipramine becomes partly converted to desmethylimipramine, a metabolite which also exhibits antidepressive activity.

The bioavailability of imipramine depends on the individual (it ranges from 25 to 50 % approximately). Because of a significant hepatic first pass effect; the bioavailability of imipramine is approximately 50% lower when administered orally than when administered via the parenteral route.

Following oral administration of 50 mg t.i.d. for 10 days, mean steady-state plasma concentrations of imipramine and desmethylimipramine were 33-85 ng/mL and 43-109 ng/mL respectively.

#### **Distribution**

About 86% of imipramine binds to plasma proteins. Concentrations of imipramine in the cerebrospinal fluid and the plasma are highly correlated.

The mean distribution volume is 21 L/kg bodyweight.

The total plasma clearance of imipramine, calculated following administration via the intravenous route, is 1 L/min. The plasma half-life elimination of imipramine depends on the individual: It ranges between 9 and 20 hours. Imipramine passes the haematoencephalic barrier as well as into maternal milk.

Imipramine and its metabolite desmethylimipramine both pass into the breast milk in concentrations similar to those found in the plasma.

#### **Biotransformation**

The liver plays a major role in the metabolism of imipramine-like antidepressants. Uptake (first pass effect) then intense biotransformation, which explains:

- The high rate of plasma clearance, which is related to the hepatic blood flow (1.5 L/min)
- The low percentage of active components present in the urine

In principle, imipramine is N-demethylated to the N-desmethylimipramine form (desipramine) (active metabolite) by CYP3A4, CYP2C19, and CYP1A2. Imipramine and desipramine undergo hydroxylation, catalysed by CYP2D6 to form 2-hydroximipramine (active metabolite) and 2-hydroxydesipramine (active metabolite). The two metabolic pathways are under genetic control.

Imipramine is extensively metabolised in the liver. It is cleared mainly by demethylation and to a lesser extent by hydroxylation. Both metabolic pathways are under genetic control.

## **Tofranil**

### **Imipramine hydrochloride 10 mg and 25 mg coated tablets**

The main metabolite of imipramine is desmethylimipramine or desipramine, an active component with a half-life which is slightly longer than that of the parent molecule. Hydroxylation of these two molecules produces other active metabolites. They are inactivated through conjugation with glucuronic acid, resulting in hydrosoluble substances that are eliminated in urine or bile.

#### **Elimination**

Imipramine is eliminated from the blood with a mean half-life of 19 hours.

About 80% is excreted in the urine and about 20% in the faeces, mainly in the form of inactive metabolites. Urinary excretion of unchanged imipramine and of the active metabolite desmethylimipramine is about 5% and 6%, respectively. Only small quantities are excreted in the faeces.

Since systemic availability is higher in elderly persons due to reduced plasma clearance, it is advisable to give them lower doses of imipramine than for patients in other age groups.

#### *Characteristics in patients*

Owing to reduced metabolic clearance, plasma concentrations of imipramine are higher in elderly patients than in younger patients. It is advisable to give them lower doses of imipramine than for patients in other age groups.

In children the mean clearance and elimination half-life does not differ significantly from adult controls, but the between-patient variability is high.

In patients with severe renal impairment, no change occurs in the renal excretion of imipramine and its biologically active unconjugated metabolites. However, steady-state plasma concentrations of the conjugated metabolites, which are considered to be biologically inactive, are elevated. The clinical significance of this finding is not known.

#### **Concentration/activity ratio**

For desipramine, the therapeutic range commonly held is between 115 and 250 ng/ml, and it is between 180 and 350 ng/ml for the total imipramine/desipramine. In current practice, it is not necessary to measure plasma levels as part of therapeutic monitoring. However, there are two groups of patients for which the monitoring of plasma concentrations may be desirable:

- Patients at risk: Elderly patients, patients with a cardiac, hepatic or renal pathology, children etc. (See section 4.4)
- Patients resisting treatment, those presenting marked undesirable effects, or those undergoing polymedication (See section 4.5).

### **5.3 Preclinical safety data**

Imipramine has no mutagenic or carcinogenic potential. Studies in four species (mouse, rat, rabbit, and monkey) led to the conclusion that orally administered imipramine has no teratogenic potential. Experiments with high doses of parenterally administered



## **Tofranil**

### **Imipramine hydrochloride 10 mg and 25 mg coated tablets**

imipramine resulted mainly in severe maternal toxicity and embryotoxic effects; they were thus inconclusive with regard to teratogenic effects.

---

## **6 PHARMACEUTICAL PARTICULARS**

---

### **6.1 List of excipients**

Tofranil tablets also contain glycerin, lactose, magnesium stearate, maize starch, stearic acid, silica, hydroxypropyl methylcellulose, vinylpyrrolidone/vinylacetate copolymer, microcrystalline cellulose, titanium dioxide, red iron oxide, macrogol 8000, polyvidone, sucrose, talc and white printing ink which contains titanium dioxide and propylene glycol.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf-life**

Tofranil 10mg - 60 months

Tofranil 25mg – 36 months

### **6.4 Special precautions for storage**

Store below 30°C. Protect from moisture and light.

Keep out of reach and sight of children

### **6.5 Nature and contents of container**

Tofranil 10 mg: Blister packs of 50 , 60 tablets or 100 tablets

Tofranil 25 mg: Blister packs of 50 tablets

### **6.6 Special precautions for disposal**

No special requirements.

---

## **7 MEDICINE SCHEDULE**

---

Prescription Medicine

---

## **8 SPONSOR**

---

AFT Pharmaceuticals Ltd

**Tofranil**  
**Imipramine hydrochloride 10 mg and 25 mg coated tablets**

Level 1, Nielson Building  
129 Hurstmere Road  
Takapuna  
Auckland

Phone: 0800 423 823  
Email:customer.service@aftpharm.com

---

## **9 DATE OF FIRST APPROVAL**

---

01 March 2001 for Tofranil 10mg coated tablet

01 February 2001 for Tofranil 25mg coated tablet

---

## **10 DATE OF REVISION OF TEXT**

---

11 December 2017

Summary table of changes

<b>Section changed</b>	<b>Summary of new information</b>
<b>3</b>	Relocation of text in line with the new Medsafe datasheet SPC format.
<b>4</b>	Relocation of text, addition of subheadings and information in line with the new Medsafe datasheet SPC format
6.1	Removal of Simethicone and inclusion of Propylene glycol
6.3	Shelf life information included in line with the new Medsafe datasheet SPC format
6.5	Inclusion of 100's blister pack as per TPDR