

# **Tofranil**

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

### **Presentation**

Tofranil 10 mg tablets are biconvex, reddish brown, sugar coated, triangular tablets printed in white with CG on one side and FT on the other. Each tablet contains 10 mg of imipramine hydrochloride.

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

### **Uses**

#### ***Actions***

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).

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.

#### ***Pharmacokinetics***

##### **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.

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 apparent distribution volume is about 21 L/kg bodyweight.

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

## **Biotransformation**

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.

## **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.

## **Characteristics in patients**

Owing to reduced metabolic clearance, plasma concentrations of imipramine are higher in elderly patients than in younger patients.

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.

## **Indications**

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

## **Dosage and 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.

### **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).

### ***Elderly patients***

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.

### ***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.

## **Contraindications**

- Hypersensitivity to imipramine and any of the excipients, 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.
- Recent myocardial infarction.
- Tofranil is contraindicated for the treatment of depression in patients 12 years of age and under.
- Tofranil is contraindicated for the treatment of nocturnal enuresis.

## **Warnings and Precautions**

### ***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.

### ***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. 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 grades I to III), or arrhythmias. Monitoring of cardiac function and the ECG is indicated in such patients, as well as in elderly patients.

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 comedication that itself can lead to a prolonged QTc interval (e.g. thioridazine).

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.

### ***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.

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.

### ***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.

### ***Anaesthesia***

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

### ***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 (see Adverse Effects).

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

Tofranil coated tablets contain lactose 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 coated tablets.

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

### ***Use during Pregnancy and Lactation***

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 fetus, treatment with Tofranil should be avoided during pregnancy, unless the anticipated benefits justify the potential risk to the fetus, 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.

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

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

Patients receiving Tofranil should be warned that blurred vision, somnolence and other CNS symptoms (see Adverse Effects) may occur, in which case they should not drive, operate machinery, or do anything else requiring alertness. Patients should also be warned that alcohol or other drugs may potentiate these effects

### ***Adverse Effects***

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

Adverse reactions (Table 1) 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 ( $< 1/10,000$ ), including isolated reports.

Table 1

|   |   |
|---|---|
| <b>Infections and infestations</b>          |   |
| Very rare:                                  | Dental caries   |
| <b>Blood and lymphatic system disorders</b> |   |
| Very rare:                                  | Leukopenia, agranulocytosis, eosinophilia, thrombocytopenia   |
| <b>Immune system disorders</b>              |   |
| Very rare:                                  | Anaphylactic reaction   |
| <b>Endocrine disorders</b>                  |   |
| Very rare:                                  | Inappropriate antidiuretic hormone secretion  |
| <b>Metabolism and nutrition disorders</b>   |   |
| Very common:                                | Weight increased  |
| Common:                                     | Anorexia  |
| Very rare:                                  | Blood glucose increase, blood glucose decrease, weight decreased  |
| <b>Psychiatric disorders</b>                |   |
| Common:                                     | Restlessness, confusion, delirium, hallucinations, anxiety, agitation, mania, hypomania, libido disorder, sleep disorder, disorientation  |
| Rare:                                       | Psychotic disorder  |
| Very rare:                                  | Aggression  |
| <b>Nervous system disorders</b>             |   |
| Very common:                                | Tremor  |
| Common:                                     | Dizziness, headache, somnolence, paraesthesias  |
| Rare:                                       | Convulsions   |
| Very rare:                                  | Myoclonus, extrapyramidal disorder, ataxia, speech disorders, electroencephalogram abnormal   |
| <b>Eye disorders</b>                        |   |
| Common:                                     | Blurred vision, disorders of visual accommodation, lacrimation decreased  |
| Very rare:                                  | Mydriasis, glaucoma   |
| <b>Ear and labyrinth disorders</b>          |   |
| Very rare:                                  | Tinnitus  |
| <b>Cardiac disorders</b>                    |   |
| Very common:                                | Sinus tachycardia, Electrocardiogram abnormalities (eg ST and T wave changes)   |
| Common:                                     | Arrhythmias, palpitations, conduction disorders (e.g. widening of QRS complex, bundle branch block, PQ changes)                           |
| Very rare:                                  | Cardiac failure, QT interval prolongation, ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation, torsades de pointes |
| <b>Vascular disorders</b>                   |   |

|   |  |
|---|--|
| Very common:  | Hot flushes, orthostatic hypotension                                   |
| Very rare:  | Purpura, petechiae, vasospasm, blood pressure increase                 |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |  |
| Very rare:  | Alveolitis allergic (with or without eosinophilia)                     |
| <b>Gastrointestinal disorders</b>                           |  |
| Very common:  | Dry mouth, constipation  |
| Common:   | Nausea, vomiting   |
| Very rare:  | Ileus paralytic, stomatitis, abdominal disorders, tongue ulceration    |
| <b>Hepatobiliary disorders</b>                              |  |
| Common:   | Liver function test abnormal   |
| Very rare:  | Hepatitis (with or without jaundice)                                   |
| <b>Skin and subcutaneous tissue disorders</b>               |  |
| Very common:  | Hyperhidrosis  |
| Common:   | Dermatitis allergic, rash, urticaria                                   |
| Very rare:  | Pruritis, photosensitivity reactions, alopecia, skin hyperpigmentation |
| <b>Renal and urinary disorders</b>                          |  |
| Common:   | Micturition disorder   |
| Very rare:  | Urinary retention  |
| <b>Reproductive system and breast disorders</b>             |  |
| Very rare:  | Hypertrophy breast, galactorrhoea                                      |
| <b>General disorders and administration site conditions</b> |  |
| Common:   | Fatigue  |
| Very rare:  | Asthenia, oedema (localised or generalised), pyrexia, sudden death     |

### ***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.

### **Interactions**

#### ***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 Contraindications).

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.

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

Co-medication may lead to additive effects on the serotonergic system. Fluoxetine and fluvoxamine may also increase plasma concentrations of imipramine, with corresponding adverse effects.

***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.

***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.

***Sympathomimetic drugs:***

Tofranil may potentiate the cardiovascular effects of adrenaline, noradrenaline, isoprenaline, ephedrine, and phenylephrine e.g. local anaesthetics.

***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.

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

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

### ***Estrogens:***

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

## **Overdosage**

### ***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: drowsiness, stupor, coma, ataxia, restlessness, agitation, enhanced reflexes, muscular rigidity and choreoathetoid movements, convulsions.

Cardiovascular system: hypotension, tachycardia, arrhythmias, 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.

### ***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.

## **Pharmaceutical Precautions**

Store below 30 °C. Protect from moisture and light.  
Keep out of reach and sight of children.

## **Medicines Classification**

Prescription Medicine

## **Package Quantities**

Blister packs of 50 tablets

## **Further Information**

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.

## **Name and Address**

AFT Pharmaceuticals Ltd  
9 Anzac Street (Level 2)  
Takapuna  
Auckland  
Email:customer.service@aftp pharm.com

## **Date of Preparation**

June 2010