Product Monograph

PrTOFRANIL*

(imipramine hydrochloride)

25, 50 and 75 mg tablets

Antidepressant

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Product Monograph

Name Of Drug

PrTOFRANIL*

(imipramine hydrochloride)

25, 50 and 75 mg tablets

Therapeutic Classification

Antidepressant

Actions And Clinical Pharmacology

TOFRANIL* (imipramine hydrochloride) is a tricyclic antidepressant with general pharmacological properties similar to those of structurally related tricyclic antidepressant drugs such as amitriptyline and doxepin.

TOFRANIL* possesses anticholinergic properties which are responsible for certain side effects. The mechanism of action of TOFRANIL* and other tricyclic antidepressants is not well established, but it is thought that it might be related to their action on the transmitter-uptake mechanism of monoaminergic neurons. The mechanism of action in childhood nocturnal enuresis is not fully known.

TOFRANIL* is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma levels are reached in 2-5 hours, and plasma half-life ranges from 9 to 20 hours. After oral administration of 50 mg three times daily for ten days, the mean steady-state plasma concentration was 33-85 ng/mL for imipramine and 43-109 ng/mL for desmethylimipramine, an active metabolite. Approximately 86% of imipramine is bound to plasma proteins. It is excreted primarily as inactive metabolites, up to 80% in the urine and up to 20% in the feces.

Owing to the lower clearance of imipramine in plasma, elderly patients require lower doses of TOFRANIL* than patients in younger age groups.

Indications And Clinical Use

TOFRANIL* (imipramine hydrochloride) is indicated for the relief of symptoms of depression.

Contraindications

TOFRANIL* (imipramine hydrochloride) is contraindicated in patients who have known or suspected hypersensitivity to the drug or its excipients, or have known or suspected hypersensitivity to tricyclic antidepressants belonging to the dibenzazepine group.

TOFRANIL* should not be given in conjunction with, or within fourteen days before or after treatment with a monoamine oxidase (MAO) inhibitor (See Drug Interactions). The concomitant treatment with selective, reversible MAO-A inhibitors, such as moclobemide, is also contraindicated. Symptoms such as hypertensive crises, hyperactivity, hyperpyrexia, spasticity, severe convulsions, and those consistent with serotonin syndrome, e.g. myoclonus, agitation, seizures, delirium or coma and death have been reported in patients receiving such combinations.

TOFRANIL* is contraindicated for use during the acute recovery phase following a myocardial infarction and in the presence of acute congestive heart failure.

TOFRANIL* is contraindicated in patients with existing liver or kidney damage and should not be administered to patients with a history of blood dyscrasias.

TOFRANIL* is contraindicated in patients with glaucoma, as the condition may be aggravated due to the atropine-like effects of the drug.

Warnings

Seizures

Tricyclic agents are known to lower the convulsive threshold and TOFRANIL* (imipramine hydrochloride) should, therefore, be used with extreme caution in patients with a history of convulsive disorders and other predisposing factors, e.g., brain damage of varying etiology, concomitant use of neuroleptics, alcoholism and withdrawal from alcohol, and concomitant use with other drugs that lower the seizure threshold. It appears that the occurrence of seizures is dose dependent. Therefore, the recommended total daily doses should not be exceeded (see Dosage And Administration).

Concurrent administration of electroconvulsive therapy and TOFRANIL* may be hazardous and such treatment should be limited to patients for whom it is essential. Physicians should discuss with patients the risk of taking TOFRANIL* while engaging in activities in which a sudden loss of consciousness could result in serious injury to the patient or others e.g., the operation of complex machinery, driving, swimming, or climbing.

Cardiovascular

Tricyclic antidepressants, particularly in high doses, have been reported to produce sinus tachycardia, changes in conduction time and arrhythmias. A few instances of unexpected death have been reported in patients with cardiovascular disorders. Myocardial infarction and stroke

have also been reported with drugs of this class. Therefore, TOFRANIL* should be administered with extreme caution to patients with a history of cardiovascular disorders, especially those with cardiovascular insufficiency, conduction disorders (e.g., atrioventricular block grades I to III) or other arrhythmias, those with circulatory lability and 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). Isolated cases have also been reported in the absence of comedication.

TOFRANIL* also has a hypotensive action which may be detrimental in these circumstances. In such cases, treatment should be initiated at low doses with progressive increases only if required and tolerated, and the patients should be under close surveillance at all dosage levels. Monitoring of cardiac function and the ECG is indicated in such patients as well as in the elderly.

Serotonin syndrome

Due to the risk of serotonergic toxicity, it is advisable to adhere to recommended doses and any increase in dose should be made with caution if other serotonergic agents are co-administered. Serotonin syndrome, with symptoms such as hyperpyrexia, myoclonus, agitation, seizures, delirium and coma, can possibly occur when imipramine is administered with serotonergic co-medications such as selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants or lithium (see Drug Interactions).

Potential Association with the Occurrence of Behavioural and Emotional Changes, Including Self-Harm

It is unknown whether increased risk of suicidal ideation and behaviour is associated with the use of older antidepressants (eg TOFRANIL*) in pediatric patients and/ or adults. However, recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer antidepressants suggest that use of these drugs in patients under the age of 25 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo. Thus, rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in <u>patients of all ages</u> given any antidepressant drug. This includes monitoring for emotional and behavioural changes.

Use in Concomitant Illness

Caution should be observed when prescribing TOFRANIL* for hyperthyroid patients or for patients receiving thyroid medication. Transient cardiac arrhythmias have occurred in rare instances in patients who have been receiving other tricyclic compounds concomitantly with thyroid medication.

Because of its anticholinergic properties, TOFRANIL* should be used with caution in patients with increased intraocular pressure, narrow angle glaucoma or urinary retention, particularly in the presence of prostatic hypertrophy.

Tricyclic antidepressants may give rise to paralytic ileus, particularly in the elderly and in hospitalized patients. Therefore, appropriate measures should be taken if constipation occurs.

Caution is called for when employing TOFRANIL* in patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma), in whom the drug may provoke hypertensive crisis.

Use in Pregnancy

The safety of use in pregnant women has not been established. Therefore, TOFRANIL* should not be administered to women of childbearing potential, or during pregnancy, unless, in the opinion of the physician, the expected benefit to the patient outweighs the potential risk to the fetus. Withdrawal symptoms including: tremors, dyspnea, lethargy, colic, irritability, hypotonia/ hypertonia, convulsions and respiratory depression have been reported in neonates whose mothers received tricyclic antidepressants during the third trimester of pregnancy. To avoid such symptoms, TOFRANIL* should, if possible, be gradually withdrawn at least 7 weeks before the calculated date of confinement.

Use during Lactation

Since imipramine passes into breast milk, TOFRANIL* should be gradually withdrawn or the infant weaned if the patient is breast-feeding.

Precautions

The possibility of a suicide attempt is inherent in depression. These patients should be carefully supervised during treatment with TOFRANIL* (imipramine hydrochloride) and hospitalization or concomitant electroconvulsive therapy may be required. Prescriptions for TOFRANIL* should be written for the smallest possible quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Psychosis, Mania-Hypomania and other Neuropsychiatric Phenomena

In patients treated with tricyclic antidepressants, activation of latent schizophrenia or aggravation of existing psychotic manifestations in schizophrenic patients may occur. Patients with manic-depressive tendencies may experience hypomanic or manic shifts. Hyperactive or agitated patients may become over-stimulated. A reduction in dose or discontinuation of TOFRANIL* should be considered under these circumstances.

In predisposed and elderly patients, tricyclic antidepressants may, particularly at night, provoke pharmacogenic (delirious) psychoses that disappear within a few days of withdrawing the drug.

Since TOFRANIL* may produce sedation, particularly during the initial phase of therapy, patients should be cautioned about the danger of engaging in activities requiring mental alertness, judgment and physical coordination.

Cardiovascular

Before initiating 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. Regular measurements of blood pressure should be performed in susceptible patients. Postural hypotension may be controlled by reducing the dosage or administering circulatory stimulants.

ECG abnormalities have been observed in patients treated with TOFRANIL*. The most common ECG changes were premature ventricular contractions (PVCs), ST-T wave changes, and abnormalities in intraventricular conduction. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary when treating patients with heart disease, as well as elderly subjects. In these patients cardiac function should be monitored and ECG examinations performed during long-term therapy. Gradual dose titration is also recommended.

Hepatic Changes

Isolated cases of obstructive jaundice have been reported. Caution is indicated in treating patients with known liver disease and periodic monitoring of hepatic function is recommended in such patients.

Hematological Changes

Isolated cases of bone marrow depression with agranulocytosis have been reported. Leukocyte and differential blood cell counts are recommended in patients receiving treatment with TOFRANIL* over prolonged periods, and should be performed for patients who develop fever, an influenzal infection or sore throat. In the event of an allergic skin reaction, TOFRANIL* should be withdrawn.

Withdrawal Symptoms

A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of TOFRANIL*, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of TOFRANIL* have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see Adverse Reactions).

Metabolic Effects

Tricyclic antidepressants have been associated with porphyrinogenicity in susceptible patients.

Renal Function

It is advisable to monitor renal function during long-term therapy with tricyclic antidepressants.

Dental Effects

Lengthy treatment with tricyclic antidepressants can lead to an increased incidence of dental caries.

Lacrimation

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.

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.

Drug Interactions

Patients should be warned that, while taking TOFRANIL*, their responses to alcoholic beverages, other CNS depressants (e.g., barbiturates, benzodiazepines or general anesthetics) or anticholinergic agents (e.g., atropine, antihistamines, biperiden, levodopa) may be exaggerated.

When tricyclic antidepressants are given in combination with anticholinergics or neuroleptics with an anticholinergic action, hyperexcitation states or delirium may occur, as well as attacks of glaucoma.

Tricyclic antidepressants should not be employed in combination with anti-arrhythmic agents of the quinidine type (See Cardiovascular section under Warnings).

Since TOFRANIL* may diminish or abolish the antihypertensive effects of guanethidine, bethanidine, clonidine, reserpine or alpha-methyldopa, patients requiring concomitant treatment for hypertension should be given antihypertensives of a different type (e.g., diuretics, vasodilators, beta-blockers).

TOFRANIL* may potentiate the cardiovascular effects of noradrenaline or adrenaline, amphetamine, as well as nasal drops and local anesthetics containing sympathomimetics (e.g., isoprenaline, ephedrine, phenylephrine).

SSRIs such as fluoxetine, paroxetine, sertraline or citalopram are inhibitors of CYP2D6. Fluvoxamine is a potent inhibitor of CYP1A2 and a moderate inhibitor of CYP2D6. Thus, coadministration of SSRIs and TOFRANIL* may result in increased exposure and accumulation of imipramine and desipramine. Dose adjustments of TOFRANIL* may therefore be necessary.

Co-medication of other serotonergic agents may lead to additive effects on the serotonergic system. Serotonin syndrome can possibly occur when imipramine is administered with serotonergic co-medications such as SSRIs, SNRIs, tricyclic antidepressants or lithium (see Warnings).

Caution should be exercised if TOFRANIL* is administered together with cimetidine or methylphenidate since these drugs have been shown to inhibit the metabolism of several tricyclic antidepressants. Clinically significant increases in plasma levels of TOFRANIL* may occur, necessitating a dosage reduction.

Substances which activate the hepatic mono-oxygenase enzyme system (e.g., barbiturates, carbamazepine, phenytoin, nicotine and oral contraceptives) may lower plasma concentrations of

tricyclic antidepressants and so reduce their antidepressive effects. In addition, TOFRANIL* may increase plasma levels of phenytoin and carbamazepine, therefore, it may be necessary to adjust the dosage of these drugs.

TOFRANIL* should not be administered for a period of at least 14 days after the discontinuation of treatment with MAO-inhibitors due to the potential for severe interactions (see Contraindications). The same caution should also be observed when administering a MAO-inhibitor after previous treatment with TOFRANIL*.

TOFRANIL* should be discontinued prior to elective surgery for as long as clinically feasible, since little is known about the interaction with general anesthetics.

Concomitant treatment with neuroleptic agents (e.g., phenothiazines and butyrophenones) may result in increased plasma concentrations of TOFRANIL*, a lowered convulsion threshold and seizures. Combination with thioridazine may produce severe cardiac arrhythmias. No such effects are known to occur in combination with diazepam, but it might be necessary to lower the dosage of imipramine if administered concomitantly with alprazolam or disulfiram.

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

If administered concomitantly with estrogens, the dose of imipramine should be reduced since steroid hormones inhibit the metabolism of imipramine.

Oral antifungal, terbinafine: Coadministration of TOFRANIL* with terbinafine, a strong inhibitor of CYP2D6, may result in increased exposure and accumulation of imipramine and desipramine. Therefore, dose adjustments of TOFRANIL* may be necessary when coadministered with terbinafine.

Adverse Reactions

If severe neurological or psychiatric reactions occur, TOFRANIL* (imipramine hydrochloride) should be withdrawn.

Elderly patients are particularly susceptible to anticholinergic, psychiatric, neurological and cardiovascular effects.

The following adverse reactions have been reported with imipramine or other tricyclic antidepressants.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports.

Infection and infestations

Very rare: dental caries

Neurological

Very common: tremors.

Common: dizziness, headache, paresthesia (numbness, tingling sensation, symptoms suggestive of peripheral neuropathy), delirium.

Rare: convulsions.

Very rare: tinnitus, incoordination, ataxia, electroencephalogram abnormal, extrapyramidal disorder, myoclonus, speech disorders, asthenia.

Behavioral

Common: somnolence, fatigue, insomnia, confusional states with hallucinations (particularly in geriatric patients and patients suffering from Parkinson's disease), anxiety, agitation, restlessness, nightmares, hypomania, mania, decrease in memory, feeling of unreality, disorientation.

Rare: psychotic disorders.

Very rare: aggression.

Anticholinergic

Very common: dry mouth and rarely associated sublingual adenitis, blurred vision, disturbances of visual accommodation, lacrimation decreased, constipation, hyperhidrosis, hot flushes.

Common: micturition disorders, dilation of the urinary tract.

Very rare: mydriasis, glaucoma, paralytic ileus, urinary retention.

Cardiovascular

Very common: hypotension, particularly orthostatic hypotension with associated vertigo, sinus tachycardia, electrocardiogram abnormalities (including flattening or inversion of T wave, depressed S-T segments).

Common: arrhythmia, disturbances in cardiac conduction (e.g., widening of QRS complex, PQ changes, bundle-branch block), palpitation, syncope.

Very rare: hypertension, congestive heart failure, myocardial infarction, heart block, asystole, stroke, vasospams, QT interval prolongation, ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation, torsades de pointes.

Hematologic

Very rare: agranulocytosis, eosinophilia, leukopenia, purpura and thrombocytopenia may occur as an idiosyncratic response.

Gastrointestinal

Common: nausea, vomiting, anorexia, abdominal cramps, liver function test abnormal.

Rare: diarrhea.

Very rare: bitter taste, stomatitis, epigastric distress, black tongue, dysphagia, increased salivation, hepatitis with or without jaundice, abdominal disorders, tongue ulceration.

Respiratory

Very rare: bronchospasm.

Endocrine

Very common: weight gain.

Common: increased or decreased libido, impotence.

Very rare: gynecomastia in the male, hypertrophy breast and galactorrhea in the female, testicular swelling, elevation or depression of blood sugar levels, weight loss, inappropriate antidiuretic hormone (SIADH) secretion syndrome.

Allergic or toxic

Common: dermatitis allergic, rash, urticaria,

Very rare: petechiae, itching, photosensitization (avoid excessive exposure to sunlight), edema (general or of face and tongue), pyrexia, obstructive jaundice, nasal congestion, alopecia, cross-sensitivity with desipramine, allergic alveolitis (pneumonia) with or without eosinophilia, systemic anaphylactic/anaphylactoid reactions including hypotension, skin hyperpigmentation.

General disorders

Very rare: sudden death

Withdrawal Symptoms

Abrupt cessation of treatment with tricyclic antidepressants after prolonged administration may occasionally produce nausea, vomiting, abdominal pain, diarrhea, insomnia, nervousness, anxiety, headache and malaise. These symptoms are not indicative of addiction.

Overdosage

Symptoms of Overdosage

These may vary in severity depending upon factors such as the amount of drug absorbed, the interval between drug ingestion and the start of treatment and the age of the patient. Accidental ingestion in children should be regarded as serious and potentially fatal.

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.

Symptoms may include drowsiness, stupor, ataxia, vomiting, cyanosis, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements and/or convulsions, serotonin syndrome. Hyperpyrexia, mydriasis, bowel and bladder paralysis, oliguria or anuria and respiratory depression may occur.

Hypotension and initial hypertension may occur. However, the usual finding is increasing hypotension which may eventually lead to shock. Serious cardiovascular disturbances are frequently present, including tachycardia, cardiac arrhythmias (flutter, atriofibrillation, premature ventricular beats and ventricular tachycardia) as well as impaired myocardial conduction, atrioventricular and intraventricular block, ECG abnormalities (such as widened QRS complexes and marked S-T shifts), signs of congestive heart failure and cardiac arrest. Coma may ensue. Isolated cases of QT prolongation, torsade de pointes and death have been reported in overdose.

Treatment of Overdosage

Patients in whom overdosage is suspected should be admitted to hospital without delay. No specific antidote is available and treatment is essentially symptomatic and supportive.

Gastric lavage or aspiration should be performed promptly and is recommended up to 12 hours or even more after the overdose, since the anticholinergic effect of the drug may delay gastric emptying. Administration of activated charcoal may help reduce absorption of the drug. As TOFRANIL* (imipramine hydrochloride) is largely protein bound, forced diuresis, peritoneal dialysis and hemodialysis are unlikely to be of value.

Treatment should be designed to insure maintenance of the vital functions. An open airway should be maintained in comatose patients and assisted ventilation instituted, if necessary, but respiratory stimulants should not be used. Hyperpyrexia should be controlled by external measures, such as ice packs and cooling sponge baths. Acidosis may be treated by cautious administration of sodium bicarbonate. Adequate renal function should be maintained.

ECG monitoring in an intensive care unit is recommended in all patients, particularly in the presence of ECG abnormalities, and should be maintained for several days after the cardiac rhythm has returned to normal. Unexpected deaths attributed to cardiac arrhythmias have been reported several days following an apparent recovery from tricyclic antidepressant overdose. Correction of hypoxia and acidosis, if present, may be beneficial. Correction of metabolic acidosis and low potassium concentrations by means of bicarbonate I.V. and potassium substitution may also be effective for treatment of arrhythmias. If bradyarrhythmia or AV-block occur, consider temporary insertion of a cardiac pacemaker. Because of its effect on cardiac conduction, digitalis should be used only, with caution. If rapid digitalization is required for the treatment of congestive heart failure, special care should be exercised in using the drug.

External stimulation should be minimized to reduce the tendency for convulsions. If convulsions occur, anticonvulsants (preferably intravenous diazepam) should be administered. Barbiturates may intensify respiratory depression and aggravate hypotension and coma. Prompt control of convulsions is essential since they aggravate hypoxia and acidosis and may thereby precipitate cardiac arrhythmias and arrest.

Shock should be treated with supportive measures such as intravenous fluids, plasma expanders, and oxygen. The use of corticosteroids in shock is controversial and may be contraindicated in tricyclic antidepressant overdose. Hypotension usually responds to elevation of the foot of the bed. Pressor agents, (but <u>not</u> epinephrine) should be given cautiously, if indicated. In the event of reduced myocardial function, consider recourse to treatment with dopamine or dobutamine by I.V. drip.

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*.

Deaths by deliberate or accidental overdosage have occurred with this class of drugs. Since the propensity for suicide is high in depressed patients, a suicide attempt by other means may occur during the recovery phase. The possibility of simultaneous ingestion of other drugs should also be considered.

Dosage and Administration

Depression

The dosage of TOFRANIL* (imipramine hydrochloride) should be individualized according to the requirements of each patient. Treatment should be initiated at the lowest recommended dose and increased gradually, noting carefully the clinical response and any evidence of intolerance, particularly when treating elderly and adolescent patients. It should be kept in mind that a lag in therapeutic response usually occurs at the onset of therapy, lasting from several days to a few weeks. Increasing the dosage does not normally shorten this latent period and may increase the incidence of side effects.

Initial dosage

Adults

The recommended initial dosage is 25 mg three times daily. This should be increased gradually as required and tolerated, up to 150 mg/day. Dosages over 200 mg/day are not recommended. In severely ill, hospitalized patients, initially 100 mg/day in divided doses, gradually increasing to 200 mg/day, if required. If no significant response is observed after 3 weeks, dosage may be increased up to 250-300 mg/day.

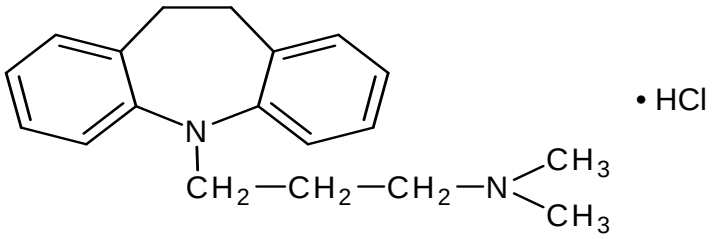
Maintenance Dosage

Dosage during maintenance therapy should be kept at the lowest effective level. Medication should be continued for the expected duration of the depressive episode in order to minimize the possibility of relapse following clinical improvement.

When a maintenance dosage has been established as described above, TOFRANIL* may be administered in a single daily dose at bedtime, provided such a dosage regimen is well tolerated.

Pharmaceutical Information

Drug Substance



Imipramine hydrochloride

Chemical Name:	5-[3-(dimethylamino)-propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride.
Molecular Formula:	$C_{19}H_{24}N_2 \cdot HCl$
Molecular Weight:	316.88
Description:	White to yellowish powder
Solubility:	Readily soluble in water, methanol, ethanol, chloroform; sparingly soluble in acetone and ethyl acetate; virtually insoluble in ether and petroleum ether
Melting Point:	173°C

Composition

PrTOFRANIL*® (imipramine hydrochloride) 25, 50 and 75 mg Tablets

Each tablet strength contains the medicinal ingredient imipramine hydrochloride and the non-medicinal ingredients: cellulose compounds, colloidal silicon dioxide, corn starch, glycerin, iron oxides, lactose, magnesium stearate, polyethylene glycol, povidone, stearic acid, sucrose, talc, titanium dioxide.

Stability and Storage Recommendations

Protect from heat (store between 2 and 30°C) and humidity.

Keep out of reach of children.

Availability of Dosage Forms

PrTOFRANIL*® (imipramine hydrochloride) 25 mg Tablets:

Reddish brown, round, biconvex, sugar-coated tablets. Available in bottles of 100 tablets.

PrTOFRANIL*® (imipramine hydrochloride) 50 mg Tablets:

Reddish brown, round, biconvex, sugar-coated tablets, branded GEIGY on one side and LB on the other side in white. Available in bottles of 100 tablets.

PrTOFRANIL*® (imipramine hydrochloride) 75 mg Tablets:

Reddish brown, round, biconvex, sugar-coated tablets, branded GEIGY on one side and ATA on the other side in white. Available in bottles of 30 tablets.

Pharmacology

The pharmacological properties of imipramine are similar to those of other tricyclic antidepressants. The pharmacological profile of imipramine includes reversal of reserpine and tetrabenazine effects, slight depressant effects on the central nervous system as manifested by behavioral, motor and electrocortical visceral activity, anticholinergic and antihistaminic effects, and potentiation of adrenergic and serotonergic functions.

In the cat and dog, the effect of acetylcholine on blood pressure, the effect of tremorine on salivation (mouse), and the effect of physostigmine on EEG arousal (rabbit), were all reduced. Doses of the order of 10 mg/kg S.C. inhibited the effects of tremorine on salivation, hypothermia, and tremor in the mouse. Imipramine also has an antihistaminic effect.

Imipramine produces changes in animal behavior. In the majority of species, the initial effect is one of sedation. As the dose is increased, autonomic disturbances, ataxia, myoclonia, and finally convulsions develop progressively. The no-effect dose for most species is 10 mg/kg S.C. Spontaneous aggressive behavior is inhibited but not provoked aggression.

Conditioned behavioral responses are enhanced by imipramine with some improvement in performance.

In doses corresponding to those used clinically, little effect is seen on reflexes. Higher doses demonstrate inhibition of spinal and supraspinal reflexes but with little or no effect on muscular contractibility.

The effects exerted by imipramine on the resting and spontaneous EEG depend on the absolute and cumulative doses employed. Slow waves of increased amplitude in the cortical leads follow small doses. With increase of the dose, spikes and dysrhythmia appear, particularly in the tracings from the amygdaloid nucleus and hippocampus.

The pattern of sleep in cats is modified by imipramine (2-4 mg/kg I.M.). The total sleeping time is increased, an increase in slow waves occurs as compared with REM sleep, fewer REM periods are seen and fewer wakeful periods occur.

Imipramine interacts with a number of drugs that act on the central nervous system. Reserpine provokes sedation (rat, mouse), catalepsy (rat), potentiation of anesthesia (mouse), ptosis (rat, rabbit), hypotension (cat), and emesis (pigeon), all of which effects are antagonized by imipramine. In a similar manner imipramine abolishes the sedation, catalepsy, and ptosis in the rat induced by treatment with tetrabenazine. Slight potentiation of barbiturate anesthetics is

evident at higher doses of imipramine. Lower doses are equivocal in their effects. Effective doses reported are 5 mg/kg I.V. (rat), 10-20 mg/kg I.P. (mouse), and 30 mg/kg S.C. (rabbit). The effects of amphetamines are enhanced by imipramine probably by reducing the breakdown of amphetamines and inhibiting reabsorption of catecholamines released by amphetamines. The sensitivity of aggregated mice to amphetamines was increased by imipramine (1 mg/kg S.C.). Imipramine has antagonistic properties to the phenothiazines. In the rat and mouse, doses of the order of 40-50 mg/kg S.C. will antagonize chlorpromazine, perphenazine, and prochlorperazine-induced catalepsy.

Imipramine has analgesic properties as shown in the mouse writhing test. 4-10 mg/kg parenterally or 120 mg/kg orally will inhibit writhing provoked by phenylquinone. 10-25 mg/kg is necessary to inhibit writhing induced by acetic acid.

The cardiovascular effects of imipramine are complex depending upon the test species and test conditions. For most tests imipramine tends to enhance hypertension in the dog and to reduce it in the cat. Effective doses are predominantly in the range of 2-5 mg/kg I.V.

When imipramine was infused into the dog at 0.2 mg/kg/min, the first ECG change was brief tachycardia, followed by bradycardia, occurring at 10 mg/kg. As infusion continued, disturbances of rhythm and conduction developed. The lethal dose in these experiments was 40-50 mg/kg. In other species the basic impairment was similar with disorders of cardiac impulse formation. Imipramine produced a diminution in central sympathetic tone in cats (0.5-1.0 mg/kg I.V.). Ganglionic blockade occurred at 5 mg/kg I.V. Also in cats, the increase in activity caused by stimulation of the amygdaloid nucleus, hypothalamus, and medulla was reduced by imipramine (1 mg/kg I.V.). The inhibitory effects of noradrenaline and of adrenaline on the post-ganglionic action potentials following pre-ganglionic stimulation of the cervical nerves were enhanced by imipramine.

Imipramine has little effect on body temperature.

Imipramine decreases gastric secretion in rats by 50% when given as 18 mg/kg I.P. 5 mg/kg I.M. protected rats against stress ulcers. Small doses of 0.3 mg/kg I.V. increased peristalsis in dogs, higher doses decreased it.

Pharmacokinetics

Even when given in high doses, only low concentrations of imipramine appear in the blood.

In fasting animals, oral doses are rapidly absorbed, maximum concentrations in the organs being reached in 1/2 - 1 hour. In man most of an orally administered dose is absorbed within two hours, blood levels are low being of the order of 0.002 to 0.005 mg% following a single 50 mg dose. Since about three quarters of the radioactivity from labelled imipramine can be detected in the urine and a portion of the dose is excreted in the bile, it may be assumed that imipramine is completely absorbed.

Imipramine is metabolized through the following pathways: Imipramine is primarily N-demethylated to form N-desmethyl imipramine (desipramine) by CYP3A4, CYP2C19, and CYP1A2. Imipramine and desipramine undergo hydroxylation catalyzed by CYP2D6 to form 2-hydroxy imipramine and 2-hydroxy desipramine.

Studies in rats showed that imipramine attains high concentrations in the lungs, liver, and heart muscle but much lower levels in the CNS.

Toxicology

Acute Toxicity

The LD_{50} values for imipramine in mice, rats, and rabbits are tabulated below. Toxicity in these species is manifested by muscular weakness, twitching, stupor, respiratory disorders, ataxia and tonic-clonic convulsions. Rabbits are less tolerant of high oral doses than rats or mice. Mice are less sensitive to high intravenous doses than rats or rabbits, which are equal in this test.

Acute LD_{50} Values for Imipramine

Species	Route	LD_{50} mg/kg
Mouse	I.V.	35
	I.P.	115
	S.C.	189
	P.O.	666
Rat	I.V.	22
	I.P.	79
	S.C.	250
	P.O.	625
Rabbit	I.V.	18
	P.O.	385

Chronic Toxicity

Oral treatment with imipramine in daily doses of 20 mg/kg was well tolerated by rats for one year and by dogs for six months. No histological changes in organ tissues were evident at autopsy.

Oral treatment with imipramine in daily doses of 60-160 mg/kg for one year in rats was associated with fatty changes in the hepatic cells. Dogs tolerated 60 mg/kg orally per day with no macroscopic or microscopic differences as compared with controls.

Teratogenicity

Extensive tests in rats, mice, and rabbits have not revealed any primary embryotoxic effects of imipramine.

Oral doses of 0, 25, 50, 100, 150 mg/kg, and subcutaneous doses of 0, 10, 20, 40 mg/kg, were used in tests in mice covering the 6th - 17th days of pregnancy. No evidence emerged indicating that imipramine caused fetal abnormality.

In the rat oral doses of 0, 5, 10, 20, 40, 60, 80, 100 mg/kg, and subcutaneous doses of 0, 20, 50, 100 mg/kg gave rise to no evidence of significant fetal abnormality, following administration during the first 16 days of pregnancy.

In the rabbit oral doses of 0, 5, 15, 25, 30, 50 mg/kg, and subcutaneous doses of 0, 5, 10, 15, 20, 30, 50 mg/kg, administered during the first 20 days of pregnancy, revealed isolated examples of fetal abnormality but no consistent teratogenic effect.

It is concluded that the safe use of imipramine in pregnancy has not been established by animal tests.

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PART III: CONSUMER INFORMATION

PrTOFRANIL*

(imipramine hydrochloride)

This leaflet is part III of a three-part "Product Monograph" published when TOFRANIL* was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TOFRANIL*. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

TOFRANIL* has been prescribed by your doctor to relieve your symptoms of depression, (feeling sad, a change in appetite or weight, difficulty concentrating or sleeping, feeling tired, headaches, unexplained aches and pains).

What it does:

TOFRANIL*belongs to the group of medicines known as tricyclic antidepressants. TOFRANIL* is thought to work by making it difficult for chemical messages to get carried by specific brain neurons.

When it should not be used:

Do not take TOFRANIL* if you:

- Are allergic to any component of TOFRANIL*, including active and non-active ingredients (see, '**What the nonmedicinal ingredients are" section).**
- Are allergic to other tricyclic antidepressants
- Are currently or have recently taken monoamine oxidase antidepressants (e.g. phenelzine sulphate, moclobemide).
- Have recently had a heart attack or if you suffer from severe heart disease
- have liver or kidney damage or any unspecified disorder of the blood
- have glaucoma

What the medicinal ingredient is:

imipramine hydrochloride

What the nonmedicinal ingredients are:

The tablets also contain the following non-medicinal ingredients: cellulose compounds, colloidal silicon dioxide, corn starch, glycerin, iron oxides, lactose, magnesium stearate, polyethylene glycol, povidone, stearic acid, sucrose, talc, titanium dioxide.

What dosage forms it comes in:

TOFRANIL* is available in tablets of 25 mg, 50 mg or 75 mg. The tablets are reddish brown, round, biconvex, sugar-coated. TOFRANIL* tablets 50mg and 75mg are branded GEIGY on one side and LB on the other side in white letters.

WARNINGS AND PRECAUTIONS

During treatment with these types of medications, it is important that you and your doctor have good ongoing communication about how you are feeling.

Before you use TOFRANIL* talk to your doctor or pharmacist:

- if you are thinking about suicide,
- if you have history of convulsive disorders and other predisposing factors, (seizures)
- if you have irregular heart beat or history of heart problems,
- if you have schizophrenia,
- if you have blood disorder (fever, influenzal infection or sore thoat),
- if you are pregnant, breast-feeding or trying to become pregnant
- if you have difficulty urinating or enlarged prostate,
- if you have overactive thyroid, or take thyroid medication
- if you take alcohol daily or in excess,
- if you have frequent constipation,
- if you have liver disease.

You should also inform your doctor if you are taking certain medicines used to treat depression (including medicines obtained without

prescription, such as St John's Wort). Examples of prescription medicines are: fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine, lithium and other tricyclic antidepressants.

TOFRANIL* coated tablets contain lactose and sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking TOFRANIL*.

Effects on Pregnancy, Newborns and Breast-feeding

The safety of use in pregnant women has not been established. Therefore, TOFRANIL* should not be administered to women of childbearing potential or during pregnancy, unless your doctor thinks that the benefits to you outweigh the risk to the unborn baby. Some newborns whose mothers took TOFRANIL* during the last 3 months of pregnancy experienced withdrawl symptoms including: tremors, shortness of breath, lethargy, colic, irritability, tight or loose muscles, convulsions. To avoid such symptoms, TOFRANIL* should, if possible be withdrawn at least 7 weeks before the baby is due to be born. Your doctor will discuss with you the potential risk of taking TOFRANIL* during pregnancy. As TOFRANIL* passes into breast milk, TOFRANIL* should be gradually withdrawn from the mother or the infant should be weaned.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicine, including herbal and non-prescription medicines.

Since many medicines interact with TOFRANIL*, it may be necessary to adjust the dosage or stop one of the medicines. TOFRANIL* should be stopped prior to elective surgery for as long as possible since little is known about its interaction with general anesthetics. It is especially important for your doctor and pharmacist to know if you drink alcohol every day or are taking any of the following: medicine for blood pressure or heart function, other antidepressants, sedatives, tranquillisers, barbiturates, antiepileptics, a medicine called terbinafine used orally to treat skin, hair or nail infections due to fungus, medicine to prevent blood-clotting (anticoagulants), medicine for asthma or allergies, medicine for Parkinson's disease, thyroid preparations, cimetidine, methylphenidate, birth control pills, estrogens.

PROPER USE OF THIS MEDICATION

Follow your doctor's instructions carefully. Do not exceed the recommended dosage. Your doctor will decide on the most suitable dosage for your particular case.

Usual dose:

The recommended initial dosage is 25 mg three times daily. This should be increased gradually as required and tolerated, up to 150 mg/day. When your doctor has found the best dose for you, TOFRANIL* may be taken once a day at bedtime.

Overdose:

If you have accidentally taken more tablets than your doctor has prescribed, seek immediate emergency medical assistance. Take your medicine to show the doctor. You may require medical attention. You may be at risk for 4-6 days.

Missed Dose:

If you forget to take a dose of TOFRANIL*, take the missed dose as soon as possible and then go back to your normal dosage schedule. If it is almost time for your next dose, skip the missed dose and continue with your normal dosage schedule. If you have any questions about this, ask your doctor. Do not double the dose to make up for the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

TOFRANIL* can have some side effects in some people. These do not normally need medical

attention, and may go away during treatment as your body adjusts to the medicine. Ask your doctor if any side effects continue or are bothersome.

The most common side effects are drowsiness, fatigue, dry mouth, blurred vision, headache, shaking, palpitations, constipation, nausea, vomiting, dizziness, restlessness, hot flushes, sweating, fall in blood pressure associated with dizziness after abrupt standing or sitting up, weight gain. At the start of treatment TOFRANIL* may increase your feelings of anxiety, but this effect generally disappears within two weeks.

Other unwanted effects may also occur, such as dental caries, confusion, disorientation, agitation, sleep disturbances, over-excitedness, irritability, aggressiveness, sexual difficulties, numbness or tingling of the extremities, involuntary movement, decreased production of tears, dilated pupils, ringing in the ears, increase in blood pressure, abdominal disorders, skin sensitivity to sunlight, darker areas of skin, skin rash, hair loss, swelling of the breasts and discharge of milk, swollen ankles,, hands and/or swelling of any other part of the body, fever.

Some patients may experience other side effects not listed above. If you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate emergency medical assistance**
		Only if severe	**In all cases**	
Common	*Allergic reactions* Skin reactions (itching or reddening)			√
	Severe confusion or delirium, hallucinations			√
Rare	Seeing or hearing things that are not really there		√	
	Fits or seizures			√
Very rare	Allergic reactions with/without coughing and difficulty in breathing			√
	Frequent infections with fever and sore throat (due to decreased number of white blood cells)		√	
	Liver disorders Jaundice Severe abdominal pain with constipation, Severe loss of appetite		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical assistance
		Only if severe	In all cases	
	Inability to coordinate movement, loss of balance Difficulty in speaking			√
	Difficulty in passing urine (signs of urinary retention)		√	
	Eye pain		√	
	Sudden contraction of the muscles, muscle stiffness, muscle spasms			√
	Fast or irregular heart beat (racing, pounding)			√

This is not a complete list of side effects. For any unexpected effects while taking TOFRANIL* contact your doctor or pharmacist.

HOW TO STORE IT

Protect from heat (store between 2 and 30^{O}C) and humidity.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:**

    Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice..

MORE INFORMATION

Please consult your doctor or pharmacist with any questions or concerns you may have regarding your individual condition.

This document plus the full product monograph, prepared for health professionals can be found at: http://www.novartis.ca
or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at:
1-800-363-8883

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IMPORTANT: PLEASE READ

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