PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr IMIPRAMINE

Imipramine hydrochloride tablets

Tablets, 10 mg, 25 mg, 50 mg and 75 mg, Oral

USP

Antidepressant

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Date of Initial Authorization:
DEC 31, 1975

Date of Revision:
JUL 26, 2024

Submission Control Number: 284437

RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

IMIPRAMINE (imipramine hydrochloride tablets) is indicated for:

- The relief of symptoms of depressive illness.

As with other tricyclic antidepressants, IMIPRAMINE may precipitate hypomanic episodes in patients with bipolar depression. These drugs are not indicated in mild depressive states and depressive reactions.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 4.2 Recommended Dose and Dosage Adjustment and 7.1.4 Geriatrics.

2 CONTRAINDICATIONS

IMIPRAMINE (imipramine hydrochloride tablets) is contraindicated in:

- Patients who are hypersensitive to imipramine hydrochloride or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with known or suspected hypersensitivity to tricyclic antidepressants (TCA) belonging to the dibenzazepine group.
- In conjunction with, or within 14 days before or after treatment with monoamine oxidase inhibitors (MAOIs) (see 9.1 Serious Drug Interactions). Hypertensive crises, hyperactivity, hyperpyrexia, spasticity, severe convulsions or coma, and death have been reported in patients receiving MAO inhibitors and TCAs (see 4.1 Dosing Considerations; 7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin toxicity/Serotonin syndrome; and 9.1 Serious Drug Interactions).
- During the acute recovery phase following a myocardial infarction and in the presence of acute congestive heart failure. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.
- Patients with narrow angle glaucoma, as the condition may be aggravated due to the atropine-like effects of the drug. See 7 WARNINGS AND PRECAUTIONS, Ophthalmologic, Angle-Closure Glaucoma.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Extreme caution should be used when IMIPRAMINE is given in the following situations:**
  - Cases of QT interval prolongation, cardiac arrhythmia and severe hypotension have been reported. A few instances of unexpected death have also been reported in patients with cardiovascular disorders. Myocardial infarction and stroke have been reported with drugs of this class. Extreme caution is advised in patients with a history of cardiovascular disorders (e.g., significant bradycardia, myocardial infarction, congestive or uncompensated heart failure), conduction abnormalities or patients with risk factors for QT interval prolongation, such as the concomitant use of those concurrently taking QT-prolonging drugs. See 2 CONTRAINDICATIONS; 5 OVERDOSAGE; 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 8.5 Post-Market Adverse Reactions; 8.1 Adverse Reaction Overview, Cardiac disorders; 9.4 Drug-Drug Interactions.
  - Unmasking of Brugada syndrome has been reported with tricyclic antidepressants. IMIPRAMINE should be avoided in patients with Brugada syndrome or those suspected of having Brugada syndrome (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 8.5 Post-Market Adverse Reactions).
  - In patients with a history or urinary retention or prostatic hypertrophy, or in patients with increased intraocular pressure or narrow angle glaucoma, because of the anticholinergic properties of IMIPRAMINE. See 7 WARNINGS AND PRECAUTIONS, General; 7 WARNINGS AND PRECAUTIONS, Ophthalmologic.
  - In patient with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias. See 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism.
  - In patients with a history of a seizure disorder, because IMIPRAMINE has been shown to lower the seizure threshold. See 7 WARNINGS AND PRECAUTIONS, Neurologic.
  - **Clinical Worsening and Suicide Risk:** Increased risk of self-harm, harm to others, suicidal thinking and behavior with antidepressant use. Closely monitor all antidepressant-treated patients for clinical worsening and for emergence of agitation-type and/or suicidal thoughts and behaviors (see 7 WARNINGS AND PRECAUTIONS, Psychiatric).

4 DOSAGE AND ADMINISTRATION

4.1 Dosage Considerations

- **Cardiovascular**

  Prior to initiating treatment with IMIPRAMINE:

- a cardiac evaluation, including blood pressure and electrocardiogram examinations, should be performed, particularly in patients with a history of cardiovascular disorders.
- Electrolyte disturbances such as hypokalemia should be treated.

See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.

Patients with circulatory liability or with cardiovascular disease should receive IMIPRAMINE in low dosage and under careful observation and only when a clear indication for the drug has been established. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.

- **Renal**

  Exercise extreme caution when IMIPRAMINE is used in patients with urinary retention, particularly in the presence of prostatic enlargement. See 7 WARNINGS AND PRECAUTIONS, Renal.

- **Pregnant women**

  IMIPRAMINE should not be used during the first trimester of pregnancy. See 7.1.1 Pregnant Women.

- **Breast-feeding**

  The use of IMIPRAMINE should be avoided during breast-feeding. See 7.1.2 Breast-feeding.

- **Elderly Patients**

  Elderly patients should receive IMIPRAMINE in low dosage and under careful observation and only when a clear indication for IMIPRAMINE has been established. See 7.1.4 Geriatrics.

- **Important interactions**

  When IMIPRAMINE is substituted for a MAOI, at least 14 days should elapse between the treatments. Administration of IMIPRAMINE should then be started cautiously and increased gradually. See 9.1 Serious Drug Interactions, 9.4 Drug-Drug Interactions.

Consider the potential for drug interactions such as monoamine oxidase inhibitors, thyroid medications, QT-prolonging drugs, and CYP450 inhibitors and inducers, prior to and during treatment with IMIPRAMINE (see 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 9 DRUG INTERACTIONS).

4.2 Recommended Dose and Dosage Adjustment

Initial dose

Adult patients: The recommended initial dosage is 25 mg three times/day. This should be increased gradually as required and tolerated, up to 150 mg/day. Dosage over 200 mg/day is not recommended for outpatients. Severely ill or hospitalized patients may require up to 300 mg/day.

Elderly patients: The recommended initial dosage is 30 to 40 mg/day. Increase the dose by 10 mg/day to a maximum of 100 mg/day. See 1.2 Geriatrics; 7.1.4 Geriatrics.

Pediatric patients (<18 years of age): Health Canada has not authorized an indication for pediatric use.

Maintenance

In suitable subjects, the maintenance dose may be administered in a single dose before bedtime. It does not have as much sedative effect as amitriptyline which may be used at bedtime for this effect.

Plasma Levels

Because of the wide variation in the absorption and distribution of tricyclic antidepressants in body fluids, it is difficult to directly correlate plasma levels and therapeutic effect. However, determination of plasma levels may be useful in identifying patients who appear to have toxic effects and may have excessively high levels, or those in whom lack of absorption or non-compliance is suspected. Because of increased intestinal transit time and decreased hepatic metabolism in elderly patients, plasma levels are generally higher for a given oral dose of imipramine hydrochloride tablets than in younger patients.

Elderly patients should be monitored carefully and quantitative serum levels obtained as clinically appropriate. Adjustments in dosage should be made according to the patient's clinical response and not on the basis of plasma levels.

Discontinuation

When discontinuing IMIPRAMINE, the dosage should be tapered gradually over several weeks (see 7 WARNINGS AND PRECAUTIONS, Dependence and Tolerance; 8.5 Post-Market Adverse Reactions.

4.4 Administration

IMIPRAMINE tablets should be swallowed whole with water.

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule.

5 OVERDOSAGE

Deaths by deliberate or accidental overdosage have occurred with this class of drugs. Children have been reported to be more sensitive than adults to an acute overdosage of IMIPRAMINE. An acute overdose in infants or young children must be considered serious and potentially fatal.

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.

Symptoms: High doses may cause temporary confusion, disturbed concentration, transient visual hallucinations, agitation, hyperactive reflexes, muscle rigidity, vomiting, or hyperpyrexia, in addition to anything listed under Adverse Effects. Based on IMIPRAMINE's known pharmacologic actions, overdosage may cause drowsiness, hypothermia, tachycardia, and other arrhythmic abnormalities such as bundle branch block, ECG evidence of impaired conduction and congestive heart failure. Other manifestations may be dilated pupils, convulsions, severe hypotension, stupor, and coma. All patients suspected of an overdose should be admitted to a hospital as soon as possible.

Treatment: No specific antidote is available, and treatment is essentially symptomatic and supportive. Cardiac arrhythmias and CNS involvement pose the greatest threat with tricyclic antidepressant overdosage and may occur suddenly even when initial symptoms appear to be mild. Therefore, patients who may have ingested an overdose of IMIPRAMINE, particularly children, should be hospitalized and kept under close surveillance.

Activated charcoal may be administered to reduce absorption of the drug.

An adequate airway should be established 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.

External stimulation should be minimized to reduce the tendency to convulsions. If convulsions occur, anticonvulsants (preferably i.v. diazepam) should be administered. Barbiturates may intensify respiratory depression, particularly in children, and aggravate hypotension and coma. Paraldehyde may be used in some children to counteract muscular hypertonus and convulsions with less likelihood of causing respiratory depression. If the patient fails to respond rapidly to

anticonvulsants, artificial ventilation should be instituted. Prompt control of convulsions is essential since they aggravate hypoxia and acidosis and may thereby precipitate cardiac arrhythmias and arrest.

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. A patient who has ingested a toxic overdose of a tricyclic antidepressant may remain medically and psychiatrically unstable for several days due to sustained excessive drug levels. Unexpected cardiac deaths have occurred up to 6 days after overdosage with other antidepressants. The QRS interval of the electrocardiogram appears to be a reliable correlate of the severity of overdosage. If the QRS interval exceeds 100 milliseconds any time during the first 24 hours after dosage, cardiac function should be continuously monitored for 5 to 6 days.

Life-threatening cardiac arrhythmias may respond to lidocaine. Quinidine, procainamide and disopyramide generally should be avoided in the management of conduction abnormalities and cardiac arrhythmias since these agents may further depress myocardial conduction and contractility. 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.

Shock should be treated with supportive measures such as intravenous fluids, plasma expanders and oxygen. The use of corticosteroids in treating shock is controversial and may be contraindicated in tricyclic antidepressant overdose. Hypotension usually responds to elevation of the foot of the bed. Pressor agents, such as norepinephrine (but not epinephrine), are rarely indicated and should be given only after careful consideration and under continuous monitoring.

Since it has been reported that physostigmine may cause severe bradycardia, asystole and seizures, its use is not recommended in cases of overdosage with tricyclic antidepressants. The use of phenytoin is also not recommended in cases of overdosage with tricyclic antidepressants.

Peritoneal and hemodialysis are of no value because of low plasma concentrations of the drug. Most of the administered dose is distributed in tissue and not in plasma. When aggressive medical management is inadequate, hemoperfusion, but not hemodialysis, has shown some good results.

For management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 10 mg ,25 mg, 50 mg and 75 mg of imipramine hydrochloride	Carnauba wax, hydroxypropyl methylcellulose, lactose monohydrate (in 25 mg, 50 mg, and 75 mg tablets only), magnesium stearate, microcrystalline cellulose, polyethylene glycol, red ferric oxide, sunset yellow aluminum lake 40%, titanium dioxide, and yellow ferric oxide.

IMIPRAMINE (imipramine hydrochloride) 10 mg tablets: Each light brown, round, biconvex, film-coated tablet, engraved “10” on one side, other side is plain, contains imipramine hydrochloride 10 mg.

IMIPRAMINE (imipramine hydrochloride) 25 mg tablets: Each light brown, round, biconvex, film-coated tablet, engraved “25” on one side, other side is plain, contains imipramine hydrochloride 25 mg.

IMIPRAMINE (imipramine hydrochloride) 50 mg tablets: Each light brown, round, biconvex, film-coated tablet, engraved “50” on one side, other side is plain, contains imipramine hydrochloride 50 mg.

IMIPRAMINE (imipramine hydrochloride) 75 mg tablets: Each light brown, round, biconvex, film-coated tablet, engraved score over “75” on one side, other side plain, contains imipramine hydrochloride 75 mg.

Available in bottles of 100 or 1000 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

- **Dental Effects**

Prolonged treatment with tricyclic antidepressants can lead to an increased incidence in dental caries.

Cardiovascular

IMIPRAMINE is contraindicated in the acute recovery period following myocardial infarction

and in the presence of acute congestive heart failure. See 2 CONTRAINDICATIONS.

Exercise extreme caution when IMIPRAMINE is given to patients with coronary thrombosis, angina pectoris, disorders of cardiac rate or rhythm or conduction.

Patients with circulatory liability or with cardiovascular disease should receive IMIPRAMINE in low dosage and under careful observation and only when a clear indication for IMIPRAMINE has been established. A few instances of unexpected death have occurred in patients with cardiovascular disorders.

Tricyclic antidepressant drugs, including amitriptyline, have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time and severe hypotension, particularly at high doses. Myocardial infarction and stroke have been reported with drugs of this class. See 8.5 Post-Market Adverse Reactions. Cardiac arrhythmias and severe hypotension may also occur at normal doses in patients with pre-existing cardiovascular disease. A few instances of unexpected deaths have been reported in patients with cardiovascular disorders. Therefore, IMIPRAMINE should be used with caution in patients with a history of cardiovascular disease, such as myocardial infarction, congestive heart failure (see 2 CONTRAINDICATIONS) and conduction abnormalities (e.g. AV block grades I to III), or arrhythmias. Close cardiovascular and ECG monitoring should be undertaken in such 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 (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 4.1 Dosing Considerations).

- **QT interval prolongation**

Cases of QT interval prolongation and arrhythmia have been reported during the post-marketing period. Caution is advised in patients with significant bradycardia, uncompensated heart failure, or in patients with other risk factors for QT interval prolongation and torsades de pointe including, but not limited to:

- congenital long QT syndrome
- Age > 65 years
- Female sex
- Concomitant use of other QTc-prolonging medicines (see 9 DRUG INTERACTIONS)

Electrolytes disturbances (e.g., hypokalemia, hyperkalemia, hypomagnesaemia, hypocalcemia). Electrolyte disturbances should be treated prior to the initiation of treatment with IMIPRAMINE.

Concurrently taking QT-prolonging drugs. Electrolyte disturbances (hypokalemia, hyperkalemia, hypomagnesaemia) are also known to increase the proarrythmic risk.

Concomitant use of IMIPRAMINE with medicines that inhibit the metabolism of amitriptyline may also increase the risk for QT interval prolongation and torsades de pointes (see 9.4 Drug-

Drug Interactions).

- **Unmasking of Brugada Syndrome**

There have been post-marketing reports of an association between treatment with tricyclic antidepressants and the unmasking of Brugada syndrome. Brugada syndrome is a disorder characterized by syncope, abnormal ECG findings, and a risk of sudden death. IMIPRAMINE should generally be avoided in patients with Brugada syndrome or those suspected of having Brugada syndrome.

Dependence/Tolerance

- **Withdrawal Symptoms**

Withdrawal symptoms may occur after abrupt cessation of treatment with IMIPRAMINE (see 8.1 Adverse Reaction Overview and 8.5 Post-Market Adverse Reactions). When discontinuing IMIPRAMINE, the dose should be tapered gradually over several weeks to minimize the risk of discontinuation symptoms, and the patient should be closely monitored.

Driving and Operating Machinery

IMIPRAMINE may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. Patients should be advised to avoid such tasks until they know how IMIPRAMINE affects them.

Endocrine and Metabolism

- **Concomitant use with thyroid medications**

Caution is recommended when IMIPRAMINE is administered to hyperthyroid patients or those receiving thyroid medication. Cardiac arrhythmias may develop when tricyclic antidepressants are used concomitantly with thyroid medications (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

- **Hyponatremia/Syndrome of inappropriate antidiuretic hormone secretion**

Hyponatremia and/or syndrome of inappropriate antidiuretic hormone secretion may occur with tricyclic antidepressants (see 8.1 Adverse Reaction Overview). Elderly patients, patients taking diuretics, and patients who are otherwise volume depleted, may be at greater risk for this event.

Gastrointestinal

IMIPRAMINE should be used with caution in patients with pylorus stenosis and paralytic ileus. Tricyclic antidepressants may give rise to paralytic ileus, particularly in elderly and in hospitalized patients. The risk may be increased in patients concurrently taking anticholinergic

drugs. Close supervision and careful adjustment of dosage are required in this situation (see 9.4 Drug-Drug Interactions). Appropriate measures should be taken if constipation occurs.

Genitourinary

IMIPRAMINE should be used with extreme caution in patients with a history of urinary retention and prostatic hypertrophy (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX). Close supervision and careful adjustment of dosage are required when IMIPRAMINE is used with other anticholinergic drugs (see 9.4 Drug-Drug Interactions).

Hematologic

Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

Isolated cases of bone marrow depression, including agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia, have been reported with tricyclic antidepressants (see 8.1 Adverse Reaction Overview).

- **Concomitant Use with Coumarin Drugs**

Tricyclic antidepressants may potentiate the anticoagulant effect of coumarin drugs (e.g., warfarin). Careful monitoring of plasma prothrombin is recommended when IMIPRAMINE is initiated or discontinued in patients concomitantly treated with coumarin drugs.

Hepatic/Biliary/Pancreatic

IMIPRAMINE should be used with caution in patients with hepatic impairment. Periodic monitoring of liver function is recommended in these patients.

Monitoring and Laboratory Tests

- Particularly in patients with a history of cardiovascular disorders, cardiac function and ECG should be periodically monitored during treatment with IMIPRAMINE, including after a dose increase or after initiating treatment with a potentially interacting medicine (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, 9 DRUG INTERACTIONS).
- In patients with a history of blood disorders, periodic monitoring of leukocyte and differential blood cell counts is recommended (see 7 WARNINGS AND PRECAUTIONS, Hematologic).
- In patients with impaired liver function, periodic monitoring of hepatic function is recommended (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Musculoskeletal

Exposure to tricyclic antidepressants may increase the risk of bone fracture. The possibility of fracture should be considered in the care of patients treated with IMIPRAMINE. Elderly patients and patients with important risk factors for bone fractures should be advised of possible adverse events which increase the risk of falls, such as dizziness and orthostatic hypotension.

Neurologic

- **Serotonin toxicity / Serotonin syndrome**

Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with tricyclic antidepressants, including IMIPRAMINE.
Serotonin toxicity is characterized by neuromuscular excitation, autonomic stimulation (e.g., tachycardia, flushing) and altered mental state (e.g., anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus

Neuroleptic malignant syndrome (NMS) has also been reported with IMIPRAMINE, with and without concomitant medications known to cause NMS (see 8.5 Post-Market Adverse Reactions). The clinical manifestations of neuroleptic malignant syndrome often overlap with those of serotonin toxicity, including hyperthermia, hypertonia, altered mental status, and autonomic instability. In contrast to serotonin toxicity, patients with neuroleptic malignant syndrome may present with “lead pipe” muscle rigidity as well as hyporeflexia.

The concomitant use of IMIPRAMINE with monoamine oxidase inhibitors is contraindicated (see 2 CONTRAINDICATIONS). IMIPRAMINE should be used with caution in patients receiving other serotonergic drugs or antipsychotics/neuroleptics. If concomitant treatment with IMIPRAMINE and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. See 2 CONTRAINDICATIONS, 4 DOSAGE AND ADMINISTRATION, and 9 DRUG INTERACTIONS.
Serotonin toxicity and neuroleptic malignant syndrome may result in potentially life-threatening conditions. If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Ophthalmologic

- **Angle-Closure Glaucoma**

IMIPRAMINE is contraindicated in patients with narrow angle glaucoma. As with other antidepressants, IMIPRAMINE can cause mydriasis, which may trigger an angle-closure attack in

a patient with anatomically narrow ocular angles. Health professionals should inform patients to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

Exercise extreme caution when IMIPRAMINE is used in patients with glaucoma.

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.

Peri-Operative Considerations

IMIPRAMINE is contraindicated in the acute recovery period following myocardial infarction (see 2 CONTRAINDICATIONS).

Anesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. IMIPRAMINE should be discontinued several days before elective surgery if possible.

Psychiatric

IMIPRAMINE should be used cautiously in hyperactive or agitated patients, in epileptic patients, or ambulatory, seriously depressed patients with suicidal tendencies.

The possibility of suicide in depressed patients remains during treatment and until significant remission occurs, this type of patient should not have access to large quantities of the drug.

- **Clinical Worsening and Suicide Risk**

Pediatrics - Placebo-Controlled Clinical Trial Data: Analyses of placebo-controlled clinical trial safety databases from SSRIs and newer antidepressants suggest that the use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo. IMIPRAMINE is not indicated for use in pediatric patients (see 1.1 Pediatrics).

Adults and Pediatrics: Patients with depression may experience worsening of their depression and/or emergence of suicidal ideation and behaviour (suicidality) or unusual changes in behaviour, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide.

Antidepressants may however have a role in inducing worsening of depression and emergence of suicidality in certain patients during the early phases of treatment. To minimize the risk of intentional overdose, prescriptions for IMIPRAMINE should be written for the smallest possible

quantity consistent with good patient management.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for depression as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, such symptoms may represent precursors to emerging suicidality.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, agitation, irritability, unusual changes in behavior, and the other symptoms described above, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Patients, families and caregivers of patients should be alerted about the need to report such symptoms immediately to health professionals

Renal

Exercise extreme caution when IMIPRAMINE is used in patients with urinary retention, particularly in the presence of prostatic enlargement.

Skin

Rare cases of drug reaction with eosinophilia and systemic symptoms (DRESS), a potentially life-threatening adverse reaction, have been reported with the use of tricyclic antidepressants. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. If DRESS is suspected, discontinue IMIPRAMINE immediately.

7.1 Special Populations

7.1.1 Pregnant Women

Exposure to tricyclic antidepressants in mid to late pregnancy may increase the risk for preeclampsia.

When considering treatment with IMIPRAMINE in pregnant women or women who may become pregnant, the potential benefits must be weighed against the possible hazards to mother and child. IMIPRAMINE is not recommended during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

Withdrawal symptoms including tremors, lethargy, colic, irritability, hypotonia/hypertonia, convulsions, poor suckling reflex, irregular breathing, respiratory depression, and possibly anticholinergic symptoms (urinary retention and constipation) have been reported in neonates whose mother received tricyclic antidepressants during the third trimester of pregnancy.

7.1.2 Breast-feeding

The use of IMIPRAMINE should be avoided during breast-feeding.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Geriatric patients are particularly sensitive to the anticholinergic side effects of tricyclic antidepressants including IMIPRAMINE. Peripheral anticholinergic effects include tachycardia, urinary retention, constipation, dry mouth, blurred vision, and exacerbation of narrow angle glaucoma. Central nervous system anticholinergic effects include cognitive impairment, psychomotor slowing, confusion, sedation, and delirium. Elderly patients taking imipramine hydrochloride may be at increased risk for falls.

Elderly patients should receive IMIPRAMINE in low dosage and under careful observation and only when a clear indication for IMIPRAMINE has been established. See 4.2 Recommended Dose and Dosage Adjustment.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Clinical trial data on which the indication was originally authorized is not available.

Although the listing which follows includes a few adverse reactions which have not been reported with this specific drug, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when IMIPRAMINE is administered.

Blood and lymphatic system disorders: bone marrow depression including agranulocytosis; eosinophilia; purpura; thrombocytopenia.

Cardiac disorders: tachycardia, palpitation, myocardial infarction, arrhythmias, heart block.

Endocrine disorders: gynecomastia in the male.

Eye disorders: blurred vision, disturbances of accommodation, mydriasis.

Gastrointestinal disorders: dry mouth, and rarely, associated sublingual adenitis, constipation, paralytic ileus, nausea and vomiting, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black tongue, parotid swelling.

General disorders and administration site conditions: edema (general or of face and tongue), drug fever, weakness, fatigue, headache.

Hepatobiliary disorders: jaundice (simulating obstructive), altered liver function.

Immune system disorders: cross-sensitivity with desipramine.

Injury, poisoning and procedural complications: falls.

Investigations: alterations in EEG patterns, elevation or depression of blood sugar levels, weight gain or loss.

Metabolism and nutrition disorders: anorexia.

Nervous system disorders: numbness, tingling, paresthesia of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, drowsiness, dizziness, tinnitus.

Psychiatric disorders: confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Renal and urinary disorders: urinary retention, delayed micturition, dilation of the urinary tract, urinary frequency.

Reproductive system and breast disorders: breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling.

Skin and subcutaneous tissue disorders: skin rash, petechiae, urticaria, itching, photosensitivity (avoid excessive exposure to sunlight), perspiration, flushing.

Vascular disorders: hypotension, hypertension, stroke.

Withdrawal symptoms: though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache and malaise.

8.5 Post-Market Adverse Reactions

Cardiac disorders: Brugada syndrome

Skin and subcutaneous tissue disorders: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Withdrawal Symptoms: Rare instances have been reported of mania or hypomania occurring within 2 to 7 days following cessation of chronic therapy with tricyclic antidepressants. These symptoms are not indicative of addiction.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• Co-Administration with Monoamine Oxidase inhibitors (MAOIs). See 2 CONTRAINDICATIONS, 9.4 Drug-Drug Interactions. • Thyroid Medication: See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism.

9.3 Drug-Behavioural Interactions

Patients should be warned that, while taking IMIPRAMINE their responses to alcoholic beverages may be exaggerated.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Adrenergic neuron blockers	T	↓Antihypertensive effects	Tricyclic antidepressants may counteract the antihypertensive effects of centrally acting antihypertensives such as guanethidine, betanidine, reserpine, clonidine and methyldopa. It is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants. There is an increased risk of hypertension on clonidine withdrawal.
Anticholinergic drugs	T	↑ Anticholinergic effects	Tricyclic antidepressants may potentiate the effects of anticholinergic drugs on the eye, central nervous system, bowel and bladder and close supervision and careful adjustment of dosage are required. Paralytic ileus, urinary retention or acute glaucoma may occur in patients taking tricyclic antidepressants in combination with anticholinergic-type drugs, particularly in elderly or hospitalized patients.
	CT	Hyperpyrexia	Hyperpyrexia has been reported when tricyclic antidepressants are administered with anticholinergic agents, particularly during hot weather.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Baclofen	T	↑muscle relaxant effect	Tricyclic antidepressants, such as amitriptyline, may enhance the muscle relaxant effect of baclofen.
Cimetidine	T	↑ imipramine	Caution should be exercised if imipramine is administered together with cimetidine since cimetidine has been shown to inhibit the metabolism of several tricyclic antidepressants and clinically significant increases in plasma levels of imipramine may occur.
CNS depressants or anticholinergic agents	T	↑ CNS depressants or anticholinergic agents	Patients should be warned that, while taking imipramine their responses to other CNS depressants or anticholinergic agents may be exaggerated.
Coumarin drugs (e.g., warfarin)	T	↑Anticoagulant effect	Tricyclic antidepressants may potentiate the anticoagulant effect of coumarin drugs. Careful monitoring of plasma prothrombin is recommended.
Iobenguane	T	Inaccurate imaging results	Antidepressants that inhibit the function of the norepinephrine transporter, such as imipramine, have the potential to interfere with iobenguane imaging results. Before iobenguane administration, drugs known or expected to interfere with iobenguane uptake should be discontinued, as clinically tolerated.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Methylphenidate	T	↑ activity and plasma concentrations of tricyclic antidepressants	
Monoamine Oxidase inhibitors (MAOIs)	T	Hyperpyretic crises, severe convulsive seizures and death may occur. The potentiation of adverse effects can be serious, or even fatal.	The concomitant use of IMIPRAMINE with MAOI is contraindicated. See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Neurologic. When IMIPRAMINE is substituted for a MAOI, at least 14 days should elapse between the treatments. Administration of IMIPRAMINE should then be started cautiously and increased gradually.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Neuroleptics (e.g., phenothiazines [fluphenazine, thioridazine[a]], butyrophenones [haloperidol])	T	↑ Seizures	Tricyclic antidepressants and neuroleptics mutually inhibit the metabolism of each other. This may result in increased tricyclic antidepressant and neuroleptic plasma level, a lowered convulsion threshold, and seizures. It may be necessary to adjust the dosage of these drugs.
		↑ risk of cardiac side effects	Combination with thioridazine may also cause cardiac arrhythmias. Co-administration of imipramine and thioridazine should be avoided.
	CT	Hyperpyrexia	Hyperpyrexia has been reported when tricyclic antidepressants are administered with neuroleptic drugs, particularly during hot weather.
Nitrates (e.g., nitroglycerin)	T	Severe hypotension	Nitrates should be used with caution in combination with tricyclic antidepressants, as it may lead to an augmentation of the hypotensive effect of nitrates. Clinical monitoring is recommended, and dose adjustment may be required.
		↓ Sublingual nitrates	Because of their anticholinergic properties, tricyclic antidepressants can cause dry mouth, which may decrease the absorption of sublingual nitrates.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Norepinephrine or epinephrine	T	↑ cardiovascular effects of norepinephrine or epinephrine	
Opioids (e.g., buprenorphine, methadone, tramadol)	T	↑ Risk for serotonin toxicity, urinary retention, and constipation ↑ Risk for seizures and opioid toxicity with concomitant use of tramadol.	Concomitant use of tricyclic antidepressants, and opioids, such as buprenorphine, methadone and tramadol, may increase the risk of serotonin toxicity, a potentially life-threatening condition. Concomitant use with opioids may also increase the risk for urinary retention and constipation. Concomitant use of tricyclic antidepressants and tramadol also increases the risk for seizures. In addition, this combination can inhibit the metabolism of tramadol to the active metabolite and thereby increasing tramadol concentrations, potentially causing opioid toxicity.
Pitolisant	T	↓effectiveness of pitolisant	Pitolisant increases the level of histamine in the brain. Concomitant use of tricyclic antidepressants with H1 receptor antagonist properties, should be avoided.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Sympathomimetic drugs	T	↑Cardiovascular effects	Tricyclic antidepressants may potentiate the cardiovascular effects of sympathomimetic drugs. Close supervision and careful adjustment of dosage are required when imipramine is administered with sympathomimetic drugs, including epinephrine combined with local anesthetics.
Valproic acid	T	↑Seizures	Concomitant use with tricyclic antidepressants may lower the seizure threshold. Dosage adjustment for valproic acid may be necessary to control seizures.

Legend: T = Theoretical, Case Study; CT

Cytochrome P450 inhibitors: Certain drugs that inhibit the activity of CYP2D6 make normal metabolizers resemble poor metabolizers. A given dose of tricyclic antidepressant may become abruptly toxic when a drug that inhibits CYP2D6 is introduced as concomitant therapy.

The drugs that inhibit CYP2D6 include some that are not metabolized by the enzyme such as cimetidine, quinidine, bupropion, duloxetine, fluoxetine, paroxetine and terbinafine, and many that are substrates for CYP2D6 such as many other antidepressants, phenothiazines (see Table 2 above), and the Type 1C antiarrhythmics propafenone and flecainide.

Cimetidine (which is also a CYP1A2 and CYP3A4 inhibitor) has been reported to reduce hepatic metabolism of certain tricyclic antidepressants, thereby delaying elimination and increasing steady-state concentrations of these drugs. Clinically significant effects have been reported with the tricyclic antidepressants when used concomitantly with cimetidine. Increases in plasma levels of tricyclic antidepressants, and in the frequency and severity of side effects, particularly anticholinergic, have been reported when cimetidine was added to the drug regimen.

Antifungals such as fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor) and terbinafine have also been observed to increase serum levels tricyclic antidepressants, and accompanying toxicity. Syncope and torsade de pointes have occurred.

Cytochrome P450 inducers: Oral contraceptives, rifampicin, phenytoin, barbiturates, and carbamazepine may increase the metabolism of tricyclic antidepressants, resulting in lowered

plasma levels of tricyclic antidepressants and reduced antidepressant response. In addition, imipramine may increase plasma levels of carbamazepine and phenytoin. Dosage adjustment of these drugs may be necessary.

QT-prolonging drugs

Concomitant use of drugs that prolong the QT interval with tricyclic antidepressants such as IMIPRAMINE may increase the likelihood of ventricular arrhythmias.

Drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide);
- Class III antiarrhythmics (e.g., amiodarone);
- Class 1C antiarrhythmics (e.g., flecainide, propafenone);
- antipsychotics (e.g., pimozide, haloperidol);
- antidepressants (e.g., fluoxetine, tricyclic/tetracyclic antidepressants);
- opioids (e.g., methadone);
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, tacrolimus);
- quinolone antibiotics (e.g., ciprofloxacin);
- antimalarials (e.g., quinine, chloroquine);
- azole antifungals (e.g., ketoconazole);
- domperidone;
- 5-HT3 receptor antagonists (e.g., ondansetron);
- tyrosine kinase inhibitors (e.g., sunitinib);
- histone deacetylase inhibitors (e.g., vorinostat);
- beta-2 adrenoceptor agonists (e.g., salmeterol).

The above list of potentially interacting drugs is not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QT/QTc interval as well as for older drugs for which these effects have recently been established.

Serotonergic agents

While selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit CYP2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs as well as in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Co-administration of IMIPRAMINE with serotonergic agents such as SSRIs, SNRIs, lithium, ozanimod, opioids and triptans may lead to additive effects on the serotonergic system and serotonin toxicity may occur (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

9.5 Drug-Food Interactions

Interactions with food have not been established. Grapefruit juice, a CYP3A4 inhibitor, may increase plasma levels of IMIPRAMINE and accompanying toxicity.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's wort, an inducer of CYP3A4, may increase the metabolism of tricyclic antidepressants, resulting in lowered plasma levels of tricyclic antidepressants and reduced antidepressant response.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The mechanism of antidepressant action of imipramine is not clear although it has been shown to block the reuptake of various neurotransmitters at the neuronal membrane. As a result, the actions of norepinephrine and serotonin may be potentiated. Imipramine has strong anticholinergic actions as well. Imipramine is not an MAO inhibitor.

10.3 Pharmacokinetics

Absorption:

Imipramine is absorbed after oral administration with peak plasma levels occurring within 1 hour to 2 hours.

Distribution:

The half-life of imipramine ranges from 8 hours to 16 hours.

Metabolism:

Imipramine is extensively metabolised by the liver. One metabolite, desipramine, is active.

Imipramine undergoes first-pass metabolism in the liver when administered orally.

Enterohepatic circulation and secretion of the drugs and their metabolites into gastric juice may occur.

Elimination

The metabolites are excreted primarily by the kidney.

Special Populations and Conditions

There is no relevant pharmacokinetic data available for special populations. The data on which the indication was originally authorized is not available.

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature (15°C-30°C).

Keep out of reach and sight of children.

IMIPRAMINE should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: imipramine hydrochloride.

Chemical name:

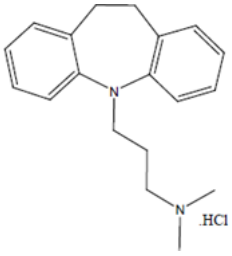
a) 10,11-Dihydro-N,N-dimethyl-5H-dibenz[b,f]azepine-5-propanamine Hydrochloride

b) 5-(3-dimethylaminopropyl)-10,11-dihydro-5H-dibenz[b,f]azepine Hydrochloride

c) N-(γ-dimethylaminopropyl)Iminodibenzyl Hydrochloride

Molecular formula and molecular mass: $C_{19}H_{24}ClN_2$ and 316.88 g/mol

Structural formula:



Physicochemical properties:

Description	White crystalline powder, slightly hygroscopic
Solubility	Soluble in water, Soluble in DMF and DMSO.
Stability	Stable, air sensitive, hygroscopic material.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether imipramine hydrochloride tablets affects fertility in males or females.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **IMIPRAMINE**

Imipramine hydrochloride tablets

Read this carefully before you start taking **IMIPRAMINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **IMIPRAMINE**.

Serious Warnings and Precautions

To help avoid side effects and ensure proper use, before you take IMIPRAMINE, talk to your healthcare professional if you:

- Are taking any other medication that may cause heart problems or affect your heart rhythm.
- Have electrolytes levels that are either too low or too high such as a low level of potassium, calcium or magnesium, or a high level of potassium in your blood. Your healthcare professional will need to treat this before you start taking IMIPRAMINE.
- Have a history of heart problems such as
    - changes in heart rhythm,
    - a slow heartbeat (bradycardia),
    - heart disease, including a condition called heart failure (a condition where your heart cannot pump the blood in your body as well as it should)

A heart problem called “prolonged QT interval” (which is shown on your electrocardiogram, ECG) and problems with the heart rhythm (rapid or irregular heartbeat) have been reported in people taking IMIPRAMINE.

IMIPRAMINE may also reveal a hidden heart problem you did not know you had, a problem called “Brugada Syndrome”. Before you start taking IMIPRAMINE, tell your healthcare professional if you have unexplained fainting or a family history of “Brugada Syndrome” or unexplained sudden death before 45 years of age, as this could indicate you may have “Brugada Syndrome”. You should not take IMIPRAMINE if you have or are suspected to have “Brugada Syndrome”.

These problems can be serious and cause sudden death. Get immediate medical help if you experience dizziness, fainting, a rapid heartbeat or heart palpitations while taking IMIPRAMINE.

- have a history of trouble emptying your bladder (urinary retention), an enlarged prostate gland, increased pressure in the eye or glaucoma as IMIPRAMINE can make these conditions worse.
- have thyroid problems or are taking thyroid medication. Heart rhythm problems may develop when IMIPRAMINE is taken with thyroid medicines.
- have a history of seizures or fits. IMIPRAMINE can make you more likely to have seizures or fits

New or worsened emotional or behavioural problems:

- When you first start taking IMIPRAMINE or when your dose is adjusted, you may feel worse instead of better. You may feel new or worsened feelings of agitation, hostility, anxiety, or impulsivity.
- During your treatment with IMIPRAMINE, it is important that you and your healthcare professional talk regularly about how you are feeling. They will closely monitor you for signs of new or worsened emotions or behaviours while you are taking IMIPRAMINE.
- You may find it helpful to tell a relative or close friend that you are depressed. Ask them to read this leaflet. You might ask them to tell you if they:
    - think your depression is getting worse, or
    - are worried about changes in your behaviour.
- If your depression worsens or you experience changes in your behaviour, tell your healthcare professional right away. Do not stop taking your medicine as it takes time for IMIPRAMINE to work.

Self-harm or suicide:

- Antidepressants, such as IMIPRAMINE, may increase the risk of suicidal thoughts and actions.

- **If you have thoughts of harming or killing yourself at any time, tell your healthcare professional or go to a hospital right away.** Close observation by a healthcare professional is necessary in this situation.

What is IMIPRAMINE used for?

IMIPRAMINE is used to relieve the symptoms of depression (feeling sad, a change in appetite or weight, difficulty concentrating or sleeping, feeling tired, headaches, unexplained aches and pain).

How does IMIPRAMINE work?

IMIPRAMINE is an antidepressant drug that belongs to a group of medicines called tricyclic antidepressant drugs. It is not known exactly how IMIPRAMINE works. It is thought to increase the concentration of certain chemicals in the brain which can help with the symptoms of depression.

What are the ingredients in IMIPRAMINE?

Medicinal ingredients: imipramine hydrochloride.

Non-medicinal ingredients: carnauba wax, hydroxypropyl methylcellulose, lactose monohydrate (in only the 25 mg, 50 mg, and 75 mg tablets), magnesium stearate, microcrystalline cellulose, polyethylene glycol, red ferric oxide, sunset yellow aluminum lake 40%, titanium dioxide, and yellow ferric oxide.

IMIPRAMINE comes in the following dosage forms:

Tablets: 10 mg, 25 mg, 50 mg, and 75 mg.

Do not use IMIPRAMINE if:

- you are allergic to imipramine hydrochloride, or any of the ingredients in IMIPRAMINE.
- you are allergic to tricyclic antidepressants that belong to the dibenzazepine group. Talk to your healthcare professional if you are not sure.
- you are taking or have taken monoamine oxidase inhibitors (MAOIs) within the last 14 days.
- you have recently had a heart attack.
- you are in heart failure.
- you have glaucoma (increased eye pressure).
- you have liver disease.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take IMIPRAMINE. Talk about any health conditions or problems you may have, including if you:

- have liver problems.
- have dental problems.
- have heart problems including:
  - blood clots that form in the blood vessels or arteries of the heart,
  - angina,
  - heart failure,
  - disorders affecting heart rate, rhythm or conduction and

    - heart or blood vessel disease.
- wear contact lenses.
- have trouble urinating.
- have an enlarged prostate.
- have thoughts of harming or killing yourself.
- have bipolar depression.
- have pylorus stenosis (narrowing of the gastric outlet) and paralytic ileus (blocked intestine).
- suffer from epilepsy or seizures.
- are pregnant, think you might be pregnant or planning to become pregnant. IMIPRAMINE should not be used during the first trimester of pregnancy.
- are breastfeeding or are planning to breastfeed.
- are taking warfarin or similar medicines, used to thin the blood.
- are taking other anticholinergic medicines (certain medicines used to treat asthma, chronic obstructive pulmonary disease, stomach and gut problems, and Parkinson's disease).
- have been told you have enzymes that do not work well (such as "CYP2D6 poor metabolizer" or "CYP2C19 poor metabolizer").
- had a recent bone fracture or were told you have osteoporosis or risk factors for osteoporosis.
- are 65 years of age or older.
- you have one of the following rare hereditary diseases:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

  Because lactose is a non-medicinal ingredient in IMIPRAMINE.

Other warnings you should know about:

Angle-closure Glaucoma: IMIPRAMINE can cause an acute attack of glaucoma. Having your eyes examined before you take IMIPRAMINE could help identify if you are at risk of having angle-closure glaucoma. Seek immediate medical attention if you experience:

- eye pain.
- changes in vision.
- swelling or redness in or around the eye.

Bone Fracture: Taking IMIPRAMINE may increase your risk of breaking a bone if you are elderly, have osteoporosis, or have other major risk factors for breaking a bone. You should take extra care to avoid falls, especially if you get dizzy or have low blood pressure.

Breastfeeding: Tell your healthcare professional if you are breastfeeding or planning to breastfeed. IMIPRAMINE is released into breast milk. It is not known if this is safe for your baby. You and your healthcare professional should decide if you should breastfeed or take

IMIPRAMINE. You should not do both.

Cavities: Long term use of IMIPRAMINE can cause dental cavities.

Laboratory Tests: Tell your healthcare professional if you develop a fever and sore throat while taking IMIPRAMINE. Your healthcare professional will do blood tests. These tests will monitor your white blood cell count.

Pregnancy: Before taking IMIPRAMINE, tell your healthcare professional if you are pregnant, think you might be pregnant or are planning to become pregnant. You should not take IMIPRAMINE if you are pregnant unless you and your healthcare professional have discussed the risks and decided that you should. Tell your healthcare professional right away if you become pregnant while taking IMIPRAMINE. Babies born to mothers that took medicines similar to IMIPRAMINE while they were pregnant have experienced withdrawal symptoms after birth. Get immediate medical help for your baby if you took IMIPRAMINE while you were pregnant, and they have any of the following symptoms:

- breathing problems, bluish skin
- seizures or fits
- body temperature changes
- stiff or floppy muscles
- jitteriness, irritability, lethargy
- drowsiness
- constant crying

Serotonin toxicity (also known as Serotonin syndrome) or Neuroleptic malignant syndrome (NMS): IMIPRAMINE can cause Serotonin toxicity or neuroleptic malignant syndrome, rare but potentially life-threatening conditions. They can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin toxicity or neuroleptic malignant syndrome if you take IMIPRAMINE with certain medications used to treat depression, migraine or other mental health problems such as schizophrenia.

Symptoms of serotonin toxicity or neuroleptic malignant syndrome include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Serious skin reactions: Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which can be serious or life-threatening, have been reported with IMIPRAMINE. Get immediate medical help if you experience:

- fever
- severe rash
- peeling skin
- swelling of the face
- swollen lymph glands
- flu-like feeling
- yellow skin or eyes
- shortness of breath
- swelling of the legs
- dry cough
- chest pain or discomfort
- feeling thirsty
- urinating less often, less urine or dark urine

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Driving and Using Machines: IMIPRAMINE can affect your ability to drive and operate machinery. Do not drive or operate machinery until you know how IMIPRAMINE affects you.

Surgery: If you have a planned surgery, talk to your healthcare professional as soon as possible. They may ask you to stop taking IMIPRAMINE.

Withdrawal symptoms: Do NOT stop taking IMIPRAMINE without talking to your healthcare professional. You may need to lower your dose gradually and careful monitoring by your healthcare professional is required. Stopping IMIPRAMINE suddenly may cause withdrawal symptoms including restlessness, nausea, headache, malaise (general discomfort), sleep disturbance, irritability and changes in behavior.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

Serious Drug Interactions
Do not take IMIPRAMINE if you are taking a monoamine oxidase inhibitor (MAOI), or if you have taken one in the last 14 days as this can cause serious side effects. Taking IMIPRAMINE and thyroid medication can cause heart rhythm problems.

The following may interact with IMIPRAMINE:

- alcohol beverages.

- medicines such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine which may be found in cough and cold medication and anesthetics used in surgery.
- other medicines used to treat depression such as other tricyclic antidepressants such as imipramine, guanethidine, betanidine, reserpine, clonidine and methyldopa, phenothiazines [fluphenazine, thioridazinea], butyrophenones [haloperidol]).
- anticholinergic agents, used to relieve stomach cramps, spasms and travel sickness.
- drugs that inhibit CYP2D
    - cimetidine used to treat stomach ulcers.
    - quinidine, used to treat certain type of irregular heartbeats.
    - bupropion, used to treat depression or for smoking cessation.
    - duloxetine, used to manage depression and anxiety, fibromyalgia, diabetic neuropathy and chronic musculoskeletal pain.
    - fluoxetine, used for depression, obsessive-compulsive disorder, panic disorder, bulimia.
    - paroxetine, used to treat depression, obsessive-compulsive disorder (OCD), panic disorder, generalized anxiety disorder (GAD), social anxiety disorder (also known as social phobia), premenstrual dysphoric disorder (PMDD), and posttraumatic stress disorder (PTSD).
    - terbinafine, fungus infections of the scalp, body, groin (jock itch), feet (athlete's foot), fingernails, and toenails.
- nitroglycerine, used for relief of chest pain (angina)
- drugs such as cytochrome P450 inducers
    - oral contraceptives
    - rifampicin, used to treat infections.
    - carbamazepine, used to manager and treat epilepsy.
- drugs that prolong the QT interval of the heat (QT-prolonging drugs)
    - quinidine, procainamide, disopyramide, amiodarone, flecainide and propafenone used to treat certain types of irregular and abnormal heartbeats
    - pimozide and haloperidol, used as an antipsychotic.
    - methadone, used as an opiod.
    - erythromycin, clarithromycin, tacrolimus, and ciprofloxacin, used as antibiotics.
    - quinine and chloroquine), used as antimalarials.
    - ketoconazole, used as antifungals.
    - domperidone used to increases the movements or contractions of the stomach and bowel.
    - ondansetron, used to prevent nausea and vomiting.
    - sunitinib and vorinostat, used to treat certain types of cancers.
    - asalmeterol, used to manage and treat asthma and COPD.
- medicines used to treat high blood pressure such as guanethidine.
- norepinephrine used to treat low blood pressure.
- epinephrine used to treat anaphylaxis, cardiac arrest, and severe asthma attacks.
- methylphenidate used to treat attention-deficit/hyperactivity disorder (ADHD).

- anticholinergic drugs such as certain medicines used to treat asthma, chronic obstructive pulmonary disease, Parkinson's disease and stomach and gut problems (stomach cramps, spasms and travel sickness), drugs like atropine and hyoscyamine*.
- cimetidine, used to treat stomach ulcers.
- pitolisant, used to treat excessive daytime sleepiness.
- high blood pressure medications such as calcium-channel blockers (e.g. diltiazem and verapamil), guanethidine*, betanidine*, reserpine*, clonidine and methyldopa.
- medicines used to treat fungal infections such as ketoconazole, itraconazole, fluconazole and terbinafine.
- opioids such as morphine, tramadol, buprenorphine, tramadol, and methadone, used to treat pain and opioid drug dependence.
- warfarin or similar medicines, used to thin the blood.
- baclofen, used to treat muscle spasms.
- nitrates, used to treat angina (chest pain).
- phenytoin, carbamazepine, topiramate, valproic acid, used to treat seizures or fits.
- St. John´s Wort (hypericum perforatum) – a herbal remedy used for depression.
- grapefruit juice.
- pitolisant, used to treat weak or paralyzed muscles or excessive daytime sleepiness (EDS) in patients with narcolepsy.

Talk to your healthcare professional as there might be newly added drugs that may interact with IMIPRAMINE.

How to take IMIPRAMINE:

- Take IMIPRAMINE exactly as your healthcare professional tells you to. Talk to your healthcare professional if you are not sure.
- Swallow the tablets whole with a glass of water.

Usual dose:

Your healthcare professional will determine the dose that is right for you and how often you should take it. Your dose will depend on your age and if you have any heart problems. Based on how you respond to IMIPRAMINE and your tolerability, your healthcare professional may change your dose.

Overdose:

Signs of an overdose may include:

- confusion
- disturbed concentration
- visual hallucinations

- restlessness
- overactive reflexes
- muscle rigidity
- vomiting
- high fever
- drowsiness
- hypothermia
- heart rhythm problems

If you think you, or a person you are caring for, have taken too much IMIPRAMINE, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of IMIPRAMINE, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time to make up for the missed dose.

What are possible side effects from using IMIPRAMINE?

These are not all the possible side effects you may have when taking IMIPRAMINE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- dry mouth
- swelling of salivary glands
- constipation
- diarrhea
- nausea, vomiting
- stomach pain, stomach cramps
- unpleasant taste in the mouth
- sore mouth
- black tongue
- change in appetite
- weight gain or loss
- fever
- weakness
- tiredness
- headache
- falls

- impaired coordination
- shaking
- drowsiness
- dizziness
- dilated pupils
- change in libido
- inability to have or maintain an erection
- swelling of testicles
- problem emptying your bladder
- frequent urination
- itching
- sweating more than usual
- flushing

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Angle-closure Glaucoma: eye pain, changes in vision, and swelling or redness in or around the eye			√
Serotonin toxicity (also known as serotonin syndrome) or Neuroleptic Malignant Syndrome (NMS): a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (> 38°C), or rigid muscles			√
UNKNOWN			
Agranulocytosis (decrease in white blood cells): frequent infection with fever, chills, sore throat			√
Bone marrow depression: easy bruising, bleeding, nose bleeds, bleeding gums, red spots on the skin, fever and chills, rash, extreme fatigue, pale skin and lips			√
Changes in feelings and behaviors:confusion, hallucinations (seeing or hearing things that are not really there), problems with attention, delusions, anxiety, restlessness, excitement, trouble sleeping, nightmares, extremely elevated and excitable mood memory problems		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Drug reaction with eosinophilia and systemic symptoms (DRESS) (serious skin reaction that may affect more than one organ): fever, severe rash, swollen lymph glands, flu-like feeling, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, urinate less often, less urine			√
Edema: unusual swelling of the arms, hands, legs, feet, ankles, face or airway passages		√	
Eosinophilia (increased numbers of certain white blood cells): abdominal pain, rash, weight loss, wheezing		√	
Extrapyramidal reactions: muscle stiffness, body spasms, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when you want, masklike face (appears to lack emotion), tremors, drooling, or dragging feet as you walk, difficultly swallowing, a feeling of restlessness, or inability to remain motionless			√
Hormonal changes: breast enlargement in men, breast enlargement and abnormal milk production in women		√	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		√	
Hypotension (low blood pressure): dizziness, fainting, lightheadedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)	√		
Hyponatremia (low sodium in the blood): lethargy, confusion, muscular twitching, achy, stiff or uncoordinated muscles, seizure, coma		√	
Increased or decreased blood sugar: frequent urination, thirst, hunger, shakiness, sweating and chills, irritability, confusion, dizziness	√		
Jaundice (buildup of bilirubin in the blood): yellowing of the skin and eyes, dark urine, light		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
colored stool, or itching all over your body			
Mania: elevated or irritated mood, decreased need for sleep, racing thoughts, uneasiness		√	
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat			√
Palpitations (fast-beating, fluttering or pounding heart): skipping beats, beating too fast, pounding, fluttering rapidly			√
Paralytic ileus (muscles that move food through the intestines are paralyzed): new or worsening constipation, nausea, vomiting, dehydration, gas, or abdominal pain		√	
Paresthesia (pins and needles): numbness, weakness, tingling, burning; occurs in the arms, hands, legs or feet.		√	
Peripheral neuropathy (damage to the nerves outside the spinal cord and the brain)**:** numbness or tingling sensation in the hands or feet		√	
QT interval prolongation and Brugada Syndrome (serious and potentially life-threatening electrical problems with the heart): dizziness, fainting, fast heartbeat, palpitations, abnormal heart rate, seizures (fits)			√
Seizures (fits): uncontrollable shaking with or without loss of consciousness			√
Skin disorders **Photosensitivity** (sensitivity to sunlight): itchy, dry, red skin when exposed to sunlight **Petechiae:** pinpoint, red or purple round spots that appear on the skin **Urticaria:** skin with red spots which burn, itch or sting		√	
Stroke: sudden numbness or weakness of your			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
arm, leg or face, especially if only on one side of the body; sudden confusion, difficulty speaking or understanding others; sudden difficulty in walking or loss of balance or coordination; suddenly feeling dizzy or sudden severe headache with no known cause			
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness			√
Tinnitus: ringing, buzzing, clicking or hissing in the ears		√	
Withdrawal symptoms: feeling or being sick, stomach discomfort, diarrhea, vomiting, difficulty sleeping, nervousness, anxiety, headache, irritability	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or

- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15°C-30°C).

Keep out of reach and sight of children.

If you want more information about IMIPRAMINE:

- Talk to your healthcare professional.

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097

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Last Revised: JUL 26, 2024