IMIPRAMINE HYDROCHLORIDE- imipramine hydrochloride tablet, film coated
PD-Rx Pharmaceuticals, Inc.

Imipramine Hydrochloride Tablets, USP
25 mg

Rx only

Prescribing Information

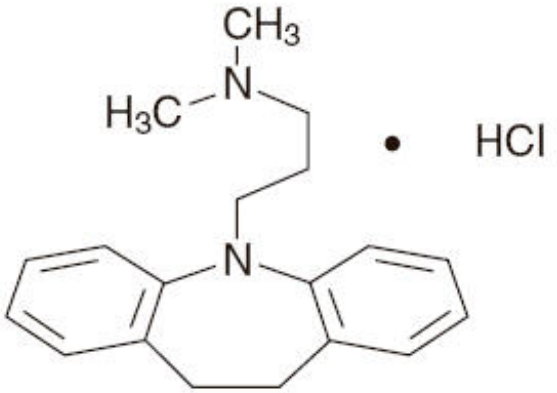
Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents , and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of imipramine hydrochloride or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Imipramine hydrochloride is not approved for use in pediatric patients (seeWARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS, Information for Patients, and PRECAUTIONS: Pediatric Use).

DESCRIPTION

Imipramine hydrochloride tablets USP are supplied in tablet form for oral administration.

Imipramine hydrochloride USP, the original tricyclic antidepressant, are a member of the dibenzazepine group of compounds. It is designated 5-3-(dimethylamino) propyl-10, 11-dihydro-5H dibenz [b,f]- azepine monohydrochloride. Its structural formula is:



C19H24N2 • HCl MW = 316.88

Imipramine hydrochloride USP is a white to off-white, odorless, or practically odorless crystalline powder. It is freely soluble in water and in alcohol, soluble in acetone, and insoluble in ether and in benzene.

*Inactive Ingredients:*Colloidal silicon dioxide, D & C red # 30 and # 40, D & C yellow # 6 and # 10, dicalcium phosphate, F D & C blue # 1 and # 2, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate, sodium starch glycolate, titanium dioxide.

CLINICAL PHARMACOLOGY

The mechanism of action of imipramine hydrochloride, is not definitely known. However, it does not act primarily by stimulation of the central nervous system. The clinical effect is hypothesized as being due to potentiation of adrenergic synapses by blocking uptake of norepinephrine at nerve endings. The mode of action of the drug in controlling childhood enuresis is thought to be apart from its antidepressant effect.

INDICATIONS AND USAGE

Depression -For the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than other depressive states. One to three weeks of treatment may be needed before optimal therapeutic effects are evident.

Childhood Enuresis -May be useful as temporary adjunctive therapy in reducing enuresis in children aged 6 years and older, after possible organic causes have been excluded by appropriate tests. In patients having daytime symptoms of frequency and urgency, examination should include voiding cystourethrography and cystoscopy, as necessary. The effectiveness of treatment may decrease with continued drug administration.

CONTRAINDICATIONS

The concomitant use of monoamine oxidase inhibiting compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur in patients receiving such combinations. The potentiation of adverse effects can be serious, or even fatal. When it

is desired to substitute imipramine hydrochloride tablets, in patients receiving a monoamine oxidase inhibitor, as long an interval should elapse as the clinical situation will allow, with a minimum of 14 days. Initial dosage should be low and increases should be gradual and cautiously prescribed.

The drug is contraindicated during the acute recovery period after a myocardial infarction. Patients with a known hypersensitivity to this compound should not be given the drug. The possibility of cross-sensitivity to other dibenzazepine compounds should be kept in mind.

WARNINGS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, 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. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in **Table 1.**

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases

Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months.However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants ants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes , either increases or decreases .

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 major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications , both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers . Such monitoring s hould include daily observation by families and caregivers . Prescriptions for imipramine hydrochloride should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder -A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric

history, including a family history of suicide, bipolar disorder, and depression. It should be noted that imipramine hydrochloride is not approved for use in treating bipolar depression.

Hyponatremia - Hyponatremia has occurred as a result of treatment with imipramine hydrochloride tablets .In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included syncope, seizure, coma, respiratory arrest, and death.

In patients with symptomatic hyponatremia, discontinue imipramine hydrochloride tablets, and institute appropriate medical intervention. Elderly patients, patients taking diuretics, and those who are volume-depleted may be at greater risk of developing hyponatremia with imipramine hydrochloride tablets.

Angle-closure Glaucoma -The pupillary dilation that occurs following use of many antidepressant drugs including imipramine hydrochloride tablets may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Children -A dose of 2.5 mg/kg/day of imipramine hydrochloride tablets, should not be exceeded in childhood. ECG changes of unknown significance have been reported in pediatric patients with doses twice this amount.

Extreme caution should be used when this drug is given to: patients with cardiovascular disease because of the possibility of conduction defects, arrhythmias, congestive heart failure, myocardial infarction, strokes, and tachycardia. These patients require cardiac surveillance at all dosage levels of the drug;

patients with history of urinary retention, or history of narrow angle glaucoma because of the drug's anticholinergic properties; hyperthyroid patients or those on thyroid medication because of the possibility of cardiovascular toxicity;

patients with a history of seizure disorder because this drug has been shown to lower the seizure threshold;

patients receiving guanethidine, clonidine, or similar agents, since imipramine hydrochloride tablets may block the pharmacologic effects of these drugs;

patients receiving methylphenidate hydrochloride. Since methylphenidate hydrochloride may inhibit the metabolism of imipramine hydrochloride tablets, downward dosage adjustment of imipramine hydrochloride may be required when given concomitantly with methylphenidate hydrochloride.

Imipramine hydrochloride tablets, may enhance the CNS depressant effects of alcohol. Therefore, it should be borne in mind that the dangers inherent in a suicide attempt or accidental overdosage with the drug may be increased for the patient who uses excessive amounts of alcohol *(see* **PRECAUTIONS).**

Since imipramine hydrochloride tablets, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned accordingly.

PRECAUTIONS

General

An ECG recording should be taken prior to the initiation of larger-than-usual doses of imipramine hydrochloride tablets, and at appropriate intervals thereafter until steady state is achieved. (Patients with any evidence of cardiovascular disease require cardiac surveillance at all dosage levels of the drug. *See***WARNINGS.)** Elderly patients and patients with cardiac disease or a prior history of cardiac disease are at special risk of developing the cardiac abnormalities associated with the use of imipramine hydrochloride tablets.

It should be kept in mind that the possibility of suicide in seriously depressed patients is inherent in the illness and may persist until significant remission occurs. Such patients should be carefully supervised during the early phase of treatment with imipramine hydrochloride tablets, and may require hospitalization. Prescriptions should be written for the smallest amount feasible. Hypomanic or manic episodes may occur, particularly in patients with cyclic disorders. Such reactions may necessitate discontinuation of the drug. If needed, imipramine hydrochloride tablets, may be resumed in lower dosage when these episodes are relieved.

Administration of a tranquilizer may be useful in controlling such episodes.

An activation of the psychosis may occasionally be observed in schizophrenic patients and may require reduction of dosage and the addition of a phenothiazine.

Concurrent administration of imipramine hydrochloride tablets, with electroshock therapy may increase the hazards; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Patients taking imipramine hydrochloride should avoid excessive exposure to sunlight since there have been reports of photosensitization.

Both elevation and lowering of blood sugar levels have been reported with imipramine hydrochloride use.

Imipramine hydrochloride should be used with caution in patients with significantly impaired renal or hepatic function.

Patients who develop a fever and a sore throat during therapy with imipramine hydrochloride should have leukocyte and differential blood counts performed. Imipramine hydrochloride should be discontinued if there is evidence of pathological neutrophil depression.

Prior to elective surgery, imipramine hydrochloride should be discontinued for as long as the clinical situation will allow.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with imipramine hydrochloride and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for imipramine hydrochloride. The prescriber or health professional should instruct patients, their families, and their

caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking imipramine hydrochloride.

Patients should be advised that taking imipramine hydrochloride tablets, can cause mild pupillary dilation,which in susceptible individuals,can lead to an episode of angle-closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle-closure glaucoma,when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle-closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible.

Clinical Worsening and Suicide Risk -Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Drug Interactions

Drugs Metabolized by P450 2D6 -The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interaction may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any

of the SSRIs and also 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).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6,

The plasma concentration of imipramine may increase when the drug is given concomitantly with hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine) and decrease by concomitant administration with hepatic enzyme inducers (e.g., barbiturates, phenytoin), and adjustment of the dosage of imipramine may therefore be necessary.

In occasional susceptible patients or in those receiving anticholinergic drugs (including antiparkinsonism agents) in addition, the atropine-like effects may become more pronounced (e.g., paralytic ileus). Close supervision and careful adjustment of dosage is required when imipramine hydrochloride is administered concomitantly with anticholinergic drugs.

Avoid the use of preparations, such as decongestants and local anesthetics, that contain any sympathomimetic amine (e.g., epinephrine, norepinephrine), since it has been reported that tricyclic antidepressants can potentiate the effects of catecholamines.

Caution should be exercised when imipramine hydrochloride is used with agents that lower blood pressure. imipramine hydrochloride may potentiate the effects of CNS depressant drugs.

Patients should be warned that imipramine hydrochloride may enhance the CNS depressant effects of alcohol *(see* **WARNINGS).**

Pregnancy

Animal reproduction studies have yielded inconclusive results *(see also***ANIMAL PHARMACOLOGY & TOXICOLOGY).**

There have been no well-controlled studies conducted with pregnant women to determine the effect of imipramine hydrochloride tablets, on the fetus. However, there have been clinical reports of congenital malformations associated with the use of the drug. Although a causal relationship between these effects and the drug could not be established, the possibility of fetal risk from the maternal ingestion of imipramine hydrochloride tablets, cannot be excluded. Therefore, imipramine hydrochloride tablets, should be used in women who are or might become pregnant only if the clinical condition clearly justifies potential risk to the fetus.

Nursing Mothers

Limited data suggest that imipramine hydrochloride tablets, is likely to be excreted in human breast milk. As a general rule, a woman taking a drug should not nurse since the possibility exists that the drug may be excreted in breast milk and be harmful to the

child.

Pediatric Use

Safety and effectiveness in the pediatric population other than pediatric patients with nocturnal enuresis have not been established *(see* **BOX WARNING** *and* **WARNINGS: Clinical Worsening and Suicide Risk).** Anyone considering the use of imipramine hydrochloride in a child or adolescent must balance the potential risks with the clinical need.

The safety and effectiveness of the drug as temporary adjunctive therapy for nocturnal enuresis in pediatric patients less than 6 years of age has not been established.

The safety of the drug for long-term, chronic use as adjunctive therapy for nocturnal enuresis in pediatric patients 6 years of age or older has not been established; consideration should be given to instituting a drug-free period following an adequate therapeutic trial with a favorable response.

A dose of 2.5 mg/kg/day should not be exceeded in childhood. ECG changes of unknown significance have been reported in pediatric patients with doses twice this amount.

Geriatric Use

In the literature, there were four well-controlled, randomized, double-blind, parallel group comparison clinical studies done with imipramine hydrochloride tablets, in the elderly population. There was a total number of 651 subjects included in these studies. These studies did not provide a comparison to younger subjects. There were no additional adverse experiences identified in the elderly.

Clinical studies of imipramine hydrochloride tablets, in the original application did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Post-marketing clinical experience has not identified differences in responses between the elderly and younger subjects. In general, dose selection for the elderly should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

(See also **DOSAGE AND ADMINISTRATION: Adoles cent and Geriatric Patients.)**

(See also **PRECAUTIONS: General.)**

ADVERSE REACTIONS

Note— 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 hydrochloride tablets, is administered.

Cardiovascular: Orthostatic hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, ECG changes, precipitation of congestive heart failure, stroke.

Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation,

delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

*Neurological:*Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alterations in EEG patterns; tinnitus.

*Anticholinergic:*Dry mouth, and, rarely, associated sublingual adenitis; blurred vision, disturbances of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

*Allergic:*Skin rash, petechiae, urticaria, itching, photosensitization; edema (general or of face and tongue); drug fever; cross-sensitivity with desipramine.

*Hematologic:*Bone marrow depression including agranulocytosis; eosinophilia; purpura; thrombocytopenia.

*Gastrointestinal:*Nausea and vomiting, anorexia, epigastric distress, diarrhea; peculiar taste, stomatitis, abdominal cramps, black tongue.

*Endocrine:*Gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; inappropriate antidiuretic hormone (ADH) secretion syndrome.

*Other:*Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing; urinary frequency; drowsiness, dizziness, weakness and fatigue; headache; parotid swelling; alopecia; proneness to falling, hyponatremia.

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

Note— In enuretic children treated with imipramine hydrochloride tablets, the most common adverse reactions have been nervousness, sleep disorders, tiredness, and mild gastrointestinal disturbances. These usually disappear during continued drug administration or when dosage is decreased. Other reactions which have been reported include constipation, convulsions, anxiety, emotional instability, syncope, and collapse. All of the adverse effects reported with adult use should be considered.

Postmarketing Experience

The following adverse drug reaction has been reported during post-approval use of imipramine. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency.

Eye disorders: angle-closure glaucoma

OVERDOSAGE

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic overdose. Therefore, hospital monitoring is required as soon as possible.

Children have been reported to be more sensitive than adults to an acute overdosage of

imipramine hydrochloride. An acute overdose of any amount in infants or young children, especially, must be considered serious and potentially fatal.

Manifestations

These may vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the interval between drug ingestion and the start of treatment. Critical manifestations of overdose include cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic toxicity.

Other CNS manifestations may include drowsiness, stupor, ataxia, restlessness, agitation, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements.

Cardiac abnormalities may include tachycardia and signs of congestive failure, Respiratory depression, cyanosis, shock, vomiting, hyperpyrexia, mydriasis, and diaphoresis may also be present.

Management

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of 6 hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at anytime during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient. Gastrointestinal Decontamination - All patients suspected of tricyclic overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated. Cardiovascular - A maximal limb-lead QRS duration of ≥ 0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH >7.60 or a pCO_2<20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium, or phenytoin, Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyrarnide, and procainamide). In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic poisoning. CNS - In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration, Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat lifethreatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center. Psychiatric Follow-up - Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery

phase. Psychiatric referral may be appropriate. Pediatric Management - The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSAGE AND ADMINISTRATION

Depression

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients as compared to hospitalized patients who will be under close supervision.Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time, at the lowest dose that will maintain remission.

Usual Adult Dose

Hospitalized Patients -Initially, 100 mg/day in divided doses gradually increased to 200 mg/day as required. If no response after two weeks, increase to 250 to 300 mg/day.

Outpatients -Initially, 75 mg/day increased to 150 mg/day. Dosages over 200 mg/day are not recommended. Maintenance, 50 to 150 mg/day.

Adolescent and Geriatric Patients -Initially, 30 to 40 mg/day; it is generally not necessary to exceed 100 mg/day.

Childhood Enuresis

Initially, an oral dose of 25 mg/day should be tried in children aged 6 and older. Medication should be given one hour before bedtime. If a satisfactory response does not occur within one week, increase the dose to 50 mg nightly in children under 12 years; children over 12 may receive up to 75 mg nightly. A daily dose greater than 75 mg does not enhance efficacy and tends to increase side effects. Evidence suggests that in early night bedwetters, the drug is more effective given earlier and in divided amounts, i.e., 25 mg in midafternoon, repeated at bedtime. Consideration should be given to instituting a drug free period following an adequate therapeutic trial with a favorable response, Dosage should be tapered off gradually rather than abruptly discontinued; this may reduce the tendency to relapse. Children who relapse when the drug is discontinued do not always respond to a subsequent course of treatment.

A dose of 2.5 mg/kg/day should not be exceeded, ECG changes of unknown significance have been reported in pediatric patients with doses twice this amount.

The safety and effectiveness of imipramine hydrochloride tablets, as temporary adjunctive therapy for nocturnal enuresis in children less than 6 years of age has not been established.

HOW SUPPLIED

Imipramine hydrochloride tablets USP, are available as follows:

Tablets 25 mg - round, brown, compressed, film-coated tablet, debossed with "EP" and

"134" on one side and plain on the other side.

Bottles of 100 ..... NDC 72789-492-01

Bottles of 1000 .....NDC 72789-492-95

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Dispense in a well-closed container as defined in the USP, using a child-resistance closure. **Keep this and all Medications out of the reach of children.**

ANIMAL PHARMACOLOGY & TOXICOLOGY

A. Acute: Oral LD_{50} ranges are as follows:

Rat 355 to 682 mg/kg
Dog 100 to 215 mg/kg

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

B. Reproduction/Teratogenic: The overall evaluation may be summed up in the following manner:

Oral: Independent studies in three species (rat, mouse, and rabbit) revealed that when imipramine hydrochloride is administered orally in doses up to approximately 2-1/2 times the maximum human dose in the first 2 species and up to 25 times the maximum human dose in the third species, the drug is essentially free horn teratogenic potential. In the three species studied, only one instance of fetal abnormality occurred (in the rabbit) and in that study there was likewise an abnormality in the control group. However, evidence does exist from the rat studies that some systemic and embryotoxic potential is demonstrable. This is manifested by reduced litter size, a slight increase in the stillborn rate, and a reduction in the mean birth weight.

Manufactured & Distributed by:

Leading Pharma, LLC
Fairfield, NJ USA 07004

Rev. 07 07/25

Medication Guide

Antidepressant Medicines , Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines.

Talk to your, or your family member's , healthcare provider about:

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines ,depression and other serious mental illnesses, and suicidal

thoughts or actions ?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers , and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions.** Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions .
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms , especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood
  Low salt (sodium) levels in the blood. Elderly people may be at greater risk for this. Symptoms may include:
  - headache
  - weakness or feeling unsteady
  - confusion, problems concentrating or thinking or memory problems
- **Visual problems:**eye pain, changes in vision, swelling or redness in or around the eye

Who should not take imipramine hydrochloride tablets?

Do not take imipramine hydrochloride tablets if you:

- take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
  - Do not take an MAOI within 2 weeks of stopping imipramine hydrochloride tablets, unless directed to do so by your physician.

- Do not start imipramine hydrochloride tablets, if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.

What else do I need to know about antidepressant medicines ?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.**Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Visual problems:**Only some people are at risk for these problems.You may want to undergo an eye examination to see if you are at risk and receive preventive treatment if you are.
- **Antidepressants are medicines used to treat depression and other illnesses.**It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects .**Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines .**Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.**Talk to your child's healthcare provider for more information.
- Tell your healthcare provider if you have low sodium levels in your blood during treatment with imipramine hydrochloride tablets.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088 OR LEADING PHARMA, LLC AT 1-844-740-7500.

Manufactured & Distributed by:
Leading Pharma, LLC
Fairfield, NJ USA 07004

Rev. 06 07/25

Imipramine 25mg

IMIPRAMINE HYDROCHLORIDE

imipramine hydrochloride tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72789-492(NDC:69315-134)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
IMIPRAMINE HYDROCHLORIDE (UNII: BKE5Q1J60U) (IMIPRAMINE - UNII:OGG85SX4E4)	IMIPRAMINE HYDROCHLORIDE	25 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
D&C RED NO. 30 (UNII: 2S42T2808B)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	

FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
ANHYDROUS DIBASIC CALCIUM PHOSPHATE (UNII: L11K75P92J)	

Product Characteristics

Color	brown	**Score**	no score
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	EP;134
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72789-492-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	03/10/2025	
2	NDC:72789-492-95	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	03/10/2025	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040903	04/07/2016	

Labeler - PD-Rx Pharmaceuticals, Inc. (156893695)

Registrant - PD-Rx Pharmaceuticals, Inc. (156893695)

Establishment

Name	Address	ID/FEI	Business Operations
PD-Rx Pharmaceuticals, Inc.		156893695	repack(72789-492)

Revised: 3/2026 PD-Rx Pharmaceuticals, Inc.