

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 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 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, Adolescent 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 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, 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

To report SUSPECTED ADVERSE REACTIONS, contact Strides Pharma Inc. at 1-877-244-9825 or go to www.strides.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

Deaths may occur from overdose 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 overdose 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 any time 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 Pco₂ < 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, disopyramide, 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 life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up: Since overdose 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 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:

10 mg are yellow, triangular, film coated tablets debossed "par" on one side and "54" on the other side and supplied in bottles of 100 (NDC 64380-169-01), and 1000 (NDC 64380-169-02) tablets.

25 mg are brown, round, film coated tablets debossed "par" on one side and "55" on the other side and supplied in bottles of 100 (NDC 64380-170-01), and 1000 (NDC 64380-170-02) tablets.

50 mg are green, round, film coated tablets debossed "par" on one side and "56" on the other side and supplied in bottles of 100 (NDC 64380-171-01), and 1000 (NDC 64380-171-02) tablets.

Store between 15° to 25°C (59° to 77°F).

ANIMAL PHARMACOLOGY & TOXICOLOGY

A. Acute: Oral LD₅₀ 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 from 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.

Medication Guide

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

Read the Medication Guide that comes with your 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 preventative 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 FDA at 1-800-FDA-1088.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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MFG. LOCATION: CR Site

ARTWORK DETAIL LABEL

Product	Imipramine HCl Tabs					
Buyer/Country	STRIDES PHARMA INC - US		Component	Outsert with Medication Guide		
Dimension	11" x 12.125"				Pack	--
New Item Code	1051998 (OS054-01-1-31)		Old Item Code	NA		
Colour Shades	 BLACK				No. of Colours	1
Change Control No.	CR-01011				Artwork Version	1.0
Design/Style	Front & Back Side Printing. To be supplied in the FOLDED BOOKLET FORM with pasting & Folded Size: 1.25" x 1.25".					
Substrate	40 GSM Bible Paper.					
Special Instructions	PRINTING CLARITY TO BE CLEAR AND SHARP.					
Autocartonator Requirements	NA					
Caution to the printer: Before processing, please ensure that the ARTWORK received for printing is exactly in line with APPROVED ARTWORK provided to you. In case of any FONTS/DESIGN are Mis-matching with the APPROVED ARTWORK, please inform PDC for further action. DO NOT MAKE ANY CHANGE TO THE ARTWORK WITHOUT WRITTEN INSTRUCTIONS FROM PDC.						

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