PRODUCT MONOGRAPH

[Pr]phl-DESIPRAMINE

(Desipramine Hydrochloride Tablets, USP)

10 mg, 25 mg, 50 mg, 75 mg and 100 mg

Antidepressant

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THERAPEUTIC CLASSIFICATION

Antidepressant

ACTION/CLINICAL PHARMACOLOGY

Desipramine Hydrochloride is a trycyclic antidepressant with actions and uses similar to those of the other tricyclic compounds. It is the principal active metabolite of imipramine and as such, shares many of imipramine's pharmacological effects.

Untoward effects are similar to those produced by imipramine, but its anticholinergic and sedative actions have been found to be less pronounced. Desipramine Hydrochloride has been found to cause ECG changes such as prolongation of the P-R interval and a decreased magnitude with an increased width of the T wave. These ECG changes were seen most frequently in elderly patients as is postural hypotension. Desipramine Hydrochloride has been known to lower the convulsive threshold.

Desipramine HCl has been shown to increase the percentage of Stage 4 sleep (deep sleep) and decrease the percentage of REM sleep. A partial recovery of REM sleep has been seen after 3 to 5 weeks of drug administration. In spite of this recovery, it has been observed that a REM rebound occurred following rapid drug withdrawal, which was experienced as an increase in dreaming.

However, the significance of these effects on the sleep cycle has not yet been clarified.

As an early manifestation of the effects of Desipramine Hydrchloride, an increase in psychomotor activity has been observed; however a significant antidepressant effect should not be expected before the end of the second week. Paths of metabolism of Desipramine Hydrochloride include hydroxylation, N-oxidation, and conjugation with glucuronic acid. Desipramine Hydrochloride is easily absorbed following oral administration is widely distributed throughout the body and is extensively bound to plasma and tissue protein.

A single dose, comparative three-way cross- over bioavailability study was performed using normal human volunteers on DESIPRAMINE Hydrochloride, 25 mg and 75 mg tablets versus Norpramin 75 mg tablets. The Summary of the results is as follows:

Parameter	Test	Geometric Mean Arithmetic Mean (C.V.) Reference		Ratio of Means (%)
	Desipramine HCl 75mg	Desipramine HCl 3 x 25mg	Nopramin 75mg	75mg; 3x25
AUC_T (ng.h/mL)	576.2098 756.3988 (82.5391)	499.3961 676.0936 (91.8881)	560.8634 708.3915 (74.6750)	102.7; 89.04
AUC_T (ng.h/mL)	725.3500 1106.3626(122.5354)	669.8623 1118.4609 (155.1593)	669.5716 940.7941 (94.7839)	103.6; 95.7
C_{max} (ng/mL)	25.5604 27.8931 (44.5166)	24.5245 26.5031 (41.6730)	26.9916 28.7331 (36.3458)	94.7; 90.8
T_{max} (h)	7.0600 (2.1032)	7.5800 (1.4045)	7.2800 (1.4866)	— —
$T_{1/2}$ (h)	23.2240 (20.0118)	24.9756 (25.5337)	20.5899 (14.3723)	— —

For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means with standard deviation in parenthesis.

INDICATIONS AND CLINICAL USE

phl-DESIPRAMINE (desipramine hydrochloride) is indicated in the treatment of endogenous depressive illness, including the depressed phase of manic depressive illness, involutional melancholia and psychotic depression. It may also be indicated in the management of depression of non-psychotic degree such as in selected cases of depressive neurosis.

Patients with normal grief reaction or transient mood disturbances are not expected to benefit from tricyclic antidepressants.

CONTRAINDICATIONS

phl-DESIPRAMINE (desipramine hydrochloride) should not be given in conjunction with, or within 2 weeks of treatment with a monoamine oxidase (MAO) inhibitor drug; hyperpyretic crises, severe onvulsions and death have occurred in patients receiving MAO inhibitors and tricyclic antidepressants.

When desipramine hydrochloride is substituted for an MAO inhibitor, at least 2 weeks should elapse between the treatments; administration of desipramine hydrochloride should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction or in cases of poorly controlled cardiac decompensation. It should not be used in those who have shown prior hypersensitivity to the drug.

Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

Extreme caution should be used when this drug is given in the following situations:

1. In patients with a history of urinary retention or glaucoma,, because of the anticholinergic properties of the drug.

2. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.

3. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes and acute myocardial infarction.

4. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.

Desipramine hydrochloride may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; therefore, the patient should be cautioned accordingly.

Use in pregnancy:

Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be administered to women of child-bearing potential, pregnant patients, or nursing mothers, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have not been conclusive.

Use in children:

Since safety and effectiveness in the pediatric age group have not been established, desipramine hydrochloride is not recommended for use in children.

PRECAUTIONS

It is important that this drug be dispensed in the least possible quantities to depressed out-patients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug, or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures.

Storage of this drug in the home must be supervised responsibly. If serious adverse effects occur, dosage should be reduced or treatment altered.

Desipramine hydrochloride may cause exacerbation of psychosis in schizophrenic patients.

Desipramine hydrochloride therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.

There is limited clinical experience in the concurrent administration of ECT and antidepressant drugs. The possibility of increased risk relative to benefits should be considered, if such a treatment is essential. Both elevation and lowering of blood sugar levels have been reported.

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.

Drug Interactions:

Desipramine Hydrochloride may potentiate the effect of a variety of drugs. When this drug is administered concomitantly with anticholinergic or sympathomimetic drugs, close supervision and careful adjustment of dosage are required. While taking Desipramine Hydrochloride, patients should be warned that their response to alcoholic beverages or other CNS depressants may be exaggerated.

This drug should be discontinued as soon as possible prior to elective surgery because of possible cardiovascular effects.

Hypertensive episodes have been observed during surgery in patients on desipramine hydrochloride.

The contraindications regarding its concomitant use with MAO inhibitors should be noted, as well as the warning regarding patients taking thyroid medication.

Desipramine hydrochloride may decrease the action of other drugs. It is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds by blocking their uptake into adrenergic neurones.

ADVERSE REACTIONS

The more common adverse reactions involve anticholinergic effects such as disturbances of visual accommodation, dry mouth, constipation and mild urinary retention. Also commonly seen are drowsiness, increased perspiration, mild tremors, insomnia, and "lightheadedness".

Adverse reactions of the cardiovascular system may be much more serious, however, these occur less frequently.

Note:
Included in the listing that follows are a few adverse reactions that have not been reported with Desipramine hydrochloride.

However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Desipramine hydrochloride is administered.

Neurologic:

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

Psychiatric:

Confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation; insomnia and nightmare; hypomania, exacerbation of psychosis.

Anticholinergic:

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

Cardiovascular

Hypotension, hypertension, tachycardia, palpitation, arrthythmias, heart block, myocardial infarction, stroke.

Premature ventricular contractions, ventricular tachycardia, ventricular fibrillation, sudden death (with reference to children).

Gastrointestinal:

Anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhoea, stomatitis, black tongue. Hepatitis, jaundice (simulating obstructive), altered liver function, elevated liver function tests, increased pancreatic enzyme.

Allergic:

Skin rash, petechiae, urticaria, itching, photosensitization (excessive exposure to sunlight should be avoided), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Haematologic:

Bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Endocrine:

Gynecomastia in the male, breast enlargement and galactorrhoea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar level.

Painful ejaculation, syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other:

Drowsiness, dizziness, weakness and fatigue, parotid swelling, headache; flushing, perspiration, urinary frequency, alopecia; weight gain or loss; jaundice (simulating obstructive), altered liver function.

Withdrawal Symptoms:

Abrupt cessation of treatment after prolonged therapy may produce nausea, headache, malaise and abdominal cramping. These symptoms are not indicative of addiction.

SYMPTOMS AND TREATMENT OF OVERDOSE

In patients presenting with signs of peripheral atropine effects, agitation and cardiac arrhythmias, the possibility of tricyclic antidepressant overdosage should be entertained.

Because of the extensive tissue and protein binding of these drugs, blood and urine levels may not accurately reflect the extent of intoxication but may be helpful in identifying the presence of the drug.

The following signs and symptoms of overdosage may occur; reflecting CNS intoxication, the patient may exhibit pressure of speech, agitation, hallucinations, hyperacusia, choreoathetoid movements and myoclonus which may be mistaken for seizure, increased tendon reflexes, Babinski

reflex, grand mal seizures and hyperactive coma progressing to flaccid coma; the cardiovascular complications are the most life threatening and may involve arrhythmias including tachycardia, nodal tachycardia vatrioventricular block, intraventricular condition delays and asystole as well as myocardial damage, congestive heart failure and shock.

In general, other signs of intoxication would also resemble those of atropine poisoning and would include flushed skin, dry mouth, dilated pupil, pyrexia, urinary retention with distended bladder and rarely, adynamic ileus.

As in other cases of coma and shock general management measures would be applicable including bladder catheterization,cardiac monitoring, etc. Early appropriate evacuation of the ingested materials and/or use of activated charcoal is indicated.

In the reversal of the more severe CNS and cardiovascular complications of poisoning from tricyclic antidepressants, injectable physostigmine salicylate is presently considered the treatment of choice.
However, in uncomplicated cases the use of this drug may not be indicated, or, may be used as a therapeutic trial only, in a reduced dosage of 1 mg injected slowly intravenously. In adults, the usual dosage of physostigmine in severe cases of poisoning would be 1 mg to 2 mg injected intravenously over a period of about 2 minutes.

The therapeutic response may be seen, often dramatically, within 5 minutes of the injection. Since physostigmine is a short-acting drug, repeat injections in more severe, responsive, cases may be needed at 30 to 60 minute intervals, provided there are no serious signs of cholinergic effects.

According to one author (B. Rumach, Pediatrics, 1973) the initial pediatric dose should be 0.5 mg administered slowly intravenously in cases of acute tricyclic antidepressant poisoning. If toxic signs persist and no serious cholinergic effects are produced, the drug can be re-administered at 5 minute intervals until a maximum dose of 2 mg is obtained.

If physostigmine salicylate is used, atropine sulfate should be available to reverse excessive cholinergic effects such as bradycardia, marked salivation, emesis and bronchospasm.

In the event of such a cholinergic crisis, atropine sulfate in a dosage equal to one-half of the physostigmine dosage may be given in order to control the muscarinic effects of the physostigmine.

The various dialysis techniques are relatively ineffective in reversing signs of overdosage because of the low free plasma levels and the firm tissue and protein binding of these drugs.

Forced diuresis is of limited value. Digitalis, if possible, should be avoided due to to its tendency to aggravate cardiac conduction problems.

Other measure of value in tricyclic antidepressant overdose may include: diazepam for the control or persistent seizures; and careful management of electrolyte and acid-base balance. Prolonged observation of at least a week is strongly recommended since deaths attributed to arrhythmias have been reported many days following an apparent recovery from a tricyclic antidepressant overdose.

DOSAGE AND ADMINISTRATION

Not recommended for use in children.

Lower dosages are recommended for elderly and debilitated patients. Lower dosages are also recommended for outpatients compared to hospitalized patients, who are closely supervised.

Dosage should be initiated at al low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication maybe required for a period of time and should be at the lowest dose that will maintain remission.

Usual Adult Dose:

The usual adult dose is 100 to 200 mg per day. In more severely ill patients, dosage may be further increased gradually to 300mg/day if necessary. Dosages above 300 mg/day are not recommended.

Dosages should be initiated at a lower level and increased according to tolerance and clinical response.

Treatment of patients requiring as much as 300 mg should generally be initiated in hospitals, where regular visits by the physician, skilled nursing care, and frequent electrocardiograms (ECG's) are available.

The best available evidence of impending toxicity from very high doses of phl-DESIPRAMINE (desipramine hydrochloride) is prolongation of the QRS or QT intervals on the ECG.

Prolongation of the PR interval is also significant, but less closely correlated with plasma levels.

Clinical symptoms of intolerance, especially drowsiness, dizziness, and postural hypotension, should also alert the physician to the need for reduction in dosage. Plasma desipramine measurement would constitute the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a single daily dose. Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

Elderly and Debilitated Patient Dose: The usual elderly and debilitated patient dose is 25 to 100 mg daily. Dosage should be initiated at a lower level and increased according to tolerance and

clinical response to a usual mamximum of 100mg daily.

In more severely ill patients, dosage may be further, increased to 150mg/day. Doses above 150 mg/day are not recommended in these patients.

Initial therapy may be administered in divided doses or a single daily dose. Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

PHARMACEUTICAL INFORMATION

Drug Substance:

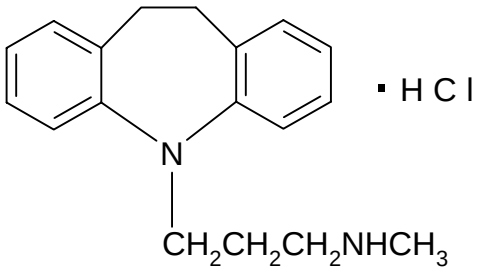
Proper Name: Desipramine Hydrochloride

Chemical Name: 10,11-Dihydro-5-3-(methylamino propyl)-5H-dibenz [b,f] azepine hydrochloride.

Molecular weight: 302.8

Molecular formula: $C_{18}H_{22}N_2$,HCl

Structural Formula:



Physical & Chemical Characteristics of Drug Substance: Desipramine hydrochloride occurs as a white to off-white crystalline powder and is soluble in water and in alcohol. It has pKas of 1.5 and 10.2.

Melting point: about 214^{o}C

Solubility:

Soluble 1 in 20 of water, 1 in 20 of alcohol and 1 in about 4 of Chloroform, practically insoluble in ether; freely soluble in methyl alcohol.

Stability and Storage recommendations:

Keep tightly closed. Store between 15^{o}-30^{o}C (59^{o}-86^{o}F).

AVAILABILITY OF DOSAGE FORMS

phl-DESIPRAMINE (desipramine hydrochloride) tablets, 10 mg are 3/16", round, biconvex, inscribed "P" in a triangle on one side, the other side plain, film coated blue: Bottles of 100.

phl-DESIPRAMINE tablets, 25 mg are 9/32", round, biconvex, pms-25 engraved on one side, film coated tropical yellow. Bottles of 100 and 500.

phl-DESIPRAMINE tablets, 50 mg are 11/32", round, biconvex, inscribed pms-50 on one side, film coated green. Bottles of 100 and 500.

phl-DESIPRAMINE tablets, 75 mg are 13/32", round, biconvex, inscribed pms-75 on one side, film coated orange. Bottles of 50.

phl-DESIPRAMINE tablets, 100 mg are 3/8”, round biconvex, inscribed pms-100 one one side, film coated beige. Bottles of 100.

PHARMACOLOGY

Desipramine hydrochloride is an antidepressant of the tricyclic class. It differs from Imipramine in its terminal N-demethylated chemical structure.

The Central Nervous System is the principal site of pharmaco-logic action of desipramine hydrochloride. In comparison with imipramine hydrochloride, its action against reserpine is more rapid and frequently more effective. It is not a monoamine oxidase (MAO) inhibitor and does not change brain catechol-amine or brain serotonin levels. It has been demonstrated that desipramine hydrochloride reverses the trophotropic syndrome produced by reserpine or by the benzoquinolizine, RO-4-1284, producing a singular type of hyperactivity.

Unlike imipramine, Desipramine Hydrochloride, alone, exerted no obvious sedation in rats even in large doses (40 mg/Kg i.p.). In very large doses (60-90 mg/Kg i.p.) it produced no coordinated hyperactivity but often elicited tremors followed by seizures. In rats, Desipramine Hydrochloride blocked or "reversed" the action of RO-4-1284 much more quickly and effectively than did imipramine.

Rats given desipramine hydrochloride and RO-4-1284 did not display an exaggeration of normal behavior patterns. Rats given reserpine (2 mg/Kg) intravenously, after treatment with desipramine hydrochloride (15 mg/Kg i.p.) displayed a similar behavior.

In dogs and cats, desipramine hydrochloride had a transient biphasic depressor-pressor response following a low i.v. dose. As the dose was increased, the depressor phase predominated. Recovery from the vasodepression began immediately upon termination of the injection, and with high doses it was often incomplete.

Initial doses of desipramine hydrochloride increased the pressor effects of epinephrine and norepinephrine in the dog. In the cat, the epinephrine pressor action was frequently decreased, whereas, the effect on the norepinephrine response was inconsistent. The contractile effect of both

amines on the nictitating membrane increased.

In dogs and cats, the vasopressor effect of serotonin was diminished or completely blocked by desipramine hydrochloride but the pressor effect was usually prolonged. Serotonin-induced contractions of the cat nictitating membrane were increased. However, serotonin's contractile effects on the isolated rat uterus were inhibited by desipramine hydrochloride.

Desipramine hydrochloride possessed weak anticholinergic, antispasmodic, and antihistaminic properties in tests in dogs and in the isolated guinea pig ileum. Pharmacologic studies have shown that desipramine hydrochloride does not inhibit monoamine oxidase or affect the release of brain amines by reserpine.

TOXICOLOGY

Acute Toxicity in mice and rats.
Dose-Volume equivalent to 10 mL/Kg

Substance	**Route**	**Mice LD50/LD5**	**Rats LD50/LD5**
Desipramine	p.os	500/325	385/175
	i.p	94/ 74	48/ 24
	s.c.	420/200	183/ 71
	i.v.	35/ 17	

Desipramine hydrochloride produced slight sedation at 325 mg/Kg orally.

Chronic Toxicity

In rats and dogs, after 6 months of chronic oral toxicity studies desipramine hydrochloride in doses of 7 and 14 mg/Kg did not produce significant evidence of toxic effects. At 30 mg/Kg, there was evidence of cloudy swelling of the renal tubular epithelium in rats and dogs that did not follow a typical dose response pattern.

After 1 year, 2 of 14 rats treated with desipramine hydrochloride (15 mg/Kg) had fatty metamorphosis of the liver, however, there was no evidence of the cloudy selling of the renal tabular epithelium at this time.

No significant toxic effects were found in the dog after 1 year of treatment at 15 mg/Kg. Convulsions occurred in dogs given daily oral doses of desipramine hydrochloride at a dose of 30 mg/Kg. Death occurred in approximately 50% of these animals.

Studies in dogs have indicated that there is a potential of toxic interaction between monoamine oxidase inhibitors and desipramine hydrochloride. Therefore, these compounds should not be combined in therapy nor should they be given in succession.

Reproduction and Teratology

Reproduction studies with desipramine hydrochloride administered orally (50 mg/Kg) or s.c. (40 mg/Kg) in rats and rabbits have not exhibited direct embryotoxic effects.

The increase of the resorption rate and number of foetuses with abnormalities (mainly signs of immaturity of the skeleton) occurred only at doses that were toxic for the mother animal.