

**PRODUCT MONOGRAPH**

**NORPRAMIN<sup>®</sup>**

(desipramine hydrochloride U.S.P.)

ANTIDEPRESSANT

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## PRODUCT MONOGRAPH

### NORPRAMIN

(desipramine hydrochloride U.S.P.)

### ANTIDEPRESSANT

#### CLINICAL PHARMACOLOGY

Norpramin (desipramine hydrochloride) displays an antidepressant property similar to that of other tricyclic antidepressants. It is the active "in vivo" metabolite of imipramine and as such, shares many of imipramine's pharmacologic effects.

The anticholinergic actions of Norpramin are responsible for many of the commonly observed side effects of the drug. Norpramin causes 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 are seen most frequently in elderly patients as is postural hypotension. Norpramin is known to lower the convulsive threshold.

Norpramin increases the percentage of Stage 4 sleep (deep sleep) and decreases the percentage of REM sleep. A partial recovery of REM sleep is seen after 3 to 5 weeks of drug administration. However, in spite of this recovery, a REM rebound occurs following rapid drug withdrawal, which is experienced as an increase in dreaming. The significance of these effects on the sleep cycle remains to be clarified.

An increase in psychomotor activity is observed as an early manifestation of the effects of Norpramin; however, a significant antidepressant effect should not be expected before the end of the second week.

Norpramin is easily absorbed from the gastrointestinal tract following oral administration and is extensively bound to tissue and plasma proteins in the order of 90 - 95%. It is inactivated by hydroxylation and by further demethylation in the liver. Norpramin is excreted as a glucuronide largely in the urine (approximately 70%) and partly in the bile.

Therapeutic actions of tricyclic antidepressants seem to be related to their plasma steady state which, given the same oral dosages, can vary considerably from one individual to another. The largest influence on steady state levels seems to be genetic, however, the influence of concomitant drug administration is also of some practical clinical significance (See the "DOSAGE AND ADMINISTRATION" section of this monograph).

## **INDICATIONS AND CLINICAL USE**

Norpramin (desipramine hydrochloride) is indicated in the treatment of endogenous depressive illness, including the depressed phase of manic depressive illness, involuntal melancholia and psychotic depression. It may also be indicated in the management of depression of a non-psychotic degree such as in selected cases of depressive neurosis. Patients with transient mood disturbances or normal grief reaction are not expected to benefit from tricyclic antidepressants.

## **CONTRAINDICATIONS**

Norpramin (desipramine hydrochloride) should not be given in conjunction with, or within 2 weeks of, treatment with a monoamine oxidase inhibitor drug; hyperpyretic crises, severe convulsions and death have occurred in patients receiving MAO inhibitors and tricyclic antidepressants. When Norpramin is substituted for an MAO inhibitor, at least 2 weeks should elapse between the treatments; administration of Norpramin 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 cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes and acute myocardial infarction. (2) In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug. (3) In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias. (4) In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.

Norpramin (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.

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

It is unknown whether increased risk of suicidal ideation and behaviour is associated with the use of older antidepressants (eg NORPRAMIN) in pediatric patients and/ or adults. However, recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer antidepressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo. Thus, rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages given any antidepressant drug. This includes monitoring for emotional and behavioural changes.

### **Use in Pregnancy:**

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

### **Use in Children:**

Norpramin is not recommended for use in children since safety and effectiveness in the paediatric age group have not been established. (See ADVERSE REACTIONS, Cardiovascular.)

## **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.

Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.

Norpramin may cause exacerbation of psychosis in schizophrenic patients.

There is limited clinical experience in the concurrent administration of ECT and antidepressant

drugs. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.

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:**

Norpramin may potentiate the effect of a variety of drugs. Close supervision and careful adjustment of dosage are required when this drug is administered concomitantly with anticholinergic or sympathomimetic drugs. Patients should be warned that, while taking Norpramin, 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 Norpramin. The contraindication regarding its concomitant use with MAO inhibitors should be noted, as well as the warning regarding patients taking thyroid medication.

Norpramin, on the other hand, 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.

There have been greater than twofold increases of previously stable plasma levels of tricyclic antidepressants when fluoxetine has been administered in combination with these agents.

### **ADVERSE REACTIONS**

The more common adverse reactions involve anticholinergic effects such as dry mouth, disturbances of visual accommodation, constipation and mild urinary retention. Also commonly seen are "light headedness", drowsiness, increased perspiration and mild tremors as well as insomnia. 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 Norpramin (desipramine hydrochloride). However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin is administered.

**Cardiovascular:**

Hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke, premature ventricular contractions, ventricular tachycardia, ventricular fibrillation, sudden death.

There has been a report of an "acute collapse" and "sudden death" in an eight-year old (18 kg) male, treated for two years for hyperactivity. There have been additional reports of sudden death in children.

**Psychiatric:**

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

**Neurologic:**

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

**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.

**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.

**Hematologic:**

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

**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 enzymes.

**Endocrine:**

Gynecomastia in the male, breast enlargement and galactorrhoea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

**Other:**

Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing, urinary frequency, nocturia; parotid swelling, drowsiness, dizziness, weakness and fatigue, headache; alopecia; elevated alkaline phosphatase.

**Withdrawal Symptoms:**

Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, malaise and abdominal cramping.

**SYMPTOMS AND TREATMENT OF OVERDOSE**

In patients presenting with signs of peripheral atropine effects, agitation and cardiac arrhythmias, the possibility of tricyclic antidepressant overdose should be entertained. In view 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 overdose may occur; reflecting CNS intoxication, the patient may exhibit pressure of speech, agitation, hallucinations, hyperacusia, choreoathetoid movements and myoclonus which may be mistaken for seizures, 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, atrioventricular block, intraventricular conduction 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 pupils, pyrexia, urinary retention with distended bladder and rarely, adynamic ileus.

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

Injectable physostigmine salicylate is presently considered the treatment of choice in the reversal of the more severe CNS and cardiovascular complications of poisoning from tricyclic antidepressants. 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 paediatric 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.

Other measures of the value in tricyclic antidepressant overdose may include: diazepam for the control of persistent seizures; and careful management of electrolyte and acid-base balance.

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 its tendency to aggravate cardiac conduction problems.

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.

Higher case fatality rates have been reported in the overdose cases with desipramine compared to other tricyclic antidepressants. However, the proportion of fatalities due to desipramine overdose alone in these reports cannot be properly assessed.

## **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 a low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication may be 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 300 mg/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 Norpramin (desipramine HCl) 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:**

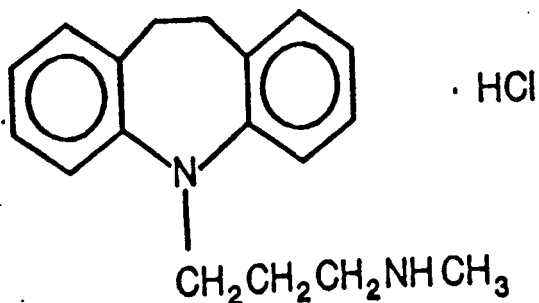
The usual elderly and debilitated patient dose is 25 to 100 mg daily. Dosage should be initiated at a lower level and increased according to tolerance and clinical response to a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to 150 mg/day. Doses above 150 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:

Norpramin (desipramine hydrochloride) is an antidepressant of the tricyclic class with the following chemical name:



5H-Dibenz [b,f]azepine-5-propanamine,10,11-dihydro-N-methyl-, monohydrochloride.

Chemical formula: C<sub>18</sub>H<sub>22</sub>N<sub>2</sub> ·HCl

Molecular weight: 302.85

Desipramine HCl is the N-demethylated form of Imipramine HCl.

### Physical Properties:

Desipramine Hydrochloride occurs as white to off-white crystalline powder which is soluble in water and in alcohol, freely soluble in methanol and in chloroform and is insoluble in ether. Its melting point is 213°. An 8% solution of desipramine HCl in water has a pH of 4.5 to 5.7.

### Storage Recommendations:

Store at room temperature in a tightly closed container. Avoid extreme heat.

## AVAILABILITY OF DOSAGE FORMS

25 mg: Yellow, round, biconvex film coated tablet, imprinted NORPRAMIN 25 in black. Available in plastic (HDPE) bottles of 100.

**Non-medicinal Ingredients:** black Ink, cornstarch, D&C Yellow #10 aluminium lake, FD&C Yellow #6/Sunset Yellow FCF aluminium lake, hydrogenated vegetable oil, hydroxypropyl methylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, pregelatinized starch, polyethylene glycol, polysorbate 80, titanium dioxide.

50 mg: Green, round, biconvex film coated tablet, imprinted NORPRAMIN 50 in black. Available in plastic (HDPE) bottles of 100.

**Non-medicinal Ingredients:** black ink, D&C Yellow #10 aluminium lake, FD&C Blue #1 brilliant blue FCF aluminium lake, FD&C Yellow #6/Sunset Yellow FCF aluminium lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, talc, titanium dioxide.

150 mg: White, round, biconvex sugar coated tablets, imprinted NORPRAMIN 150 in black. Available in plastic (HDPE) bottles of 50.

**Non-medicinal Ingredients:** acacia white, black ink, calcium carbonate, corn starch, FD&C Blue #1, hydrogenated soy oil, magnesium stearate, mannitol powder, petrolatum light liquid, pregelatinized corn starch, polyethylene glycol, sucrose, talc, titanium dioxide, wax.

## **PHARMACOLOGY**

The central nervous system is the principal site of pharmacologic action of Norpramin (desipramine hydrochloride) (DMI). In comparison with imipramine hydrochloride (IMI), its action against reserpine is more rapid and frequently more effective. It is not an MAO inhibitor and does not change brain catecholamine or brain serotonin levels.

In mice and rats, DMI antagonized and in some instances "reversed" the depressant effects of reserpine and a synthetic benzoquinolizine derivative (RO-1284).

In dogs and cats, DMI 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 DMI 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.

The vasopressor effect of serotonin in dogs and cats was diminished or completely blocked by DMI 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 DMI.

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

## **TOXICOLOGY**

The acute oral toxicity (LD<sub>50</sub>) of DMI is approximately 300 mg/kg in mice and rats. This is similar to that of IMI. The i.v. LD<sub>50</sub> is approximately 20 mg/kg in mice, rats, and dogs.

After 6 months of chronic oral toxicity studies in rats and dogs, DMI in doses of 7 and 15 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 DMI (15 mg/kg) had fatty metamorphosis of the liver, however, there was no evidence of the cloudy swelling of the renal tubular 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 DMI 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 DMI. Therefore, these compounds should not be combined in therapy nor should they be given in succession.

Reproductive and teratologic studies with DMI in rats and rabbits have not produced evidence of adverse effects on the development and viability of fetuses during 2 successive generations.

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