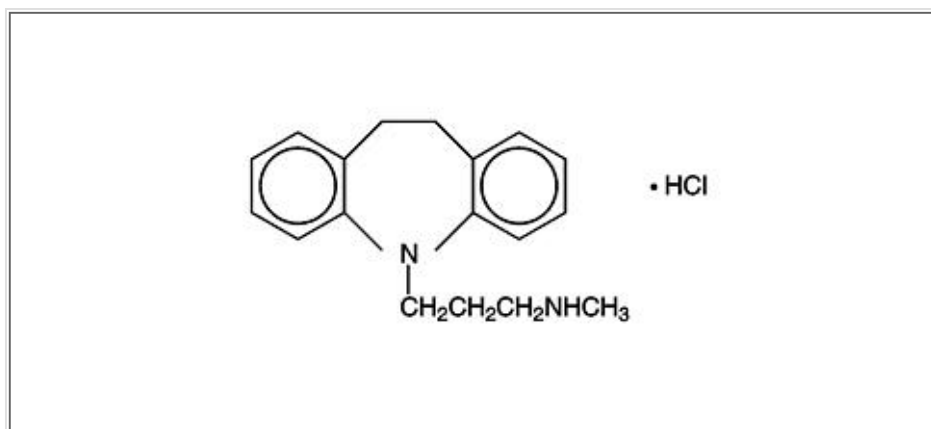


NORPRAMIN® (Aventis)
(desipramine hydrochloride tablets USP)

Prescribing Information as of July 2000

DESCRIPTION

NORPRAMIN® (desipramine hydrochloride USP) is an antidepressant drug of the tricyclic type, and is chemically:



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

Inactive Ingredients

The following inactive ingredients are contained in all dosage strengths: acacia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1 (except 50 mg, 75 mg, and 100 mg), hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Mechanism of Action

Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindoleacetic acid.

While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the re-uptake of these substances from the synapse in the central nervous system. Evidence indicates that the secondary amine tricyclic antidepressants, including NORPRAMIN, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on serotonin re-uptake.

NORPRAMIN (desipramine hydrochloride) is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imipramine. Earliest

therapeutic effects may occasionally be seen in 2 to 5 days, but full treatment benefit usually requires 2 to 3 weeks to obtain.

Metabolism

Tricyclic antidepressants, such as desipramine hydrochloride, are rapidly absorbed from the gastrointestinal tract. Tricyclic antidepressants or their metabolites are to some extent excreted through the gastric mucosa and reabsorbed from the gastrointestinal tract. Desipramine is metabolized in the liver, and approximately 70% is excreted in the urine.

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. Up to a 36-fold difference in plasma level may be noted among individuals taking the same oral dose of desipramine. The ratio of 2-hydroxydesipramine to desipramine may be increased in the elderly, most likely due to decreased renal elimination with aging.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine, which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Research on the relationship of plasma level to therapeutic response with the tricyclic antidepressants has produced conflicting results. While some studies report no correlation, many studies cite therapeutic levels for most tricyclics in the range of 50 to 300 nanograms per milliliter. The therapeutic range is different for each tricyclic antidepressant. For desipramine, an optimal range of therapeutic plasma levels has not been established.

INDICATIONS AND USAGE

NORPRAMIN (desipramine hydrochloride) is indicated for the treatment of depression.

CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When NORPRAMIN (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. NORPRAMIN should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. 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:

- a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
- b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
- c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
- d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.

This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.

The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdose.

Use in Pregnancy

Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing 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 (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric

age group have not been established. (See ADVERSE REACTIONS , Cardiovascular).

Geriatric Use

Clinical studies of NORPRAMIN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Lower doses are recommended for elderly patients. (See DOSAGE AND ADMINISTRATION).

The ratio of 2-hydroxydesipramine to desipramine may be increased in the elderly, most likely due to decreased renal elimination with aging.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. NORPRAMIN use in the elderly has been associated with a proneness to falling as well as confusional states. (See ADVERSE REACTIONS).

PRECAUTIONS

General

It is important that this drug be dispensed in the least possible quantities to depressed outpatients, 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 should be altered.

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

The drug may cause exacerbation of psychosis in schizophrenic patients.

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.

Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.

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 taking desipramine hydrochloride.

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 IC antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs 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.

Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or

sympathomimetic drugs.

Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.

If NORPRAMIN (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of NORPRAMIN and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of NORPRAMIN.

ADVERSE REACTIONS

Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when NORPRAMIN (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, palpitations, heart block, myocardial infarction, stroke, arrhythmias, premature ventricular contractions, tachycardia, ventricular tachycardia, ventricular fibrillation, sudden death

There has been a report of an "acute collapse" and "sudden death" in an 8-year-old (18 kg) male, treated for 2 years for hyperactivity.

There have been additional reports of sudden death in children. (See WARNINGS , Use 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; alterations in EEG patterns; tinnitus

Symptoms attributed to Neuroleptic Malignant Syndrome have been reported during desipramine use with and without concomitant neuroleptic therapy.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of urinary tract

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), 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, diarrhea, 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 galactorrhea 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: weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; fever; alopecia; elevated alkaline phosphatase

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

OVERDOSAGE*

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant 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 antidepressant overdose; therefore, hospital monitoring is required as soon as possible. There is no specific antidote for desipramine overdose.

Oral LD₅₀

The oral LD₅₀ of desipramine is 290 mg/kg in male mice and 320 mg/kg in female rats.

Manifestations of Overdosage

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

antidepressant toxicity.

Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the symptoms listed under ADVERSE REACTIONS.

Management

Aggressive supportive care and serum alkalinization are the mainstays of therapy.

General. 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. Follow ECG, renal function, CPK, and arterial blood gasses as clinically indicated. 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 antidepressant 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. Serum alkalinization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate and hyperventilation (as needed) should be instituted for patients with dysrhythmias and/or QRS widening. A pH >7.60 or a $pCO_2 < 20$ mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type IA and IC antiarrhythmics are generally contraindicated (eg, 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 antidepressant poisoning.

CNS. In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines. If these are ineffective or seizures recur, other anticonvulsants (eg, phenobarbital, phenytoin) may be used. 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 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 overdoses are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

*Poisindex®: Toxicologic Management
Topic: Antidepressants, Tricyclic
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DOSAGE AND ADMINISTRATION

Not recommended for use in children (see WARNINGS).

Lower dosages are recommended for elderly patients and adolescents. 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.

Dosage 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 (ECGs) are available.

The best available evidence of impending toxicity from very high doses of NORPRAMIN 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.

Adolescent and Geriatric Dose

The usual adolescent and geriatric 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 age groups.

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.

HOW SUPPLIED

10 mg blue coated tablets imprinted 68-7

NDC 0068-0007-01: bottles of 100

25mg yellow coated tablets imprinted NORPRAMIN 25

NDC 0068-0011-01: bottles of 100

50mg green coated tablets imprinted NORPRAMIN 50

NDC 0068-0015-01: bottles of 100

75mg orange coated tablets imprinted NORPRAMIN 75

NDC 0068-0019-01: bottles of 100

100mg peach coated tablets imprinted NORPRAMIN 100

NDC 0068-0020-01: bottles of 100

150mg white coated tablets imprinted NORPRAMIN 150

NDC 0068-0021-50: bottles of 50

NORPRAMIN tablets should be stored at room temperature, preferably below 86°F (30°C). Protect from excessive heat.

Rx only

Prescribing Information as of July 2000

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