



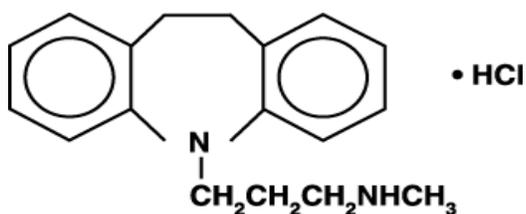
NORPRAMIN[®] (desipramine hydrochloride tablets USP)

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 NORPRAMIN 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. NORPRAMIN is not approved for use in pediatric patients (*see WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.*)

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.



Each NORPRAMIN tablet contains 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, or 150 mg of desipramine hydrochloride for oral administration.

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 25 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 is not a monoamine oxidase inhibitor (MAOI) 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 is indicated for the treatment of depression.

CONTRAINDICATIONS

The use of MAOIs intended to treat psychiatric disorders with NORPRAMIN or within 14 days of stopping treatment with NORPRAMIN is contraindicated because of an increased risk of serotonin syndrome. The use of NORPRAMIN within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated (*see WARNINGS and DOSAGE AND ADMINISTRATION*).

Starting NORPRAMIN in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome (*see WARNINGS and DOSAGE AND ADMINISTRATION*).

NORPRAMIN 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

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 (selective serotonin re-uptake inhibitors [SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 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
	<i>Increases Compared to Placebo</i>
<18	14 additional cases
18-24	5 additional cases
	<i>Decreases Compared to Placebo</i>
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 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 should include daily observation by families and caregivers. Prescriptions for NORPRAMIN 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 NORPRAMIN is not approved for use in treating bipolar depression.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome has been reported with serotonin norepinephrine re-uptake inhibitors (SNRIs) and SSRIs, including NORPRAMIN, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular changes (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of NORPRAMIN with MAOIs intended to treat psychiatric disorders is contraindicated. NORPRAMIN should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There

may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking NORPRAMIN. NORPRAMIN should be discontinued before initiating treatment with the MAOI (*see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION*).

If concomitant use of NORPRAMIN with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome particularly during treatment initiation and dose increases.

Treatment with NORPRAMIN and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

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

General

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 who have a family history of sudden death, cardiac dysrhythmias, or cardiac conduction disturbances.
- c. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
- d. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
- e. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold. Seizures precede cardiac dysrhythmias and death in some patients.

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.

Pregnancy

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including NORPRAMIN, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants

at 1-844-405-6185 or visiting online at <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants>

Safe use of NORPRAMIN 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.

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

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 NORPRAMIN and should counsel them in its appropriate use. A patient Medication Guide about “Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions” is available for NORPRAMIN. 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 NORPRAMIN.

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 observe 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.

Patients should be advised that taking Norpramin 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.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (*see BOX WARNING and WARNINGS-Clinical Worsening and Suicide Risk*). Therefore, NORPRAMIN (desipramine hydrochloride) is not recommended for use in children.

Anyone considering the use of NORPRAMIN in a child or adolescent must balance the potential risks with the clinical need (*see also ADVERSE REACTIONS-Cardiovascular*).

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 (*see WARNINGS-Clinical Worsening and Suicide Risk*). 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 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 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 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.

Concomitant use of Monoamine Oxidase Inhibitors (MAOIs) and serotonergic drugs may potentially cause life threatening adverse events (*see CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION*).

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 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 PRECAUTIONS-Pediatric Use*).

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, proneness to falling, 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.

To report SUSPECTED ADVERSE REACTIONS, contact Validus Pharmaceuticals LLC at 1-866-982-5438 (1-866-9VALIDUS) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

Deaths may occur from overdose with this class of drugs. Overdose of desipramine has resulted in a higher death rate compared to overdoses of other tricyclic antidepressants. 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. Early changes in the QRS complex include a widening of the terminal 40 msec with a rightward axis in the frontal plane, recognized by the presence of a terminal S wave in Lead I and AVL and an R wave in AVR.

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 alkalization 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 gases 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. Emesis is contraindicated. Activated charcoal should be administered to patients who present early after an overdose.

Cardiovascular. A maximal limb-lead QRS duration widening to greater than 100 msec is a significant indicator of toxicity, specifically for the risk of seizures and, eventually, cardiac dysrhythmias. Serum alkalization with intravenous sodium bicarbonate and hyperventilation (as needed) should be instituted in patients manifesting significant toxicity such as QRS widening. Dysrhythmias despite adequate alkalemia may respond to overdrive pacing, beta-agonist infusions, and magnesium therapy. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

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 (e.g., phenobarbital, propofol) may be used.

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.

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 mg 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.

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 mg 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.

Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders: At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with NORPRAMIN. Conversely, at least 14 days should be allowed after stopping NORPRAMIN before starting an MAOI intended to treat psychiatric disorders (*see CONTRAINDICATIONS*).

Use of NORPRAMIN With Other MAOI's Such as Linezolid or Methylene Blue:

Do not start NORPRAMIN in a patient who is being treated with linezolid or intravenous methylene blue because there is increased risk of serotonin syndrome. In a patient who

requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered (*see CONTRAINDICATIONS*).

In some cases, a patient already receiving NORPRAMIN therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, NORPRAMIN should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with NORPRAMIN may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue (*see WARNINGS*).

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with NORPRAMIN is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use (*see WARNINGS*).

HOW SUPPLIED

10 mg blue coated tablets imprinted 68-7
NDC 30698-007-01: bottles of 100

25 mg yellow coated tablets imprinted NORPRAMIN 25
NDC 30698-011-01: bottles of 100

50 mg green coated tablets imprinted NORPRAMIN 50
NDC 30698-015-01: bottles of 100

75 mg orange coated tablets imprinted NORPRAMIN 75
NDC 30698-019-01: bottles of 100

100 mg peach coated tablets imprinted NORPRAMIN 100
NDC 30698-020-01: bottles of 100

150 mg white coated tablets imprinted NORPRAMIN 150
NDC 30698-021-05-: bottles of 50

Store at 77°F (25°C); excursions permitted to 59° to 86°F (15° to 30°C) [See USP Controlled Room Temperature].

Dispense in a tight container. Protect from excessive heat.

Rx Only

Manufactured for and Distributed by:

Validus Pharmaceuticals LLC
119 Cherry Hill Road, Suite 310
Parsippany, NJ 07054
info@validuspharma.com
www.validuspharma.com
1-866-982-5438 (1-866-9VALIDUS)

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Medication Guide

Norpramin® (desipramine hydrochloride tablets USP)

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.

Who should not take NORPRAMIN?

- You should not take NORPRAMIN 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 NORPRAMIN unless directed to do so by your physician.
- Do not start NORPRAMIN if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.

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

Visual Problems

- eye pain
- changes in vision
- swelling or redness in or around the eye

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.

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.
- **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 are pregnant or plan to become pregnant during treatment with Norpramin.**
 - If you become pregnant during treatment with Norpramin, talk to your healthcare provider about registering with the National Pregnancy Registry for Antidepressants. You can register by calling 1-844-405-6185 or visit <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants>

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Validus Pharmaceuticals LLC U.S. at 1-866-982-5438 (1-866-9VALIDUS).

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

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