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APPROVED

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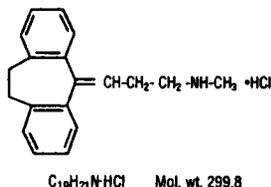
Pamelor®(nortriptyline HCl) capsules, USP
(nortriptyline HCl) oral solution, USP

Rx only

DESCRIPTION

Pamelor® (nortriptyline HCl) is 1-Propanamine, 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-N-methyl-, hydrochloride.

The structural formula is as follows:

**10 mg, 25 mg, 50 mg, and 75 mg Capsules**

Active Ingredient: nortriptyline HCl, USP

10 mg, 25 mg, and 75 mg Capsules

Inactive Ingredients: D&C Yellow #10, FD&C Yellow #6, gelatin, silicone fluid, sodium lauryl sulfate, starch, and titanium dioxide.

May Also Include: benzyl alcohol, butylparaben, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, and sodium propionate.

50 mg Capsules

Inactive Ingredients: gelatin, silicone fluid, sodium lauryl sulfate, starch, and titanium dioxide.

May Also Include: benzyl alcohol, butylparaben, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, sodium bisulfite (capsule shell only), and sodium propionate.

Solution

Active Ingredient: nortriptyline HCl, USP

Inactive Ingredients: alcohol, benzoic acid, flavoring, purified water, and sorbitol.

ACTIONS

The mechanism of mood elevation by tricyclic antidepressants is at present unknown. Pamelor® (nortriptyline HCl) is not a monoamine oxidase inhibitor. It inhibits the activity of such diverse agents as histamine, 5-hydroxytryptamine, and acetylcholine. It increases the pressor effect of norepinephrine but blocks the pressor response of phenethylamine. Studies suggest that Pamelor® (nortriptyline HCl) interferes with the transport, release, and storage of catecholamines. Operant conditioning techniques in rats and pigeons suggest that Pamelor® (nortriptyline HCl) has a combination of stimulant and depressant properties.

INDICATIONS

Pamelor® (nortriptyline HCl) is indicated for the relief of symptoms of depression. Endogenous depressions are more likely to be alleviated than are other depressive states.

CONTRAINDICATIONS

The use of Pamelor® (nortriptyline HCl) or other tricyclic antidepressants concurrently with a monoamine oxidase (MAO) inhibitor is contraindicated. Hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations. It is advisable to have discontinued the MAO inhibitor for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. Patients hypersensitive to Pamelor® (nortriptyline HCl) should not be given the drug.

Cross-sensitivity between Pamelor® (nortriptyline HCl) and other dibenzazepines is a possibility.

Pamelor® (nortriptyline HCl) is contraindicated during the acute recovery period after myocardial infarction.

WARNINGS

Patients with cardiovascular disease should be given Pamelor® (nortriptyline HCl) only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong the conduction time. Myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, Pamelor® (nortriptyline HCl) should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely when Pamelor® (nortriptyline HCl) is administered, inasmuch as this drug is known to lower the

convulsive threshold. Great care is required if Pamelor® (nortriptyline HCl) is given to hyperthyroid patients or to those receiving thyroid medication, since cardiac arrhythmias may develop.

Pamelor® (nortriptyline HCl) may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly.

Excessive consumption of alcohol in combination with nortriptyline therapy may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher AUC, and lower clearance of nortriptyline.

Use in Pregnancy

Safe use of Pamelor® (nortriptyline HCl) during pregnancy and lactation has not been established; therefore, when the drug is administered to pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards. Animal reproduction studies have yielded inconclusive results.

Pediatric Use

This drug is not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

PRECAUTIONS

The use of Pamelor® (nortriptyline HCl) in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms. If the drug is given to overactive or agitated patients, increased anxiety and agitation may occur. In manic-depressive patients, Pamelor® (nortriptyline HCl) may cause symptoms of the manic phase to emerge.

Troublesome patient hostility may be aroused by the use of Pamelor® (nortriptyline HCl). Epileptiform seizures may accompany its administration, as is true of other drugs of its class.

When it is essential, the drug may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery.

The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time.

Both elevation and lowering of blood sugar levels have been reported.

Drug Interactions

Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients.

Close supervision and careful adjustment of the dosage are required when Pamelor® (nortriptyline HCl) is used with other anticholinergic drugs and sympathomimetic drugs.

Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. The patient should be informed that the response to alcohol may be exaggerated.

A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropramide (250 mg/day), after the addition of nortriptyline (125 mg/day).

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%-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 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and 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.

Geriatric Use

Clinical studies of Pamelor® (nortriptyline HCl) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience indicates that, as with other tricyclic antidepressants, hepatic adverse events (characterized mainly by jaundice and elevated liver enzymes) are observed very rarely in geriatric patients and deaths associated with cholestatic liver damage have been reported in isolated instances. Cardiovascular function, particularly arrhythmias and fluctuations in blood pressure, should be monitored. There have also been reports of confusional states following tricyclic antidepressant administration in the elderly. Higher plasma concentrations of the active nortriptyline metabolite, 10-hydroxynortriptyline, have also been reported in elderly patients. As with other tricyclic antidepressants, dose selection for an elderly patient should usually be limited to the smallest effective total daily dose (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Note: Included in the following list 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 nortriptyline is administered.

Cardiovascular – Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric – Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, 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 the urinary tract.

Allergic – Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs.

Hematologic – Bone marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia.

Gastrointestinal – Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, blacktongue.

Endocrine – Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion.

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

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

DOSAGE AND ADMINISTRATION

Pamelor® (nortriptyline HCl) is not recommended for children.

Pamelor® (nortriptyline HCl) is administered orally in the form of capsules or liquid. Lower than usual dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients than for hospitalized patients who will be under close supervision. The physician should initiate dosage at a low level and increase it gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time at the lowest dose that will maintain remission.

If a patient develops minor side effects, the dosage should be reduced. The drug should be discontinued promptly if adverse effects of a serious nature or allergic manifestations occur.

Usual Adult Dose – 25 mg three or four times daily; dosage should begin at a low level and be increased as required. As an alternate regimen, the total daily dosage may be given once a day. When doses above 100 mg daily are administered, plasma levels of nortriptyline should be monitored and maintained in the optimum range of 50-150 ng/mL. Doses above 150 mg/day are not recommended.

Elderly and Adolescent Patients – 30-50 mg/day, in divided doses, or the total daily dosage may be given once a day.

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.

Manifestations:

Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, shock, congestive heart failure, pulmonary edema, 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, restlessness, disturbed concentration,

transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the acute symptoms listed under ADVERSE REACTIONS. There have been reports of patients recovering from nortriptyline overdoses of up to 525 mg.

Management:

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 six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination: All patients suspected of tricyclic 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. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH > 7.60 or a $pCO_2 < 20$ mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic 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, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up: Since 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.

HOW SUPPLIED

Pamelor® (nortriptyline HCl) Capsules, USP

Pamelor® (nortriptyline HCl) Capsules, USP, equivalent to 10 mg, 25 mg, 50 mg, and 75 mg base, are available in bottles of 100 (10 mg: NDC 0078-0086-05; 25 mg: NDC 0078-0087-05; 50 mg: NDC 0078-0078-05; 75 mg: NDC 0078-0079-05). 10 mg, 25 mg, and 50 mg are available in a unit dose package of 100 individually labeled blisters, each containing 1 capsule (10 mg: NDC 0078-0086-06; 25 mg: NDC 0078-0087-06; 50 mg: NDC 0078-0078-06). Pamelor® (nortriptyline HCl) Capsules, USP 25 mg is also available in bottles of 500 (NDC 0078-0087-08).

10 mg capsules branded "  SANDOZ" on one half, "  PAMELOR 10 mg" other half; 25 mg capsules branded "  SANDOZ" on one half, "  PAMELOR 25 mg" other half; 50 mg capsules branded "  SANDOZ" on one half, "  PAMELOR 50 mg" other half; and 75 mg capsules branded "  SANDOZ" on one half, "  PAMELOR 75 mg" other half.

Store and Dispense

Below 86°F (30°C); tight container.

Pamelor® (nortriptyline HCl) Solution, USP

Pamelor® (nortriptyline HCl) Solution, USP, equivalent to 10 mg base per 5 mL, is supplied in 16-fluid-ounce bottles (NDC 0078-0016-33). Alcohol content 4%.

Store and Dispense

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

Solution Manufactured by:

Novartis Consumer Health, Inc.
Lincoln, Nebraska 68517

Capsules Manufactured by:

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

Distributed by:

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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