PRODUCT MONOGRAPH

PrNORVENTYL®

Nortriptyline HCl Capsules, USP

10 mg & 25 mg capsules

TRICYCLIC ANTIDEPRESSANT

Valeant Canada limitée/Limited
4787 Levy Street
Montreal, Quebec
H4R 2P9

Date of Preparation: April 15, 2005

Control No.: 098074

PRODUCT MONOGRAPH

PrNORVENTYL®

Nortriptyline Hydrochloride Capsules, USP

10 mg & 25 mg

Tricyclic Antidepressant

ACTION AND CLINICAL PHARMACOLOGY

Nortriptyline is the major metabolite of amitriptyline and belongs to the group of tricyclic antidepressants. Nortriptyline does not inhibit monoamine oxidase.

Although the exact mechanism of action in the treatment of depression is unclear, tricyclic antidepressants have been thought to increase the synaptic concentration of norepinephrine and/or serotonin in the central nervous system. These neurotransmitters are increased through inhibition of their reuptake by the presynaptic neuronal membrane. Nortriptyline mainly inhibits the reuptake of norepinephrine.

Recent research has shown that after long-term treatment with antidepressants, changes in postsynaptic beta-adrenergic receptor sensitivity and increased responsiveness of the adrenergic and serotonergic systems to physiologic and environmental stimuli contribute to the mechanism of action. Antidepressants may produce a downregulation (desensitization) of $alpha_2$- or beta-adrenergic and serotonin receptors, equilibrating the noradrenergic system, and thus correcting the dysregulated monoamine output of depressed patients. Receptor changes resulting from chronic administration of tricyclic antidepressants appear to correlate better with antidepressant action than does the synaptic reuptake blockade of neurotransmitters, and may also account for

the delay of 2 to 4 weeks in therapeutic response.

Nortriptyline also produces low peripheral and central anticholinergic effects due to its binding affinity for muscarinic receptors. In addition, it exhibits moderate sedative effects due its binding affinity for histamine H1-receptors, and a low orthostatic hypotension due to alpha blockade. Tricyclic antidepressants are antiarrhythmic agents which, like quinidine, moderately slow ventricular conduction in therapeutic doses, and in overdosage may cause severe conduction block and occasional ventricular arrhythmia.

PHARMACOKINETICS

Absorption: Nortriptyline HCl is well absorbed from the GI tract. Plasma concentrations exhibit considerable interpatient variation. A relationship of plasma concentrations to clinical response and acute toxicity has not been fully established but has been reported by other study groups. Peak plasma concentrations occur within 7 to 8.5 hours after oral administration. Optimal response to the drug appears to be associated with plasma concentrations of 50 to 150 ng/ml. Adverse effects appear within a few hours after administration of the drug, but full antidepressant effects may not occur for several weeks.

Distribution: Nortriptyline HCl is distributed to the lungs, heart, brain, and liver. Nortriptyline and its metabolite is highly bound to plasma and tissue proteins. Nortriptyline readily crosses the placenta and nortriptyline is distributed into breast milk where it appears in similar or slightly greater concentrations than those present in the maternal serum.

Elimination: Nortriptyline, when administered orally, undergoes first-pass metabolism in the liver. The primary route of elimination is urinary excretion, approximately one-third of the dose as metabolites within 24 hours, but it is also excreted in feces via the bile. The plasma half-life of nortrip-tyline ranges from 16 to more than 90 hours.

Comparative pharmacokinetic parameters for nortriptyline, comparing Aventyl (Lilly) and Norventyl (ICN Canada) are shown in the table below:

Summary Table of the Comparative Bioavailability Data
NORVENTYL
(25 mg)
From measured data
Geometric Mean
Arithmetic Mean (CV%)

PARAMETER	TEST ICN Canada	REFERENCE Lilly Canada	*RATIO OF MEANS
AUC_T (ng.hr/mL)	640.11 696.20(40.47)	685.25 741.35(38.43)	93
AUC_I (ng.hr/mL)	724.04 778.25(37.47)	767.28 834.46(41.01)	94
C_{max} (ng/mL)	16.40 16.92(24.58)	16.91 17.48(24.67)	97
T_{max} (h)	7.63(14.88)	7.63(20.03)	--
$T_{1/2}$ (h)	30.46(27.86)	32.75(34.26)	--

The T_{max} and $T_{1/2}$ parameters are expressed as the arithmetic means.

INDICATIONS AND CLINICAL USE

Norventyl (Nortriptyline hydrochloride) is indicated for the relief of symptoms of depression. Endogenous depressions are more likely to be alleviated than are other depressive states.

CONTRAINDICATIONS

Nortriptyline and other tricyclic antidepressants are contraindicated in the acute recovery phase following myocardial infarction.

The use of nortriptyline or other tricyclics is contraindicated in patients with proven hypersensitivity to the drug or any compound in the formulation. Cross-sensitivity among the

drugs has been reported, and should be considered when switching patients from one tricyclic antidepressant to another because of a hypersensitivity reaction.

Concomitant administration of tricyclic antidepressants and MAO inhibitor antidepressants is contraindicated since hyperpyretic crises, severe seizures, and death, have been reported. These effects have usually occurred following over-dosage or parenteral administration of 1 or both drugs. Following the oral administration of both drugs in therapeutic dosage, nonfatal hyperpyrexia, hypertension, tachycardia, confusion, and seizures have been reported. It is advisable to discontinue the MAO inhibitor at least 2 weeks before treatment with **Norventyl** is started.

WARNINGS

Cardiovascular: patients with preexisting cardiovascular disease may be especially sensitive to nortriptyline. Hypertensive episodes have occurred during surgery in patients receiving tricyclic antidepressants, and the drugs should be discontinued several days prior to selective surgery. Patients should be closely monitored since nortriptyline tends to produce sinustachycardia and to prolong the conduction time. Stroke and congestive heart failure, myocardial infarction and arrhythmias have been reported.

Anticholinergic Effects: adverse CNS and neuromuscular effects occur frequently. Drowsiness is the most frequent adverse reaction to tricyclic antidepressants. Peripheral neuropathy, dizziness, incoordination, ataxia or unsteadiness, and falling have been reported and patients taking nortriptyline should be advised of not operating heavy machinery or driving a car to avoid injury.

Hepatic Effects: in some rare cases, asymptomatic increases in serum aminotransferase concentrations, changes in serum alkaline phosphatase concentrations and hepatitis of the allergic type have been reported. Jaundice and hepatitis are reversible following discontinuation of the drug.

Pregnancy and Lactation: safe use of nortriptyline in pregnancy has not been established. Nortriptyline should not be used in pregnant women or women who may become pregnant

unless the possible benefits outweigh the potential risks to the fetus. Nortriptyline is distributed into milk. Because of the potential for serious adverse reactions to tricyclic antidepressants in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the women.

DRUG INTERACTIONS

Monoamine Oxidase Inhibitors: interactions between MAO inhibitors and nortriptyline may be severe (refer to Contraindications Section)

Histamine H_2 Receptor Antagonists: steady-state serum concentrations of tricyclic antidepressants are reported to fluctuate significantly when cimetidine is either added or deleted from the drug regimen. Serious anticholinergic symptoms (severe dry mouth, urinary retention, blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressants when cimetidine is added to the drug regimen. In addtion, higher than expected steady-state serum concentrations of tricyclic antidepressants have been observed when therapy is initiated in patients already taking cimetidine.

In well-controlled patients undergoing concurrent therapy with cimetidine, a decrease in the steady-state serum concentrations of tricyclic antidepressants may occur when cimetidine therapy is discontinued. The therapeutic efficacy of tricyclic antidepressant may be compromised in these patients when cimetidine is discontinued. Several of the tricyclic antidepressants have been cited in these reports.

Hypotensive Agents: tricyclic antidepressants block the uptake of guanethidine and similarly acting agents into adrenergic neurons, and thus prevent their hypotensive activity. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients.

CNS Depressants: tricyclic antidepressants may be additive with or may potentiate the action of CNS depressants such as alcohol, sedatives, or hypnotics. Concurrent administration of

nortriptyline and fluoxetine reportedly has resulted in adverse effects associated with tricyclic toxicity (including sedation, decreased energy, lightheadedness, psychomotor retardation, dry mouth, constipation, memory impairment) and/or greater than twofold elevations in plasma tricyclic antidepressant concentrations.

Antipsychotic Agents: various phenothiazines and haloperidol have been shown to inhibit metabolism and increase blood concentrations of tricyclic antidepressants. Although the clinical importance has not been established, dosages of both drugs should be carefully adjusted whenever antipsychotics are given with tricyclic antidepressants.

Sympathomimetic and Anticholinergic Agents: concomitant administration of tricyclic antidepressants with sympathomimetic drugs such as isoproterenol, phenylephrine, norepinephrine, epinephrine, or amphetamines may increase sympathetic activity. Concomitant administration of tricyclic antidepressants and anticholinergic agents has been reported to produce hyperthermia, particularly during hot weather, and paralytic ileus.

Other Drugs: tricyclic antidepressants may delay gastric emptying as a result of their anticholinergic activity. Absorption of drugs such as levodopa and phenylbutazone which are absorbed from the intestine may be delayed sufficiently to permit inactivation in the stomach. Careful dosage monitoring is essential when such drugs are administered with tricyclic antidepressants. Nortriptyline has been reported to increase plasma concentrations of dicumarol.

The onset of therapeutic effect of tricyclic antidepressants has been reported to be accelerated by thyroid agents and patients who are hyperthyroid or are on thyroid agents should be closely monitored.

Drugs metabolized by P450IID6:

A subset (3% to 10%) of the population has reduced activity of certain drug metabolizing enzymes such as the cytochrome P450 isoenzyme P450IID6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants. These individuals may have higher than expected plasma concentrations of

tricyclic antidepressants when given usual doses. In addition, certain drugs that are metabolized by this isoenzyme, including many antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, and others), may inhibit the activity of this isoenzyme, and thus may make normal metabolizers resemble poor metablizers with regard to concomitant therapy with other drugs metabolized by this enzyme system, leading to drug interactions.

Concomitant use of tricyclic antidepressants with other drugs metabolized by cytochrome P450IID6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Therefore, co-administration of tricyclic antidepressants with other drugs that are metabolized by this isoenzyme, including other antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibits this enzyme (e.g., quinidine), should be approached with caution.

PRECAUTIONS

* Nortriptyline should be used with caution in patients for whom excess anticholinergic activity could be harmful, such as those with benign prostatic hypertrophy, a history of urinary retention, increased intraocular pressure, or angle-closure glaucoma. Patients who exhibit symptoms of angle-closure glaucoma should not receive the drug until the cause of the symptoms is determined, and glaucoma should be corrected before treatment with nortriptyline is initiated. Patients with adequately controlled glaucoma should be closely monitored during therapy with nortriptyline because nortriptyline may precipitate an attack of angle-closure glaucoma.

* The patient taking nortriptyline and concomitantly drugs possessing anticholinergic activity which affect the thermoregulation (e.g., antimuscarinics, phenothiazines) should be advised of the risk of hyperthermia, particularly during hot weather.

* Patients should be warned that nortriptyline might impair their ability to perform hazardous activities requiring mental alertness or physical coordination such as operating machinery or driving a motor vehicle.

* Nortriptyline may lower the seizure threshold and should be used with caution in patients with a history of epileptic seizure disorders, organic brain disease, or who may be predisposed to seizures (e.g., in the acute withdrawal phase of alcoholism).

* Depressed patients are especially prone to suicidal tendencies and the possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; therefore, it is important that large quantities of nortriptyline should not be prescribed and dispensed at one time. 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 patient should be informed that the response to alcohol may be exaggerated.

* If necessary, the drug may be administered concurrently with electroconsulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery.

* Nortriptyline may exacerbate psychosis or may activate latent schizophrenic symptoms in schizophrenic patients. Nortriptyline may increase anxiety and agitation when given to overactive or agitated patients. In manic-depressive patients, **Norventyl** may cause symptoms of the manic phase to emerge. Troublesome patient hostility may be aroused by the use of **Norventyl**.

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

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

Pediatric Precautions

The safe use of nortriptyline for the treatment of depression in children younger than 12 years of age has not been established.

ADVERSE REACTIONS

Minor adverse reactions associated with the use of nortriptyline generally reflects the drugs' anticholinergic and CNS activities. Tolerance usually develops to sedative and anticholinergic effects and to postural hypotension; therefore, these adverse reactions can be minimized by starting therapy with low doses and titrating dosage gradually upwards.

1. Anticholinergic Effects: dry mouth, rarely associated with sublingual adenitis; blurred vision; disturbance of accommodation; mydriasis; constipation; paralytic ileus; urinary retention; delayed micturition; dilation of the urinary tract.

2. Nervous System Effects: paresthesias of extremities; tingling; numbness; incoordination; tremor; ataxia; peripheral neuropathy; extrapyramidal symptoms; seizures; alterations of EEG patterns and tinnitus.

3. Cardiovascular Effects: hypotension; hypertension; tachycardia; palpitation; myocardial infarction; arrhythmias; heart block; stroke.

4. Hematologic Effects: bone marrow depression, including agranulocytosis, aplastic anemia; eosinophilia; purpura; thrombocytopenia.

5. Hepatic Effects: jaundice; altered liver function; hepatitis, and liver necrosis.

6. Psychiatric Effects: confusion, hallucinations; disorientation; delusion; anxiety; restlessness; agitation; insomnia; panic; nightmares; hypomania; exacerbation of psychosis.

7. Allergic Reactions: skin rash; petechiae; urticaria; itching; photosensitization (avoid excessive exposure to sun light); edema (local or generalized); drug fever; cross-sensitivity with other tricyclic drugs.

8. Gastrointestinal Effects: nausea; vomiting; epigastric distress; anorexia; diarrhea; stomatitis; black tongue; change of taste; constipation; abdominal cramps; paralytic ileus.

9. Endocrine Effects: gynecomastia in men; breast enlargement and galactorrhea in females; impotence; increase or decrease of libido; elevation or depression of blood sugar levels; ADH

(antidiuretic hormone) changes; testicular swelling.

10. Other Effects: perspiration; urinary frequency, nocturia; weight gain; hot flushes; drowsiness; dizziness; weakness; fatigue; headache; parotid swelling; alopecia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: overdosage with tricyclic antidepressants may be manifest with doses as small as 50 mg in children. A mortality rate of between 0% and 15 % has been reported for patients admitted to the hospital alive. Symptoms of overdosage of tricyclic antidepressants may begin within several hours of oral ingestion. Signs and symptoms may include blurred vision, confusion, restlessness, dizziness, hypothermia, hyperthermia; agitation; vomiting, hyperactive reflexes; dilated pupils, fever, rapid heart beat, bowel atonia, dry mouth, inability to void, myoclonic jerks, seizures, respiratory depression, myoglobulinuric renal failure, nystagmus, ataxia, dysarthria, choreoathetosis, coma, hypotension, and cardiac arrhythmias. A quinidine-like reaction on cardiac conduction as are slowing of conduction, prolongation of the QRS complex and QT intervals, right bundle branch and AV block, ventricular tachyarrhythmias (including Torsade de pointes and fibrillation), and death have been reported. A prolongation of the QRS duration to more than 0.1 seconds is predictive of more severe toxicity. The absence of sinus tachycardia does not predict a benign course. Hypotension may be caused by vasodilation, central and peripheral a-adrenergic blockade, and cardiac depression. In a healthy young person, prolonged resuscitation may be effective; one patient was reported to survive after 5 hours of cardiac massage.

Treatment: In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc.

Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Ventricular arrhythmias, especially when accompanied by lengthened QRS intervals, may respond to alkalinization by hyperventilation or administration of sodium bicarbonate. It is important to monitor and manage serum electrolyte levels. Refractory arrhythmias may respons to propranolol, bretylium, or lidocaine. Quinidine and procainamide usually should not be used because they may exacerbate arrhythmias and conduction already slowed by the overdosage.

Seizures may respond to diazepam. Phenytoain has pharmacologic properties that may be helpful in dealing with both the seizures and cardiac rhythm disturbances of tricyclic antidepressant overdose. Although the prophylactic use of phenytoin has been suggested, it is not yet of proven value.

In some patients, physostigmine may antagonize such effects of tricyclic antidepressant overdose as atrial tachycardia, gut immotility, myoclinic jerks, and somnolence. It is less effective for seizures and ventricular arrhythmias. When physostigmine is given, the patient's condition should be carefully monitored and ventilation and cardiac rhythm should be supported. Cholinergic toxicity from physostigmine may include bronchospasm, bronchorrhea, bradycardia, asystole, diaphoresis, incontinence, and seizures. If physostigmine is used, give it slowly because rapid injection may cause seizures. The effects of physostigmine may be short-lived; repeated doses may lead to continued improvement.

Diuresis and dialysis remove little of the tricyclic antidepressant present in the body of a patient who has taken an overdose. Hemoperfusion is of unproven benefit. The patient who has taken a tricyclic overdose should be monitored closely, at least until the QRS duration is normal.

DOSAGE AND ADMINISTRATION

Norventyl (nortriptyline hydrochloride) is administered orally in capsule form. Lower than usual dosages are recommended for elderly patients and adolescents. The use of lower dosages for outpatients is more important than for hospitalized patients who will be treated under close supervision. **Norventyl** dosage should be initiated at a low level and increased gradually, checking the clinical response carefully and recording 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: orally, 25 mg three or four times a day, the dosage being adjusted as needed and tolerated. As an alternate regimen, the total daily dose may be given once a day. When doses above 100 mg daily are administered, plasma levels of nortriptyline hydrochloride should be monitored and maintained in the optimum range of 50 to 150 ng/mL. Doses above 150 mg per day are not recommended.

Usual Adult Prescribing Limits: up to 150 mg a day.

Geriatric and Adolescent Dose: 30 to 50 mg a day in divided doses, the dosage being adjusted as needed and tolerated.

Plasma Levels: Optimal responses to nortriptyline have been associated with plasma concentrations of 50 to 150 ng/mL (see Pharmacology Section). Higher concentrations may be associated with more adverse experiences. Plasma concentrations are difficult to measure, and physicians should consult with the laboratory professional staff.

Larger plasma concentrations of the active nortriptyline metabolite 10-hydroxynortriptyline have been reported in older patients. In one case, such a condition was associated with apparent cardiotoxicity despite the fact that nortriptyline concentrations were within the "therapeutic

range". Clinical findings should predominate over plasma concentrations as primary determinations of dosage changes.

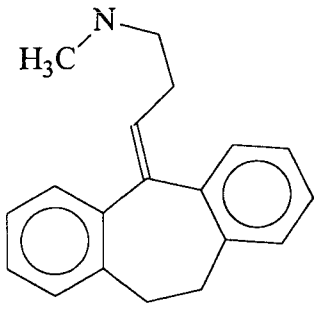
PHARMACEUTICAL INFORMATION

Drug Substance: Nortriptyline hydrochloride, USP

Chemical Name: (1) 1-Propanamine, 3-(10,11-dihydro-5H -dibenzo[a,d]-cyclohepten-5-ylidene)-N-methyl-,hydrochloride;

(2) 10,-11-Dihydro-N-methyl-5Hdibenzo[a,d]cycloheptene-5,g-propylamine hydrochloride.

Structural Formula:



• **HCI**

Molecular Formula: $C_{19}H_{21}N.HCl$

Molecular Weight : 299.84

Description: nortriptyline hydro-chloride is a white or off-white powder with a slight characteristic odour. Nortriptyline hydrochloride 22.8 mg is approximately equivalent to 20 mg of nortriptyline.

Solubility: USP: soluble 1 in 90 of water, 1 in 30 of alcohol, 1 in 20 of chloroform, and 1 in 10 of methyl alcohol; practically insoluble in ether and in most other organic solvents. A 1 % solution in water has a pH of about 5.

Composition: **Norventyl** 10 mg & 25 mg capsules contain:

* nortriptyline hydrochloride, USP

Non-medicinal ingredients:

* colloidal silicon dioxide, NF
* pregelatinized starch, NF
* sodium lauryl sulfate, NF.

Norventyl capsule shells contain:

Body: white opaque: titanium dioxide and gelatin

Cap: light green opaque: FD&C green #3, D&C yellow #10, titanium dioxide and gelatin. The cap is imprinted with black ink S-1-8114/S-1-8115.

Stability and Storage Recommendations:

Store **Norventyl** capsules in a tight container at controlled temperature between 15 and 30^{o} C. Protect from light.

AVAILABILITY

Each **Norventyl** 10 mg capsule, light opaque green cap and white opaque body imprinted with "ICN N31" contains 11.38 mg nortriptyline hydrochloride, USP. Supplied in bottles of 100 and 500 capsules.

Each **Norventyl** 25 mg capsule, light opaque green cap and white opaque body imprinted with "ICN N32" contains 28.45 mg nortriptyline hydrochloride, USP. Supplied in bottles of 100 and 500 capsules.

INFORMATION TO THE CONSUMER

Description:

Norventyl (nortriptyline) is a tricyclic antidepressant and is used to relieve mental depression. **Norventyl** is available in capsule form by prescription only.

It is very important that you read and understand the following information. If any of it causes you special concern, check with your physician. Also, if you have any questions or if you want more information about **Norventyl** or your medical problem, ask you physician, or pharmacist.

Before Using Norventyl

In deciding to use **Norventyl**, the risks of taking the drug must be weighed against the good it will do. This is a decision you and your physician will make. For **Norventyl**, the following should be considered and your physician should be informed if you have or have had:

* **Allergies** - or any unusual reaction to any tricyclic antidepressant, or if you are allergic to any other substances, such as foods, preservatives, or dyes.

* **Pregnancy** - studies have not be done in pregnant women. However, there have been reports of newborns suffering from muscle spasms, heart, breathing, and urinary problems when their mothers had taken tricyclic antidepressants immediately before delivery. Also, animal studies have shown that some tricyclic antidepressants may cause unwanted effects in the fetus.

***Breast-feeding** - tricyclic anti-depressants pass into the breast milk, and might cause drowsiness in the nursing baby.

***Children** - children are especially sensitive to the effects of tricyclic antidepressants. This may increase the chance of side effects during treatment. The most common side effects reported in children are: nervousness, sleeping problems, tiredness, and mild stomach upset. If these side effects continue or are bothersome, check with your physician. These side effects normally subside after discontinuation of the medication.

*__Older Adults__ - drowsiness, dizziness, confusion, vision problems, dryness of the mouth, constipation, and problems in urinating are more likely to occur in elderly patients, who are usually more sensitive than younger adults to the effects of tricyclic antidepressants.

*__Other medicines__ - when more than one medicine is taken, drug interactions may occur which can lead to a decrease in well-being, impairment of functioning or even hospitalization. When you are taking **Norventyl**, it is of importance that your physician or pharmacist know if you are taking any of the following medications:

*antipsychotics (medicines for mental illness);

*Clonidine (high blood pressure treatment) - using clonidine with **Norventyl** may increase the CNS depressant effect and increase the chance of serious side effects;

*antithyroid agents (treatment of overactive thyroid);

*Cimetidine (histamine antagonist) - increased risk of serious side effects;

* amphetamines;

* appetite suppressants (diet pills);

* ephedrine (bronchodilator);

* epinephrine (glaucoma treatment);

* isoproterenol (bronchodilator);

* medicines to treat asthma or other breathing problems;

*medicines for colds, sinus problems, hay fever or other allergies;

*phenylephrine (cough and cold medicine)

-using this medicine with **Norventyl** may increase the risk of serious effects on the heart;

*central nervous system (CNS) de-pressants - a combination of these medications may increase the CNS depressant effect;

*guanadrel (antihypertensive); or

*guanethidine (antihypertensive) - a combination of Norventyl and the antihypertensives may reduce the effectiveness of the antihypertensives;

*methyldopa; or

*metoclopramide; or

*metyrosine; or

*pemoline; or

*pimozide; or

*promethazine; or

*rauwolfia alkaloids; or

*trimeprazine - tricyclic antidepress-ants may cause certain side effects to be more severe and occur more often;

*metrizamide - the risk of seizures may be increased;

*monoamine oxidase inhibitors - taking tricyclic antidepressants while you are taking or within 2 weeks of taking monoamine oxidase inhibitors may cause sudden highly elevated body temperature, extremely high blood pressure, severe convulsions, and death; however, sometimes certain of these medicines may be used together under close supervision by your physician.

*** Other medical problems** - the presence of other medical problems may affect the use of tricyclic antidepressants. Make sure you tell your physician if you have any other medical problems, especially:

* alcohol abuse or history of alcohol abuse;

* asthma;

* bipolar disorder (manic-depressive illness);

* blood disorders;

* convulsions;

* difficult urination;

* enlarged prostate;

* glaucoma or increased eye pressure;

* heart disease;

* high blood pressure;

* schizophrenia - tricyclic antidepressants may make the condition worse;

* kidney disease;

* liver disease - higher blood levels of **Norventyl** may result, increasing the chance of side effects;

* overactive thyroid;

* stomach or intestinal problems - tricyclic antidepressants may cause an increased chance of serious side effects;

Before you begin using any new medicine (prescription or nonprescription) or if you develop any new medical problem while you are using **Norventyl,** check with your physician, or pharmacist.

Proper Use of Norventyl

* To lessen stomach upset, take **Norventyl** with food, unless your doctor has told you otherwise.

Take **Norventyl** only as directed by your physician, to benefit your condition as much as possible. Do not take more of it, do not take it more often, and do not take it for a longer time than your physician ordered.

* Sometimes **Norventyl** must be taken for several weeks before you begin to feel better. Your physician should check your progress at regular visits.

* Missed dose - if you miss a dose of **Norventyl,** take the missed dose as soon as possible. However, if it is almost time for your next dose, skip the missed dose, and go back to your regular dosing schedule. Do not double dose.

Storage of Norventyl

* keep out of reach of children. Overdose of this medicine is very dangerous in young children.

* store away from heat and direct light.

* do not store the capsules in the bathroom, near the kitchen sink, or in other damp places. Heat or moisture may cause the medicine to break down.

* do not keep outdated medicine or medicine no longer needed. Be sure that any discarded medicine is out of the reach of children.

Precautions while you are taking Norventyl

It is very important that your physician check your progress at regular visits to allow dosage adjustments and to help reduce side effects.

Norventyl will add to the effect of alcohol and other CNS depressants.

Norventyl may cause some people to become drowsy. **If this occurs, do not drive, use machines, or do anything else that could be dangerous if you are not alert.**

Dizziness, lightheadedness, or fainting may occur, especially when you get up from a lying or sitting position. Getting up slowly may help. If this problem continues or gets worse, check with your physician.

Norventyl may cause dryness of the mouth. For temporary relief, use sugarless gum or candy, melt bits of ice in your mouth, or use a saliva substitute. However, if your mouth continues to feel dry for more than 2 weeks, check with your physician or dentist. Continuing dryness of the mouth may increase the chance of dental disease, including tooth decay, gum disease, and fungus infections.

Norventyl may cause your skin to be more sensitive to sunlight than it is normally. Exposure to sunlight, even for a brief period of time, may cause a skin rash, itching, redness or other discoloration of the skin, or a severe sunburn. When you begin taking **Norventyl**

* stay out of direct sunlight, especially between the hours of 10:00 a.m. and 3:00 p.m..
* wear protective clothing including a hat. Also wear sunglasses.
* apply a sun block product that has a skin protection factor of at least 15.

Before you have any medical tests, tell the physician that you take Norventyl. Before having any kind of surgery, dental treatment, or emergency treatment, tell the physician or dentist in charge that you take Norventyl.

If you suffer from diabetes let your physician know. **Norventyl** may affect blood sugar levels.

Do not stop taking **Norventyl** without first consulting with your physician. Your physician may want you to reduce gradually the amount you are taking before stopping completely. This may prevent a possible worsening of your condition and reduce the possibility of withdrawal symptoms such as headache, nausea, and/or an overall feeling of discomfort.

The effects of **Norventyl** may last for 3 to 7 days after you have stopped taking it.

Side Effects of Norventyl

Along with its needed effects, some medications may cause some unwanted effects. Not all of the side effects listed below may occur, however, if you experience some, report them to your physician:

Less common:

* blurred vision
* confusion or delirium
* constipation
* difficulty in speaking or swallowing
* eye pain
* fainting
* fast or irregular heartbeat
* loss of balance
* nervousness
* problem in urinating
* slowed movements

Rare:

* anxiety
* increased sensitivity to sunlight
* irritability
* buzzing in the ear

* skin rash and itching
* sore throat and fever
* swelling of tongue and face
* weakness
* yellow skin or eyes

ANIMAL PHARMACOLOGY

Nortriptyline hydrochloride labeled with radiocarbon in the N-methyl group has been prepared, and its metabolism, distribution, and excretion have been studied in the rat. About 25% of an administered dose undergoes N-demethylation in the whole animal. Another 40% of the dose is excreted in urine as conjugates of the cis-isomer and trans-isomer of 10-hydroxynortriptyline.

Studies indicate that the drug undergoes wide distribution, and the highest levels are found in the lungs and liver. Identification of nortriptyline hydrochloride in the brain shows that it does pass the blood-brain barrier. It was slowly but efficiently absorbed from the intestinal tract in rats.

TOXICOLOGY

In both acute and chronic toxicity studies, nortriptyline hydrochloride has a degree of toxicity comparable to that of other members of the tricyclic antidepressant group. In acute experiments, the oral LD_{50} is 327 mg/kg in mice, and 502 mg/kg in rats. When the drug was administered intravenously, the LD_{50} was 25.7 mg/kg in mice and 22.2 mg/kg in rats.

In chronic toxicity studies, rats tolerated a concentration of nortriptyline hydrochloride in the diet equivalent to 150 mg/kg/day for one year. They showed some growth retardation but no visceral damage. Dogs receiving nortriptyline hydrochloride orally for twelve months tolerated as much as 20 mg/kg/day. However, a large oral dose (40 mg/kg/day) caused signs of depression and ataxia and, with continued treatment, death at the end of the first month.

REFERENCES

1. Baumann P., Jonzier-Perey M., Koeb L., LÈ P.K., Tinguely D., Schopf J. Amitriptyline pharmacokinetics and clinical response: I. Free and total plasma amitriptyline and nortriptyline. International Clinical Psychopharmacology 1986; 1:89-101.

2. Corona G.L., Cucchi M.L., Frattini P., Santagostino G., Schinelli S., Zerbi F., Savoldi F. Aspects of amitriptyline and nortriptyline plasma levels monitoring in depression. Psychopharmacology 990; 100:334-338.

3. Cutler N.R., Narang P.K. Implications of dosing tricyclic antidepressants and benzodiazepines in geriatrics. Psychiatric Clinics of North America 1984; 7:845-861.

4. Dawling S., Crome P., Braithwaite R.S., Lewis R.R. Nortriptyline therapy in elderly patients: dosage prediction after single dose pharmacokinetic study. European Journal of Clinical Pharmacology 1980; 18:147-150.

5. Fabre L.F., Scharf M.B., Itil T.M. Comparative efficacy and safety of nortriptyline and fluoxetine in the treatment of major depression: a clinical study. J Clin Psychiatry 1991; 52:6(suppl)62-67.

6. Fant W.K., Ritschel W.A., Alwis S.K., Roe S., Ehret J. Prediction of steady-state nortriptyline plasma levels by the repeated one-point method. Clinical Pharmacokinetics 1984; 9:450-456.

7. Georgotas A., McCue R.E., Cooper T., Chang I., Mir P., Welkowitz J. Clinical predictors of response to antidepressants in elderly patients. Biological Psychiatary 1987; 22:733-740.

8. Georgotas A., McCue R.E., Friedman E., Cooper T.B. Electrocardiographic effects of nortriptyline, phenelzine, and placebo under optimal treatment conditions. Am J Psychiatry 1987; 144(6):798-801.

9. Georgotas A., McCue R.E., Friedman E., Cooper T.B. Response of depressive

symptoms to nortriptyline, phenelzine and placebo. British Journal of Psychiatry 1987; 515:102-106.

10. Georgotas A., McCue R.E., Friedman E., Cooper T.B. A placebo-controlled comparison of the effect of nortriptyline and phenelzine on orthostatic hypotension in elderly depressed patients. J Clin Psychopharmacol 1987; 7(6):413-416.
11. Katz M.M., Koslow S.H., Maas J.W., Frazer A., Kocsis J., Secunda S., Bowden C.L., Casper R.C. Identifying the specific clinical actions of amitriptyline: interrelationships of behaviour, affect and plasma levels in depression. Psychological Medicine 1991; 21:599-611.
12. Kragh-Sorensen P. Monitoring plasma concentration of nortriptyline. Danish Medical Bulletin 1985; 32(1):29-53.
13. Malmgren R., Aberg-Wistedt A., Bertilsson L. Serotonin uptake inhibition during treatment of depression with nortriptyline caused by parent drug and not by 10-hydroxymetabolites. Psychopharmacology 1987; 92:169-172.
14. Miller M.D., Pollock B.G., Rifai A.H., Paradis C.F., Perel J.M., George C., Stack J.A., Reynolds III C.F. Longitudinal analysis of nortriptyline side effects in elderly depressed patients. Journal of Geriatric Psychiatry and Neurology 1991; 4(4):226-230.
15. Murphy G.E., Simons A.D., Wetzel R.D. Plasma nortriptyline and clinical response in depression. Journal of Affective Disorders 1985; 9:123-129.
16. Nordin C., Bertilsson L., Siwers B. Clinical and biochemical effects during treatment of depression with nortriptyline: The role of 10-hydroxynortriptyline. Clin Pharmacol Ther 1987; 42(1):10-19.
17. Perry P.J., Browne J.L., Alexander B., Tsuang M.T., Sherman A.D., Dunner F.J. Two prospective dosing methods for nortriptyline. Clinical Pharmacokinetics 1984; 9:555-563.
18. Rosen J., Sweet R., Pollock B.G., Mulsant B.H. Nortriptyline in the hospitalized

elderly: tolerance and side effect reduction. Psychopharmacology Bulletin 1993; 29(2):327-331.

19. Sjöqvist F., Bertilsson L. Slow hydroxylation of tricyclic antidepressants - relationship to polymorphic drug oxidation. Progress Clinical Biological Research 1986; 214:169-188.
20. Sunderrajan S., Brooks C.S., Sunderrajan E.V. Nortriptyline-induced severe hyperventilation. Arch Intern Med 1985; 145(4):746-747.
21. Warner M.D., Griffin M., Peabody C.A. High initial nortriptyline doses in the treatment of depression. J Clin Psychiatry 1993; 54(2):67-69.
22. Task Force on the Use of Laboratory Tests in Psychiatry. Tricyclic antidepressants - blood level measurements and clinical outcome: An APA Task Force Report. Am J Psychiatary 1985; 142(2):155-162.
23. Antidepressants, Tricyclic - Systemic. In: Drug Information for the Health Care Professional, 14th Edition. USP DI 1994; 262-268.
24. Nortriptyline Hudrochloride. In: AHFS 94 (American Hospital Formulary Service), Drug Informaton 1994:1393-1394.

Updated References

25. Aventyl: Product Monograph, Eli Lilly Canada Inc. Toronto 1994
26. Corona G.L., Pinelli P., Zerbi F., Fenoglio L., Santagostino G., Frattini P. and Cucchi M.L. Amitriptyline, nortriptyline plasma levels and clinical response in women with affective disorders. Pharmakopsychiat 1980;13(3):102-110
27. Geller B., Fox L.W. and Fletcher M. Effect of tricylcic antidepressants on switching to mania and on the onset of bipolarity in depressed 6- to 12-year-olds. J Am Acad Child Adolesc Psychiatry 1993;32(1):43-50
28. Geller B., Cooper T.B., Chestnut E.C., Anker J.A. and Schluchter M.D. Preliminary data on the relationship between nortriptyline plasma level and response in depressed

children. Am J Psychiatry 1986;143(10):1283-1286