PRODUCT MONOGRAPH

Pr TEVA-NORTRIPTYLINE
(Nortriptlyline Hydrochloride Capsules)

10 mg and 25 mg

USP

Antidepressant

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9
www.tevacanada.com

Date of Preparation:
December 7, 2011

Submission Control No: 151598

PRODUCT MONOGRAPH

Pr TEVA-NORTRIPTYLINE

(Nortriptyline Hydrochloride Capsules)

10 mg and 25 mg

THERAPEUTIC CLASSIFICATION

Antidepressant

ACTION AND CLINICAL PHARMACOLOGY

The mood elevating mechanism of tricyclic antidepressants is at present unknown. TEVA-NORTRIPTYLINE (nortriptyline hydrochloride) 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 nortriptyline hydrochloride interferes with the transport, release, and storage of catecholamines. Operant conditioning techniques in rats and pigeons suggest that nortriptyline has a combination of stimulant and depressant properties.

Absorption:

Nortriptyline is the principal active metabolite of amitriptyline. Nortriptyline has a longer plasma half-life than amitriptyline. Nortriptyline is subject to extensive first-pass metabolism in the liver to 10-hydroxynortriptyline, which is active.

Plasma Concentrations:

Nortriptyline appears to have a specific therapeutic window between 50 and 150 ng per mL within which favourable antidepressant responses occur. Above and below this specific plasma concentration range, there is a poor clinical response. Plasma concentration

measurements were unequivocally useful in problem patients who did not respond to usual oral doses or in high-risk patients who, because of age or medical illness, would best be treated with the lowest possible effective dose of the drug.

In a study of 18 depressed patients with steady-state total nortriptyline hydrochloride plasma concentrations between 50 and 150 ng per mL, regression analyses predicted that the probability of antidepressant response would be 68% or more if the free nortriptyline hydrochloride concentration is between 7 and 10 ng per mL.

Metabolism:

There is evidence that individuals with a slow debrisoquine hydroxylation phenotype may be at greater risk of confusional states when taking nortriptyline hydrochloride. This was thought to be because the polymorphic hydroxylation of debrisoquine and nortriptyline hydrochloride are mediated by similar enzymatic mechanisms, with slow oxidizers having higher plasma nortriptyline hydrochloride concentrations. There was no significant correlation between hydroxylation phenotype and amitriptyline serum concentrations, suggesting that demethylation is mediated by a different cytochrome P-450 isoenzyme to hydroxylation. (See **PRECAUTIONS**)

A comparative bioavailability study was conducted on two nortriptyline hydrochloride 25 mg capsule products, TEVA-NORTRIPTYLINE 25 mg capsules and Aventyl® 25 mg capsules. The pharmacokinetic data calculated is summarized below.

Nortriptyline (1 x 25mg) Geometric Mean Arithmetic Mean (CV %)				
	TEVA-NORTRIPTYLINE 1x25 mg	AVENTYL®** 1x25 mg	(%)Ratio of Geometric Means	90% Confidence Interval
$AUC_{T(0-72)}$ ng.h/mL	672.5 714.5 (35)	666.6 705.4 (34)	101	95.52-103.87
AUC_I ng.h/mL	838.5 932.6 (51)	815.0 882.1 (39)	103	95.53-108.02
C_{max} ng/mL	19.80 20.46 (26.66)	19.48 20.13 (26.37)	102	96.91-103.90
T_{max}* h	7.94 (2.73)	7.03 (1.07)		
$T_{1/2}$* h	29.4 (10.5)	27.5 (8.95)		

*For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation)
**AVENTYL® 25 mg capsules (Eli Lilly Canada Inc. Canada)

INDICATIONS AND CLINICAL USE

TEVA-NORTRIPTYLINE (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

The concurrent use of TEVA-NORTRIPTYLINE (nortriptyline hydrochloride) or other tricyclic antidepressants 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 discontinue the MAO inhibitor at least 2 weeks before treatment with TEVA-NORTRIPTYLINE is started.

Patients hypersensitive to TEVA-NORTRIPTYLINE should not be given the drug. Cross-sensitivity between TEVA-NORTRIPTYLINE and other dibenzazepines is possible.

TEVA-NORTRIPTYLINE is contraindicated during the acute recovery period after myocardial infarction.

WARNINGS

Patients with cardiovascular disease should be given TEVA-NORTRIPTYLINE (nortriptyline hydrochloride) 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, TEVA-NORTRIPTYLINE 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 TEVA-NORTRIPTYLINE is administered, because this drug is known to lower the convulsive threshold. Great care is required if TEVA-NORTRIPTYLINE is given to hyperthyroid patients or to those receiving thyroid medication, because cardiac arrhythmias may develop.

TEVA-NORTRIPTYLINE 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.

Use in Pregnancy :

Safe use of TEVA-NORTRIPTYLINE 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.

PRECAUTIONS

General:

The use of TEVA-NORTRIPTYLINE (nortriptyline hydrochloride) in schizophrenic patients may result in 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, TEVA-NORTRIPTYLINE may cause symptoms of the manic phase to emerge.

Troublesome patient hostility may be aroused by the use of TEVA-NORTRIPTYLINE. As may happen with other drugs of its class, epileptiform seizures may accompany its administration.

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 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.

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).

Drug Interactions:

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 addition, 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.

There have been greater than two-fold increases in previously stable plasma levels of other antidepressants, including nortriptyline hydrochloride, when fluoxetine has been administered in combination with these agents. Fluoxetine and its active metabolite, norfluoxetine, have long half-lives (4 to 16 days for norfluoxetine) that may affect strategies during conversion from one drug to the other. 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 TEVA-NORTRIPTYLINE is used with other anticholinergic drugs or sympathomimetic drugs.

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 metabolizers 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 (eg, propafenone, flecainide, and encainide), or that inhibit this enzyme (eg, quinidine), should be approached with caution.

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 these 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 of EEG patterns; tinnitus.

Anticholinergic:

Dry mouth, and rarely, associated sublingual adenitis or gingivitis; 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; aplastic anemia; eosinophilia; purpura; thrombocytopenia.

Gastrointestinal:

Nausea and vomiting, anorexia, epigastric distress, diarrhea; peculiar taste, stomatitis, abdominal cramps, black tongue, constipation, paralytic ileus.

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, hepatitis, and liver necrosis; 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.

SYMPTOMS AND TREATEMENT OF 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, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.

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

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

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 (eg, quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

CNS: In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (eg, 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 overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSAGE AND ADMINISTRATION

TEVA-NORTRIPTYLINE (nortriptyline hydrochloride) is not recommended for children. TEVA-NORTRIPTYLINE is administered orally in the form of capsules. 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. The physician should initiate dosage at a low level and increase it gradually, checking the clinical response carefully and noting 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.

Recommended Adult Dose: 25 mg 3 or 4 times daily; dosage should begin at a low level and be increased as required. 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.

Elderly and Adolescent Patients: 30 to 50 mg/day, in divided doses.

Plasma Levels:

Optimal responses to nortriptyline have been associated with plasma concentrations of 50 to

150 ng/mL (see **PHARMACOLOGY**). 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 determinants of dosage changes.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Tedva Canada Limited at:
1-800-268-4127 ext. 5005 (English);
1-877-777-9117 (French)
or druginfo@tevacanada.com

This leaflet was prepared by:
Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9
Canada
Last revised: November 11, 2011

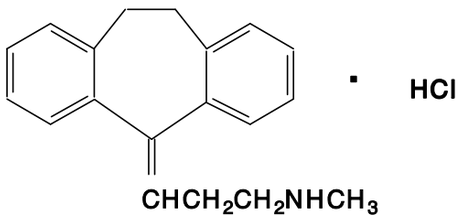
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper name: Nortriptyline Hydrochloride

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

Structural Formula:



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

Molecular Weight: 299.8

Description: White to off-white powder with a slight characteristic odor.

Solubility: Soluble in water and in chloroform; sparingly soluble in methanol; practically insoluble in ether, in benzene and in most other organic solvents.

The pH of a 1% solution is approximately 5.

Composition:

TEVA-NORTRIPTYLINE 10 mg capsules contain: nortriptyline hydrochloride equivalent to 10 mg of nortriptyline, white dextrin, corn starch, lactose monohydtare (modified spray dried), colloidal silicon dioxide and magnesium stearate. The capsule shell contains gelatin, FD&C Yellow No. 6, D&C Yellow No. 10, titanium dioxide, and gelatin.

TEVA-NORTRIPTYLINE 25 mg capsules contain: nortriptyline hydrochloride equivalent to 25 mg of nortriptyline, white dextrin, corn starch, lactose monohydtare (modified spray dried), colloidal silicon dioxide and magnesium stearate. The capsule shell contains gelatin, FD&C Yellow No. 6, D&C Yellow No. 10, titanium dioxide, and gelatin.

AVAILABILITY OF DOSAGE FORM

Availability:

TEVA-NORTRIPTYLINE (nortriptyline hydrochloride) capsules are available as:

10 mg: White to off –white powder mix in white opaque body and maize opaque cap, size #3 hard gelatin capsules. Imprinted in black ink **N** and **10** on opposing cap and body portions of the capsules.

25 mg: White to off –white powder mix in white opaque body and maize opaque cap, size #1 hard gelatin capsules. Imprinted in black ink **N** and **25** on opposing cap and body portions of the capsules.

Both strengths are supplied in bottles of 100.

Storage:

Store between 15°C and 30°C.

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 percent of an administered dose undergoes N-demethylation in the whole animal. Another 40 percent 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 per kg daily) caused signs of depression and ataxia and, with continued treatment, death at the end of the first month.

REFERENCES

1. Bonaccorsi A, Franco R, Garattini S, et al. Plasma nortriptyline and cardiac responses in young and old rats. Br J Pharmac 1977; 60:21-27

2. Cairncross KD, McCulloch MW, Story DF, Trinker, F. Modification of synaptic transmission in the superior cervical ganglion by epinephrine, norepinephrine and nortriptyline. Int J Neuropharmacol 1967; 6:293-300

3. Hyttel J, Christensen A, Fjalland B. Neuropharacological properties of amitriptyline, nortriptyline and their metabolites. Acta Pharmacol et Toxicol 1980; 47:53-57

4. Meyers DB, Small RM, Anderson RC. Toxicology of nortriptyline hydrochloride. Toxicol Appl Pharmacol 1966; 9:152-159

5. Pollock BG, Everett G, Perel, JM. Comparative cardiotoxicity of nortriptyline and its isomeric 10-hydroxymetabolites. Neuropsychopharmacology 1992; 6:1-10

6. AHFS Drug Information 1994. American Hospital Formulary Services. Bethesda MD USA 1994; 1383-1387; 1393-1394

7. CPS Twenty-ninth edition. Canadian Pharmaceutical Association. Ottawa, Canada. 1994; 128-129

8. USP Drug Information 1994 United States Pharmacopeial Convention Inc. Rochville MD, USA. 1994; 278-289

9. A Two-Way Single Dose Fasting Bioavailability Study of Teva-Nortriptyline HCl 25mg Capsules and Aventyl® 25mg Pulvule Capsules in Normal Healthy Non-Smoking Male Volunteers (Study# 1484-1). Data on file at Teva Canada Limited.

10. Aventyl® Product Monograph, September 17, 2009; Eli Lilly Canada Inc., Toronto, Ontario