PRODUCT MONOGRAPH

PrTEVA-AMITRIPTYLINE

(Amitriptyline Hydrochloride Tablets, USP)

10 mg, 25 mg, and 50 mg

Antidepressant

Teva Canada Limited
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Control Number: **190590**

ACTION

Amitriptyline hydrochloride is a tricyclic antidepressant with sedative properties. Its mechanism of action in man is not known. Amitriptyline inhibits the membrane pump mechanism responsible for the re-uptake of transmitter amines, such as norepinephrine and serotonin, thereby increasing their concentration at the synaptic clefts of the brain. Amitriptyline has pronounced anticholinergic properties and produces EKG changes and quinidine-like effects on the heart (See ADVERSE REACTIONS). It also lowers the convulsive threshold and causes alterations in EEG and sleep patterns.

Orally administered amitriptyline is readily absorbed and rapidly metabolized. Steady-state plasma concentrations vary widely and this variation may be genetically determined. Amitriptyline is primarily excreted in the urine, mostly in the form of metabolites, with some excretion also occurring in the feces.

INDICATIONS

TEVA-AMITRIPTYLINE (amitriptyline hydrochloride USP) is indicated for the relief of symptoms of depressive illness.

CONTRAINDICATIONS

Known hypersensitivity. Amitriptyline should not be given concomitantly with or within at least 14 days following the discontinuance of a MAO inhibitor. Then initiate dosage of amitriptyline cautiously with gradual increase in dosage until optimum response is achieved. Amitriptyline is not recommended during the acute recovery phase following myocardial infarction, and in the presence of acute congestive heart failure.

WARNINGS

Arrhythmias, sinus tachycardia, and prolongation of the conduction time have been reported, particularly with high doses of amitriptyline. A few instances of unexpected death have been reported in patients with cardiovascular disorders. Myocardial infarction and stroke have also been reported with drugs of this class. Therefore, these drugs should be used with extreme caution in patients with a history of cardiovascular disease, those with circulatory liability, and elderly patients. In such cases, treatment should be initiated with low doses, with progressive increases only if required and tolerated, and the patient should be under close surveillance at all dosage levels.

Close supervision is required for hyperthyroid patients or those receiving thyroid medication, because of the possibility of cardiovascular toxicity.

Amitriptyline should be used with caution in patients with a history of seizures. Concurrent

electroshock therapy may increase the hazards of therapy; such treatment, therefore, should be limited to patients for whom it is essential.

Because of its anticholinergic activity it should be used with caution in patients with a history of urinary retention, or patients with narrow-angle glaucoma or increased intraocular pressure. Paralytic ileus may occur, especially in elderly or hospitalized patients taking tricyclic antidepressants alone, or in combination with other anticholinergic drugs. Therefore, appropriate measures should be taken if constipation occurs.

This drug may impair mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Amitriptyline should be used with caution in patients with a history of hepatic or renal damage or of blood dyscrasias. Periodic leukocyte and differential blood counts and liver function tests should be performed when patients receive amitriptyline in large doses, or over prolonged periods.

Use in Pregnancy and Lactation: The safety of amitriptyline use during pregnancy and lactation has not been established, and therefore it should not be administered to women of child-bearing potential or nursing mothers, unless, in the opinion of the physician, the expected benefit to the patient outweighs the potential hazard to the fetus or child.

Use in Children: In view of the lack of experience with amitriptyline in the treatment of depression in children, this drug is not recommended for patients under 12 years of age.

PRECAUTIONS

In schizophrenic patients and those with paranoid symptomatology, activation of latent or aggravation of existing symptoms may occur; manic-depressive patients may experience a shift to the manic phase. In these circumstances, it may be necessary to reduce the dosage or discontinue amitriptyline therapy, and to administer an antipsychotic agent, such as a phenothiazine.

The possibility of suicide in depressed patients remains during treatment and until significant remission occurs; this type of patient should not have easy access to large quantities of the drug.

When amitriptyline is given with anticholinergic agents or CNS-depressant or sympathomimetic drugs, close supervision and careful adjustment of dosages are required.

When possible, discontinue the drug several days before elective surgery.

Drug Interactions: Amitriptyline may block the antihypertensive action of guanethidine or similarly acting compounds.

The drug may enhance the response to alcohol and the effects of barbiturates and other CNS depressants. Caution is advised if patients receive large doses of ethchlorvynol concurrently.

Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75-150 mg of amitriptyline.

Caution should be exercised if amitriptyline is administered together with cimetidine, since the latter has been shown to inhibit the metabolism of several tricyclic antidepressants, including amitriptyline, and clinically significant increases in plasma levels of amitriptyline may occur.

ADVERSE REACTIONS

The following adverse reactions have been reported with amitriptyline or other tricyclic antidepressants:

Neurologic: Dizziness, weakness, headache, tinnitus, extrapyramidal symptoms such as tremor, ataxia and incoordination, slurred speech, seizures, changes in EEG patterns, numbness, tingling, paresthesia of the limbs, peripheral neuropathy.

Behavioural: Drowsiness, fatigue, giddiness, excitement, agitation, restlessness, hypomania or manic episodes, insomnia nightmares, jitteriness, anxiety, activation of latent schizophrenia, confusion, disorientation, hallucinations, delusions, disturbed concentration, impaired memory.

Autonomic: Dry mouth and, rarely, associated sublingual adenitis, blurred vision, disturbance of accommodation, mydriasis, constipation, paralytic ileus, urinary retention, dilatation of the urinary tract, disturbances of micturition, excessive sweating, flushing, precipitation of latent and aggravation of existing glaucoma.

Cardiovascular: Hypotension and associated vertigo, hypertension, tachycardia, palpitations, syncope. A quinidine-like effect and other reversible EKG changes, such as flattening or inversion of T-waves, bundle branch block, depressed S-T segments, prolonged conduction time and asystole, arrhythmias, heart block, fibrillation, myocardial infarction and stroke have been reported. Unexpected death in patients with cardiovascular disorders has occurred during administration of tricyclic antidepressants.

Gastrointestinal: Nausea, vomiting, disturbances of appetite, epigastric distress, heartburn, abdominal pain, diarrhea.

Endocrine: Impotence, testicular swelling and gynecomastia in the male, breast enlargement and galactorrhea in the female, changes in libido, weight gain or loss, changes in blood sugar levels, syndrome of inappropriate antidiuretic hormone (ADH) secretion.

Allergic or Toxic: Skin rash, petechiae, urticaria, pruritus, edema, photosensitization; bone marrow depression, including agranulocytosis, eosinophilia, leukopenia, purpura and thrombocytopenia; obstructive jaundice and disorders of hepatic function, drug fever.

Miscellaneous: Alopecia, parotid swelling, peculiar taste, stomatitis, black tongue, hyperpyrexia.

Withdrawal Symptoms: Abrupt cessation of treatment after prolonged administration may produce nausea, headache and malaise; these symptoms are not indicative of addiction.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

Symptoms: High doses of amitriptyline may cause temporary confusion, disturbed concentration, or transient visual hallucinations. Manifestations of overdosage are: drowsiness, severe hypotension, hypertension, hypothermia, or hyperpyrexia, tachycardia, arrhythmic abnormalities, EKG evidence of impaired conduction (such as bundle branch block), congestive heart failure, agitation, hyperactive reflexes, muscle rigidity, vomiting, perspiration, rapid thready pulse, respiratory depression, dilated pupils, general weakness, convulsions, stupor and coma. In patients with glaucoma, even average doses may precipitate an attack.

Treatment: Treatment is symptomatic and supportive. Cardiac arrhythmias and CNS involvement pose the greatest threat and may occur suddenly even when initial symptoms appear to be mild. Therefore, patients who may have ingested an overdosage of amitriptyline, particularly children, should be hospitalized and kept under close surveillance. Induced emesis and gastric lavage are recommended in the alert and conscious patient. It may be helpful to leave the tube in the stomach, with irrigation (with an electrolyte balanced fluid) and continual

aspiration of stomach contents possibly promoting more rapid elimination of the drug from the body. If the patient is not alert, a cuffed endotracheal tube should be inserted before lavage is performed and emesis should not be induced. An open airway should be maintained.

Standard measures (oxygen, intravenous fluids, corticosteroids) may be used to manage circulatory shock. Noradrenaline or other pressor agents (but not adrenaline) by i.v. drop infusion under continuous monitoring may be used, if necessary. Failing respiration must be maintained by artificial means, but respiratory stimulants should not be used. Hyperpyrexia should be controlled by external measures, such as ice packs and cooling sponge baths. Bladder catheterization should be performed in the unconscious patient.

Continuous cardiac monitoring should be instituted in all patients, particularly in the presence of EKG abnormalities, and should be maintained for several days after the cardiac rhythm has returned to normal. Because of its effect on cardiac conduction, digitalis should be used only with caution. If rapid digitalization is required for the treatment of congestive heart failure, special care should be exercised in using the drug.

The room should be darkened, with minimal amount of external stimulation, to reduce the tendency to convulsions. If convulsions occur, they should preferably be controlled by non-barbiturate sedatives, such as chlordiazepoxide or diazepam, or by an inhalation anesthetic (amitriptyline increases the CNS depressant but not the anticonvulsant action of barbiturates). It has been reported that the slow intravenous administration of physostigmine salicylate may reverse some of the CNS and cardiovascular effects of tricyclic antidepressant overdosage. The dosage that has been recommended for adults is 1 to 2 mg in very slow intravenous injection. In children, the initial dosage should not exceed 0.5 mg and should be adjusted to age and response. Since physostigmine has a short duration of action, administration may have to be repeated at 30 to 60 minute intervals. Physostigmine is not innocuous and carries the risk of inducing seizures and cholinergic crisis. It should not be used routinely. If excessive sweating, nausea, or vomiting occurs, dosage of physostigmine should be reduced. Atropine in a dose of 50% of the amount of injected physostigmine should be kept at hand and administered if excessive cholinergic symptoms develop.

Deaths by deliberate or accidental overdosage have occurred with this class of drugs. Since the propensity for suicide is high in depressed patients, a suicide attempt by other means may occur during the recovery phase. The possibility of simultaneous ingestion of other drugs should also be considered. Dialysis has not been found to be of value for intoxication by amitriptyline alone due to low plasma concentrations of the drug.

DOSAGE AND ADMINISTRATION

As with other psychotropic drugs, the dosage of TEVA-AMITRIPTYLINE (amitriptyline hydrochloride USP) should be adapted to the requirements of each individual patient. Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance. It should be kept in mind that a lag in therapeutic response occurs at the onset of therapy, lasting from several days to a few weeks. Increasing the dosage does not normally shorten this latent period and may increase the incidence of side effects.

Initial Dosage: Adults: The recommended initial dose for ambulatory patients is 75 mg daily in two or three divided doses. This should be increased as required by 25 mg increments, usually up to 150 mg daily, and preferably by adding to the late afternoon and/or bedtime doses. Doses in excess of 200 mg daily are not recommended for outpatients. In the case of severely depressed or hospitalized patients, a higher initial dose of 100 mg daily in two or three divided doses may be indicated. The usual optimal dose is 150 mg daily, but some patients may require up to 300 mg daily, depending on tolerance and response of each individual patient.

Elderly or Debilitated Patients: In general, lower dosages are recommended for these patients. Initially, 20 to 30 mg daily in divided doses is suggested, with very gradual increments, depending on tolerance and response. Blood pressure and cardiac rhythm should be checked frequently, particularly in patients who have unstable cardiovascular function.

Maintenance Dosage: Once a satisfactory response has been obtained, the dosage should be adjusted to the lowest level required to maintain symptomatic relief. Medication should be continued for the expected duration of the depressive episode in order to minimize the possibility of relapse following clinical improvement.

AVAILABILITY

TEVA-AMITRIPTYLINE tablets are available in film-coated tablet as the following:

10 mg amitriptyline hydrochloride as blue, circular biconvex, film-coated tablets having an embossing of ‘rph’ on one side and ‘A114’ on the other side. Available in bottles of 100 and 1000.

25 mg amitriptyline hydrochloride as yellow, circular biconvex, film-coated tablets having an embossing of ‘rph’ on one side and ‘A113’ on the other side. Available in bottles of 100 and 1000.

50 mg amitriptyline hydrochloride as beige, circular biconvex, film-coated tablets having an embossing of ‘rph’ on one side and ‘A112’ on the other side. Available in bottles of 100 and 1000.

COMPOSITION

TEVA-AMITRIPTYLINE (amitriptyline hydrochloride USP) tablets are available in 3 strengths containing 10 mg, 25 mg, and 50 mg amitriptyline per tablet.

The following non-medicinal ingredients are common to all tablet strengths:
colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, pregelatinised starch, titanium dioxide, triacetin and triacetate.

Colourants are present in the tablets as follows:

10 mg: FD&C Blue #1 Aluminum Lake, FD&C Yellow # 6 Aluminum Lake

25 mg: D&C Yellow #10 Aluminum Lake, FD&C Blue #1 Aluminum Lake, FD&C Yellow # 6 Aluminum Lake

50 mg: Black Iron Oxide, Iron Oxide Red, Yellow Iron Oxide

STORAGE

Store at room temperature (15-30°C). Keep in a tightly closed container. Protect from moisture.

CHEMISTRY AND PHARMACOLOGY

A two-way crossover, blinded, single-dose, fasting, bioequivalence study of amitriptyline 50 mg tablets versus Apo®-amitriptyline 50 mg tablets in 23 normal, healthy, non-smoking male subjects was conducted. The summary of results is in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

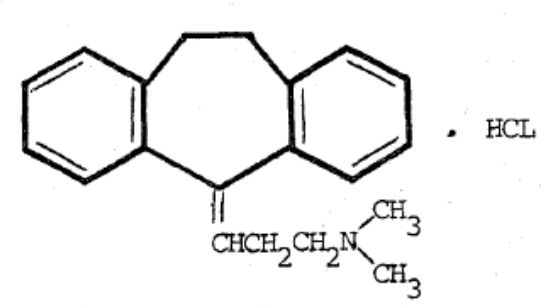
Amitriptyline (1 x 50 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	607.7 662.8 (41.5)	571.0 648.6 (46.4)	106.4	99.78 – 113.5
AUC_I (ng·h/mL)	684.7 752.5 (42.4)	647.1 744.0 (47.9)	105.8	99.20 – 112.9
C_{max} (ng/mL)	33.32 35.50 (37.01)	32.15 35.63 (43.68)	103.6	94.98 – 113.1
T_{max}§ (h)	4.22 (39.62)	4.46 (42.64)		
$T_{½}$§ (h)	23.60 (16.86)	23.71 (21.66)		

* Amitriptyline Hydrochloride Tablets USP 50 mg (Teva Canada Limited, formally ratiopharm inc. Canada) purchased in Canada

† Apo-Amitriptyline (Amitriptyline Hydrochloride Tablets USP) 50 mg (Apotex, Canada)

§ Expressed as median (range) only

Amitriptyline hydrochloride is 3-[10,11-dihydro-5H-dibenzo(a,d)-eyclohepten-5-ylidene]-N,N-dimethyl-1-propanamine hydrochloride, and has the following structural formula:



Amitriptyline has qualitatively similar pharmacologic actions to other tricyclic antidepressants in experimental animals. It is more sedative than imipramine, reducing spontaneous motor activity at lower doses. It also prolongs hexobarbital sleeping time, produces ataxia and has a disruptive effect on EEG activity and conditioned behaviour. Amitriptyline antagonizes or reverses the depressant effects of reserpine and tetrabenazine and potentiates the pressor effects

of norepinephrine and various behavioural effects of amphetamine. It possesses anticholinergic, antihistaminic and weak antiserotonin action. Amitriptyline also decreases body temperature, lowers blood pressure in the anesthetized dog and has a quinidine-like effect on the heart.

Amitriptyline is absorbed slowly from the gastrointestinal tract in experimental animals. The drug is distributed in liver, lung, and brain tissue. Amitriptyline is detoxified in the liver where it undergoes N-demethylation to nortriptyline, which is further demethylated. Amitriptyline is excreted in the urine and bile as conjugates of the cis and trans isomers of 10-hydroxynortriptyline.

TOXICOLOGY

Acute:

Species	Route	Sex	LD_{50} (mg of base/kg)	95% Fiducial Limits
Mice	PO	F	289	(249-335)
	IP	F	76	(71-81)
	SC	F	328	(279-386)
Rats	PO	F	464	(370-583)
	PO	M	600	(403-872)
	IP	F	67	(59-76)
	IP	M	77	(67-88)
	SC	F	1350	(1130-1162)
	SC	M	1235	(1010-1510)

Signs of toxicity included sedation, ataxia, ptosis, lacrimation, decreased respiratory rate, partial loss of righting reflex and convulsions.

Subacute and Chronic: Dogs: Oral doses of 20 and 40 mg/kg/day were tolerated for 6 months without hematologic, biochemical or anatomical evidence of drug toxicity. Signs of drug effect included slight to marked sedation, a slight tachycardia, slight ataxia, and occasionally, excessive salivation and emesis. Oral doses of 80 mg/kg/day in a 6-month study were not well tolerated: 2 of 4 dogs died within 3 weeks after exhibiting severe ataxia and sedation. No other drug-related effects were observed. Doses of 100 mg/kg/day or greater were not tolerated for more than a few days. The only effect observed was a small amount of fat in the periportal region of the liver without evidence of necrosis.

Rats: 0, 15, 30 or 60 mg/kg/day were given orally by gavage, 5 days a week, for periods up to 48 weeks. Doses of 60 mg/kg/day produced a moderate depression of body weight and a slight increase in liver weight.

REFERENCES:

1. Product Monograph, Apo-Amitriptyline (amitriptyline hydrochloride) Tablets, Apotex Inc., June 8, 1987.

2. A Two-Way Crossover, Blinded, Single-Dose, Fasting, Bioequivalence Study of Amitriptyline 50mg Tablets Versus Apo®-Amitriptyline 50mg Tablets in Normal Healthy Non-Smoking Male Subjects (Study# 3300). Data on File at Teva Canada Limited.