PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]TEVA-AMITRIPTYLINE

Amitriptyline Hydrochloride Tablets, USP

10 mg, 25 mg, and 50 mg

Antidepressant

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PRODUCT MONOGRAPH

TEVA-AMITRIPTYLINE

Amitriptyline Hydrochloride Tablets, USP
10 mg, 25 mg, and 50 mg

THERAPEUTIC CLASSIFICATION

Antidepressant

ACTIONS AND CLINICAL PHARMACOLOGY

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 AND CLINICAL USE

TEVA-AMITRIPTYLINE (amitriptyline hydrochloride) is indicated in the drug management of depressive illness.

TEVA-AMITRIPTYLINE may be used in depressive illness of psychotic or endogenous nature and in selected patients with neurotic depression. Endogenous depression is more likely to be alleviated than are other depressive states. TEVA-AMITRIPTYLINE, because of its sedative action, is also of value in alleviating the anxiety component of depression.

As with other tricyclic antidepressants, TEVA-AMITRIPTYLINE may precipitate hypomanic episodes in patients with bipolar depression. These drugs are not indicated in mild depressive states and depressive reactions.

CONTRAINDICATIONS

TEVA-AMITRIPTYLINE (amitriptyline hydrochloride) is contraindicated in:

- Patients who are hypersensitive to amitriptyline hydrochloride or to any ingredient in the formulation (see PHARMACEUTCIAL INFORMATION, Composition) or component of the container.
- Patients with recent myocardial infarction or acute congestive heart failure.

- Patients with severe liver impairment.

Amitriptyline should not be used in combination with a monoamine oxidase inhibitor (MAOI) due to the risk of serotonin syndrome (a combination of symptoms that may include agitation, confusion, tremor, myoclonus, and hyperthermia). Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving concomitant tricyclic, antidepressants and MAOIs.

Treatment with a MAOI should be discontinued at least 14 days before initiating treatment with amitriptyline. Similarly, amitriptyline treatment should be discontinued at least 14 days before starting a MAOI (see DOSAGE AND ADMINISTRATION).

WARNINGS

Amitriptyline should be used with caution in patients with a history of seizures, impaired liver function or blood dyscrasias. Due to its anticholinergic activity, amitriptyline should be used with caution in patients with a history of urinary retention, or with narrow-angle glaucoma or increased intraocular pressure.

As with other antidepressants, TEVA-AMITRIPTYLINE can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles (see ADVERSE REACTIONS). Healthcare providers should inform patients to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye. In patients with narrow-angle glaucoma, even average doses may precipitate an attack.

Patients with cardiovascular disorders should be closely monitored. Tricyclic antidepressant drugs, including amitriptyline have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time and severe hypotension, particularly at high doses. Myocardial infarction and stroke have been reported with drugs of this class (see ADVERSE REACTIONS). Cardiac arrhythmias and severe hypotension may also occur at normal doses in patients with pre-existing cardiovascular disease. A few instances of unexpected death have been reported in patients with cardiovascular disorders. Therefore, these drugs should be used with caution in patients with a history of cardiovascular disease, such as myocardial infarction, congestive heart failure (see CONTRAINDICATIONS) and conduction abnormalities.

There has been a report of fatal dysrhythmia occurring as late as 56 hours after amitriptyline overdose.

Caution is recommended when amitriptyline is administered to hyperthyroid patients or those receiving thyroid medication. Cardiac arrhythmias may develop when tricyclic antidepressants are used concomitantly with thyroid medications.

QT interval prolongation
Cases of QT interval prolongation and arrhythmia have been reported during the post-marketing period (see ADVERSE REACTIONS, Cardiovascular). Caution is advised in patients with significant bradycardia, in patients with uncompensated heart failure, or in patients concurrently taking QT-prolonging drugs (see PRECAUTIONS, Drug Interactions). Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) are also known to increase the proarrythmic risk.
Concurrent administration of amitriptyline and electroconvulsive therapy may increase the hazards of therapy. Such treatment should be limited to patients for whom it is essential.

Amitriptyline may impair mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a motor vehicle. Patients should be advised to avoid such tasks until they know how amitriptyline affects them.

Fertility: Amitriptyline reduced the pregnancy rate in rats. No data on the effects of amitriptyline on human fertility are available.

Pregnant Women::
There are no adequate and well-controlled studies in pregnant women. When considering treatment with amitriptyline in pregnant women or women who may become pregnant, the potential benefits must be weighed against the possible hazards to mother and child. Amitriptyline is not recommended during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

Nursing Women: Amitriptyline and its metabolites are excreted in breast milk. Because of the potential for serious adverse reactions in infants from amitriptyline, a decision should be made whether to discontinue nursing or discontinue the drug.

Pediatrics:
The safety and efficacy of amitriptyline have not been established in patients under 12 years of age. The use of amitriptyline in pediatric patients is not recommended (see DOSAGE and ADMINISTRATION).

Geriatrics (> 65 years of age): Geriatric patients are particularly sensitive to the anticholinergic side effects of tricyclic antidepressants including amitriptyline hydrochloride. Peripheral anticholinergic effects include tachycardia, urinary retention, constipation, dry mouth, blurred vision, and exacerbation of narrow angle glaucoma. Central nervous system anticholinergic effects include cognitive impairment, psychomotor slowing, confusion, sedation, and delirium.

Elderly patients taking amitriptyline hydrochloride may be at increased risk for falls.

Elderly patients should be started on low doses of amitriptyline and observed closely due to the greater frequency of decreased hepatic function, concomitant disease and other drug therapy in elderly patients (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS

The potency of amitriptyline is such that addition of other antidepressant drugs generally does not result in any additional therapeutic benefit. Untoward reactions have been reported after the combined use of antidepressant agents having varying modes of activity. Accordingly, combined use of amitriptyline and other antidepressant drugs should be undertaken only with due recognition of the possibility of potentiation and with a thorough knowledge of the pharmacology of both drugs. There have been no reports of untoward events when patients receiving amitriptyline were changed immediately to protriptyline or vice versa.

When amitriptyline is used to treat the depressive component of schizophrenia, activation or exacerbation of existing psychotic manifestation may occur. Likewise, patients with bipolar disorder may experience hypomanic or manic episodes and hyperactive or agitated patients may become overstimulated when treated with amitriptyline. Paranoid delusions, with or without associated hostility, may be exaggerated. A reduction in dose or discontinuation of amitriptyline may be indicated and administration of a neuroleptic such as a phenothiazine, be considered under these circumstances.

The possibility of suicide is inherent in depression and remains during treatment High risk patients should be closely supervised throughout treatment. To minimize the risk of intentional overdose, prescriptions for TEVA-AMITRIPTYLINE should be written for the smallest possible quantity consistent with good patient management.

Discontinue the drug several days before elective surgery if possible.

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

Drug Interactions:

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS

Tricyclic antidepressants may potentiate the cardiovascular effects of sympathomimetic drugs. Close supervision and careful adjustment of dosage are required when amitriptyline is administered with sympathomimetic drugs, including epinephrine combined with local anesthetics.

Tricyclic antidepressants may potentiate the effects of anticholinergic drugs on the eye, central nervous system, bowel and bladder and close supervision and careful adjustment of dosage are required. Paralytic ileus, urinary retention or acute glaucoma may occur in patients taking tricyclic antidepressants in combination with anticholinergic-type drugs, particularly in elderly or hospitalized patients.

Hyperpyrexia has been reported when tricyclic antidepressants are administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.

Tricyclic antidepressants may counteract the antihypertensive effects of centrally acting antihypertensives such as clonidine and methyldopa. It is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants.

Amitriptyline may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Delirium has been reported with concurrent administration of amitriptyline and disulfiram.

Drugs Metabolized by P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (CYP 2D6) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by CYP 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 that inhibit the activity of CYP 2D6 make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given a

drug that inhibits CYP 2D6 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 CYP 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit CYP 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 coadministration 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 CYP 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 cotherapy, an increased dose of tricyclic antidepressant may be required. Monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of CYP 2D6.

Drugs which prolong the QT-interval including antiarrhythmics (e.g., quinidine, sotalol, disopyramide, amiodarone, some antipsychotics (e.g., pimozide, haloperidol), antidepressants (e.g., fluoxetine, tricyclic/tetracyclic antidepressants); macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, tacrolimus); quinolone antibiotics (e.g., ciprofloxacin); antimalarials (e.g., quinine, chloroquine); azole antifungals (e.g., ketoconazole); domperidone; 5-HT3 receptor antagonists (e.g., ondansetron); tyrosine kinase inhibitors (e.g., sunitinib); histone deacetylase inhibitors (e.g., vorinostat); and, beta-2 adrenoceptor agonists (e.g., salmeterol) may increase the likelihood of ventricular arrhythmias when taken with tricyclic antidepressants.

Use caution when using amitriptyline and methadone concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.

Caution is also advised for co-administration of amitriptyline and diuretics inducing hypokalaemia (e.g. furosemide) (see WARNINGS, QT Interval Prolongation).

ADVERSE REACTIONS

Note: Included in the listing which follows are a few adverse reactions which have not been reported with this specific drug. However, pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when amitriptyline is administered.

Psychiatric: drowsiness, fatigue, activation of latent schizophrenia, disorientation, confusional states, hallucinations, delusions, hypomanic reactions, disturbed concentration, nightmares, insomnia, restlessness, agitation, excitement, jitteriness, anxiety, giddiness.

Neurologic: epileptiform seizures, coma, dizziness, tremors, numbness, tingling, parasthesias of the extremities, peripheral neuropathy, headache, ataxia, alteration in EEG patterns, extrapyramidal symptoms including abnormal involuntary movements and tardive dyskinesia, dysarthria, tinnitus, incoordination, and slurred speech.

Anticholinergic: urinary retention, dilatation of the urinary tract, constipation, paralytic ileus, especially in the elderly, hyperpyrexia, dry mouth, blurred vision, disturbance of accommodation, increased intraocular pressure, precipitation of latent glaucoma, aggravation of existing glaucoma, and mydriasis. Amitriptyline hydrochloride tablets can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma.

Cardiovascular: myocardial infarction, stroke, non-specific ECG changes and changes in AV conduction, prolonged conduction time, asystole, hypotension, syncope, hypertension, palpitation, QT interval prolongation, arrhythmias, heart block, ventricular tachycardia, fibrillation, unexpected death in patients with cardiovascular disorders.

Hematologic: bone marrow depression, including agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia.

Allergic: skin rash, urticaria, photosensitization, edema of the face and tongue, itching.

Gastrointestinal: nausea, epigastric distress, heartburn, vomiting, hepatitis (including altered liver function and jaundice), anorexia, stomatitis, peculiar taste, diarrhea, parotid swelling, black tongue.

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

Miscellaneous: weakness, increased perspiration, edema, urinary frequency, alopecia, increased appetite, weight gain, weight loss.

Withdrawal Symptoms: Abrupt cessation of treatment after prolonged administration may produce nausea, headache and malaise. Gradual dosage reduction has been reported to produce, within 2 weeks, transient symptoms including irritability, restlessness, and dream and sleep disturbance. These symptoms are not indicative of addiction. Rare instances have been reported of mania or hypomania occurring within 2 to 7 days following cessation of chronic therapy with tricyclic antidepressants.

Other reported adverse reactions for which a relationship could not be established include lupus-like syndrome (migratory arthritis, positive ANA and rheumatoid factor), hepatic failure and ageusia.

Post-market Adverse Events
A syndrome resembling neuroleptic malignant syndrome (NMS) has been very rarely reported after starting or increasing the dose of amitriptyline, with and without concomitant medications known to cause NMS. Symptoms have included muscle rigidity, fever, mental status changes, diaphoresis, tachycardia, and tremor.

Very rare cases of serotonin syndrome have been reported with amitriptyline in combination with other drugs that have a recognized association with serotonin syndrome.

Very rare cases of cardiomyopathy have been reported with amitriptyline.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

SYMPTOMS

High doses may cause temporary confusion, disturbed concentration, or transient visual hallucinations. Overdosage may cause drowsiness, hypothermia, tachycardia and other arrhythmic abnormalities, such as bundle branch block, ECG evidence of impaired conduction, congestive heart failure, disorders of ocular motility, convulsions, severe hypotension, stupor, coma, polyradiculoneuropathy and constipation. Other symptoms may be agitation, hyperactive reflexes, muscle rigidity, vomiting, hyperpyrexia, or any of those listed under ADVERSE REACTIONS. Symptoms of overdose may vary in severity depending on various factors such as the amount of drug absorbed, the interval between drug ingestion and start of treatment, and the age of the patient. In patients with glaucoma, even average doses may precipitate an attack.

TREATMENT

For the most current information for management of a suspected overdose, contact your regional Poison Control Centre immediately.

Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose; therefore, hospital monitoring is required as soon as possible.

In managing overdose, consider the possibility of multiple drug overdose, interactions among drugs, and unusual drug kinetics.

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.

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 the period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose (see WARNINGS); these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination
EMESIS IS CONTRAINDICATED. 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.

Cardiovascular
A maximal limb lead QRS duration of $\geq$ 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 < 20 mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine or bretylium. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide and procainamide and flecainide).

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).

DOSAGE AND ADMINISTRATION

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Outpatient Adults: The recommended initial dose for ambulatory patients is 25 mg 3 times a day. Depending upon tolerance and response, this may be increased to a total of 150 mg a day.

Increases are made preferably in the late afternoon and/or bedtime doses. The sedative effect is usually rapidly apparent. The antidepressant activity may be evident within 3 or 4 days or may take up to 30 days to develop adequately.

Hospitalized Patients: Severely ill or hospitalized patients may require 100 mg a day initially. This can be increased gradually to 200 mg a day if necessary. A small number of hospitalized patients may need as much as 300 mg a day.

Pediatric Patients: The use of amitriptyline in pediatric patients is not recommended (see WARNINGS, Pediatrics).

Adolescent and Elderly Patients: When considering the use of amitriptyline in adolescent or elderly patients, the potential risks must be balanced with clinical need (see WARNINGS). In general, lower dosages are recommended for these patients. In those patients who may not tolerate higher doses, 50 mg daily may be satisfactory. The dose may be administered in divided doses or as a single dose preferably in the evening or at bedtime.
Maintenance: When satisfactory improvement has been reached, dosage should be reduced to the lowest amount that will maintain relief of symptoms. The usual maintenance dose is 50 to 100 mg/day in divided doses; however, in suitable patients, the total daily dosage may be given in a single dose, preferably at bedtime. It is appropriate to continue maintenance therapy throughout the active phase of the depression and for the expected duration of the depressive episode, in order to minimize the possibility of relapse.

Plasma Levels: Because of the wide variation in the absorption and distribution of tricyclic antidepressants in body fluids, it is difficult to directly correlate plasma levels and therapeutic effect. However, determination of plasma levels may be useful in identifying patients who appear to have toxic effects and may have excessively high levels, or those in whom lack of absorption or non-compliance is suspected. Adjustments in dosage should be made according to the patient's clinical response and not on the basis of plasma levels.

AVAILABILITY

TEVA-AMITRIPTYLINE tablets are available in film-coated tablets 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, magnesium stearate, microcrystalline cellulose, pregelatinised starch.

Coating ingredients are present in the tablets as follows:

10 mg: Hypromellose, Titanium Dioxide, Triacetin, FD&C Blue #1 Aluminum Lake, FD&C Yellow # 6 Aluminum Lake

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

50 mg: Polyvinyl Alcohol, Titanium Dioxide, Polyethylene Glycol, Talc, 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

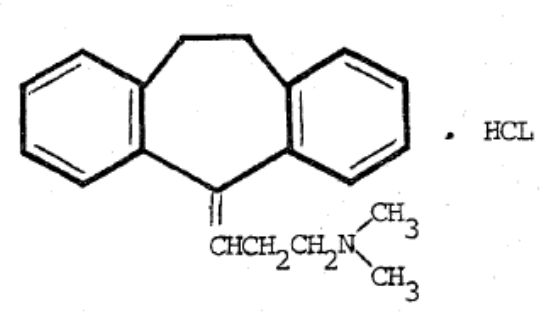
Amitriptyline (1 x 50 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	Ratio of Geometric Means %	90% Confidence Interval
AUC_T (ng·h/mL)	607.7 662.8 (41.5)	571.0 648.6 (46.4)	106.4	99.78 – 113.5
AUC_I (ng·h/mL)	684.7 752.5 (42.4)	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., February 11, 2019.

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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

TEVA-AMITRIPTYLINE

Amitriptyline Hydrochloride Tablets

Read this carefully before you start taking TEVA-AMITRIPTYLINE and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about TEVA-AMITRIPTYLINE.

Serious Warnings and Precautions

- **Electrical problems with the heart (QT interval prolongation) -** A heart problem called "prolonged QT interval" (which is shown on your electrocardiogram, ECG) and problems with the heart rhythm (rapid or irregular heart beat) have been reported in people taking TEVA-AMITRIPTYLINE. This can be serious and cause sudden death. If you experience dizziness, fainting, a rapid heart beat or heart palpitations while taking TEVA-AMITRIPTYLINE get immediate medical help.

- **Thoughts of suicide and worsening of your depression -** If you are depressed, you can sometimes have thoughts of harming or killing yourself. These thoughts may be increased when first starting antidepressants like TEVA-AMITRIPTYLINE, since these medicines take time to work. If you have thoughts of suicide or harming yourself while taking TEVA-AMITRIPTYLINE get immediate medical help.

What is TEVA-AMITRIPTYLINE used for?

TEVA-AMITRIPTYLINE is used in adults to treat depression.

How does TEVA-AMITRIPTYLINE work?

TEVA-AMITRIPTYLINE is an antidepressant that belongs to a group of medicines known as tricyclic antidepressants. It is not known exactly how TEVA-AMITRIPTYLINE works. It is thought to increase the concentration of certain chemicals in the brain which can help with the symptoms of depression.

What are the ingredients in TEVA-AMITRIPTYLINE?

Medicinal ingredients: amitriptyline hydrochloride
Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, pregelatinised starch.

Coating ingredients are present in the tablets as follows:

10 mg: Hypromellose, Titanium Dioxide, Triacetin, FD&C Blue #1 Aluminum Lake, FD&C Yellow # 6 Aluminum Lake

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

50 mg: Polyvinyl Alcohol, Titanium Dioxide, Polyethylene Glycol, Talc, Black Iron Oxide, Iron Oxide Red, Yellow Iron Oxide.

TEVA-AMITRIPTYLINE comes in the following dosage forms:
tablets: 10 mg, 25 mg, 50 mg

Do not use TEVA-AMITRIPTYLINE if you:
- are allergic to amitriptyline or any of the other ingredients of this medicine
- have recently experienced a heart attack or heart failure
- have a severe liver disease
- are taking a medicine known as monoamine oxidase inhibitors (MAOIs), also used to treat depression
- have taken a MAOI within the last 14 days

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-AMITRIPTYLINE. Talk about any health conditions or problems you may have, including if you:
- have heart problems such as changes in heart rhythm which are seen on an electrocardiogram (ECG), heart block, or heart disease
- have a slow heart beat (bradycardia)
- have glaucoma or increased pressure in your eyes
- have liver problems.
- have or have had a history of epilepsy, seizures or fits.
- have difficulty passing urine
- have an enlarged prostate
- have thyroid problems or are taking thyroid medication
- have bipolar disorder
- have schizophrenia
- have a blood disease with abnormal particles in the blood called "blood discrasia"
- have problems with your electrolytes including low levels of calcium, potassium or magnesium in your blood
- are dehydrated or suffer from excessive sweating, vomiting or diarrhea, or an eating disorder
- are undergoing electroconvulsive therapy (ECT) to treat mental health problems
- are scheduled to have surgery
- are pregnant or planning to become pregnant
- are breastfeeding or planning to breastfeed. You and your healthcare professional should decide if you should breastfeed or take TEVA-AMITRIPTYLINE. You should not do both.
- are 65 years of age or older

Other warnings you should know about:
Driving and Using Machines: TEVA-AMITRIPTYLINE can affect your ability to drive and operate machinery. Do not drive or operate machinery until you know how TEVA-AMITRIPTYLINE affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TEVA-AMITRIPTYLINE:
- monoamine oxidase inhibitors (MAOIs) also used to treat depression, such as selegiline and phenelzine
- medicines such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine which may be found in cough and cold medication and anesthetics used in

surgery

- other medicines used to treat depression such as other tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) like fluoxetine, sertraline, and paroxetine.
- anticholinergenic drugs such as certain medicines used to treat glaucoma, Parkinson's disease and stomach and gut problems, like atropine and hyoscyamine
- cimetidine, used to treat stomach ulcers
- sedatives used to treat anxiety and sleep disorders
- disulfiram, used to treat alcoholism
- medicines used to treat schizophrenia and other mental health problems, such as primozide, sertindole and haloperidol
- high blood pressure medications such as clonidine and methyldopa
- medicines used to treat irregular heartbeat such as quinidine, propafenone, flecainide, disopyramide, amiodarone and sotalol
- astemizole and terfenadine, used to treat allergies and hayfever
- cisapride, used to treat certain types of indigestion
- methadone, used to treat pain and for detoxification
- diuretics or "water pills" such as furosemide
- thyroid medication
- medicines used to treat bacterial infections such as erythromycin, clarithromycin, tacrolimus and ciprofloxacin.
- medicines used to treat malaria such as quinine, halofantrine and chloroquine
- medicines used to treat fungal infections such as ketoconazole
- domperidone used to treat nausea and vomiting and increase milk supply in breastfeeding mothers
- medicines used to treat nausea and vomiting in cancer patients such as ondansetron
- medicines used to treat cancer such as sunitinib and vorinostat
- medicines used to treat breathing problems like asthma and COPD such as salmeterol

You should avoid drinking alcohol while taking TEVA-AMITRIPTYLINE.

How to take TEVA-AMITRIPTYLINE:

- Always take TEVA-AMITRIPTYLINE exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- TEVA-AMITRIPTYLINE can be taken with or without food.
- Swallow the tablets whole with water. Do not chew them.

Even if you feel better, do not stop taking TEVA-AMITRIPTYLINE without first talking to your healthcare professional. Stopping TEVA-AMITRIPTYLINE suddenly can cause serious withdrawal symptoms.

Usual adult dose:

The recommended initial dose is 25 mg three times a day.

Depending on your response to TEVA-AMITRIPTYLINE, your healthcare professional may gradually increase your dose to 150 mg per day divided in two doses.

The usual maintenance dose is 50 to 100 mg per day.

Overdose:

If you think you have taken too much **TEVA-AMITRIPTYLINE**, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take TEVA-AMITRIPTYLINE, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Do not take two doses at the same time to make up for a missed dose.

What are possible side effects from using TEVA-AMITRIPTYLINE?
These are not all the possible side effects you may feel when taking TEVA-AMITRIPTYLINE. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- nausea, vomiting
- stomach pain
- constipation
- diarrhea
- drowsiness
- dizziness
- fatigue
- restlessness
- headache
- dry mouth, sore mouth
- unpleasant taste in the mouth
- black tongue
- itching
- changes in weight (loss or gain)
- weakness
- increased sweating

TEVA-AMITRIPTYLINE can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Mental health problems: confusion, hallucinations, trouble sleeping, excitement, nightmares, problems with attention, anxiety		√	

Nervous system problems: shaking, numbness and tingling of the hands and feet, clumsiness and lack of coordination, loss of balance, uncontrolled twitching or jerking, slurred speech, ringing in the ears, coma		√	
Neuroleptic malignant syndrome: very high fever, irregular heartbeat, rapid breathing, muscle stiffness, altered mental state			√
Difficulty passing urine	√		
Glaucoma: increased pressure in the eye, blurred vision, eye pain		√	
Electrical problems with the heart (QT interval prolongation): dizziness, fainting, fast heartbeat, palpitations			√
Heart attack: chest pain, tightness or pressure that may spread to your neck, jaw or back, nausea, indigestion, shortness of breath, cold sweat, fatigue, dizziness			√
Stroke: sudden numbness or weakness in the face, arm or leg, confusion, trouble speaking, blurred vision, trouble walking, dizziness, loss of balance			√
High blood pressure: headache, fatigue, vision problems		√	
Heart problems (enlarged heart, heart disease): weakness, fatigue, shortness of breath especially during exercise, light-headedness, chest pain, palpitations, fainting, swelling in your feet, ankles and legs		√	
Bone marrow depression: easy bruising, bleeding, nose bleeds, bleeding gums, red spots on the skin, fever and chills, rash, extreme fatigue, pale skin and lips			√
Increased sensitivity of the skin to sun	√		
Allergic reaction: rash, hives, swelling of the face, lips and tongue or throat, difficulty swallowing or breathing.			√
Liver problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
Reproductive problems: swelling of testicles, impotence in men, increase in breast tissue (in men and women), change in sex drive		√	
Increased or decreased blood sugar: frequent urination, thirst, hunger, shakiness, sweating and chills, irritability, confusion, dizziness	√		
Unusual hair loss or thinning		√	
Mania: elevated or irritated mood, decreased need for sleep, racing thoughts		√	
Serotonin syndrome: a combination of most or all of the following: confusion, restlessness, sweating, shaking, shivering, hallucinations, sudden			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
jerking of the muscles, fast heartbeat			
Seizures or fits			√
New or worsened emotional or behavioural problems: feeling angry, aggressive, worried, agitated, hostile or impulsive, feeling violent or suicidal, thoughts of hurting yourself or other people, feeling like you are not yourself or that you are less inhibited			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:

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

Keep out of reach and sight of children.

If you want more information about TEVA-AMITRIPTYLINE:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email

druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9

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