

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**PrAmitriptyline Hydrochloride Tablets USP**

Amitriptyline hydrochloride tablets

Tablets, 10 mg, 25 mg, 50 mg and 75 mg, Oral

USP

Antidepressant

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## RECENT MAJOR LABEL CHANGES

[7 Warnings and precautions, Neurologic](#)

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### TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES.....	2
TABLE OF CONTENTS.....	2
<b>PART I: HEALTH PROFESSIONAL INFORMATION .....</b>	<b>4</b>
<b>1 INDICATIONS.....</b>	<b>4</b>
1.1 Pediatrics .....	4
1.2 Geriatrics.....	4
<b>2 CONTRAINDICATIONS.....</b>	<b>4</b>
<b>3 SERIOUS WARNINGS AND PRECAUTIONS BOX.....</b>	<b>5</b>
<b>4 DOSAGE AND ADMINISTRATION .....</b>	<b>5</b>
4.1 Dosing Considerations .....	5
4.2 Recommended Dose and Dosage Adjustment .....	5
4.4 Administration .....	6
4.5 Missed Dose.....	7
<b>5 OVERDOSAGE.....</b>	<b>7</b>
<b>6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.....</b>	<b>8</b>
<b>7 WARNINGS AND PRECAUTIONS .....</b>	<b>9</b>
7.1 Special Populations.....	12
7.1.1 Pregnant Women.....	12
7.1.2 Breast-feeding.....	13
7.1.3 Pediatrics.....	13
7.1.4 Geriatrics.....	13
<b>8 ADVERSE REACTIONS.....</b>	<b>13</b>
8.1 Adverse Reaction Overview.....	13
8.5 Post-Market Adverse Reactions .....	14
<b>9 DRUG INTERACTIONS.....</b>	<b>15</b>

9.1	Serious Drug Interactions .....	15
9.2	Drug Interactions Overview .....	15
9.3	Drug-Behavioural Interactions .....	15
9.4	Drug-Drug Interactions .....	15
9.5	Drug-Food Interactions.....	19
9.6	Drug-Herb Interactions .....	19
9.7	Drug-Laboratory Test Interactions.....	19
<b>10</b>	<b>CLINICAL PHARMACOLOGY .....</b>	<b>19</b>
10.1	Mechanism of Action .....	19
10.2	Pharmacodynamics.....	19
10.3	Pharmacokinetics.....	19
<b>11</b>	<b>STORAGE, STABILITY AND DISPOSAL .....</b>	<b>20</b>
<b>12</b>	<b>SPECIAL HANDLING INSTRUCTIONS .....</b>	<b>20</b>
<b>PART II: SCIENTIFIC INFORMATION.....</b>		<b>21</b>
<b>13</b>	<b>PHARMACEUTICAL INFORMATION.....</b>	<b>21</b>
<b>14</b>	<b>CLINICAL TRIALS .....</b>	<b>21</b>
14.3	Comparative Bioavailability Studies .....	21
<b>15</b>	<b>MICROBIOLOGY .....</b>	<b>21</b>
<b>16</b>	<b>NON-CLINICAL TOXICOLOGY .....</b>	<b>21</b>
<b>17</b>	<b>SUPPORTING PRODUCT MONOGRAPHS .....</b>	<b>22</b>
<b>PATIENT MEDICATION INFORMATION.....</b>		<b>23</b>

## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **1 INDICATIONS**

Amitriptyline Hydrochloride Tablets USP (amitriptyline hydrochloride) is indicated for:

- Drug management of depressive illness.
- 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. Amitriptyline Hydrochloride Tablets USP, because of its sedative action, is also of value in alleviating the anxiety component of depression.

As with other tricyclic antidepressants, Amitriptyline Hydrochloride Tablets USP may precipitate hypomanic episodes in patients with bipolar depression. These drugs are not indicated in mild depressive states and depressive reactions.

#### **1.1 Pediatrics**

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use.

#### **1.2 Geriatrics**

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

### **2 CONTRAINDICATIONS**

Amitriptyline Hydrochloride Tablets USP (amitriptyline hydrochloride) is contraindicated in:

- Patients who are hypersensitive to amitriptyline hydrochloride or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).
- Patients with recent myocardial infarction or acute congestive heart failure.
- Patients with severe liver impairment.
- Combination with a monoamine oxidase inhibitor (MAOI) due to the risk of serotonin toxicity (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 [7 WARNINGS AND PRECAUTIONS, Neurologic](#).

### 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

#### Serious Warnings and Precautions

- **Extreme caution should be used when Amitriptyline Hydrochloride Tablets USP is given in the following situations:**
  - Cases of QT interval prolongation, cardiac arrhythmia and severe hypotension have been reported. A few instances of unexpected death have also been reported in patients with cardiovascular disorders. Myocardial infarction and stroke have been reported with drugs of this class. Extreme caution is advised in patients with a history of cardiovascular disorders (e.g., significant bradycardia, myocardial infarction, congestive or uncompensated heart failure), conduction abnormalities or those concurrently taking QT-prolonging drugs. See [2 CONTRAINDICATIONS](#); [5 OVERDOSAGE](#); [7 WARNINGS AND PRECAUTIONS, Cardiovascular](#); [8.1 Adverse Reaction Overview, Cardiac disorders](#); [9.4 Drug-Drug Interactions](#).
  - In patients with a history or urinary retention or in patients with increased intraocular pressure or narrow angle glaucoma, because of the anticholinergic properties of amitriptyline hydrochloride. See [7 WARNINGS AND PRECAUTIONS, General](#); [7 WARNINGS AND PRECAUTIONS, Ophthalmologic](#).
  - In patient with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias. See [7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism](#).
  - In patients with a history of a seizure disorder, because amitriptyline hydrochloride has been shown to lower the seizure threshold. See [7 WARNINGS AND PRECAUTIONS, Neurologic](#).
- **Potential association with behavioural and emotional changes, including self-harm and suicidal ideation and behaviour.** See [7 WARNINGS AND PRECAUTIONS, Psychiatric](#).

### 4 DOSAGE AND ADMINISTRATION

#### 4.1 Dosing Considerations

Dosage should be initiated at a low level and increased gradually according to tolerance and clinical response.

##### Cardiac

Prior to initiating treatment with Amitriptyline Hydrochloride Tablets USP, a cardiac evaluation, including blood pressure and electrocardiogram examinations, should be performed, particularly in patients with a history of cardiovascular disorders (see [7 WARNINGS AND PRECAUTIONS, Cardiovascular](#)).

#### 4.2 Recommended Dose and Dosage Adjustment

##### 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 gradually 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**

Health Canada has not authorized an indication for pediatric use.

### **Elderly Patients**

When considering the use of amitriptyline in elderly patients, the potential risks must be balanced with clinical need. See [7.1.4 Geriatrics](#). 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 lessen 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.

### **Concomitant use with CYP2D6 inhibitors**

Dosage adjustments may be required if Amitriptyline Hydrochloride Tablets USP is co-administered with CYP2D6 inhibitors (see [9.2 Drug Interactions Overview](#) and [9.4 Drug-Drug Interactions](#)).

## **4.4 Administration**

Amitriptyline Hydrochloride Tablets USP tablets should be swallowed whole with water. Amitriptyline Hydrochloride Tablets USP can be administered with or without food.

#### 4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule.

### 5 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 [8 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

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 overdose 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 [7 WARNINGS AND PRECAUTIONS, Cardiovascular](#)); 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).

For management of a suspected drug overdose, contact your regional poison control centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 1 – Dosage Forms, Strengths, Composition and Packaging**

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 10 mg, 25 mg, 50 mg, and 75 mg of amitriptyline hydrochloride	Colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, purified talc and titanium dioxide.  In addition to the above ingredients the tablets also contain the following non-medicinal ingredients:  Amitriptyline Hydrochloride Tablets USP 10 mg tablets: triacetin and the dye FD&C Blue No. A1. Lake.  Amitriptyline Hydrochloride Tablets USP 25 mg tablets:



		<p>polyethylene glycol and the dye D&amp;C Yellow No. 10 Lake.</p> <p>Amitriptyline Hydrochloride Tablets USP 50 mg tablets: triacetin and the dyes FD&amp;C Yellow No.6 and FD&amp;C Blue No. 2 A1 Lake.</p> <p>Amitriptyline Hydrochloride Tablets USP 75 mg tablets: polyethylene glycol and the dye Lake Sunset Yellow.</p>
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**Amitriptyline Hydrochloride Tablets USP 10 mg:** Round, blue colored, biconvex tablets, debossed "A" on one side and "10" on other side. Contains 10 mg of amitriptyline hydrochloride. Available in HDPE bottles of 100 and 1000 tablets, and blisters of Alu/Alu 10 x 10 tablets.

**Amitriptyline Hydrochloride Tablets USP 25 mg:** Round, yellow colored, biconvex tablets debossed "A" on one side and "25" on other side. Contains 25 mg of amitriptyline hydrochloride. Available in HDPE bottles of 100 and 1000 tablets, and blisters of Alu/Alu 10 x 10 tablets.

**Amitriptyline Hydrochloride Tablets USP 50 mg:** Round, brown colored, biconvex tablets debossed "A" on one side and "50" on other side. Contains 50 mg of amitriptyline hydrochloride. Available in HDPE bottles of 100 and 1000 tablets, and blisters of Alu/Alu 10 x 10 tablets.

**Amitriptyline Hydrochloride Tablets USP 75 mg:** Round, orange colored, biconvex tablets debossed "A" on one side and "75" on other side. Contains 75 mg of amitriptyline hydrochloride. Available in HDPE bottles of 100 and 1000 tablets, and blisters of Alu/Alu 10 x 10 tablets.

## 7 WARNINGS AND PRECAUTIONS

Please see [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#).

### General

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.

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.

### Cardiovascular

Patients with cardiovascular disorders should be closely monitored (see [7 WARNINGS AND](#)

[PRECAUTIONS, Monitoring and Laboratory Tests](#) and [4.1 Dosing Considerations](#)). 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 [8.1 Adverse Reaction Overview, Cardiac disorders](#) and [8.1 Adverse Reaction Overview, Vascular disorders](#). Cardiac arrhythmias and severe hypotension may also occur at normal doses in patients with pre-existing cardiovascular disease. A few instances of unexpected deaths have been reported in patients with cardiovascular disorders. Therefore, Amitriptyline Hydrochloride Tablets USP should be used with caution in patients with a history of cardiovascular disease, such as myocardial infarction, congestive heart failure (see [2 CONTRAINDICATIONS](#)) and conduction abnormalities.

There has been a report of a fatal dysrhythmia occurring as late as 56 hours after amitriptyline overdose (see [5 OVERDOSAGE](#)).

#### ***QT interval prolongation***

Cases of QT interval prolongation and arrhythmia have been reported during the post-marketing period. Caution is advised in patients with significant bradycardia, uncompensated heart failure, or in patients concurrently taking QT-prolonging drugs. Electrolyte disturbances (hypokalemia, hyperkalemia, hypomagnesaemia) are also known to increase the proarrhythmic risk.

#### **Dependence/Tolerance**

#### ***Withdrawal Symptoms***

Withdrawal symptoms may occur after abrupt cessation of treatment with Amitriptyline Hydrochloride Tablets USP (see [8.1 Adverse Reaction Overview, Withdrawal Symptoms](#)).

#### **Driving and Operating Machinery**

Amitriptyline may impair mental and/or physical abilities required for 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.

#### **Endocrine and Metabolism**

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

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.

#### **Hematologic**

Amitriptyline should be used with caution in patients with a history of blood dyscrasias.

#### **Hepatic/Biliary/Pancreatic**

Amitriptyline Hydrochloride Tablets USP is contraindicated in patients with severe liver impairment (see [2 CONTRAINDICATIONS](#)). Amitriptyline should be used with caution in patients with impaired liver function.

## Monitoring and Laboratory Tests

Cardiac function, including blood pressure and ECG, should be periodically monitored during treatment with Amitriptyline Hydrochloride Tablets USP, particularly in patients with a history of cardiovascular disorders (see [7 WARNINGS AND PRECAUTIONS, Cardiovascular](#)).

## Neurologic

### *Seizures*

Amitriptyline hydrochloride is known to lower the convulsive threshold. Amitriptyline Hydrochloride Tablets USP should be used with extreme caution patients with a history of seizure disorder.

### *Serotonin toxicity/Neuroleptic Malignant Syndrome*

Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with amitriptyline hydrochloride (see [8.5 Post-Market Adverse Reactions](#)).

Serotonin toxicity is characterized by neuromuscular excitation, autonomic stimulation (e.g. , tachycardia, flushing) and altered mental state (e.g., anxiety, agitation, hypomania). In accordance with the Hunter criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus

Neuroleptic malignant syndrome (NMS) has also been reported with amitriptyline hydrochloride, with and without concomitant medications known to cause NMS (see [8.5 Post-Market Adverse Reactions](#)). The clinical manifestations of neuroleptic malignant syndrome often overlap with those of serotonin toxicity, including hyperthermia, hypertonia, altered mental status, and autonomic instability. In contrast to serotonin toxicity, patients with neuroleptic malignant syndrome may present with “lead pipe” muscle rigidity as well as hyporeflexia.

The concomitant use of Amitriptyline Hydrochloride Tablets USP with monoamine oxidase inhibitors is contraindicated (see [2 CONTRAINDICATIONS](#)). Amitriptyline Hydrochloride Tablets USP should be used with caution in patients receiving other serotonergic drugs or antipsychotics/neuroleptics. If concomitant treatment with Amitriptyline Hydrochloride Tablets USP and other serotonergic agents and/or antipsychotics/neuroleptics is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see [9.4 Drug-Drug Interactions](#)). Serotonin toxicity and neuroleptic malignant syndrome may result in potentially life-threatening conditions. If serotonin toxicity or neuroleptic malignant syndrome is suspected, discontinuation of Amitriptyline Hydrochloride Tablets USP should be considered.

## **Ophthalmologic**

As with other antidepressants, amitriptyline hydrochloride can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. See [8.1 Adverse Reaction Overview, Eye disorders](#). Healthcare professionals 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.

## **Peri-Operative Considerations**

Discontinue the drug several days before elective surgery if possible.

## **Psychiatric**

### ***Electroconvulsive therapy***

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.

### ***Psychosis, Mania/Hypomania and Other Neuropsychiatric Phenomena***

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.

### ***Clinical Worsening and Suicide***

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 Amitriptyline Hydrochloride Tablets USP should be written for the smallest possible quantity consistent with good patient management.

## **Reproductive Health: Female and Male Potential**

- **Fertility**

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

## **7.1 Special Populations**

### **7.1.1 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.

### 7.1.2 Breast-feeding

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.

### 7.1.3 Pediatrics

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use.

### 7.1.4 Geriatrics

Geriatrics ( $\geq$  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 [4.2 Recommended Dose and Dosage Adjustment](#).

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

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.

**Blood and lymphatic system disorders:** bone marrow depression, including agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia.

**Cardiac disorders:** myocardial infarction, changes in AV conduction, asystole, syncope, palpitation, arrhythmias, heart block, ventricular tachycardia, fibrillation, unexpected death in patients with cardiovascular disorders.

**Endocrine disorders:** gynecomastia in the male, syndrome of inappropriate ADH (antidiuretic hormone) secretion.

**Eye disorders:** blurred vision, disturbance of accommodation, 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.

**Gastrointestinal disorders:** nausea, epigastric distress, heartburn, vomiting, stomatitis, peculiar taste, diarrhea, parotid swelling, black tongue, constipation, paralytic ileus especially in the elderly, dry mouth.

**General disorders and administration site conditions:** fatigue, jitteriness, hyperpyrexia, weakness, increased perspiration, edema.

**Hepatobiliary disorders:** hepatitis (including altered liver function and jaundice).

**Investigations:** alteration in EEG patterns, increased intraocular pressure, non-specific ECG changes, prolonged conduction time, QT interval prolongation, elevation and lowering of blood sugar levels, weight gain, weight loss.

**Metabolism and nutrition disorders:** anorexia, increased appetite.

**Nervous system disorders:** epileptiform seizures, coma, dizziness, tremors, numbness, tingling, parasthesia of the extremities, peripheral neuropathy, headache, ataxia, extrapyramidal symptoms including abnormal involuntary movements and tardive dyskinesia, dysarthria, tinnitus, incoordination, giddiness and slurred speech.

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

**Renal and urinary disorders:** urinary retention, dilatation of the urinary tract, urinary frequency.

**Reproductive system and breast disorders:** testicular swelling, impotence in the male, breast enlargement and galactorrhea in the female, increased or decreased libido.

**Skin and subcutaneous tissue disorders:** skin rash, urticaria, photosensitization, edema of the face and tongue, itching, alopecia.

**Vascular disorders:** stroke, hypotension, hypertension.

**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.

## **8.5 Post-Market Adverse Reactions**

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 (see [7 WARNINGS AND PRECAUTIONS, Neurologic](#)).

Very rare cases of serotonin toxicity have been reported with amitriptyline in combination with other drugs that have a recognized association with serotonin toxicity (see [7 WARNINGS AND PRECAUTIONS, Neurologic](#)).

Very rare cases of cardiomyopathy have been reported with amitriptyline.

## 9 DRUG INTERACTIONS

### 9.1 Serious Drug Interactions

#### Serious Drug Interactions

- Monoamine Oxidase Inhibitors: Amitriptyline Hydrochloride Tablets USP should be not administered for a period of at least 14 days after the discontinuation of treatment with MAO inhibitors due to the potential for severe interactions. The same caution should also be observed when administering a MAO inhibitor after previous treatment with Amitriptyline Hydrochloride Tablets USP. See [2 CONTRAINDICATIONS](#) and [7 WARNINGS AND PRECAUTIONS, Neurologic](#).
- Thyroid Medication: See [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#) and [7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism](#).

### 9.2 Drug Interactions Overview

#### 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).

### 9.3 Drug-Behavioural Interactions

Amitriptyline may enhance the response to alcohol.

### 9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

**Table 2 - Established or Potential Drug-Drug Interactions**

Proper/Common name	Source of Evidence	Effect	Clinical comment
Anticholinergic drugs	T	↑ Anticholinergic effects	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.
Anticholinergic agents or neuroleptic drugs	CT	Hyperpyrexia	Hyperpyrexia has been reported when tricyclic antidepressants are administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.
Barbiturates and CNS depressants	T	↑ Effects of barbiturates and CNS depressants	Amitriptyline may enhance the effects of barbiturates and other CNS depressants.
Cimetidine	CT	↑ Tricyclic antidepressants	Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants.
Clonidine and methyldopa	T	↓ Antihypertensive effects	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.
Disulfiram	CT	Delirium	Delirium has been reported with concurrent administration of amitriptyline and disulfiram.



Proper/Common name	Source of Evidence	Effect	Clinical comment
Diuretics	T	Hypokalemia	Caution is advised for co-administration of amitriptyline and diuretics inducing hypokalemia (e.g., furosemide). See <a href="#">7 WARNINGS AND PRECAUTIONS, Cardiovascular</a> .
Methadone	T	↑ Cardiovascular effects. Additive effects on the QT interval	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.
Sympathomimetic drugs	T	↑ Cardiovascular effects	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.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

### CYP2D6 inhibitors

Certain drugs that inhibit the activity of CYP2D6 make normal metabolizers resemble poor metabolizers. A given dose of tricyclic antidepressant may become abruptly toxic when a drug that inhibits CYP2D6 is introduced as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme such as quinidine and cimetidine (see [Table 2](#) above) and many that are substrates for CYP 2D6 such as many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide. 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 co-therapy, an increased dose of tricyclic antidepressant may be required. Monitor tricyclic antidepressant plasma levels whenever a tricyclic antidepressant is going to be co-administered with another drug known to be an inhibitor of CYP2D6.

### **Serotonergic agents**

While selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit CYP 2D6 (see previous subsection), they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs as well as 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).

Co-administration of Amitriptyline Hydrochloride Tablets USP with serotonergic agents such as SSRIs, SNRIs and triptans may lead to additive effects on the serotonergic system and serotonin toxicity may occur (see [7 WARNINGS AND PRECAUTIONS, Neurologic](#)).

### **QT-prolonging drugs**

Concomitant use of drugs that prolong the QT interval with tricyclic antidepressants such as Amitriptyline Hydrochloride Tablets USP may increase the likelihood of ventricular arrhythmias.

Drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide);
- Class III antiarrhythmics (e.g., amiodarone);
- Class 1C antiarrhythmics (e.g., flecainide, propafenone);
- antipsychotics (e.g., pimozide, haloperidol);
- antidepressants (e.g., fluoxetine, tricyclic/tetracyclic antidepressants);
- opioids (e.g., methadone);
- 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-HT<sub>3</sub> receptor antagonists (e.g., ondansetron);
- tyrosine kinase inhibitors (e.g., sunitinib);
- histone deacetylase inhibitors (e.g., vorinostat);
- beta-2 adrenoceptor agonists (e.g., salmeterol).

The above list of potentially interacting drugs is not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QT/QTc interval as well as for older drugs for which these effects have recently been established.

### **9.5 Drug-Food Interactions**

Interactions with food have not been established.

### **9.6 Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **9.7 Drug-Laboratory Test Interactions**

Interactions with laboratory tests have not been established.

## **10 CLINICAL PHARMACOLOGY**

### **10.1 Mechanism of 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 [8 ADVERSE REACTIONS](#). It also lowers the convulsive threshold and causes alterations in EEG and sleep patterns.

### **10.2 Pharmacodynamics**

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 antiserotonergic action. Amitriptyline also decreases body temperature, lowers blood pressure in the anesthetized dog and has a quinidine-like effect on the heart.

### **10.3 Pharmacokinetics**

#### **Absorption**

Amitriptyline is absorbed slowly from the gastrointestinal tract in experimental animals.

Orally administered amitriptyline is readily absorbed and rapidly metabolized. Steady-state plasma concentrations vary widely and this variation may be genetically determined.

#### **Distribution:**

The drug is distributed in liver, lung, and brain tissue.

#### **Metabolism:**

Amitriptyline is detoxified in the liver where it undergoes N-demethylation to nortriptyline,

which is further demethylated.

### Elimination

Amitriptyline is primarily excreted in the urine, mostly in the form of metabolites, with some excretion also occurring in the feces.

Amitriptyline is excreted in the urine and bile as conjugates of the cis and trans isomers of 10-hydroxynortriptyline.

### Special Populations and Conditions

- **Pediatrics (< 18 years of age):** Health Canada has not authorized an indication for use in pediatric patients.
- **Geriatrics:** Information is not available. 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 [7.1.4 Geriatrics](#) and [4.2 Recommended Dose and Dosage Adjustment](#).
- **Sex:** Information is not available.
- **Genetic Polymorphism:** 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).
- **Ethnic Origin:** Information is not available.
- **Hepatic Insufficiency:** Information is not available. Amitriptyline Hydrochloride Tablets USP is contraindicated in patients with severe liver impairment (see [2 CONTRAINDICATIONS](#)). Amitriptyline should be used with caution in patients with impaired liver function.
- **Renal Insufficiency:** Information is not available.
- **Obesity:** Information is not available.
- 

### 11 STORAGE, STABILITY AND DISPOSAL

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

Amitriptyline Hydrochloride Tablets USP should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

### 12 SPECIAL HANDLING INSTRUCTIONS

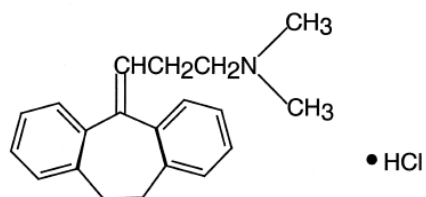
None.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name:	Amitriptyline hydrochloride
Chemical name:	1-propanamine, 3-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidene)-N,N-dimethyl-hydrochloride
Molecular formula and molecular mass:	C <sub>20</sub> H <sub>23</sub> N • HCl and 313.86 g/mol
Structural formula:	



Physicochemical properties:	Amitriptyline hydrochloride is a white or practically white, odorless or practically odorless, crystalline powder or small crystals. Freely soluble in water, in alcohol, in chloroform, and in methanol; insoluble in ether.
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### 14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

#### 14.3 Comparative Bioavailability Studies

A double blinded, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, two-way crossover, oral bioequivalence study of Amitriptyline Hydrochloride Tablets USP (amitriptyline hydrochloride) 10 mg (Strides Pharma Canada Inc.) and Elavil® (amitriptyline hydrochloride) 10 mg tablets (AA Pharma Inc., Canada) in 34 healthy, adult, human subjects under fasting conditions was conducted. The summary of results is in the following table.

**SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA**

<b>Amitriptyline Hydrochloride Tablets USP 10 mg</b> From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval
<b>AUC<sub>0-72</sub></b> <b>(ng.hr/mL)</b>	152.03 166.24 (45.00)	146.15 161.63 (47.98)	104.12	99.55 to 108.89
<b>C<sub>max</sub></b> <b>(ng/mL)</b>	7.08 7.63 (40.12)	6.86 7.42 (39.45)	103.59	97.44 to 110.13
<b>T<sub>max</sub><sup>§</sup></b> <b>(hr)</b>	4.50 (2.00-8.00)	4.50 (2.00-10.00)		
<b>T<sub>½</sub><sup>€</sup></b> <b>(hr)</b>	30.09 31.85 (36.52)	29.16 31.22 (42.49)		
<b>K<sub>el</sub> (hr<sup>-1</sup>)<sup>€</sup></b>	0.023 0.024 (32.59)	0.024 0.025 (33.00)		

\* Test: Amitriptyline Hydrochloride Tablets USP 10 mg (Strides Pharma Canada Inc.)

† Reference: PrElavil® (amitriptyline hydrochloride) 10 mg Tablets (AA Pharma Inc., Vaughan, Canada)

§ Expressed as median (range) only

€ Expressed as the arithmetic mean (CV%) only

In addition, a double blinded, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, two-way crossover, oral bioequivalence study of Amitriptyline Hydrochloride Tablets USP (amitriptyline hydrochloride) 75 mg (Strides Pharma Canada Inc.) and Elavil® (amitriptyline hydrochloride) 75 mg tablets (AA Pharma Inc., Canada) in 34 healthy, adult, human subjects under fasting conditions was conducted. The summary of results is in the following table.

**SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA**

<b>Amitriptyline Hydrochloride Tablets USP 75 mg</b> From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval
<b>AUC<sub>0-72</sub></b> <b>(ng.hr/mL)</b>	1464.64 1557.15 (35.46)	1394.94 1479.25 (35.43)	105.00	100.57 to 109.62
<b>C<sub>max</sub></b> <b>(ng/mL)</b>	74.20 81.46 (46.19)	70.84 74.61 (34.59)	104.73	96.37 to 113.83
<b>T<sub>max</sub><sup>§</sup></b> <b>(hr)</b>	3.50 (2.00-8.00)	4.50 (1.50-8.00)		

Amitriptyline Hydrochloride Tablets USP 75 mg From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval
$T_{1/2}^{\text{€}}$ (hr)	29.61 30.67 (26.79)	29.19 30.26 (27.49)		
$K_{el}$ (hr <sup>-1</sup> ) <sup>€</sup>	0.023 0.024 (26.73)	0.024 0.025 (27.51)		

\* Test: Amitriptyline Hydrochloride Tablets USP 75 mg (Strides Pharma Canada Inc.)

† Reference: PrElavil® (amitriptyline hydrochloride) 75 mg Tablets (AA Pharma Inc., Vaughan, Canada)

§ Expressed as median (range) only

€ Expressed as the arithmetic mean (CV%) only

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

### General Toxicology:

#### ACUTE

SPECIES	ROUTE	SEX	LD <sub>50</sub> (mg of base/kg)	95% FUDUCIAL LIMITS
Mice	PO	F	289	(249 – 335)
	IP	F	76	(71 – 81)
	SO	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.

**Carcinogenicity:** Information is not available.

**Genotoxicity:** Information is not available.

**Reproductive and Developmental Toxicology:** Information is not available.

**Special Toxicology:** Information is not available.

**Juvenile Toxicity:** Information is not available.

## **17 SUPPORTING PRODUCT MONOGRAPHS**

1. ELAVIL, amitriptyline hydrochloride tablets 10 mg, 25 mg, 50 mg, and 75 mg, submission control 259735, Product Monograph, AA PHARMA INC. (MAY 31, 2022)



## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

#### PrAmitriptyline Hydrochloride Tablets USP

#### Amitriptyline Hydrochloride Tablets

Read this carefully before you start taking **Amitriptyline Hydrochloride Tablets USP** 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 **Amitriptyline Hydrochloride Tablets USP**.

#### Serious Warnings and Precautions

**To help avoid side effects and ensure proper use, before you take Amitriptyline Hydrochloride Tablets USP, talk to your healthcare professional if you have:**

- a history of heart problems such as changes in heart rhythm, a slow heartbeat (bradycardia), heart disease or are taking medicines that effect your heart rhythm. A heart problem called “prolonged QT interval” (which is shown on your electrocardiogram, ECG) and problems with the heart rhythm (rapid or irregular heartbeat) have been reported in people taking amitriptyline hydrochloride. This can be serious and cause sudden death. If you experience dizziness, fainting, a rapid heart beat or heart palpitations while taking Amitriptyline Hydrochloride Tablets USP get immediate medical help.
- a history of trouble emptying your bladder (urinary retention) or increased pressure in the eye (glaucoma) as Amitriptyline Hydrochloride Tablets USP can make these conditions worse.
- thyroid problems or are taking thyroid medication. Heart rhythm problems may develop when Amitriptyline Hydrochloride Tablets USP is taken with thyroid medicines.
- a history of seizures or fits. Amitriptyline Hydrochloride Tablets USP can make you more likely to have seizures or fits.

#### **New or worsened emotional or behavioural problems:**

- **Get immediate medical help if you have any thoughts of suicide or harming yourself while you are taking Amitriptyline Hydrochloride Tablets USP. Close observation by a healthcare professional is necessary in this situation.**
- When you first start taking Amitriptyline Hydrochloride Tablets USP or when your dose is adjusted, you may feel worse instead of better. This can include new or worsened feelings of agitation, hostility, anxiety, or impulsivity. Do not stop taking your medicine as it takes time for Amitriptyline Hydrochloride Tablets USP to work.
- It is important that you and your healthcare professional talk regularly during your treatment about how you are feeling. If your depression worsens or you experience changes in your behaviour, tell your healthcare professional right away.
- You may find it helpful to tell a relative or close friend that you are depressed. Ask them to read this leaflet. You might ask them to tell you if they:
  - think your depression is getting worse, or
  - are worried about changes in your behaviour

**What is Amitriptyline Hydrochloride Tablets USP used for?**

Amitriptyline Hydrochloride Tablets USP is used in adults to treat depression.

**How does Amitriptyline Hydrochloride Tablets USP work?**

Amitriptyline Hydrochloride Tablets USP is an antidepressant that belongs to a group of medicines known as tricyclic antidepressants. It is not known exactly how amitriptyline hydrochloride 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 Amitriptyline Hydrochloride Tablets USP?**

Medicinal ingredients: amitriptyline hydrochloride

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, purified talc and titanium dioxide.

In addition to the above ingredients, the tablets also contain the following non-medicinal ingredients:

10 mg tablets: triacetin and the dye FD&C Blue A1. Lake

25 mg tablets: polyethylene glycol and the dye D&C Yellow No. 10 Lake

50 mg tablets: triacetin and the dyes FD&C Yellow No.6 A1 Lake and FD&C Blue No.2 A1 Lake

75 mg tablets: polyethylene glycol and the dye Lake Sunset Yellow

**Amitriptyline Hydrochloride Tablets USP comes in the following dosage forms:**

Tablets: 10 mg, 25 mg, 50 mg and 75 mg

**Do not use Amitriptyline Hydrochloride Tablets USP 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 Amitriptyline Hydrochloride Tablets USP. Talk about any health conditions or problems you may have, including if you:**

- have liver problems.
- have an enlarged prostate.
- have bipolar disorder.
- have schizophrenia.
- have a blood disease with abnormal particles in the blood called “blood dyscrasia”.
- 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 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 Amitriptyline Hydrochloride Tablets USP. You should not do both.
- are 65 years of age or older.

**Other warnings you should know about:**

**Withdrawal symptoms:** Do NOT stop taking Amitriptyline Hydrochloride Tablets USP without talking to your healthcare professional. You may need to lower your dose gradually and careful monitoring by your healthcare professional is required. Stopping Amitriptyline Hydrochloride Tablets USP suddenly may cause withdrawal symptoms including restlessness, nausea, headache, malaise (general discomfort), sleep disturbance, irritability and changes in behavior.

**Amitriptyline Hydrochloride Tablets USP can cause serious side effects, including:**

- **Angle-closure glaucoma:** Amitriptyline Hydrochloride Tablets USP can cause angle-closure glaucoma (sudden eye pain). Having your eyes examined before you take Amitriptyline Hydrochloride Tablets USP could help identify if you are at risk of having angle-closure glaucoma. Talk to your healthcare professional rightaway if you have:
  - eye pain;
  - changes in vision;
  - swelling or redness in or around the eye.
- **Serotonin toxicity (also known as Serotonin syndrome) or Neuroleptic malignant syndrome:** Amitriptyline Hydrochloride Tablets USP can cause serotonin toxicity or neuroleptic malignant syndrome, rare but potentially life-threatening conditions. They can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity or neuroleptic malignant syndrome if you take Amitriptyline Hydrochloride Tablets USP with certain medications used to treat

depression, migraine or other mental health problems such as schizophrenia.

Symptoms of serotonin toxicity or neuroleptic malignant syndrome include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, changes in reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

See the [Serious side effects and what to do about them table](#), below, for more information on these and other serious side effects.

**Driving and Using Machines:** Amitriptyline Hydrochloride Tablets USP can affect your ability to drive and operate machinery. Do not drive or operate machinery until you know how Amitriptyline Hydrochloride Tablets USP affects you.

**Blood tests and monitoring:** Amitriptyline Hydrochloride Tablets USP can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results. Your healthcare professional will also monitor your blood pressure and the health of your heart while you are taking Amitriptyline Hydrochloride Tablets USP.

**Surgery:** If you have a planned surgery, talk to your healthcare professional as soon as possible. They may ask you to stop taking Amitriptyline Hydrochloride Tablets USP.

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

#### Serious Drug Interactions

- **Do not** take Amitriptyline Hydrochloride Tablets USP if you are taking a monoamine oxidase inhibitor (MAOI), or if you have taken one in the last 14 days as this can cause serious side effects.
- Taking Amitriptyline Hydrochloride Tablets USP and thyroid medication can cause heart rhythm problems.

**The following may interact with Amitriptyline Hydrochloride Tablets USP:**

- 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.
- triptans, used to treat migraine.
- anticholinergic 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 pimozide, 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, procainamide 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.
- 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 Amitriptyline Hydrochloride Tablets USP.

#### **How to take Amitriptyline Hydrochloride Tablets USP:**

- Always take Amitriptyline Hydrochloride Tablets USP exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Amitriptyline Hydrochloride Tablets USP 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 Amitriptyline Hydrochloride Tablets USP without first talking to your healthcare professional. Stopping Amitriptyline Hydrochloride Tablets USP suddenly can cause serious withdrawal symptoms.

#### **Usual dose:**

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

Depending on your response to Amitriptyline Hydrochloride Tablets USP, 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:**

Signs of an overdose may include:

- temporary confusion
- drowsiness
- low body temperature (hypothermia)
- heart rhythm problems such as an irregular heartbeat
- heart failure
- abnormal eye movement
- convulsions
- severe low blood pressure
- constipation
- coma

If you think you, or a person you are caring for, have taken too much Amitriptyline Hydrochloride Tablets USP, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

If you forget to take Amitriptyline Hydrochloride Tablets USP, 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 Amitriptyline Hydrochloride Tablets USP?**

These are not all the possible side effects you may have when taking Amitriptyline Hydrochloride Tablets USP. If you experience any side effects not listed here, tell 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

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	
<b>RARE</b>			
<b>Mania:</b> elevated or irritated mood, decreased need for sleep, racing thoughts, uneasiness		√	
<b>VERY RARE</b>			
<b>Serotonin Toxicity or Neuroleptic Malignant Syndrome:</b> Reactions which may cause feelings of agitation or restlessness, muscle twitching, involuntary eye movements, flushing, heavy sweating, high body temperature (>38°C), or rigid muscles.			√
<b>UNKNOWN FREQUENCY</b>			
<b>Allergic reaction:</b> rash, hives, swelling of the face, lips and tongue or throat, difficulty swallowing or breathing.			√
<b>Bone marrow depression:</b> easy bruising, bleeding, nose bleeds, bleeding gums, red spots on the skin, fever and chills, rash, extreme fatigue, pale skin and lips			√
<b>Difficulty passing urine</b>	√		
<b>Electrical problems with the heart (QT interval prolongation):</b> dizziness, fainting, fast heartbeat, palpitations, abnormal heart rate			√
<b>Gastrointestinal disorders:</b> Heart burn, diarrhoea, black tongue, constipation, dry mouth, unpleasant taste, swollen salivary gland, bowel obstruction, change in weight (loss or gain)	√		
<b>Glaucoma:</b> increased pressure in the eye, pupil dilation, blurred vision, eye pain		√	

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	
<b>Heart attack:</b> chest pain, tightness or pressure that may spread to your neck, jaw or back, nausea, indigestion, shortness of breath, cold sweat, fatigue, dizziness			√
<b>Heart problems (enlarged heart, heart disease):</b> weakness, fatigue, shortness of breath especially during exercise, light-headedness, chest pain, palpitations, fainting, swelling in your feet, ankles and legs		√	
<b>High blood pressure:</b> headache, fatigue, vision problems		√	
<b>Increased or decreased blood sugar:</b> frequent urination, thirst, hunger, shakiness, sweating and chills, irritability, confusion, dizziness	√		
<b>Liver problems:</b> yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
<b>Mental health problems:</b> confusion, hallucinations, trouble sleeping, excitement, nightmares, problems with attention, anxiety		√	
<b>Nervous system problems:</b> 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		√	
<b>New or worsened emotional or behavioural problems:</b> feeling angry, aggressive, worried, agitated, hostile or impulsive, feeling violent, feeling like you are not yourself or that you are less inhibited		√	
<b>Photosensitivity:</b> Increased sensitivity of the skin to sun	√		



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	
<b>Reproductive problems:</b> swelling of testicles, impotence in men, increase in breast tissue (in men and women), change in sex drive		√	
<b>Stroke:</b> sudden numbness or weakness in the face, arm or leg, confusion, trouble speaking, blurred vision, trouble walking, dizziness, loss of balance			√
<b>Seizures or fits:</b> uncontrollable shaking with or without loss of consciousness			√
<b>Thoughts of death or suicide:</b> thoughts about hurting or killing yourself or other people			√
<b>Unusual hair loss or thinning</b>		√	
<b>Withdrawal symptoms:</b> nausea, headache, irritability, restlessness, dream and sleep disturbance, generally feeling unwell, irritability, behavioural changes		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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. Keep out of reach and sight of children.

**If you want more information about Amitriptyline Hydrochloride Tablets USP:**

- 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); Find the Patient Medication Information on the manufacturer's website (<https://strides.com/>), or by calling 1-888-318-0234.

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