PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]pms-AMITRIPTYLINE

Amitriptyline Hydrochloride Tablets

Tablets, 10 mg, 25 mg, 50 mg, 75 mg and 100 mg, Oral

USP

Antidepressant

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RECENT MAJOR LABEL CHANGES

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7 WARNINGS AND PRECAUTIONS	07/2023
7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women	07/2023
7 WARNINGS AND PRECAUTIONS, Neurologic	02/2023

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

pms-AMITRIPTYLINE (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. pms-AMITRIPTYLINE, because of its sedative action, is also of value in alleviating the anxiety component of depression.

As with other tricyclic antidepressants, pms-AMITRIPTYLINE 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 (≥ 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 4.2 Recommended Dose and Dosage Adjustment and 7.1.4 Geriatrics.

2 CONTRAINDICATIONS

pms-AMITRIPTYLINE (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. Cross-sensitivity with other dibenzazepine compounds is a possibility.
- Patients with recent myocardial infarction or acute congestive heart failure.
- Patients with severe liver impairment.
- Combination with cisapride (no longer marketed in Canada) due to the increased risk for QT interval prolongation and arrhythmia.
- 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 pms-AMITRIPTYLINE 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 patients with risk factors for QT interval prolongation, such as the concomitant use of QT-prolonging drugs. See 2 CONTRAINDICATIONS; 5 OVERDOSAGE; 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 8.5 Post-Market Adverse Reactions; 9.4 Drug-Drug Interactions.
  - Unmasking of Brugada syndrome has been reported with tricyclic antidepressants. pms-AMITRIPTYLINE should be avoided in patients with Brugada syndrome or those suspected of having Brugada syndrome (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 8.5 Post-Market Adverse Reactions).
  - In patients with a history or urinary retention or prostatic hypertrophy, or in patients with increased intraocular pressure or narrow angle glaucoma, because of the anticholinergic properties of pms-AMITRIPTYLINE. 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.
- **Clinical Worsening and Suicide Risk**: Increased risk of self-harm, harm to others, suicidal thinking and behavior with antidepressant use. Closely monitor all antidepressant-treated patients for clinical worsening and for emergence of agitation-type and/or suicidal thoughts and behaviors (see 7 WARNINGS AND PRECAUTIONS, Psychiatric).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

As with other psychotropic drugs, the dosage of pms-AMITRIPTYLINE (amitriptyline hydrochloride) should be adapted to the requirements of each individual patient. Dosage should be initiated at a low level and increased gradually, carefully assessing the clinical response and potential intolerance. It is noteworthy that a lag between the onset of therapy and the therapeutic response (several days to a few weeks) is to be expected. Increasing the initial dose will not shorten this latent period but will increase the risk of side effects.

Cardiac
Prior to initiating treatment with pms-AMITRIPTYLINE:
- a cardiac evaluation, including blood pressure and electrocardiogram examinations, should be performed, particularly in patients with a history of cardiovascular disorders.
- Electrolyte disturbances such as hypokalemia should be treated.

See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.

Cardiac function and ECG should also be periodically monitored during treatment with pms-AMITRIPTYLINE, including after a dose increase or after initiating treatment with a potentially interacting medicine, particularly in patients with a history of cardiovascular disorders (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; 9 DRUG INTERACTIONS).

Drug Interactions
Consider the potential for drug interactions such as monoamine oxidase inhibitors, thyroid medications, QT-prolonging drugs, and CYP450 inhibitors and inducers, prior to and during treatment with pms-AMITRIPTYLINE (see 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 9 DRUG INTERACTIONS).

Monitor for agitation, suicidal tendencies
Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages, especially when initiating therapy or during any change in dose or dosage regimen. This includes monitoring for agitation-type, emotional and behavioural changes. See 7 WARNINGS AND PRECAUTIONS, Psychiatric, Clinical Worsening and Suicide Risk.

Discontinuation
When discontinuing pms-AMITRIPTYLINE, the dosage should be tapered gradually (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance; 8.5 Post-Market Adverse Reactions).

4.2 Recommended Dose and Dosage Adjustment

Initial Dosage:
- **Adults:** The recommended initial dose for ambulatory patients is 75 mg daily in three divided doses of 25 mg. The dose can be increased as required for symptomatic relief by 25 mg increments up to 150 mg daily, preferably by adding to the late afternoon and/or bedtime doses. Severely depressed and hospitalized patients may require an initial dose of 100 mg a day. This dose can be increased gradually to 200 mg a day in two or three divided doses. A small number of hospitalized patients may need as much as 300 mg a day. Doses in excess of 200 mg daily are not recommended for outpatients.

- **Pediatric Patients (< 18 years):** Health Canada has not authorized an indication for pediatric use.

- **Geriatric (> 65 years) or Debilitated Patients:** In general, lower doses are recommended for these patients. Initially, 20 to 30 mg daily in divided doses is suggested, with very gradual increments,

depending on tolerance and response. A daily dose of 50 mg may be satisfactory in the elderly. Blood pressure and cardiac rhythm should be checked frequently, particularly in patients who have unstable cardiovascular function.

Maintenance Dosage (Adult and Geriatric Patientd)
Maintenance dose is usually given as a single dose preferably in the evening or at bedtime. Once a satisfactory response has been obtained, the therapy should be continued for at least 3 months or more if needed in order to minimize the possibility of relapse following clinical improvement.

Concomitant use with inhibitors or inducers of cytochrome P450 enzymes:
Increased levels of amitriptyline have been observed when amitriptyline was co-administered with inhibitors of cytochrome P450 enzymes (see 9.4 Drug-Drug Interactions).

Consider monitoring amitriptyline plasma levels when pms-AMITRIPTYLINE is co-administered with another drug known or expected to inhibit the metabolism of amitriptyline. Dosage adjustments of amitriptyline may be required. When one of these other drugs is withdrawn from co-therapy, an increased dose of amitriptyline may be required.

Dosage adjustments may also be required when pms-AMITRIPTYLINE is co-administered with inducers of cytochrome P450 enzymes (see 9.4 Drug-Drug Interactions).

Use in CYP2D6 or CYP2C19 poor metabolizers
These patients may have higher plasma concentrations of amitriptyline (see 9.2 Drug Interactions Overview). Dosage adjustment should be considered.

Hepatic Insufficiency
Amitriptyline is primarily metabolized in the liver. In patients with mild or moderate hepatic impairment, use caution when initiating treatment with pms-AMITRIPTYLINE. Lower doses may be required.

pms-AMITRIPTYLINE is contraindicated in patients with severe hepatic impairment (see 2 CONTRAINDICATIONS).

4.4 Administration

pms-AMITRIPTYLINE tablets should be swallowed whole with water. pms-AMITRIPTYLINE 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

Deaths by deliberate or accidental overdosage have occurred with this class of drugs. There has been a report of a fatal dysrhythmia occurring as late as 56 hours after amitriptyline overdose. Since the propensity for suicide is high in depressed patients, a suicide attempt by other means may occur during the recovery phase. The possibility of simultaneous ingestion of other drugs (including alcohol) should also be considered.

Symptoms
High doses may cause temporary confusion, disturbed concentration, or transient visual hallucinations.

Cardiac symptoms: ECG abnormalities such as prolongation of the PR, QRS and QT intervals, rightward axis shift in the terminal QRS complex, changes to ST-segment and T-wave, bundle branch block, ventricular tachycardia and fibrillation, congestive heart failure.

Overdosage may also cause tachycardia, severe hypotension, drowsiness, convulsions, CNS depression including stupor and coma, hyperthermia or hypothermia, flushing, urinary retention, constipation, dilated pupils, disorders of ocular motility, polyradiculoneuropathy, agitation, hyperactive reflexes, muscle rigidity, vomiting, 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 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; 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: Administration of activated charcoal may help to reduce the absorption of the drug. EMESIS IS CONTRAINDICATED. If consciousness is impaired, the airway should be secured prior to gastrointestinal decontamination.

Cardiovascular: A maximal limb lead QRS duration of ≥ 0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH > 7.60 or a pCO_2 < 20 mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine 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).

Since it has been reported that physostigmine may cause severe bradycardia, asystole and seizures, its use is not recommended in cases of overdosage with tricyclic antidepressants. The use of phenytoin is also not recommended in cases of overdosage with tricyclic antidepressants.

Pediatric Management: The principles of management of pediatric and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment."

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, 75 mg and 100 mg of amitriptyline hydrochloride	Colloidal Silicon Dioxide, Croscarmellose Sodium, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Titanium Dioxide. In addition to the above ingredients the tablets also contain the following non-medicinal ingredients: 10 mg tablets: FD&C blue No. 1 Aluminum Lake. 25 mg tablets: FD&C Blue No. 2 Aluminum Lake, FD&C Yellow No.5 (Tartrazine) Aluminum Lake. 50 mg tablets: Black Iron Oxide, Red Iron Oxide and Yellow Iron Oxide. 75 mg tablets: FD&C Yellow No. 6 Aluminum Lake 100 mg tablets: FD&C Blue No. 2 Aluminum Lake and Red Iron Oxide non-irradiated.

10 mg: Each blue, round, coated tablets debossed with “AM” on one side and “10” on the other side contains 10 mg Amitriptyline Hydrochloride. Available in HDPE bottles of 100 and 1000 tablets.

25 mg: Each yellow, round, coated tablet debossed with “AM” on one side and “25” on the other side contains 25 mg Amitriptyline Hydrochloride. Available in HDPE bottles of 100 and 1000 tablets.

50 mg: Each brown, round, coated tablet debossed with “AM” on one side and “50” on the other side contains 50 mg Amitriptyline Hydrochloride. Available in HDPE bottles of 100 and 1000 tablets.

75 mg: Each orange, round, coated tablet debossed with “AM” on one side and “75” on the other side contains 75 mg Amitriptyline Hydrochloride. Available in HDPE bottles of 100 tablets.

100 mg: Each light purple, round coated tablet debossed with “AM” above “100” on one side and nothing on the other side contains 100 mg Amitriptyline Hydrochloride. Available in HDPE bottles of 100 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

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

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 8.5 Post-Market 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 deaths have been reported in patients with cardiovascular disorders. Therefore, pms-AMITRIPTYLINE 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 (e.g., AV block grades I to III), or arrhythmias. Close cardiovascular and ECG monitoring should be undertaken in such patients. An ECG should be performed prior to starting treatment, at steady state, after an increase in dose or after starting any potentially interacting medicine (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; and 4.1 Dosing Considerations).

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 with other risk factors for QT interval prolongation and torsades de pointe including, but not limited to:

- congenital long QT syndrome
- Age > 65 years
- Female sex
- Concomitant use of other QTc-prolonging medicines (see 9 DRUG INTERACTIONS)
- Electrolytes disturbances (e.g., hypokalemia, hyperkalemia, hypomagnesaemia, hypocalcemia). Electrolyte disturbances should be treated prior to the initiation of treatment with pms-AMITRIPTYILINE.

Concomitant use of pms-AMITRIPTYILINE with medicines that inhibit the metabolism of amitriptyline may also increase the risk for QT interval prolongation and torsades de pointes (see 9.4 Drug-Drug Interactions).

Consideration should be given to stopping amitriptyline treatment or reducing the dose if the QTc interval is > 500ms or increases by > 60ms.

Unmasking of Brugada Syndrome
There have been post-marketing reports of an association between treatment with tricyclic antidepressants and the unmasking of Brugada syndrome. Brugada syndrome is a disorder characterized by syncope, abnormal ECG findings, and a risk of sudden death. pms-AMITRIPTYLINE should generally be avoided in patients with Brugada syndrome or those suspected of having Brugada syndrome.

Dental Effects
Prolonged treatment with tricyclic antidepressants can lead to an increased incidence in dental caries.

Dependence/Tolerance
Withdrawal Symptoms
Withdrawal symptoms may occur after abrupt cessation of treatment with pms-AMITRIPTYLINE (see 8.5 Post-Market Adverse Reactions). When discontinuing pms-AMITRIPTYILINE, the dose should be tapered gradually over several weeks to minimize the risk of discontinuation symptoms, and the patient should be closely monitored.

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
Changes in blood glucose levels
Both elevation and lowering of blood glucose levels have been reported with amitriptyline (see 8.5 Post-Market Adverse Reactions). Dosage adjustments of antidiabetic agents may be required with concomitant amitriptyline hydrochloride treatment.

Concomitant use with thyroid medications
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 (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

Hyponatremia/Syndrome of inappropriate antidiuretic hormone secretion
Hyponatremia and/or syndrome of inappropriate antidiuretic hormone secretion may occur with tricyclic antidepressants, including amitriptyline (see 8.5 Post-Market Adverse Reactions). Elderly patients, patients taking diuretics, and patients who are otherwise volume depleted, may be at greater risk for this event.

Gastrointestinal
Amitriptyline should be used with caution in patients with pylorus stenosis and paralytic ileus. Tricyclic antidepressants may give rise to paralytic ileus, particularly in elderly and in hospitalized patients. The risk may be increased in patients concurrently taking anticholinergic drugs. Close supervision and careful adjustment of dosage are required in this situation (see 9.4 Drug-Drug Interactions). Appropriate measures should be taken if constipation occurs.

Genitourinary
Due to its anticholinergic activity, amitriptyline should be used with extreme caution in patients with a history of urinary retention and prostatic hypertrophy (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX). Close supervision and careful adjustment of dosage are required when amitriptyline is used with other anticholinergic drugs (see 9.4 Drug-Drug Interactions).

Hematologic
Isolated cases of bone marrow depression, including agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia, have been reported with tricyclic antidepressants (see 8.5 Post-Market Adverse Reactions).

Amitriptyline should be used with caution in patients with a history of blood disorders. Periodic monitoring of leukocyte and differential blood cell counts is recommended in these patients.

Concomitant Use with Coumarin Drugs
Tricyclic antidepressants may potentiate the anticoagulant effect of coumarin drugs (e.g., warfarin). Careful monitoring of plasma prothrombin is recommended when pms-AMITRIPTYLINE is initiated or discontinued in patients concomitantly treated with coumarin drugs.

Hepatic/Biliary/Pancreatic
pms-AMITRIPTYLINE is contraindicated in patients with severe liver impairment (see 2 CONTRAINDICATIONS).

Hepatic adverse events, such as altered liver function, hepatic failure, hepatitis and jaundice, have been reported with amitriptyline (see 8.5 Post-Market Adverse Reactions). Amitriptyline should be used with caution in patients with impaired liver function. Periodic monitoring of hepatic function is recommended in these patients.

Monitoring and Laboratory Tests

- Particularly in patients with a history of cardiovascular disorders, cardiac function and ECG should be periodically monitored during treatment with pms-AMITRIPTYLINE, including after a dose increase or after initiating treatment with a potentially interacting medicine (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 9 DRUG INTERACTIONS).
- In patients with a history of blood disorders, periodic monitoring of leukocyte and differential blood cell counts is recommended (see 7 WARNINGS AND PRECAUTIONS, Hematologic).
- In patients with impaired liver function, periodic monitoring of hepatic function is recommended (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Musculoskeletal
Exposure to tricyclic antidepressants may increase the risk of bone fracture. The possibility of fracture should be considered in the care of patients treated with pms-AMITRIPTYLINE. Elderly patients and patients with important risk factors for bone fractures should be advised of possible adverse events which increase the risk of falls, such as dizziness and orthostatic hypotension.

Neurologic

Seizures

pms-AMITRIPTYLINE is known to lower the convulsive threshold. pms-AMITRIPTYLINE 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 particularly during combined use with other serotonergic drugs (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 pms-AMITRIPTYLINE with monoamine oxidase inhibitors is contraindicated (see 2 CONTRAINDICATIONS). pms-AMITRIPTYLINE should be used with caution in patients receiving other serotonergic drugs or antipsychotics/neuroleptics. If concomitant treatment with pms-AMITRIPTYLINE 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 pms-AMITRIPTYLINE should be considered.

Ophthalmologic

Due to its anticholinergic activity, amitriptyline should be used with extreme caution in patients with increased intraocular pressure and narrow-angle glaucoma (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX). Close supervision and careful adjustment of dosage are required when amitriptyline is used with other anticholinergic drugs (see 9.4 Drug-Drug Interactions).

As with other antidepressants, pms-AMITRIPTYLINE can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. See 8.5 Post-Market Adverse Reactions. 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.

Decreased lacrimation and accumulation of mucoid secretions, due to the anticholinergic properties of tricyclic antidepressants, may cause damage to the corneal epithelium in patients with contact lenses.

Peri-Operative Considerations
pms-AMITRIPTYILINE is contraindicated in the acute recovery period following myocardial infarction (see 2 CONTRAINDICATIONS).

Anesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. pms-AMITRIPTYILINE should be discontinued several days before elective surgery if possible.

Psychiatric

Clinical Worsening and Suicide Risk
Pediatrics - Placebo-Controlled Clinical Trial Data: Analyses of placebo-controlled clinical trial safety databases from SSRIs and newer antidepressants suggest that the use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo. pms-AMITRIPTYILINE is not indicated for use in pediatric patients (see 1.1 Pediatrics).

Adults and Pediatrics: Patients with depression may experience worsening of their depression and/or emergence of suicidal ideation and behaviour (suicidality) or unusual changes in behaviour, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. Antidepressants may however have a role in inducing worsening of depression and emergence of suicidality in certain patients during the early phases of treatment. To minimize the risk of intentional overdose, prescriptions for pms-AMITRIPTYILINE should be written for the smallest possible quantity consistent with good patient management.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for depression as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, such symptoms may represent precursors to emerging suicidality.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, agitation, irritability, unusual changes in behavior, and the other symptoms described above, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Patients, families

and caregivers of patients should be alerted about the need to report such symptoms immediately to healthcare professionals.

Psychosis, Mania/Hypomania and Other Neuropsychiatric Phenomena
A major depressive episode may be the initial presentation of bipolar disorder. Patients with bipolar disorder may be at an increased risk of experiencing manic episodes when treated with antidepressants alone. Therefore, the decision to initiate symptomatic treatment of depression should only be made after patients have been adequately assessed to determine if they are at risk for bipolar disorder.

When amitriptyline is used to treat the depressive component of schizophrenia, activation or exacerbation of existing psychotic manifestation may occur. 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 should be considered under these circumstances.

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.

Renal
pms-AMITRIPTYLINE should be used with caution in patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma), in whom the drug may provoke a hypertensive crisis.

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.

Skin
Rare cases of drug reaction with eosinophilia and systemic symptoms (DRESS), a potentially life-threatening adverse drug reaction, have been reported with the use of tricyclic antidepressants, including amitriptyline. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. If DRESS is suspected, discontinue amitriptyline immediately.

7.1 Special Populations

7.1.1 Pregnant Women

Amitriptyline and its main metabolite nortriptyline have been shown to cross the placental barrier. There are no adequate and well-controlled studies in pregnant women to establish the safety of amitriptyline during pregnancy. Although a causal relationship has not been established, there have been a few reports

of adverse events, including CNS effects, limb deformities, or developmental delay, in infants whose mothers had taken amitriptyline during pregnancy.

Exposure to tricyclic antidepressants in mid to late pregnancy may increase the risk for preeclampsia.

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.

Withdrawal symptoms including tremors, lethargy, colic, irritability, hypotonia/hypertonia, convulsions, poor suckling reflex, irregular breathing, respiratory depression, and possibly anticholinergic symptoms (urinary retention and constipation) have been reported in neonates whose mother received tricyclic antidepressants during the third trimester of pregnancy.

7.1.2 Breast-feeding

Amitriptyline and its metabolites are excreted in breast milk. A risk to the suckling child cannot be excluded. 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 taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

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 4.2 Recommended Dose and Dosage Adjustment.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Clinical trial data on which the indication was originally authorized is not available. Adverse reactions associated with amitriptyline use are listed in 8.5 Post-Market Adverse Reactions.

The most serious adverse effects include unexpected death in patients with cardiovascular disorders, asystole, syncope, ventricular arrhythmias, heart block, myocardial infarction, stroke, paralytic ileus, glaucoma, increased intraocular pressure, bone marrow depression, hepatitis.

8.2 Clinical Trial Adverse Reactions

Clinical trial data on which the indication was originally authorized is not available.

8.3 Less Common Clinical Trial Adverse Reactions

Clinical trial data on which the indication was originally authorized is not available.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical trial data on which the indication was originally authorized is not available.

8.5 Post-Market 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.

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

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

Very rare cases of cardiomyopathy have been reported with amitriptyline.

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), hepatic failure.

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.

Musculoskeletal and connective tissue disorders: lupus-like syndrome (migratory arthritis, positive ANA and rheumatoid factor).

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

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).

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 drug reaction with eosinophilia and systemic symptoms (DRESS).

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. Rare instances have been reported of mania or hypomania occurring within 2 to 7 days following cessation of chronic therapy with tricyclic antidepressants. These symptoms are not indicative of addiction.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Monoamine Oxidase Inhibitors: pms-AMITRIPTYLINE 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 pms-AMITRIPTYLINE. See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Neurologic.
- Cisapride: See 2 CONTRAINDICATIONS.
- Thyroid Medication: See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism.

9.2 Drug Interactions Overview

Metabolism of amitriptyline
Tricyclic antidepressants (TCA) including amitriptyline are primarily metabolized by the hepatic cytochrome P450 isozymes CYP2D6 and CYP2C19, which are polymorphic in the population.

The biochemical activity of the drug metabolizing isozyme CYP2D6 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. The biochemical activity of the drug metabolizing isozyme CYP2C19 is also reduced in a subset of the population (CYP2C19 poor metabolizers). Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. For instance, in CYP2D6 poor metabolizers the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA), depending on the fraction of the drug metabolized by CYP2D6.

Other isozymes involved in the metabolism of amitriptyline are CYP3A4, CYP1A2 and CYP2C9.

9.3 Drug-Behavioural Interactions

Alcohol: Amitriptyline may enhance the response to alcohol.

In addition, concomitant use of alcohol and amitriptyline may result in increased amitriptyline plasma concentrations. Patients should be advised to avoid alcohol during treatment with amitriptyline.

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
Adrenergic neurone blockers	T	↓ Antihypertensive effects	Tricyclic antidepressants may counteract the antihypertensive effects of centrally acting antihypertensives such as guanethidine, betanidine, reserpine, clonidine and methyldopa. It is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants. There is an increased risk of hypertension on clonidine withdrawal.
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. Amitriptyline for enuresis should not be combined with an anticholinergic drug.
	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.
Baclofen	T	↑ muscle relaxant effect	Tricyclic antidepressants, such as amitriptyline, may enhance the muscle relaxant effect of baclofen.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Coumarin drugs (e.g., warfarin)	T	↑ Anticoagulant effect	Tricyclic antidepressants may potentiate the anticoagulant effect of coumarin drugs. Careful monitoring of plasma prothrombin is recommended.
Disulfiram[a]	CT	Delirium	Delirium has been reported with concurrent administration of amitriptyline and disulfiram.
Diuretics	T	Hypokalemia	Combination of amitriptyline with diuretics may lead to hypokalemia, which in turn increases the risk of QTc prolongation. Hypokalemia should be treated prior to administration of amitriptyline. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.
Iobenguane	T	Inaccurate imaging results	Antidepressants that inhibit the function of the norepinephrine transporter, such as amitriptyline, have the potential to interfere with iobenguane imaging results. Before iobenguane administration, drugs known or expected to interfere with iobenguane uptake should be discontinued, as clinically tolerated.
Neuroleptics (e.g., phenothiazines [fluphenazine, thioridazine[a]], butyrophenones [haloperidol])	T	↑ Seizures	Tricyclic antidepressants and neuroleptics mutually inhibit the metabolism of each other. This may result in increased tricyclic antidepressant and neuroleptic plasma level, a lowered convulsion threshold, and seizures. It may be necessary to adjust the dosage of these drugs.
		↑ risk of cardiac side effects	Combination with thioridazine may also cause cardiac arrhythmias. Co-administration of amitriptyline and thioridazine should be avoided.
		Hyperpyrexia	Hyperpyrexia has been reported when tricyclic antidepressants are administered with neuroleptic drugs, particularly during hot weather.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Nitrates (e.g., nitroglycerin)	T	Severe hypotension	Nitrates should be used with caution in combination with tricyclic antidepressants, such as amitriptyline, as it may lead to an augmentation of the hypotensive effect of nitrates. Clinical monitoring is recommended, and dose adjustment may be required.
		↓ Sublingual nitrates	Because of their anticholinergic properties, tricyclic antidepressants can cause dry mouth, which may decrease the absorption of sublingual nitrates
Opioids (e.g., buprenorphine, methadone, tramadol)	T	↑ Risk for serotonin toxicity, urinary retention, and constipation	Concomitant use of tricyclic antidepressants, such as amitriptyline, and opioids, such as buprenorphine, methadone and tramadol, may increase the risk of serotonin toxicity, a potentially life-threatening condition. Concomitant use with opioids may also increase the risk for urinary retention and constipation.
		↑ Risk for seizures and opioid toxicity with concomitant use of tramadol.	Concomitant use of tricyclic antidepressants, such as amitriptyline, and tramadol also increases the risk for seizures. In addition, this combination can inhibit the metabolism of tramadol to the active metabolite and thereby increasing tramadol concentrations, potentially causing opioid toxicity.
		↑ Risk for serious cardiovascular effects with concomitant use of methadone	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.
Pitolisant	T	↓ effectiveness of pitolisant	Pitolisant increases the level of histamine in the brain. Concomitant use of tricyclic antidepressants with H1 receptor antagonist properties, such as amitriptyline, should be avoided.

Proper/Common name	Source of Evidence	Effect	Clinical comment
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.
Topiramate	T	↑ Amitriptyline	Some patients may experience a large increase in amitriptyline concentration in the presence of topiramate and any adjustments in amitriptyline dose should be made according to the patient's clinical response and not on the basis of plasma levels.
Valproic acid	T	↑ Amitriptyline ↑ Seizures	Amitriptyline plasma concentration can be increased by valproic acid. Clinical monitoring is therefore recommended. Concomitant use with tricyclic antidepressants may lower the seizure threshold. Dosage adjustment for valproic acid may be necessary to control seizures.
[a] no longer markete din Canada			

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

Cytochrome P450 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 CYP2D6 include some that are not metabolized by the enzyme such as cimetidine, quinidine, bupropion, duloxetine, fluoxetine, paroxetine and terbinafine, and many

that are substrates for CYP2D6 such as many other antidepressants, phenothiazines (see Table 2 above), and the Type 1C antiarrhythmics propafenone and flecainide.

Cimetidine (which is also a CYP1A2 and CYP3A4 inhibitor) has been reported to reduce hepatic metabolism of certain tricyclic antidepressants, thereby delaying elimination and increasing steady-state concentrations of these drugs. Clinically significant effects have been reported with the tricyclic antidepressants when used concomitantly with cimetidine. Increases in plasma levels of tricyclic antidepressants, and in the frequency and severity of side effects, particularly anticholinergic, have been reported when cimetidine was added to the drug regimen.

Antifungals such as fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor) and terbinafine have also been observed to increase serum levels tricyclic antidepressants, including amitriptyline, and accompanying toxicity. Syncope and torsade de pointes have occurred.

Fluvoxamine (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 inhibitor) was also shown to increase amitriptyline plasma concentrations and this combination should be avoided.

Other CYP450 inhibitors, such as ketoconazole, itraconazole, protease inhibitors (e.g., ritonavir), diltiazem, verapamil (all CYP3A4 inhibitors), methylphenidate and modafinil, may also increase plasma levels of amitriptyline and accompanying toxicity.

Concomitant use of amitriptyline with drugs that can inhibit the cytochrome P450 enzymes involved in its metabolism may require lower doses than usually prescribed for either amitriptyline or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of amitriptyline may be required. Monitoring of amitriptyline plasma levels should be considered whenever pms-AMITRIPTYLINE is going to be co- administered with another drug known or expected to inhibit amitriptyline metabolism.

Cytochrome P450 inducers: Oral contraceptives, rifampicin, phenytoin, barbiturates, and carbamazepine may increase the metabolism of tricyclic antidepressants, resulting in lowered plasma levels of tricyclic antidepressants and reduced antidepressant response. In addition, amitriptyline may increase plasma levels of carbamazepine and phenytoin. Dosage adjustment of these drugs may be necessary.

Serotonergic agents
While selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit CYP2D6 (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 pms-AMITRIPTYLINE with serotonergic agents such as SSRIs, SNRIs, lithium, ozanimod, opioids 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 pms-AMITRIPTYLINE 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-HT3 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

Grapefruit juice, known to be a CYP3A4 inhibitor, may increase plasma levels of amitriptyline and accompanying toxicity.

9.6 Drug-Herb Interactions

St. John's Wort, an inducer of CYP3A4, may increase the metabolism of tricyclic antidepressants, resulting in lowered plasma levels of tricyclic antidepressants and reduced antidepressant response.

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, antihistaminergic 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:** Tricyclic antidepressants (TCA) including amitriptyline are primarily metabolised by the hepatic cytochrome P450 isozymes CYP2D6 and CYP2C19, which are polymorphic in the population. Patients known to be poor CYP2D6 or CYP2C19 metabolisers may have higher plasma levels of amitriptyline (see 9.2 Drug Interactions Overview). Dosage adjustments should be considered (see 4.2 Recommended Dose and Dosage Adjustment).

- **Ethnic Origin:** Information is not available.

- **Hepatic Insufficiency:** Information is not available. pms-AMITRIPTYLINE 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 between 15°C and 30°C. Keep in a tightly closed container.

12 SPECIAL HANDLING INSTRUCTIONS

None.

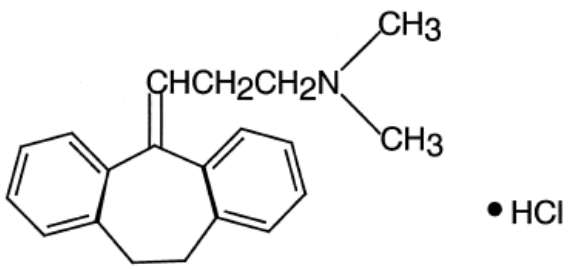
PART II: SCIENTIFIC INFORMATION

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:	$C_{20}H_{23}N$ • 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.

14 CLINICAL TRIALS

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

14.2 Comparative Bioavailability Studies

A blinded, randomized, two-treatment, two-period, two-sequence, single oral dose (1 x 50 mg), crossover comparative bioavailability study of pms-AMITRIPTYLINE tablets 50 mg (PHARMASCIENCE INC.) and ELAVIL® tablets 50 mg (AA PHARMA INC.), was conducted in healthy, adult male subjects under fasting conditions. Comparative bioavailability data from 26 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Amitriptyline (1 x 50 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	626.9 662.5 (33.5)	609.1 664.0 (43.3)	102.9	97.1 - 109.1
AUC_I (ng·h/mL)	742.5 806.8 (42.4)	712.7 789.4 (46.2)	104.2	98.2 - 110.6
C_{max} (ng/mL)	29.8 30.9 (26.3)	28.7 30.7 (38.6)	104.0	93.4 – 115.9
T_{max}[3] (h)	4.50 (2.50 - 7.00)	5.25 (2.50 - 6.00)		
$T_{½}$[4] (h)	26.6 (31.2)	25.1 (25.8)		

[1] pms-AMITRIPTYLINE (amitriptyline hydrochloride) tablets, 50 mg (PHARMASCIENCE INC.)
[2] ELAVIL® (amitriptyline hydrochloride) tablets, 50 mg (AA PHARMA INC., Canada)
[3] Expressed as the median (range) only
[4] 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_{50} (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®, Tablets, 10 mg, 25 mg, 50 mg and 75 mg, submission control 268308, Product Monograph, AA PHARMA INC. (May 9, 2023).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]pms-AMITRIPTYLINE

Amitriptyline Hydrochloride Tablets

Read this carefully before you start taking **pms-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 **pms-AMITRIPTYLINE**.

Serious Warnings and Precautions

To help avoid side effects and ensure proper use, before you take pms-AMITRIPTYLINE, talk to your healthcare professional if you:

- Are taking any other medication that may cause heart problems or affect your heart rhythm.
- Have electrolytes levels that are either too low or too high such as a low level of potassium, calcium or magnesium, or a high level of potassium in your blood. Your healthcare professional will need to treat this before you start taking pms-AMITRIPTYLINE.
- Have a history of heart problems such as
  - changes in heart rhythm,
  - a slow heartbeat (bradycardia),
  - heart disease, including a condition called heart failure (a condition where your heart cannot pump the blood in your body as well as it should)

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.

pms-AMITRIPTYLINE may also reveal a hidden heart problem you did not know you had, a problem called “Brugada Syndrome”. Before you start taking pms-AMITRIPTYLINE, tell your healthcare professional if you have unexplained fainting or a family history of “Brugada Syndrome” or unexplained sudden death before 45 years of age, as this could indicate you may have “Brugada Syndrome”. You should not take pms-AMITRIPTYLINE if you have or are suspected to have “Brugada Syndrome”.

These problems can be serious and cause sudden death. Get immediate medical help if you experience dizziness, fainting, a rapid heartbeat or heart palpitations while taking pms-AMITRIPTYLINE.

- have a history of trouble emptying your bladder (urinary retention), an enlarged prostate gland, increased pressure in the eye or glaucoma as pms-AMITRIPTYLINE can make these conditions worse.
- have thyroid problems or are taking thyroid medication. Heart rhythm problems may develop when pms-AMITRIPTYLINE is taken with thyroid medicines.
- have a history of seizures or fits. pms-AMITRIPTYLINE can make you more likely to have seizures or fits.

New or worsened emotional or behavioural problems:
- When you first start taking pms-AMITRIPTYLINE or when your dose is adjusted, you may feel worse instead of better. You may feel new or worsened feelings of agitation, hostility, anxiety, or impulsivity.
- During your treatment with pms-AMITRIPTYLINE, it is important that you and your healthcare professional talk regularly about how you are feeling. They will closely monitor you for signs of new or worsened emotions or behaviours while you are taking pms-AMITRIPTYLINE.
- 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
- If your depression worsens or you experience changes in your behaviour, tell your healthcare professional right away. Do not stop taking your medicine as it takes time for pms-AMITRIPTYLINE to work.

Self-harm or Suicide
- Antidepressants, such as pms-AMITRIPTYLINE, can increase the risk of suicidal thoughts or actions.
- If you have thoughts of harming or killing yourself at any time, tell your healthcare professional or go to a hospital right away. You will be closely observed by your healthcare professional in this situation.

What is pms-AMITRIPTYLINE used for?
pms-AMITRIPTYLINE is used in adults to treat depression.

How does pms-AMITRIPTYLINE work?
pms-AMITRIPTYLINE is an antidepressant that belongs to a group of medicines known as tricyclic antidepressants. It is not known exactly how pms-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 pms-AMITRIPTYLINE?
Medicinal ingredients: amitriptyline hydrochloride
Non-medicinal ingredients: Colloidal Silicon Dioxide, Croscarmellose Sodium, Hypromellose,

Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Titanium Dioxide.

In addition to the above ingredients, the tablets also contain the following non-medicinal ingredients:
10 mg tablets: FD&C blue No. 1 Aluminum Lake
25 mg tablets: FD&C Blue No. 2 Aluminum Lake, FD&C Yellow No.5 (Tartrazine) Aluminum Lake
50 mg tablets: Black Iron Oxide, Red Iron Oxide and Yellow Iron Oxide
75 mg tablets: FD&C Yellow No. 6 Aluminum Lake
100 mg tablets: FD&C Blue No. 2 Aluminum Lake and Red Iron Oxide non-irradiated

pms-AMITRIPTYLINE comes in the following dosage forms:
Tablets: 10 mg, 25 mg, 50 mg, 75 mg and 100 mg

Do not use pms-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.
- are taking cisapride

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-AMITRIPTYLINE. Talk about any health conditions or problems you may have, including if you:
- have liver problems.
- have dental problems.
- wear contact lenses.
- have a tumour (cancer) of the adrenal gland (such as pheochromocytoma or neuroblastoma).
- have bipolar disorder.
- have schizophrenia.
- have or have had a blood disease such as low platelet or white blood cell counts.
- have pylorus stenosis (narrowing of the gastric outlet) and paralytic ileus (blocked intestine).
- have diabetes as you might need an adjustment of your antidiabetic medicine.
- 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 taking warfarin or similar medicines, used to thin the blood.
- are taking other anticholinergic medicines (certain medicines used to treat asthma, chronic obstructive pulmonary disease, stomach and gut problems, and Parkinson's disease).
- have been told you have enzymes that do not work well (such as "CYP2D6 poor

metabolizer" or "CYP2C19 poor metabolizer").
- had a recent bone fracture or were told you have osteoporosis or risk factors for osteoporosis.
- are 65 years of age or older.

Other warnings you should know about:

Pregnancy: Before taking pms-AMITRIPTYLINE, tell your healthcare professional if you are pregnant, think you might be pregnant or are planning to become pregnant. You should not take pms-AMITRIPTYLINE if you are pregnant unless you and your healthcare professional have discussed the risks and decided that you should. Tell your healthcare professional right away if you become pregnant while taking pms-AMITRIPTYLINE.

Babies born to mothers that took medicines similar to pms-AMITRIPTYLINE while they were pregnant have experienced withdrawal symptoms after birth. Get immediate medical help for your baby if you took pms-AMITRIPTYLINE while you were pregnant, and they have any of the following symptoms:
- breathing problems, bluish skin
- seizures or fits
- body temperature changes
- stiff or floppy muscles
- jitteriness, irritability, lethargy
- drowsiness
- constant crying

Breastfeeding: Tell your healthcare professional if you are breastfeeding or planning to breastfeed. pms-AMITRIPTYLINE is released into breast milk. It is not known if this is safe for your baby. You and your healthcare professional should decide if you should breastfeed or take pms-AMITRIPTYLINE. You should not do both.

Cavities: Long-term use of pms-AMITRIPTYLINE can cause dental cavities.

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

Bone Fracture: Taking pms-AMITRIPTYLINE may increase your risk of breaking a bone if you are elderly, have osteoporosis, or have other major risk factors for breaking a bone. You should take extra care to avoid falls, especially if you get dizzy or have low blood pressure.

pms-AMITRIPTYLINE can cause serious side effects, including:

- **Angle-closure glaucoma:** pms-AMITRIPTYLINE can cause angle-closure glaucoma (sudden eye pain). Having your eyes examined before you take pms-AMITRIPTYLINE could help identify if you are at risk of having angle-closure glaucoma. Talk to your healthcare professional right away if you have:
  - eye pain;
  - changes in vision;
  - swelling or redness in or around the eye.

- **Serious skin reactions:** Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which can be serious or life-threatening, have been reported with amitriptyline hydrochloride. Get immediate medical help if you experience:
  - fever
  - severe rash
  - peeling skin
  - swelling of the face
  - swollen lymph glands
  - flu-like feeling
  - yellow skin or eyes
  - shortness of breath
  - swelling of the legs
  - dry cough
  - chest pain or discomfort
  - feeling thirsty
  - urinating less often, less urine or dark urine

- **Serotonin toxicity (also known as Serotonin syndrome) or Neuroleptic malignant syndrome:** pms-AMITRIPTYLINE 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 pms-AMITRIPTYLINE 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: pms-AMITRIPTYLINE can affect your ability to drive and operate

machinery. Do not drive or operate machinery until you know how pms-AMITRIPTYLINE affects you.

Blood tests and monitoring: pms-AMITRIPTYLINE 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 pms-AMITRIPTYLINE.

Surgery: If you have a planned surgery, talk to your healthcare professional as soon as possible. They may ask you to stop taking pms-AMITRIPTYLINE.

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 pms-AMITRIPTYLINE 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.
- **Do not** take pms-AMITRIPTYLINE if you are taking cisapride*, as this can cause serious side effects.
- Taking pms-AMITRIPTYLINE and thyroid medication can cause heart rhythm problems.

The following may interact with pms-AMITRIPTYLINE:

- alcohol. You should avoid drinking alcohol while taking pms-AMITRIPTYLINE.
- 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, fluvoxamine, sertraline, and paroxetine.
- bupropion, used to treat depression or for smoking cessation.
- ozanimod, used to treat multiple sclerosis or ulcerative colitis.
- triptans, used to treat migraine.
- anticholinergic drugs such as certain medicines used to treat asthma, chronic obstructive pulmonary disease, 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.
- pitolisant, used to treat excessive daytime sleepiness.
- modafinil, used to treat excessive sleepiness.
- disulfiram*, used to treat alcoholism.
- medicines used to treat schizophrenia and other mental health problems, such as pimozide, sertindole*, fluphenazine, thioridazine* and haloperidol.

- high blood pressure medications such as calcium-channel blockers (e.g. diltiazem and verapamil), guanethidine*, betanidine*, reserpine*, 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.
- diuretics or “water pills” such as furosemide.
- medicines used to treat bacterial infections such as erythromycin, clarithromycin, tacrolimus, rifampicin* and ciprofloxacin.
- medicines used to treat malaria such as quinine, halofantrine* and chloroquine.
- medicines used to treat fungal infections such as ketoconazole, itraconazole, fluconazole and terbinafine.
- 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.
- opioids such as morphine, tramadol, buprenorphine, and methadone, used to treat pain and opioid drug dependence.
- warfarin or similar medicines, used to thin the blood.
- baclofen, used to treat muscle spasms.
- nitrates, used to treat angina (chest pain).
- phenytoin, carbamazepine, topiramate, valproic acid, used to treat seizures or fits.
- methylphenidate, used to treat ADHD.
- protease inhibitors such as ritonavir, used to treat HIV and COVID-19.
- oral contraceptives, used to prevent pregnancy.
- St. John´s Wort (hypericum perforatum) – a herbal remedy used for depression.
- grapefruit juice.

* Product is not or no longer marketed in Canada.

How to take pms-AMITRIPTYLINE:
- Always take pms-AMITRIPTYLINE exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- pms-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 pms-AMITRIPTYLINE without first talking to your healthcare professional. Stopping pms-AMITRIPTYLINE suddenly can cause serious withdrawal symptoms.

Usual dose:
Adults: The recommended initial dose is 75 mg daily in three divided doses of 25 mg.

Depending on how you respond, your doctor may gradually increase your dose.

Maximum daily dose: 150 mg a 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 pms-AMITRIPTYLINE, 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 pms-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 pms-AMITRIPTYLINE?
These are not all the possible side effects you may have when taking pms-AMITRIPTYLINE. 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**	
RARE			
Mania: elevated or irritated mood, decreased need for sleep, racing thoughts, uneasiness, excessive physical activity		✓	
VERY RARE			
Serotonin Toxicity (also called serotonin syndrome) or Neuroleptic Malignant Syndrome: 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.			✓
UNKNOWN FREQUENCY			
Allergic reaction: rash, hives, swelling of the face, lips and tongue or throat, difficulty swallowing or breathing.			✓
Angle-closure glaucoma: increased pressure in the eye, pupil dilation, blurred vision, eye pain		✓	
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			✓
Difficulty passing urine	✓		
Drug reaction with eosinophilia and systemic symptoms (DRESS) (serious skin reaction that may affect more than one organ): fever, severe rash, swollen lymph glands, flu-like feeling, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, urinate less often, less urine			✓
QT interval prolongation and Brugada Syndrome (serious and potentially life- threatening electrical problems with the heart): dizziness, fainting, fast heartbeat, palpitations, abnormal heart rate, seizures (fits)			✓
Gastrointestinal disorders: Heartburn, diarrhea, black tongue, constipation, dry mouth, unpleasant taste, swollen salivary gland, bowel obstruction, change in weight (loss or gain)	✓		

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**	
Heart attack: chest pain, tightness or pressure that may spread to your neck, jaw or back, pain in the arm or shoulder, nausea, indigestion, shortness of breath, cold sweat, fatigue, dizziness			✓
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		✓	
High blood pressure: headache, fatigue, vision problems		✓	
Hyponatremia (low sodium in the blood): lethargy, confusion, muscular twitching, achy, stiff or uncoordinated muscles, seizure, coma		✓	
Increased or decreased blood sugar: frequent urination, thirst, hunger, shakiness, sweating and chills, irritability, confusion, dizziness	✓		
Liver problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
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		✓	
New or worsened emotional or behavioural problems: feeling angry, aggressive, worried, agitated, hostile or impulsive, feeling violent, feeling like you are not yourself or that you are less inhibited		✓	
Photosensitivity: Increased sensitivity of the skin to sun	✓		
Reproductive problems: swelling of testicles, impotence in men, increase in breast tissue (in men and women), change in sex drive		✓	
Stroke: sudden numbness or weakness in the face, arm or leg, confusion, trouble speaking, blurred vision, trouble walking, dizziness, loss of balance			✓
Seizures or fits: uncontrollable shaking with or without loss of			✓

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	
consciousness			
Thoughts of death or suicide: thoughts about hurting or killing yourself or other people			✓
Unusual hair loss or thinning		✓	
Withdrawal symptoms: 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 between 15°C and 30°C. Keep in a tightly closed container.

Keep out of reach and sight of children.

If you want more information about pms-AMITRIPTYLINE:
- Talk to your healthcare professional.
- Find the full prescribing information 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), or by contacting the sponsor Pharmascience Inc. at: 1-888-550-6060.

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