PREScribing INFORMATION

Pr

pms-AMITRIPtyline
Amitriptyline Hydrochloride Tablets, USP
10 mg, 25 mg, 50 mg, 75 mg and 100 mg

Antidepressant

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THERAPEUTIC CLASSIFICATION
Antidepressant

ACTIONS AND CLINICAL PHARMACOLOGY

Pharmacodynamics
Amitriptyline is a tricyclic antidepressant. These drugs block the re-uptake of noradrenaline and serotonin (5HT) into presynaptic nerve terminals and this has been thought to be their mode of action. However the antidepressant effect does not appear until 10-14 days after starting treatment whereas a block in activity can be shown within an hour. This suggests that other pharmacological actions may also contribute.

Pharmacokinetics
Amitriptyline is readily absorbed from the GI tract, peak plasma levels occurring within approximately 6 hours of oral administration. The bioavailability of amitriptyline is 48 ± 11 %, it is 94.8 ± 0.8 % plasma bound. Neither parameter is age dependant. Half-life is 16 ± 6 hours with a volume of distribution of 14 ± 2 L/kg. Both of these parameters will significantly increase with age.

Amitriptyline is extensively demethylated in the liver to its primary metabolite, nortriptyline. Paths of metabolism include hydroxylation, N-oxidation and conjugation with glucuronic acid. It is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form. Clearance is 12.5 ± 2.8 mL/min/kg (not age dependant) and less than 2 % is excreted in the urine.
INDICATIONS AND CLINICAL USE

pms-AMITRIPTYLINE is indicated for the treatment of depression, especially when sedation is required.

CONTRAINDICATIONS

- Patients who are hypersensitive to tricyclic antidepressants or to any of the ingredients in the tablets;
- Patients who are taking monoamine oxidase inhibitors (MAOIs) or who have taken them within the last 14 days;
- A history of myocardial infarction, arrhythmias, particularly heart block of any degree, congestive heart failure, coronary artery insufficiency; severe liver disease;
- Children under 18 years;
- During breast-feeding (see section WARNINGS AND PRECAUTIONS-Pregnancy and lactation);
- Mania.

WARNINGS AND PRECAUTIONS

pms-AMITRIPTYLINE should be used with great caution in patients with a history of epilepsy or recent convulsions, porphyria, pheochromocytoma, impaired liver function, blood dyscrasias, urinary retention, symptoms suggestive of prostatic hypertrophy, narrow angle glaucoma, or increased intra-ocular pressure. In patients with narrow angle glaucoma, even average doses may precipitate an attack of glaucoma.

Patients with hyperthyroidism, cardiovascular disorders, and patients receiving thyroid hormone medication or anticholinergic agents may need the dosage of all medications carefully adjusted when amitriptyline is given concurrently (see section DRUG INTERACTIONS).
Cardiac arrhythmias and severe hypotension are likely to occur with high dosages or in patients with pre-existing heart disease.

If possible pms-AMITRIPTYLINE therapy should be discontinued several days before surgery, but if emergency surgery is required, the anaesthetist should be informed that the patient is taking pms-AMITRIPTYLINE as anaesthetics may increase the risk of arrhythmias and hypotension (see section DRUG INTERACTIONS).

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

The elderly or debilitated are particularly liable to experience toxic effects, especially agitation, confusion and postural hypotension. The initial dose should be increased with great caution under close supervision.

Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant.

When amitriptyline is given for the depressive component of schizophrenia, psychotic symptoms may be aggravated. In manic-depressives, a shift towards the manic phase may occur; paranoid delusions, with or without associated hostility, may be aggravated. In these cases, a major tranquilliser should be given concurrently, or the dosage of pms-AMITRIPTYLINE reduced.

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

**Occupational Hazards:** Drowsiness (impaired alertness) is not uncommon in the early stages of treatment and patients should be warned not to drive or operate machinery until it has been established that their alertness is not impaired.

**Pregnancy and lactation:** Safety in pregnancy and lactation has not been established. Do not use during the first and third trimester or in nursing mothers unless there are compelling reasons. Clinical experience of the use of amitriptyline in pregnancy is limited. Animal studies have shown harmful effects at exceptionally high doses. Withdrawal symptoms, including respiratory depression and agitation have been reported in neonates whose mothers had taken tricyclic antidepressants during the last trimester of pregnancy. Urinary retention in the neonate has also been associated with maternal use of amitriptyline.

Amitriptyline is detectable in breast milk. Because of the potential risk of serious adverse reactions to breast-fed infants, a decision should be made to either discontinue pms-AMITRIPTYLINE or breast-feeding.
**DRUG INTERACTIONS**

_Altretamine_: there is a risk of severe postural hypotension when amitriptyline and altretamine are used concurrently.

_Alpha2-adrenoceptor stimulants_: Concomitant use of apraclonidine and brimonidine should be avoided.

_Anaesthetics_: anaesthetics may increase the risk of arrhythmias and hypotension in patients taking amitriptyline (see section WARNINGS AND PRECAUTIONS).

_Antiarethyrmics_: there is an increased risk of ventricular arrhythmias with drugs which prolong the QT interval, including amiodarone (avoid concomitant use), disopyramide, procainamide, propafenone and quinidine.

_Antibacterials_: the plasma concentrations of some tricyclic antidepressants may be reduced by rifampicin, leading to a reduced antidepressant effect. Concomitant use with linezolid may result in CNS excitation and hypertension.

_Antidepressants_: Concomitant use of reboxetine should be with caution. The plasma concentrations of some tricyclics are increased by SSRIs.
Fluoxetine markedly inhibits Cytochrome P450 II D6, which is involved in the metabolism of a number of tricyclic antidepressants. Patients should be monitored for increased antidepressant plasma levels and toxicity when fluoxetine is used concurrently. Adjustment of the antidepressant dosage may be necessary.
Antiepileptics: amitriptyline may antagonise antiepileptics e.g. barbiturates, carbamazepine thereby reducing the convulsive threshold. The plasma concentrations of some tricyclics may be reduced resulting in a reduced antidepressant effect.

Antihistamines: antimuscarinic and sedative effects may be increased. Avoid concomitant use with terfenadine as the risk of ventricular arrhythmias may be increased.

Antihypertensives: in general the hypotensive effect is enhanced; however, amitriptyline may decrease the antihypertensive effect of guanethidine, debrisoquine, bethanidine and possibly clonidine. There is an increased risk of hypertension on withdrawal of clonidine. It is advisable to review all anti-hypertensive therapy during treatment with tricyclic antidepressants.

Antimuscarinics: antimuscarinic side effects may be increased. Paralytic ileus, urinary retention or acute glaucoma may occur in patients taking tricyclic antidepressants concurrently with drugs having an anticholinergic action, especially in elderly patients.

Antipsychotics: the risk of ventricular arrhythmias is increased (avoid concomitant use with pimozide or thioridazine); plasma concentrations of some tricyclics are increased. Antimuscarinic side effects may be increased with phenothiazines and possibly clozapine.

Antivirals: Based on the known metabolism of amitriptyline, the protease inhibitor, ritonavir, may increase the serum levels of amitriptyline. Therefore, careful monitoring of therapeutic and adverse effects is recommended when these drugs are administered concomitantly.

Anxiolytics and hypnotics: Concomitant use enhances the sedative effect.

Other CNS Depressants: amitriptyline may potentiate the central nervous depressant action of alcohol, barbiturates, and other CNS depressants. In turn, the antidepressant action of amitriptyline may be decreased by barbiturates. Caution is also advised in patients who receive large doses of ethchlorvynol concurrently with amitriptyline, as transient delirium has been reported in patients receiving 1 g ethchlorvynol and 75 - 150 mg of amitriptyline.
Beta-blockers: the risk of ventricular arrhythmias associated with sotalol is increased.

Calcium-channel Blockers: diltiazem and verapamil may increase the plasma concentration of amitriptyline.

Disulfiram: Delirium has been reported in patients taking amitriptyline with disulfiram. Concomitant use may inhibit the metabolism of tricyclics. Increased plasma concentrations and increased disulfiram reaction has been reported in patients taking amitriptyline, alcohol and disulfiram concomitantly.

Diuretics: there is an increased risk of postural hypotension.

Dopaminergics: Concomitant use with entacapone should be avoided. CNS toxicity has been reported with selegiline.

Monoamine oxidase inhibitors (MAOIs): MAOIs can potentiate the effects of amitriptyline, and cases of hyperpyretic crises, severe convulsions and fatalities have been reported. Amitriptyline should not be given with and until a minimum of two weeks after discontinuing treatment with a monoamine oxidase inhibitor. The amitriptyline should be introduced cautiously and the dosage increased gradually. CNS excitation and hypertension have occurred with MAOIs.

Muscle Relaxants: the muscle relaxant effect of baclofen may be enhanced by concomitant use.

Nitrites: the effect of sublingual nitrates may be reduced (owing to the effect of dry mouth).

Oestrogens and Progestogens: oral contraceptives antagonise the antidepressant effect but side effects may be increased due to the increased plasma concentration of amitriptyline.
Ritonavir: based on the known metabolism of amitriptyline, the protease inhibitor ritonavir may increase the serum levels of amitriptyline. Therefore careful monitoring of therapeutic and adverse effects is recommended when these drugs are administered concomitantly.

Sibutramine: Concomitant use is not recommended due to the increased risk of CNS toxicity.

Sympathomimetic Agents: amitriptyline should not be given with sympathomimetic agents such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine due to hypertension and arrhythmias. Local anaesthetics with adrenaline appear to be safe. Methylphenidate may inhibit the metabolism of tricyclics and therefore increase the antidepressant action of amitriptyline.

Thyroid preparations e.g. levothyroxine: the action of tricyclic antidepressants such as amitriptyline may be accelerated by the concurrent use of thyroid hormone medication (see section WARNINGS AND PRECAUTIONS).

Ulcer-healing Drugs: cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants when taken concurrently resulting in increased plasma concentration of amitriptyline.

Concurrent administration of amitriptyline with electroconvulsive therapy should be limited to patients for whom it is considered essential, as the hazards of each treatment may be increased.

ADVERSE REACTIONS

In general, amitriptyline is well tolerated. The following adverse effects although not necessarily all reported with amitriptyline, have occurred with tricyclic antidepressants.

Blood and lymphatic system disorders: bone marrow depression including agranulocytosis, leucopenia, eosinophilia, purpura, and thrombocytopenia.
Immune system disorders: Allergic reactions, oedema of the face and tongue.

Endocrine disorders: syndrome of inappropriate ADH (antidiuretic hormone) secretion (see section WARNINGS AND PRECAUTIONS)

Metabolism and nutrition disorders: increased appetite may be a drug reaction or due to relief of depression.

Psychiatric disorders: confusional states, disorientation, delusions, hallucinations, hypomania, excitement, anxiety, restlessness, insomnia, nightmares.

Cases of suicidal ideation and suicidal behaviours have been reported during amitriptyline therapy or early after treatment discontinuation (see section WARNINGS AND PRECAUTIONS).

Nervous system disorders: Dizziness, headache, drowsiness, disturbed concentration, numbness, tingling and paresthesias of the extremities, peripheral neuropathy, incoordination, ataxia, tremors, coma, convulsions, alteration of the EEG, extrapyramidal symptoms, including abnormal involuntary movements and tardive dyskinesia, dysarthria,

Ear and labyrinth disorders: tinnitus
Anticholinergic effects reported are dry mouth, blurred vision, mydriasis, disturbance of accommodation, increased intra-ocular pressure, constipation, paralytic ileus, hyperpyrexia, urinary retention, and urinary tract dilatation.

Cardiac disorders: syncope, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke, and non-specific ECG changes in AV conduction. Cardiac arrhythmias and severe hypotension are likely to occur with high dosage or in deliberate overdosage. They may also occur in patients with pre-existing heart disease taking normal dosage.

Vascular disorders: hypotension, postural hypotension, hypertension


*Gastrointestinal disorders:* nausea, epigastric distress, vomiting, anorexia, stomatitis, taste disturbance, diarrhoea, parotid swelling, black tongue.

*Hepato-biliary disorders:* Rarely hepatitis (including altered liver function and jaundice).

*Skin and subcutaneous tissue disorders:* skin rash, urticaria, photosensitisation, increased perspiration and alopecia.

*Renal and urinary disorders:* Urinary frequency.

*Reproductive system and breast disorders:* testicular swelling, gynaecomastia, breast enlargement, galactorrhoea, increased or decreased libido, impotence, interference with sexual function

*General disorders and administration site conditions:* fatigue, weakness

*Investigations:* elevation or lowering of blood sugar levels, weight gain may be a drug reaction or due to relief of depression.

Confusion may occur at high doses or in elderly patients requiring reduction of dosage. Withdrawal symptoms which may occur on abrupt cessation of therapy include nausea, headache and malaise. Gradual withdrawal is associated with reports of transient symptoms including irritability, restlessness, as well as dream and sleep disturbances during the first two weeks of dosage reduction. These symptoms are not indicative of addiction. There have also been reports of withdrawal symptoms, respiratory depression and agitation in neonates, whose mothers received tricyclic antidepressants.

Mania or hypomania has been reported rarely within 2 - 7 days of stopping chronic treatment with tricyclic antidepressants.


Class effects

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

<table>
<thead>
<tr>
<th>Reporting Side Effects</th>
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</thead>
<tbody>
<tr>
<td>You can report any suspected side effects associated with the use of health products to Health Canada by:</td>
</tr>
<tr>
<td>• Visiting the Web page on Adverse Reaction Reporting (<a href="http://www.hc-sc.gc.ca/dhpmps/medeff/report-declaration/index-eng.php">http://www.hc-sc.gc.ca/dhpmps/medeff/report-declaration/index-eng.php</a>) for information on how to report online, by mail or by fax; or</td>
</tr>
<tr>
<td>• Calling toll-free at 1-866-234-2345.</td>
</tr>
</tbody>
</table>

*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.*

**OVERDOSAGE**

High dosage may cause transient visual hallucinations, temporary confusion and disturbed concentration. Overdosage may cause tachycardia, other arrhythmic abnormalities such as bundle branch block, ECG evidence of impaired conduction, congestive heart failure, severe hypotension, dilated pupils, drowsiness, hypothermia, convulsions, stupor and coma. Other symptoms may include agitation, hyperactive reflexes, muscle rigidity, vomiting, hyperpyrexia, or any of the other side effects listed previously.

There is no specific antidote for tricyclic antidepressant poisoning. Patients should be hospitalised and treatment should be symptomatic and based on cardiac (including ECG monitoring) and respiratory support.

The stomach should be emptied as quickly as possible by emesis, followed by gastric lavage and aspiration. Following lavage, activated charcoal at a dose of 20-30g every four to six hours may be
given for the first 24-48 hours. An open airway and an adequate fluid intake should be maintained, and body temperature regulated.

Intravenous physostigmine salicylate, 1-3mg has been reported to reverse the symptoms of tricyclic antidepressant poisoning. As physostigmine is rapidly metabolised, the dosage should be repeated as required, particularly if life-threatening signs such as arrhythmias, convulsions and deep coma recur or persist after the initial dose. As physostigmine itself may be toxic, it is not recommended for routine use.

Standard measures should be used to manage circulatory shock and metabolic acidosis. Cardiac arrhythmias may be treated with neostigmine, pyridostigmine or propranolol. Should cardiac failure occur, use of digitalis should be considered. Close monitoring of cardiac function for not less than five days is advisable.

If convulsions occur, they should be treated with paraldehyde, diazepam or an inhalation anaesthetic. Barbiturates should not be used because amitriptyline increases their CNS-depressant action.

Dialysis is of no value because of low plasma concentrations of amitriptyline. Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdosage have occurred with this class of medicament.

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

As with other psychotropic drugs, the dosage of PMS-AMITRIPTYLINE (amitriptyline hydrochloride USP) should be adapted to the requirements of each individual patient. Dosage should be initiated at a low level and increased gradually, 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.

Initial Dosage: Adults
The recommended initial dose for ambulatory patients is 75 mg daily in two or three divided doses. 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.

Children (< 18 years)
Amitriptyline should not be used in children under 18 years of age.

Elderly (> 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 Dose (Adult and Elderly)
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.
**Drug Substance**

Proper/Common Name: Amitriptyline Hydrochloride

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

Molecular Formula: $C_{20}H_{23}N \cdot HCl$

Molecular Weight: 313.86 g/mol

Structural Formula:

![Structural Formula](image)

Description: 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.
CLINICAL TRIALS

A single-dose, randomized, two-way comparative bioavailability study was conducted to compare pms-AMITRIPTYLINE tablets to the Canadian reference product, ELAVIL® (amitriptyline hydrochloride) tablets (AA Pharma Inc., Canada). The study drugs were administered as a 1 x 50 mg dose to healthy adult male subjects in the fasted state.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test† (ng·h/mL)</th>
<th>Reference† (ng·h/mL)</th>
<th>% Ratio of Geometric Means</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCₜ</td>
<td>662.5 (33.5)</td>
<td>664.0 (43.3)</td>
<td>102.9</td>
<td>97.1 – 109.1</td>
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<tr>
<td>Cmax</td>
<td>742.5</td>
<td>712.7</td>
<td>104.2</td>
<td>98.2 – 110.6</td>
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<tr>
<td>Tmax ‡</td>
<td>4.50 (2.50 – 7.00)</td>
<td>5.25 (2.50 – 6.00)</td>
<td></td>
<td></td>
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<tr>
<td>T1/2  §</td>
<td>26.6 (31.2)</td>
<td>25.1 (25.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† pms-Amitriptyline 50 mg tablets, Pharmascience Inc., Montreal, QC, Canada
‡ ELAVIL® 50 mg tablets, AA Pharma Inc., Vaughan, ON, Canada
§ Expressed as the median (range)
§ Expressed as the arithmetic mean (CV%)
AVAILABILITY OF DOSAGE FORMS

**Tablets**

**10 mg:** Each blue, round, coated tablets debossed with “AM” on one side and “10” on the other side contains 10 mg Amitriptyline Hydrochloride, and the following non-medicinal ingredients: Colloidal Silicon Dioxide, Croscarmellose Sodium, FD&C blue No. 1 Aluminum Lake, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Titanium Dioxide. Available in HDPE bottles of 100 and 1000.

**25 mg:** Each yellow, round, coated tablet debossed with “AM” on one side and “25” on the other side contains 25 mg Amitriptyline Hydrochloride, and the following non-medicinal ingredients: Colloidal Silicon Dioxide, Croscarmellose Sodium, FD&C Blue No. 2 Aluminum Lake, FD&C Yellow No.5 (Tartrazine) Aluminum Lake, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Titanium Dioxide. Available in HDPE bottles of 100 and 1000

**50 mg:** Each brown, round, coated tablet debossed with “AM” on one side and “50” on the other side contains 50 mg Amitriptyline Hydrochloride, and the following non-medicinal ingredients: Black Iron Oxide, Colloidal Silicon Dioxide, Croscarmellose Sodium, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Red Iron Oxide, Titanium Dioxide, and Yellow Iron Oxide. Available in HDPE bottles of 100 and 1000

**75 mg:** Each orange, round, coated tablet debossed with “AM” on one side and “75” on the other side contains 75 mg Amitriptyline Hydrochloride, and the following non-medicinal ingredients: Colloidal Silicon Dioxide, Croscarmellose Sodium, FD&C Yellow No. 6 Aluminum Lake, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Titanium Dioxide. Available in HDPE bottles of 100.
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, and the following non-medicinal ingredients: Colloidal Silicon Dioxide, Croscarmellose Sodium, FD&C Blue No. 2 Aluminium Lake, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol/Macrogol, Red Iron Oxide non-irradiated, Titanium Dioxide. Available in HDPE bottles of 100.

**Stability and Storage Recommendations**

Store between 15°C and 30°C. Keep in a tightly closed container.