PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]AVENTYL

Nortriptyline Hydrochloride Capsules

Capsules, 10 mg and 25 mg, Oral

USP

Antidepressant

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RECENT MAJOR LABEL CHANGES

N/A	N/A

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATION

AVENTYL (nortriptyline hydrochloride) is indicated for the relief of symptoms of depression. Endogenous depressions are more likely to be alleviated than are other depressive states.

1.1 Pediatrics

Pediatrics (< 18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of AVENTYL in pediatric patients has not been established. Therefore, Health Canada has not authorized an indication for pediatric use (see 4.2. Recommended Dose and Dosage Adjustment; 7.1.3. Pediatrics).

1.2 Geriatrics

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; 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

AVENTYL is contraindicated:

- in patients with hypersensitivity to this drug 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 between nortriptyline and other dibenzazepines is a possibility.
- with concomitant use of a MAO inhibitor or use within 14 days of discontinuing treatment with a MAO inhibitor (see 9.4 Drug-Drug Interactions; 5 OVERDOSAGE).
- during the acute recovery period following myocardial infarction.

3 SERIOUS WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Increased risk of self-harm, harm to others, suicidal thinking and behaviour 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, Potential association with behavioural and emotional changes, including self-harm).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- AVENTYL is not recommended for use in children (see 1.1 Pediatrics; 7.1.3 Pediatrics).

- AVENTYL is contraindicated for concomitant use with MAO inhibitors (see 2 CONTRAINDICATIONS). AVENTYL should not be used within 14 days of initiating or discontinuing MAO inhibitors.

- The maximum recommended daily dose is 100 mg/day.

- Clinical findings should predominate over plasma concentrations as primary determinants of dosage changes.

- Dosage adjustments are recommended for elderly patients and adolescents (see 4.2 Recommended Dose and Dosage Adjustment).

- The use of lower dosages for outpatients is more important than for hospitalized patients, who will be treated under close supervision.

- Dosages should be titrated, beginning at a low level and increasing gradually over several weeks, while carefully monitoring for clinical response and noting any evidence of intolerance. Improvement may not occur during the first few weeks or more of treatment.

- When discontinuing AVENTYL, the dosage should be tapered gradually (see 7 WARNINGS AND PRECAUTIONS; 8.5 Post-Market Adverse Reactions).

- Following remission, maintenance medication may be required for a long period of time at the lowest dose that will maintain remission.

- If a patient develops minor side effects, the dosage should be reduced. The drug should be discontinued promptly if adverse effects of a serious nature or allergic manifestations occur.

4.2 Recommended Dose and Dosage Adjustment

- **Adults (≥ 18 years):** The recommended dose of AVENTYL is 25 mg, taken orally 3 - 4 times daily. When initiating treatment with AVENTYL, dosage should begin at a low level and increase gradually, as required. Doses above 100 mg/day are not recommended (see 1.1 Pediatrics; 7.1.3 Pediatrics).

- **Pediatrics (< 18 years):** Health Canada has not authorized an indication for pediatric use. The use of AVENTYL in children is not recommended. When considering the use of

nortriptyline in adolescents, the clinical need should outweigh the potential risks and uncertainties. Dosing in adolescents should be reduced to 30 to 50 mg/day, in divided doses.

- **Geriatrics:** There is limited data available involving the use of nortriptyline in patients aged 65 and over. Caution should be exercised when using AVENTYL in elderly patients. Dosing for elderly patients should be limited to 30 to 50 mg/day, in divided doses (see 7.1.4 Geriatrics).

- **Hepatic Insufficiency:** Nortriptyline is extensively metabolized in the liver (see 10.3 Pharmacokinetics). In patients with hepatic impairment, use caution when initiating treatment with AVENTYL. Lower doses may be required.

4.4 Administration

AVENTYL is administered orally, in the form of capsules.

4.5 Missed Dose

If the patient misses a dose of AVENTYL, the patient should be instructed to skip the missed dose and take the next dose at the regular dosing schedule.

5 OVERDOSAGE

Overdose of tricyclic antidepressants may manifest with doses as small as 50 mg in a child. Of patients who are alive at initial presentation, a mortality rate of between 0% and 15% has been reported. Symptoms of overdose of tricyclic antidepressants may begin within several hours of oral ingestion. Symptoms and signs may include blurred vision, confusion, restlessness, dizziness, hypothermia, hyperthermia, agitation, vomiting, hyperactive reflexes, dilated pupils, fever, rapid heart rate, decreased bowel sounds, dry mouth, inability to void, myoclonic jerks, seizures, respiratory depression, myoglobinuric renal failure, nystagmus, ataxia, dysarthria, choreoathetosis, coma, hypotension, and cardiac arrhythmias (see 8.1 Adverse Reaction Overview).

An effect on cardiac conduction, similar to that of quinidine, may be seen with slowing of conduction, prolongation of the QRS complex and QT intervals, right bundle branch and AV block, ventricular tachyarrhythmias (including Torsade de pointes and fibrillation), and death. Prolongation of the QRS duration to more than 0.1 seconds is predictive of more severe toxicity. The absence of sinus tachycardia does not ensure a benign course. Hypotension may be caused by vasodilation, central and peripheral a.- adrenergic blockade, and cardiac depression. In a healthy young person, prolonged resuscitation may be effective; one patient was reported to survive 5 hours of cardiac massage.

In managing overdose, consider the possibility of multiple drug overdose, interactions among drugs, and unusual drug kinetics in your patients. Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Ventricular arrhythmias, especially when accompanied by lengthened QRS intervals, may respond to alkalinization by hyperventilation or administration of sodium bicarbonate. It is important to monitor and manage serum electrolyte levels. Refractory arrhythmias may respond to propranolol, bretylium, or lidocaine. Quinidine and procainamide usually should not be used because they may exacerbate arrhythmias and conduction already slowed by the overdosage (see 9.4 Drug-Drug Interactions).

Seizures may respond to diazepam. Phenytoin has pharmacologic properties that may be helpful in dealing with both the seizures and cardiac rhythm disturbances of tricyclic antidepressant overdose. Although the prophylactic use of phenytoin has been suggested, it is not yet of proven value.

In some patients, physostigmine may antagonize such effects of tricyclic antidepressant overdose as atrial tachycardia, gut immotility, myoclonic jerks, and somnolence. It is less effective for seizures and ventricular arrhythmias. When giving physostigmine, the patient's condition should be carefully monitored and ventilation and cardiac rhythm should be supported. Cholinergic toxicity from physostigmine may include bronchospasm, bronchorrhea, bradycardia, asystole, diaphoresis, incontinence, and seizures. If physostigmine is used, give it slowly because rapid injection may cause seizures. The effects of physostigmine may be short-lived; repeated doses may lead to continued improvement.

Diuresis and dialysis remove little of the tricyclic antidepressant present in the body of a patient who has taken an overdose. Hemoperfusion is of unproven benefit. The patient who has taken a tricyclic antidepressant overdose should be monitored closely, at least until the QRS duration is normal.

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	Capsules, 10 mg, 25 mg	Corn starch, D&C yellow #10, FD&C yellow #6, gelatin, lactose, stearic acid, talc and titanium dioxide

AVENTYL 10 mg Capsules: Each white, opaque body, maize opaque cap, hard gelatin capsule, imprinted "NT" and "10 mg" over "709", with white to off-white powder fill, contains nortriptyline hydrochloride equivalent to 10 mg nortriptyline base.

AVENTYL 25 mg Capsules: Each white, opaque body, maize opaque cap, hard gelatin capsule, imprinted "NT" and "25 mg" over "710", with white to off-white powder fill, contains nortriptyline hydrochloride equivalent to 25 mg nortriptyline base.

Tartrazine-free. Available in bottles of 100, 250, 500 and 1000 capsules.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS.

General

POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM

- **Pediatrics:** Placebo-Controlled Clinical Trial Data

Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer anti-depressants suggest that 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.
The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among the drugs in the class.

- **Adults and Pediatrics:** Additional data

There are clinical trial and post-marketing reports with SSRIs and other newer antidepressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia/psychomotor restlessness, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients ages 18 to 24 years with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo.

Cardiovascular

AVENTYL is contraindicated in the acute recovery period following myocardial infarction (see 2 CONTRAINDICATIONS).

Patients with cardiovascular disease should be given nortriptyline only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong the conduction time (see 8.1 Adverse Reaction Overview, Cardiovascular). Myocardial infarction, arrhythmia and strokes have occurred.

The antihypertensive action of guanethidine and similar agents may be blocked with concomitant use of nortriptyline (see 8 ADVERSE REACTIONS, Cardiovascular; 9.4 Drug-Drug Interactions).

Great care is required if nortriptyline is administered to hyperthyroid patients or those receiving thyroid medication, because cardiac arrhythmias may develop (see 9.4 Drug-Drug Interactions).

Dependence/Tolerance

Though not indicative of addiction, abrupt cessation of treatment following prolonged therapy may produce withdrawal symptoms, including flu-like symptoms, dizziness, nausea, headache, agitation, malaise, and abdominal cramping. As with other antidepressants, sudden discontinuation of nortriptyline treatment may also increase the risk of relapse. When discontinuing AVENTYL, the patient should be closely monitored, while the dosage is gradually tapered over several weeks (see 4.1 Dosing Considerations; 8 ADVERSE REACTIONS, Withdrawal).

Driving and Operating Machinery

Nortriptyline may cause somnolence, dizziness, and confusion. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

In hyperthyroid patients or those receiving thyroid medication, NORTIPTYLINE may cause cardiac arrhythmias (see 8 ADVERSE REACTIONS, Cardiovascular).

Nortriptyline may affect blood sugar levels. Both elevation and lowering of blood sugar levels

have been reported with nortriptyline (see 8 ADVERSE REACTIONS, Endocrine). A case of significant hypoglycemia has been reported in a Type II diabetic patient maintained on chlorpropamide (250 mg/day) after the addition of nortriptyline (125 mg/day).

Those patients with reduced activity of drug metabolizing enzymes, such as the cytochrome P450 isoenzyme P450 2D6 (debrisoquin hydroxylase), may have higher plasma concentrations of nortriptyline when given usual doses. These patients may require lower doses than usually prescribed for AVENTYL (see 10.3 Pharmacokinetics).

Genitourinary

Due to its anticholinergic activity, nortriptyline may cause urinary retention (see 8 ADVERSE REACTIONS, Anticholinergic). Extreme caution should be used when AVENTYL is given to patients with a history of urinary retention. Close supervision and careful adjustment of the dosage are required when nortriptyline is used with other anticholinergic drugs (see 9.4 Drug-Drug Interactions).

Monitoring and Laboratory Tests

Plasma concentrations are difficult to measure. Healthcare providers should consult with laboratory professional staff. Clinical findings should predominate over plasma concentration as primary determinants of dosage change (see 4.1 Dosing Considerations).

Neurologic

- Seizures

  Nortriptyline is known to lower convulsive threshold. Extreme caution should be exercised when using AVENTYL in patients with a history of seizures. Patients should be followed closely when nortriptyline is administered in these patients.

  Troublesome patient hostility may be aroused by the use of nortriptyline. Epileptiform seizures may accompany its administration, as may happen with other drugs of its class.

- Serotonin toxicity/Serotonin syndrome

  Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with tricyclic antidepressants.
  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

If concomitant treatment with AVENTYL and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 2 CONTRAINDICATIONS; 4.1 Dosing Considerations; 9.4 Drug-Drug Interactions). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

- Electroconvulsive Therapy (ECT)

There is limited clinical experience in the concurrent administration of ECT and antidepressant drugs. When it is essential, AVENTYL may be administered concurrently with ECT, if such treatment is essential. However, the possibility of increased risk, relative to benefits, should be considered. Discontinue the drug for several days, if possible, prior to ECT.

Ophthalmologic

Due to anticholinergic activity, nortriptyline may cause an increase in intraocular pressure. AVENTYL should not be used in patients with or at risk of glaucoma (see 8.1 Adverse Reaction Overview, Anticholinergic; 9.4 Drug-Drug Interactions).

Peri-Operative Considerations

AVENTYL should be discontinued as soon as possible (for several days, if possible) prior to elective surgery due to possible drug interactions and cardiovascular effects (see 8 ADVERSE REACTIONS, Cardiovascular; 9.4 Drug-Drug Interactions).

Psychiatric

All patients being treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behaviour, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Closely monitor all antidepressant-treated patients for clinical worsening and for emergence of agitation-type

and/or suicidal thoughts and behaviors (see 3 SERIOUS WARNINGS AND PRECAUTIONS).

The use of nortriptyline in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms.

If the drug is given to overactive or agitated patients, increased anxiety and agitation may occur. In manic depressive patients, nortriptyline may cause symptoms of the manic phase to emerge.

Inform the patient that their response to alcohol may be exaggerated. Excessive consumption of alcohol in combination with nortriptyline therapy may have a potentiating effect, which may increase the risk of suicidal thinking and behaviour (see 3 SERIOUS WARNINGS AND PRECAUTIONS) and/or overdosage, especially in patients with a history of emotional disturbances or suicidal ideation (see 9.3. Drug-Behavioural Interactions).

The possibility of a suicidal attempt by depressed patients remains even after initiation of treatment. In this regard, it is important that the least possible quantity of drug be dispensed at any given time.

7.1 Special Populations

7.1.1 Pregnant Women

Safe use of nortriptyline during pregnancy has not been established; therefore, when the drug is administered to pregnant patients or women of childbearing age, the potential benefits must be weighed against the possible hazards. Animal reproduction studies have yielded inconclusive results.

7.1.2 Breast-feeding

Safe use of nortriptyline during lactation has not been established; therefore, when the drug is administered to nursing mothers, the potential benefits must be weighed against the possible hazards.

7.1.3 Pediatrics

Pediatrics (<18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of AVENTYL in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. Nortriptyline is not recommended for use in children (see 1.1. Pediatrics; 3 SERIOUS WARNINGS AND PRECAUTIONS).

7.1.4 Geriatrics

There is limited data available involving the use of nortriptyline in patients aged 65 and over.

Elderly patients may respond differently to AVENTYL and may be more liable to experience adverse reactions, especially agitation, confusion and postural hypotension.

Higher plasma concentrations of the active nortriptyline metabolite, 10-hydroxynortriptyline, have also been reported in elderly patients, associated with apparent cardiotoxicity (see 10.3 Pharmacokinetics). Cardiovascular function, particularly arrhythmias and fluctuations in blood pressure, should be monitored.

There have been reports of confusional states following tricyclic antidepressant administration to the elderly (see 8.5 Post-Market Adverse Reactions). Dose selection for an elderly patient should usually be limited to the smallest effective total daily dose (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 nortriptyline use are listed in 8.5 Post-Market Adverse Reactions.

The most serious adverse effects include orthostatic hypotension, syncope, ventricular arrhythmias, AV block, myocardial infarction, stroke, paralytic ileus, glaucoma, increased intraocular pressure, agranulocytosis, leukopenia, thrombocytopenia, hepatitis, angioedema.

8.2 Clinical Trial Adverse Reactions

The clinical trial data on which the indication was originally authorized is not available. See 8.5 Post-Market Adverse Reactions below.

8.3 Less Common Clinical Trial Adverse Reactions

The 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

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

8.5 Post-Market Adverse Reactions

Note: Included in the following list are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of these reactions be considered when nortriptyline is administered.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross- sensitivity with other tricyclic drugs.

Anticholinergic: dry mouth and, rarely, associated sublingual adenitis or gingivitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke, QT prolongation (especially in the elderly).

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

Gastrointestinal: nausea and vomiting, anorexia, epigastric distress, diarrhea; peculiar taste, stomatitis, abdominal cramps, black tongue, constipation, paralytic ileus.

Hematologic: bone-marrow depression, including agranulocytosis, aplastic anemia; eosinophilia; purpura; thrombocytopenia.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy, extrapyramidal symptoms; seizures, alteration of EEG patterns; tinnitus.

Other: jaundice (simulating obstructive); altered liver function, hepatitis, and liver necrosis; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia.

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbations of psychosis.

Withdrawal Symptoms: though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce flu-like symptoms, dizziness, nausea, headache, agitation, malaise, and abdominal cramping. Relapse of depression and anxiety may also occur.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Concomitant use of AVENTYL with monoamine oxidase (MAO) inhibitors, such as linezolid, and IV methylene blue, is contraindicated as it can lead to an increased risk of developing serotonin toxicity, which can be life-threatening (see 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS; 9.4 Drug-Drug Interactions).

9.2 Drug Interactions Overview

Concomitant use of AVENTYL with monoamine oxidase (MAO) inhibitors is contraindicated (see 2 CONTRAINDICATIONS). AVENTYL should not be co-administered with, or within 2 weeks of, a MAO inhibitor drug.

Concomitant use of nortriptyline with other serotonergic agents, particularly MAO inhibitors, increases the risk of serotonin toxicity.

Prescribe AVENTYL with extreme caution for hyperthyroid patients or for patients receiving thyroid medication. Transient cardiac arrhythmias have occurred in rare instances in patients who have been receiving other tricyclic compounds concomitantly with thyroid medication.

AVENTYL has anticholinergic actions. Close supervision and careful adjustment of dosage are required when this drug is administered concomitantly with other anticholinergic or sympathomimetic drugs.

AVENTYL may decrease the effect of drugs that rely upon neuronal uptake via the norepinephrine transporter, such as the antihypertensive, guanethidine.

Co-administration of tricyclic antidepressants with other drugs that are metabolized by the cytochrome P450 isoenzyme CYP2D6, including other antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g. quinidine), should be approached with caution.

Nortriptyline can exaggerate the response to alcohol.

9.3 Drug-Behavioural Interactions

The patient should be warned their response to alcohol may be exaggerated (see 7 WARNINGS AND PRECAUTIONS, Psychiatric).

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	Potential Effect	Clinical comment
MAO inhibitors (e.g. selegiline, phenelzine, linezolid, iv methylene blue)	CT	Increase in nortriptyline exposure.	The concomitant use of nortriptyline or other tricyclic antidepressants with a MAO inhibitor is contraindicated (see 2 CONTRAINDICATIONS).
Serotonergic drugs (e.g. triptans, tricyclic antidepressants, SSRIs, SNRIs, fentanyl, lithium, tramadol, tryptophan, buspirone)	CT	Potentiated serotonin levels. Possible increase in nortriptyline exposure.	The concomitant use of nortriptyline with other serotonergic drugs increases the risk of serotonin toxicity (see 7 WARNINGS AND PRECAUTIONS). If concomitant treatment with AVENTYL and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases and when switching from one class to the other.
Fluoxetine	CT	>2 fold increase in nortriptyline exposure	Fluoxetine and its active metabolite, norfluoxetine, have a long half-life (7 to 9 days for norfluoxetine) which might affect strategies during conversion from one drug to another.
Reserpine (adrenergic blocking agent)	C	Increase in nortriptyline exposure.	Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a “stimulating” effect in some depressed patients.
Histamine H2 blockers (e.g. cimetidine)	CT	Increase in nortriptyline exposure.	Serious anticholinergic symptoms (severe dry mouth, urinary retention, blurred vision) may occur (see 7 WARNINGS AND PRECAUTIONS). The therapeutic efficacy of AVENTYL may be compromised, upon cimetidine discontinuation.

Proper/Common name	Source of Evidence	Potential Effect	Clinical comment
Anticholinergic	CT	Additive effect	Concomitant use should be avoided due to an increased risk of adverse reactions, including paralytic ileus and hyperpyrexia. Close supervision and careful adjustment of the dosage are required.
Sympathomimetic drugs (as found in anaesthetics) (e.g. adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine)	CT	Increased pressor response to sympathomimetics.	May produce severe hypertension (see 7 WARNINGS AND PRECAUTIONS). Concomitant use with sympathomimetic agents is not recommended. Close supervision and careful adjustment of the dosage are required.
Antihypertensives (e.g. guanethidine, debrisoquine, betanidine, methyldopa, clonidine)	T	Reduced uptake of antihypertensive drugs.	Nortriptyline may decrease the efficacy of antihypertensive drugs (see 7 WARNINGS AND PRECAUTIONS).
Thyroid medications (e.g. levothyroxine)	C	Mutual effects on exposure.	The risk or severity of adverse reactions associated with either drug may be increased. Cardiac arrhythmias may develop (see 7 WARNINGS AND PRECAUTIONS).
Phenothiazines (e.g. chlorpromazine, thioridazine, trifluoperazine)	T	Increase in nortriptyline exposure.	Use caution with concomitant use. Dosage adjustments may be required.
Carbamazepine	CT	Reduced nortriptyline exposure.	May reduce the efficacy of nortriptyline.
Type 1C antiarrhythmics (e.g. quinidine)	CT	>2 fold increase in nortriptyline exposure	Concomitant use increases the risk of serotonin toxicity and anticholinergic symptoms and should be avoided (see 7 WARNINGS AND PRECAUTIONS).

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal remedies have not been established.

Herbal remedies such as milk thistle, kava kava, black cohosh, Echinacea, and St. John's wort are mild modulators of human CYP2D6 and not expected to significantly alter nortriptyline exposure. However, exercise caution when using these herbal remedies with AVENTYL. Goldenseal should be avoided while taking AVENTYL, as it is a potent CYP2D6 inhibitor and may give rise to significant pharmacokinetic herb-drug interactions, resulting in increased adverse reactions.

Herbal remedies known to regulate serotonin, such as St. John's wort, Garcinia cambogia (HCA), and ashwagandha should be avoided, as concomitant use may increase the risk of serotonin toxicity (see 7 WARNINGS AND PRECAUTIONS).

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The mechanism of mood elevation of tricyclic antidepressants is at present unknown. AVENTYL (nortriptyline hydrochloride) is not an MAO inhibitor. It inhibits the activity of such diverse agents as histamine, 5-hydroxytryptamine, and acetylcholine. It increases the pressor effect of norepinephrine but blocks the pressor response of phenethylamine. Studies suggest that nortriptyline hydrochloride interferes with the transport, release and storage of catecholamines.

10.2 Pharmacodynamics

There are post-marketing reports of QT prolongation, particularly in the elderly (see 8.5 Post-Market Adverse Reactions).

10.3 Pharmacokinetics

Absorption
Nortriptyline HCl is well absorbed from the GI tract. Plasma concentrations exhibit considerable inter-patient variation. A relationship of plasma concentrations to clinical response and acute toxicity has not been fully established but has been reported by other study groups. Peak plasma concentrations occur within 7 to 8.5 hours after oral administration. Optimal response to the drug appears to be associated with plasma concentrations of 50 to 150 ng/ml. Adverse effects appear within a few hours after administration of the drug, but full antidepressant

effects may not occur for several weeks.

Distribution
Nortriptyline HCl is distributed to the lungs, heart, brain, and liver. Nortriptyline and its metabolite are highly bound to plasma and tissue proteins. Nortriptyline readily crosses the placenta and is distributed into breast milk where it appears in similar or slightly greater concentrations than those present in the maternal serum.

Metabolism
Nortriptyline is subject to extensive first-pass metabolism in the liver by CYP2D6 to its active metabolite, 10- hydroxynortriptyline, which is active.

Elimination
Nortriptyline, when administered orally, undergoes first-pass metabolism in the liver. The primary route of elimination is urinary excretion, approximately one-third of the dose as metabolites within 24 hours, but it is also excreted in feces via the bile. The plasma half-life of nortriptyline ranges from 16 to more than 90 hours.

Special Populations and Conditions

- **Pediatrics (<18 yrs):** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of AVENTYL in pediatric patients has not been established. Therefore, Health Canada has not authorized an indication for pediatric use
- **Geriatrics:** There is limited data available involving the use of nortriptyline in patients aged 65 and over. However, elderly patients may be more sensitive to the effects of tricyclic antidepressants. Dosing adjustments are recommended (see 4.2 Recommended Dose and Dosage Adjustment). Higher plasma concentrations of the active nortriptyline metabolite, 10-hydroxynortriptyline, have also been reported in elderly patients.
- **Sex:** The data upon which the indication was originally authorized is not available.
- **Pregnancy and Breast-feeding:** Nortriptyline is known to cross the placenta. Nortriptyline should only be used in pregnancy if the potential benefits outweigh the possible hazards (see 7.1.1 Pregnant Women).

  Nortriptyline is present in breast milk. The safe use of nortriptyline during breast-feeding has not been established. Nortriptyline should only be used in nursing mothers if the potential benefits outweigh the possible hazards (see 7.1.2 Breast-feeding).
- **Genetic Polymorphism:** A subset (3 to 10%) of the population has reduced activity of certain drug metabolizing enzymes such as the cytochrome P450 isoenzyme P450 2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan and the tricyclic antidepressants. These individuals may have higher than expected plasma concentrations of tricyclic antidepressants when given usual doses.

- **Ethnic Origin:** The data upon which the indication was originally authorized is not available.
- **Hepatic Insufficiency:** The data upon which the indication was originally authorized is not available. However, nortriptyline is primarily metabolized in the liver and impairments in hepatic function may increase drug exposure.
- **Renal Insufficiency:** The data upon which the indication was originally authorized is not available.
- **Obesity**: The data upon which the indication was originally authorized is not available.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C-30°C). Keep tightly closed.

AVENTYL should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

12 SPECIAL HANDLING INSTRUCTIONS

None

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Nortriptyline hydrochloride

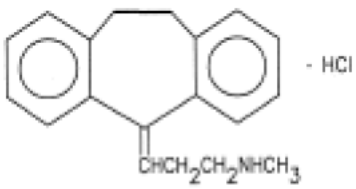
Chemical Names:

1) 1-Propanamine, 3-(10,11-dihydro-5*H*-dibenzo-[a,d]-cyclohepten-5-ylidene)-*N*-methyl-, hydrochloride;

2) 10,11-Dihydro-*N*-methyl-*5H*-dibenzo-[a,d]-cycloheptene- $\Delta^{5,\gamma}$-propylamine hydrochloride.

Molecular Formula and Molecular Mass: $C_{19}H_{21}N \bullet HCl$ and 299.84 g/mol

Structural formula:



Physicochemical properties: Nortriptyline hydrochloride is a white to off-white powder, having a slight, characteristic odor. Its solution (1 in 100) has a pH of about 5. Soluble in water and in chloroform; sparingly soluble in methanol; practically insoluble in ether, in benzene, and in most other organic solvents.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The data upon which the indication was originally authorized is not available.

14.2 Comparative Bioavailability Studies

A randomized, two-treatment, two-period, single-dose, crossover comparative bioavailability study of AVENTYL 25 mg capsules (AA Pharma Inc.) and Aventyl® 25 mg capsules (Eli Lilly Canada Inc.) was conducted in healthy adult male subjects under fasting conditions. Comparative bioavailability data from 16 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Nortriptyline (3 x 25 mg) Geometric Least Square Mean Arithmetic Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-72} (ng·h/mL)	1188 1264 (33)	1216 1267 (33)	98	91 – 105
AUC_T (ng·h/mL)	1436 1575 (40)	1476 1593 (41)	97	91 – 104
AUC_I (ng·h/mL)	1589 1730 (40)	1683 1746 (42)	94	90 – 99
C_{max} (ng/mL)	36.76 38.36 (30)	38.50 39.27 (29)	95	85 – 107
T_{max}[3] (h)	7.9 (23)	8.0 (27)		
$T_{1/2}$[3] (h)	37.8 (41)	36.1 (38)		

[1] AVENTYL (nortriptyline hydrochloride) capsules, 25 mg (AA Pharma Inc.)
[2] Aventyl® (nortriptyline hydrochloride) capsules, 25 mg (Eli Lilly Canada Inc.)
[3] Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

The data upon which the indication was originally authorized is not available.

17 SUPPORTING PRODUCT MONOGRAPHS

1. AVENTYL®, capsules, 10 mg and 25 mg, submission control 173243, Product Monograph AA Pharma Inc. (April 29, 2014).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]AVENTYL

Nortriptyline Hydrochloride Capsules

Read this carefully before you start taking **AVENTYL** 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 **AVENTYL**.

Serious Warnings and Precautions

New and worsened emotional or behaviour problems:

- **When you first start taking AVENTYL or when your dose is adjusted, you may feel worse instead of better. You may feel new or worsened feelings of agitation, hostility, anxiety, aggression or impulsivity.**
- **During your treatment with AVENTYL, 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 AVENTYL.**
- **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 AVENTYL to work.**

Self-harm or suicide:

- **Antidepressants, such as AVENTYL, may increase the risk of suicidal thoughts and actions.**
- **If you have thoughts of harming or killing yourself at any time, tell your healthcare professional or go to a hospital right away. Close observation by a healthcare professional is necessary in this situation.**

What is AVENTYL used for?

AVENTYL is used in adults to relieve the symptoms of depression (feeling sad, a change in appetite or weight, difficulty concentrating or sleeping, feeling tired, headaches, unexplained

aches and pain).

How does AVENTYL work?

AVENTYL is a medicine that belongs to a group of medicines known as tricyclic antidepressants. It is not known exactly how AVENTYL 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 AVENTYL?

Medicinal ingredients: Nortriptyline hydrochloride

Non-medicinal ingredients: Corn starch, D&C yellow #10, FD&C yellow #6, gelatin, lactose, stearic acid, talc and titanium dioxide.

AVENTYL comes in the following dosage forms:

Capsules: 10 mg and 25 mg.

Do not use AVENTYL if:

- you are allergic to nortriptyline or any of the non-medicinal ingredients in AVENTYL
- you are taking or have taken within the last 14 days medicines for depression called monoamine oxidase inhibitors (MAOIs)
- you have recently experienced a heart attack or heart failure

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AVENTYL. Talk about any health conditions or problems you may have, including if you:

- have heart problems
- have low blood pressure
- have high pressure in the eyes (glaucoma)
- have or have a history of difficulty passing urine
- have a history of epilepsy or seizures
- have a thyroid condition or are taking thyroid medication
- have schizophrenia, bipolar disorder or any other mental health problems
- are taking other anticholinergic medicines (certain medicines used to treat asthma, chronic obstructive pulmonary disease, stomach and gut problems, and Parkinson's disease) or sympathomimetic medicines such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine
- have ever had suicidal thoughts

- consume alcohol. Drinking alcohol while taking AVENTYL may exaggerate your response to alcohol
- are going to have electroconvulsive therapy (electric shock)
- have diabetes
- have lactose intolerance
- are pregnant, think you might be pregnant or are planning to become pregnant
- are breastfeeding or are planning to breastfeed
- are taking medicines used to treat high blood pressure such as guanethidine
- are 65 years of age or older
- have liver problems

Other warnings you should know about:

Withdrawal symptoms: Do NOT stop taking AVENTYL without talking to your healthcare professional first. You may need to lower your dose gradually and careful monitoring by your healthcare professional is required. Stopping AVENTYL suddenly may cause withdrawal symptoms including dizziness, nausea, headache, malaise (general discomfort), agitation and stomach cramps.

Driving and using machines: AVENTYL can cause you to feel drowsy, dizzy, and confused. Do not drive or operate machinery until you know how AVENTYL affects you.

Serotonin toxicity (also known as Serotonin Syndrome): AVENTYL can cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take AVENTYL with certain anti-depressants or migraine medications. Serotonin toxicity symptoms include:

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

Glaucoma: AVENTYL can cause angle-closure glaucoma (sudden eye pain). Having your eyes examined before you take AVENTYL 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.

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

Check-ups and testing: Your healthcare professional may do tests to monitor your health while

you are taking NORTIPTYLINE. This may include tests to monitor your blood pressure and check for problems with your heart.

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 AVENTYL 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.

The following may interact with AVENTYL:

- cimetidine, used to treat stomach ulcers
- anticholinergic medications such as certain medicines used to treat asthma, chronic obstructive pulmonary disease, stomach and gut problems, and Parkinson's disease
- medicines called sympathomimetics such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine
- dextromethorphan used to treat cough
- other antidepressants such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) like fluoxetine, and serotonin and norepinephrine reuptake inhibitors (SNRIs)
- medicines used to treat mental and emotional problems called phenothiazines, such as chlorpromazine, thioridazine, trifluoperazine
- carbamazepine used to treat seizures
- medicines used to treat irregular heartbeats such as propafenone, flecainide, encainide and quinidine
- medicines used to treat thyroid problems such as levothyroxine
- medicines used to treat high blood pressure such as guanethidine, reserpine, debrisoquine, betanidine, methyldopa, and clonidine
- medicines used to treat pain called opioids, such as tramadol and fentanyl
- lithium, used to treat bipolar disorder
- buspirone, used to treat generalized anxiety disorder
- medicines called triptans, used to treat migraines or headaches
- alcohol
- herbal medicines such as goldenseal, garcinia cambogia, ashwagandha, and St. John's wort

How to take AVENTYL:

- Always take AVENTYL exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- You should continue to take your medicine even if you do not feel better. It may take a number of weeks for your medicine to start working.

- Do not stop taking or change your dose without talking to your healthcare professional. If you are stopping this medication you may need to lower the dose gradually. Stopping AVENTYL suddenly can cause withdrawal symptoms.

Usual dose:

Your healthcare professional will determine the dose that is right for you. Take AVENTYL exactly as directed. Based on how you respond to AVENTYL and your tolerability, your healthcare professional may change your dose. If you are elderly or have other health problems such as problems with your liver, your healthcare professional may prescribe a lower dose.

Overdose:

Signs of overdose may include blurred vision, confusion, restlessness, changes in body temperature, agitation, vomiting, uncontrolled movements, dilated pupils, fever, rapid heartbeats, constipation, dry mouth, difficulties passing water, fits, difficulty breathing, renal failure, repetitive, uncontrolled eye movements, impaired coordination, slurred speech, involuntary twitching or writhing movements, coma, low blood pressure, and abnormal heart rhythms

If you think you, or a person you are caring for, have taken too much AVENTYL, 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 AVENTYL, skip the missed dose and take the next dose as scheduled.

What are possible side effects from using AVENTYL?

These are not all the possible side effects you may have when taking AVENTYL. If you experience any side effects not listed here, tell your healthcare professional.

The side effects may include:

- restlessness
- constipation
- nausea and vomiting
- decrease appetite
- stomach pain
- diarrhea
- changes in taste
- black tongue
- changes in weight (gain or loss)

- increased sweating
- drowsiness
- dizziness
- weakness
- tiredness
- headache
- hair loss
- trouble sleeping

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**	
UNKNOWN			
Stomatitis (mouth sores, redness and swelling of the lining of the mouth)	✓		
Digestive system problems: diarrhea, loss of appetite, nausea, stomach pain, unpleasant taste in the mouth, upset stomach, vomiting, black tongue, constipation	✓		
Dry mouth, sometimes with a swollen salivary gland (enlargement, pain and redness of salivary glands) or gingivitis (inflammation of gums)		✓	
Urticarial reaction: skin with red spots which burn, itch or sting	✓		
Nocturia (excessive urination at night)	✓		
Feeling weak, dizzy, tired or have a headache	✓		
Insomnia: trouble falling asleep, staying asleep, waking up too early and not being able to get back to sleep	✓		
Mania: elevated or irritable mood, decreased need for sleep, racing thoughts		✓	
Allergic reaction: rash, hives,		✓	

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**	
swelling of the face, lips and tongue or throat, difficulty swallowing or breathing, fever			
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, tremors		✓	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		✓	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		✓	
Increased or decreased blood sugar: frequent urination, thirst, hunger, shakiness, sweating and chills, irritability, confusion, dizziness		✓	
Photosensitivity: Increased sensitivity of the skin to sun		✓	
Reproductive problems: swelling of testicles, impotence in men, increase in breast tissue (in men and women), increased production or outflow of breast milk without breast feeding, change in sex drive		✓	

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 rhythm problems: palpitations (rapid, pounding, or irregular heartbeat), changes in the rhythm or rate of the heartbeat, abnormal fast heartbeat, dizziness, fainting		✓	
Paralytic ileus (muscles of the intestines do not allow food to pass through causing blocked intestine): stomach bloating, gas, constipation, nausea and vomiting, dehydration		✓	
Difficulty passing urine		✓	
Mental health problems: confusion, hallucinations, excitement, nightmares, problems with attention, anxiety		✓	
Withdrawal symptoms: nausea, headache, irritability, restlessness, dream and sleep disturbance, generally feeling unwell, irritability, behavioural changes		✓	
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat.			✓
Stroke: Sudden numbness or weakness of your arm, leg or face, especially if only on one side of the body; sudden			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
confusion, difficulty speaking or understanding others; sudden difficulty in walking or loss of balance or coordination; suddenly feeling dizzy or sudden severe headache with no known cause.			
Seizures (fit): uncontrollable shaking with or without loss of consciousness			✓
SIADH—syndrome of inappropriate antidiuretic hormone secretion: concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits (seizures) which may be due to inappropriate secretion of ADH (antidiuretic hormone).			✓
Aplastic anemia (when cells meant to develop into mature blood cells are damaged): fatigue, weakness, pale skin			✓
Eosinophilia (increased numbers of certain white blood cells): abdominal pain, rash, weight loss, wheezing			✓
Agranulocytosis (decrease in white blood cells): frequent infection with fever, chills, sore throat			✓
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness			✓
Jaundice (build up of bilirubin in the blood): yellowing of the skin and eyes, dark urine, light coloured stool, itching all over			✓

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	
your body			
Hepatitis (Inflammation of liver): Abdominal pain, fatigue, fever, itchiness, light coloured stool, trouble thinking clearly, yellowing of the skin			✓
Hepatic necrosis (death of liver cells): abdominal pain and dark urine, fever, light-colored stool, and jaundice (a yellow appearance of the skin and white portion of the eyes)			✓
Glaucoma: increased pressure in the eye, pupil dilation, blurred vision, eye pain			✓
New or worsened emotional or behavioural problems: feeling very agitated or restless, acting aggressive, being angry or violent, acting on dangerous impulses, thoughts of harming others, thoughts of suicide or dying attempts to commit suicide			✓
Serotonin toxicity (also known as serotonin syndrome): a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (above 38°C), or rigid muscles			✓

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

Reporting Side Effects

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

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

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

Storage:

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

Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

Keep out of reach and sight of children.

If you want more information about AVENTYL:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc., 1165 Creditstone Road Unit #1, Vaughan, Ontario, L4K 4N7.

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