PRESCRIBING INFORMATION

^{Pr}pms-BENZTROPINE

Benztropine Mesylate Tablets, USP
2 mg

Antiparkinson Agent

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Benztropine Mesylate Tablets, USP
2 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Tablet, 2 mg	Lactose monohydrate, magnesium stearate, microcrystalline cellulose and pregelatinized starch

INDICATIONS AND CLINICAL USE

pms-BENZTROPINE (benztropine mesylate) is indicated for the symptomatic treatment of all etiologic groups of Parkinsonism and drug-induced extrapyramidal disorders (except tardive dyskinesia).

Geriatrics: (> 65 years of age):
Generally, older patients cannot tolerate large doses of pms-BENZTROPINE (see DOSAGE AND ADMINISTRATION).

Pediatrics: (3 - 18 years of age):
pms-BENZTROPINE is contraindicated in infants and children less than 3 years of age (see CONTRAINDICATIONS) and should be used with caution in older children.

CONTRAINDICATIONS

pms-BENZTROPINE (benztropine mesylate) is contraindicated in:

- Patients who are hypersensitive to benztropine mesylate or to any ingredient in the formulation or component of the container.
- Children less than 3 years of age.
- Patients with narrow angle glaucoma.

WARNINGS AND PRECAUTIONS

General
Since benztropine mesylate has cumulative action, continued supervision is advisable.

Dry mouth, blurred vision, nausea, vomiting and nervousness may develop. Adjustment of dosage or time of administration sometimes helps to control these reactions. If dry mouth is so severe that there is difficulty in swallowing or speaking or there is loss of appetite and weight, reduce dosage or discontinue temporarily. Vomiting may be controlled by temporary discontinuation, followed by resumption at a lower dosage.

Cardiovascular
Since benztropine mesylate has cumulative action, continued supervision is advisable especially in patients with a tendency to tachycardia.

Endocrine and Metabolism
Benztropine mesylate may produce anhidrosis. Therefore, it should be given with caution during hot weather, especially to elderly, the chronically ill, the alcoholic, those with Central Nervous System (CNS) disease and those who do manual labour in a hot environment. Anhidrosis may be anticipated to occur more readily when some disturbance of sweating already exists. If there is evidence of anhidrosis, dosage should be decreased at the discretion of the physician so that the ability to maintain body heat equilibrium by perspiration is not impaired.

Gastrointestinal
When benztropine mesylate is given concomitantly with phenothiazines or other drugs with anticholinergic activity, advise patients to report gastrointestinal complaints promptly. Paralytic ileus, sometimes fatal, has occurred in patients taking anticholinergic type antiparkinson drugs, including benztropine, in combination with phenothiazines and/or tricyclic antidepressants.

Genitourinary
Dysuria may occur. Since benztropine mesylate has cumulative action, continued supervision of patient is advisable, especially in patients with prostatic hypertrophy.

Immune
Occasionally, an allergic reaction develops (*e.g.* skin rash). This may be controlled by reducing the dosage, but, occasionally, the drug may need to be discontinued.

Musculoskeletal
The starting daily dosage of benztropine is 0.5 – 1 mg with a maximum of 6 mg. In large doses (upper range), benztropine mesylate may cause complaints of weakness and inability to move particular muscle groups. For example, if the neck has been rigid and suddenly relaxes, it may feel weak, causing some concerns. In this event, dosage adjustment is required.

Neurologic
Mental confusion, visual hallucinations and agitation may occur with large doses, or in susceptible patients.

Tardive dyskinesia may appear in some patients on long-term therapy with phenothiazines and related agents, or may occur after therapy with these drugs has been discontinued. Antiparkinson drugs usually do not alleviate the symptoms of tardive dyskinesia, and in some instances may aggravate or unmask such symptoms. Benztropine mesylate is not recommended in tardive dyskinesia.

Occupational Hazards
Benztropine mesylate may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Ophthalmologic
The occurrence of glaucoma is possible. Although the drug does not appear to have any adverse effect on simple glaucoma, it should not be used in narrow angle glaucoma (see CONTRAINDICATIONS).

Psychiatric
The psychotogenic potential of antiparkinson drugs should be considered when managing patients with mental disorders. When benztropine mesylate is used to treat extrapyramidal symptoms due to CNS drugs such as phenothiazine derivatives and reserpine in patients with a mental disorder, occasionally, there may be intensification of mental disorders. When using benztropine mesylate in these patients, they should be kept under careful observation, especially at the beginning of treatment or if dosage is increased.

Special Populations

Pregnant Women: The use of this drug in pregnancy has not been studied.

Pediatrics: Because of its atropine-like side effects, pms-BENZTROPINE is contraindicated in children less than 3 years of age, and should be used with caution in older children.

Geriatrics: Generally, older patients cannot tolerate large doses (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The adverse reactions below, most of which are anticholinergic or antihistaminic in nature, have been reported and are listed below by body system in order of decreasing severity.

Cardiovascular: Tachycardia.

Digestive: Paralytic ileus, constipation, vomiting, nausea, dry mouth.

Nervous System: Toxic psychosis, including confusion, disorientation, memory impairment, visual hallucinations; exacerbation of pre-existing psychotic symptoms; nervousness; depression; listlessness; numbness of fingers.

Special Senses: Blurred vision, dilated pupils.

Urogenital: Urinary retention, dysuria.

Metabolic/Immune or Skin: Occasionally, an allergic reaction, e.g., skin rash, develops.

Other: Heat stroke, hyperthermia, fever.

DRUG INTERACTIONS

Drug-Drug Interactions

Occasionally, there may be an intensification of mental disorders when benztropine mesylate is used to treat extrapyramidal symptoms due to CNS drugs, such as phenothiazine derivatives and reserpine, in patients with a mental disorder. The psychotogenic potential of antiparkinson drugs should be considered when planning the management of patients with mental disorders. When using benztropine mesylate in these patients, keep them under careful observation, especially at the beginning of the treatment or if dosage is increased.

Additive anticholinergic effects (*e.g.* fatal paralytic ileus) may occur if benztropine mesylate is used concurrently with other drugs such as phenothiazines and/or tricyclic antidepressants.

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Anticholinergics / antispasmodics – Additive anticholinergic effects may occur if benztropine is used concurrently with other drugs with anticholinergic effects such as amantadine, clidinium antihistamines, antipsychotics, muscle relaxants, tricyclic antidepressants.

Certain antiarrhythmics (e.g. disopyramide, procainamide, quinidine)

Cholinesterase inhibitors – Theoretically, anticholinergics such as benztropine may interfere with the action of centrally acting cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine) and vice versa. In cases where both classes of drugs may be indicated, such as patients with both dementia and urge urinary incontinence, monitor for signs of decreased response to either drug if they are used concurrently.

MAO inhibitors (e.g. moclobemide, phenelzine, tranylcypromine, methylene blue)

Motion sickness medication (e.g. scopolamine, dimenhydrinate) – decrease cholinergic effects/transmission. Additive anticholinergic adverse effects may be seen with concurrent use.

Narcotic pain relievers (e.g. codeine, meperidine, morphine)

Potassium Chloride – Slowed gastric emptying due to the anticholinergic effect of benztropine

can increase the risk of gastrointestinal irritation or ulceration associated with solid oral potassium dosage forms. Avoid concurrent use when possible. Liquid forms of potassium may be preferable.

Tricyclic antidepressants (e.g., amitriptyline, doxepin) – decrease cholinergic effects/transmission. Additive anticholinergic adverse effects may be seen with concurrent use.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
False test results may result with certain medical/laboratory tests (including brain scan for Parkinson's disease).

Drug-Lifestyle Interactions
Ethanol can increase the sedative effects of benztropine.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Benztropine mesylate has cumulative action, thus, therapy should be initiated with a low dose which is increased gradually at 5 or 6 day intervals to the smallest amount necessary for optimal relief. Initially, 0.5 mg is given daily. Increases should be made in increments of 0.5 mg until optimal results are obtained without excessive adverse effects (maximum dose of 6 mg).

There are no adequate and well controlled studies on benztropine mesylate use in pediatric or geriatric patients. The dosage should be individualized based on severity of symptoms, patient characteristics and the type of Parkinsonism being treated. Dosing recommendations are based on clinical experience. In general, treatment should begin at the lowest dose, with gradual increases until maximum improvements are noted or intolerable adverse events occur.

Recommended Dose and Dosage Adjustment

Arteriosclerotic, idiopathic and postencephalitic Parkinsonism:

Adults
The usual daily dose is 1 to 2 mg with a range of 0.5 to 6 mg.

Patients with a poor mental outlook are usually poor candidates for therapy.

In arteriosclerotic and idiopathic Parkinsonism, therapy may be initiated with a single daily dose

of 0.5 to 1 mg (low dose) at bedtime. In some patients, this will be adequate; in others, 4 to 6 mg a day may be required. Generally, older patients, thin patients and those with arteriosclerotic Parkinsonism cannot tolerate large doses.

In postencephalitic Parkinsonism, therapy may be initiated with 2 mg a day in 1 or more doses. In highly sensitive patients, therapy may be initiated with 0.5 mg at bedtime, and increased as necessary. Most patients with postencephalitic Parkinsonism need fairly large doses and tolerate them well.

Some patients experience greatest relief by taking the entire daily dose at bedtime; others react more favourably to divided doses (2 to 4 times a day).

Therapy with other agents should not be terminated abruptly when therapy with benztropine mesylate is initiated, but may be reduced or discontinued gradually. Benztropine mesylate may be administered concomitantly with levodopa or a levodopa/carbidopa combination, in which case the dose of each may need adjustment.

Pediatric > 3 years
The usual dose is 0.02 – 0.05 mg/kg administered orally 1-2 times a day.

Drug-induced extrapyramidal symptoms:
In treating extrapyramidal disorders due to phenothiazine derivatives or reserpine, the recommended dosage is 1 to 4 mg once or twice a day. Dosage must be individualized according to the need of the patient.

In acute dystonic reactions, 2 mg of benztropine mesylate given i.v. quickly relieves the condition. Then, 1 to 2 mg given orally twice a day usually prevents recurrence.

When extrapyramidal disorders develop soon after initiation of treatment with phenothiazine derivatives or reserpine, they are likely to be transient. One (1) to 2 mg, 2 or 3 times a day usually provides relief within 1 to 2 days. After 1 or 2 weeks, benztropine mesylate should be withdrawn to determine the continued need for it. If Parkinsonism recurs, benztropine mesylate can be reinstituted.

Benztropine mesylate should not be used beyond the period necessary to counteract the extrapyramidal manifestations. Consider reducing the dosage of neuroleptic agents or reserpine when adjunctive benztropine mesylate therapy is required.

Patients must be closely observed for severe reactions and benztropine mesylate discontinued temporarily if they appear (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Missed Dose:
If a tablet is missed, it should be taken as soon as possible. If it is almost time to take the next tablet, the missed tablet should not be taken, and the normal schedule should be resumed.

OVERDOSAGE

Symptoms: May be any of those seen in atropine poisoning or antihistamine overdosage: CNS depression, preceded or followed by stimulation; confusion; nervousness; listlessness; intensification of mental symptoms, or toxic psychosis, in patients with mental illness being treated with phenothiazine derivatives or reserpine; hallucinations (especially visual); dizziness; muscle weakness; ataxia; dry mouth; mydriasis; photophobia; tachycardia; dysuria; vomiting; giddiness; staggering; rapid pulse and breathing; drowsiness; stupor; blurred vision; palpitations; nausea; numbness of fingers; dysphagia; allergic reactions (e.g., skin rash); headache; hot, dry, flushed skin; delirium; shock; convulsions; coma; circulatory failure; respiratory arrest; anhidrosis; hyperthermia; glaucoma; constipation.

Treatment: Benzodiazepine agonists should be used to treat agitation and seizures. Although patients with very minor anticholinergic toxicity may respond well to small doses of benzodiazepines, those with moderate to severe agitation will likely respond better to physostigmine. Physostigmine salicylate, 1 to 2 mg, by s.c. or i.v. routes to reverse symptoms of anticholinergic intoxication. A second injection may be given after 2 hours if required. Otherwise, treatment is symptomatic and supportive. Induce emesis or perform gastric lavage (contraindicated in precomatose, convulsive, or psychotic states). Give a saline purgative, e.g., sodium sulfate 30 g in 250 mL water, to promote peristalsis. Maintain respiration; supportive care for depression (avoid convulsant stimulants); artificial respiration for severe respiratory depression; a local miotic for mydriasis and cycloplegia; ice bags and alcohol sponges for hyperpyrexia, a vasopressor and fluids for circulatory collapse; catheterize for anuria. Darken room for photophobia.

For management of a suspected drug overdose, contact your Regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Benztropine mesylate contains the tropine portion of the atropine molecule and the benzohydryl portion of diphenhydramine. Thus, it possesses both anticholinergic and antihistaminic effects, although only the former has been established as therapeutically significant in the management of Parkinsonism.

Pharmacokinetics
The mean C_{max} of 1.5 PO single dose is 2.5 ng/mL with a mean elimination half-life ($t_{1/2}$) of 7 hours.

Benztropine is well-absorbed from the gastrointestinal tract. When given orally, benztropine has an onset of action of between 1 to 2 hours, though the pharmacologic effects of the drug may not be apparent for 2 to 3 days after initiation of therapy. The duration of action of benztropine, when given orally, is approximately 24 hours. Benztropine is highly protein bounded (95%), has a hepatic metabolism in animals, and is excreted primarily through the urine and bile unchanged.

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Supplied in bottles of 100 and 1000 tablets. Each round, cylindrical, bevelled-edge, flat faced, white tablet. Cross-scored on one side and identified "PMS-2" on the other side contains 2 mg benztropine mesylate and the following non-medicinal ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose and pregelatinized starch.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

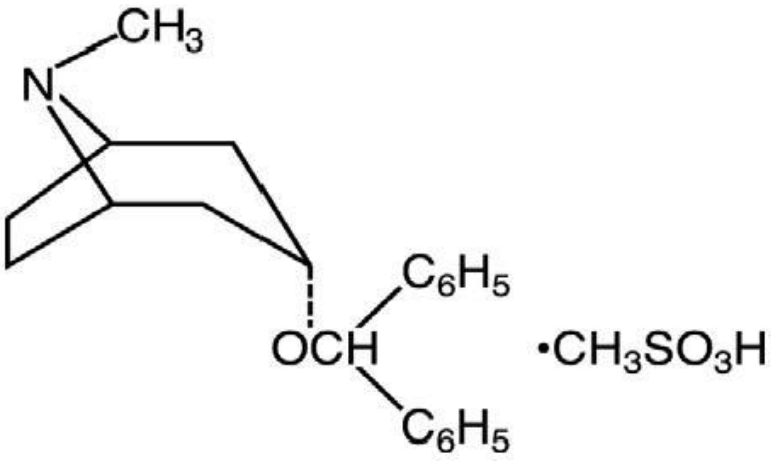
Drug Substance

Proper name: Benztropine mesylate

Chemical name: 8-azabicyclo[3.2.1] octane, 3-(diphenylmethoxy)-,endo, methanesulfonate.

Molecular formula and molecular mass: $C_{21}H_{25}NO \cdot CH_4O_3S$ 403.54

Structural formula:



Physicochemical properties: Crystalline white powder, very soluble in water.

DETAILED PHARMACOLOGY

In the laboratory, the antihistaminic activity of benztropine mesylate approaches that of pyrilamine maleate. Its duration of action also approaches that of pyrilamine maleate.

In the isolated guinea pig ileum, benztropine mesylate anticholinergic activity is about equal to that of atropine; however, when administered orally to unanesthetized cats, it is only about half as active as atropine.

TOXICOLOGY

In animals, benztropine mesylate produces about the same degree of sedation as pyrilamine maleate and tripelennamine, but much less than diphenhydramine HC and promethazine.

Direct application to the eyes of cats and rabbits produces substantially the same mydriatic effect and paralysis of the light reflex as atropine sulfate, although benztropine mesylate is somewhat more irritating.

In anesthetized cats, i.v. injection causes a moderate decrease in blood pressure. Large doses decrease the heart rate but do not appreciably affect the respiratory tract.

No significant effects on growth, organ weights, or hemograms of adult rats were observed in a chronic toxicity study.

REFERENCE

1. pdp-BENZTROPINE Prescribing Information, PENDOPHARM, Division of Pharmascience Inc. Control number 179633. November 14, 2014.

PART III: CONSUMER INFORMATION

[Pr]pms-BENZTROPINE

Benztropine Mesylate Tablets, USP, 2 mg

Read this carefully before you start taking pms-BENZTROPINE and each time you get a refill. This leaflet is a summary and will not tell you everything about pms-BENZTROPINE. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about pms-BENZTROPINE.

ABOUT THIS MEDICATION

What the medication is used for:
pms-BENZTROPINE is recommended for:

- **Symptoms of Parkinson's Disease**
- **Movement Disorders:** to reduce some movement disorders that were caused by other medications

What it does:
pms-BENZTROPINE is an Antiparkinson drug. It acts on the nervous system to correct some of the chemical imbalances that cause the symptoms of Parkinson's disease and movement disorders.

When it should not be used:

- If you are allergic to benztropine mesylate or to any non-medicinal ingredients
- In children less than 3 years of age
- If you have narrow angle glaucoma (eye disease)

What the medicinal ingredient is:
Benztropine mesylate.

What the non-medicinal ingredients are:
Lactose monohydrate, magnesium stearate, microcrystalline cellulose and pregelatinized starch.

What dosage forms it comes in:
Tablets.

WARNINGS AND PRECAUTIONS

BEFORE you use pms-BENZTROPINE talk to your doctor or pharmacist if:

- You have glaucoma (eye disease)
- You have heart rhythm problems (such as a racing heart rate)
- You have prostate problems
- You have difficulty or pain while urinating
- You have a tardive dyskinesia (uncontrollable movements or twitches of the body, face, eyes or tongue, stretching the neck and body)
- You are pregnant, plan to become pregnant or are breast-feeding

pms-BENZTROPINE may affect your ability to sweat. This can lead to dangerous increases in body temperature. Tell your doctor if you have a condition that affects your ability to sweat, and:

- you have a chronic illness or a nervous system disease,
- consume excessive amounts of alcohol,
- do labour in a hot environment.

This is particularly important during hot weather.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to pms-BENZTROPINE.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Drugs that may interact with pms-BENZTROPINE include:

- other drugs used to treat movement disorders and symptoms of Parkinson's Disease such as amantadine
- drugs used to treat bowel problems such as clidinium, dicyclomine
- drugs used to treat Alzheimer's Disease, such as donepezil, galantamine, rivastigmine
- drugs used to treat asthma and Chronic Obstructive Pulmonary Disease (COPD) such as tiotropium
- drugs used to treat urinary and bladder difficulties such as oxybutynin
- drugs used to treat allergies such as diphenhydramine
- muscle relaxants such as cyclobenzaprine
- drugs used to treat generalized anxiety disorders such as lorazepam and diazepam.
- tricyclic antidepressants such as amitriptyline, doxepin
- drugs that help maintain a regular heart rhythm such as disopyramide, procainamide, quinidine
- MAO inhibitors such as moclobemide, phenelzine, tranylcypromine, methylene blue (used in medical procedures)
- motion sickness medication such as scopolamine, dimenhydrinate
- narcotic pain relievers such as codeine, meperidine, morphine
- potassium tablets/capsules
- psychiatric medicines such as pimozide and phenothiazine derivatives such as chlorpromazine

If you already take other drugs to treat Parkinson's disease, the doctor may decide to adjust or gradually discontinue them. Do not suddenly stop taking them. Always follow your doctor's instructions.

PROPER USE OF THIS MEDICATION

Dosage must be individualized according to the need of the patient. pms-BENZTROPINE is usually started at a low dose and increased gradually every 5 or 6 days until the smallest effective dose is found. pms-BENZTROPINE is taken by mouth.

Many factors can affect the dose of medication that a person

needs, such as age, body weight, other medical conditions, and other medications. **If your doctor has recommended a dose different from the ones listed here**, do not change the way you are taking the medication without consulting your doctor.

Usual adult dose:
Symptoms of Parkinson's Disease:
Initial dose: 0.5 mg a day.
Maximum dose: 6 mg a day.

Usual Dose: 1 to 2 mg a day.
The dose can range from 0.5 to 6 mg a day depending on circumstances.

Your doctor may recommend you take:
- one dose at bedtime
- multiple doses spread throughout the day.

Dose for children more than 3 years old:
Dosage should be individualised based on the weight of the child.
Usual dose: 0.02 – 0.05 mg/kg 1-2 times a day.

Movement Disorders:
Recommended dose: 1 to 4 mg once or twice a day.

Your doctor may recommend you take your dose as one, two or three doses in a day. After 1 or 2 weeks, your doctor may stop pms-BENZTROPINE to determine if you still need it. pms-BENZTROPINE may need to be restarted if your movement disorder returns.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. If it is near the time of the next dose, skip the missed dose and resume your usual dosing schedule. Do not double the dose to catch up.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:
- blurred vision
- nervousness, listlessness, agitation
- constipation
- numbness of the fingers
- fever

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	**Severe dry mouth:** difficulty swallowing or speaking, loss of appetite and weight	√		
	Nausea	√		
	Vomiting		√	
Frequency Unknown	**Dysuria:** Painful or difficult urination		√	
	Paralytic ileus: (Bowel Obstruction): abdominal pain and discomfort, constipation, nausea, vomiting, excessive burping		√	
	Tachycardia: fast heartbeat.	√		
	Weakness and an inability to move certain muscle groups		√	
	Mental Confusion		√	
	Worsening of Mental Disorders	√		
	Hallucinations: see or hear things that are not there		√	
	Glaucoma: increased pressure in your eyes, eye pain			√
	Depression: Feeling sad, unexplained weight change, sleep disturbances, lack of interest in usual activities		√	
Uncommon	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√

This is not a complete list of side effects. For any unexpected effects while taking pms-BENZTROPINE, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15°C-30°C).
Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full prescribing information, prepared for health professionals can be found by contacting the sponsor, Pharmascience Inc., at: 1-800-550-6060

This leaflet was prepared by Pharmascience Inc.

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