PRODUCT MONOGRAPH

pms-IPRATROPIUM
Ipratropium Bromide Nebulizer Solution
250 mcg/mL (0.025%) in 20 mL Bottles

Bronchodilator

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Inhalation	Solution 20 ml bottle (0.025%)	Benzalkonium Chloride Solution (50% w/v), Edetate Disodium Dihydrate, Hydrochloric Acid, Purified Water and Sodium Chloride

INDICATIONS AND CLINICAL USE

pms-IPRATROPIUM (ipratropium bromide) nebulizer solution is indicated for:

- the treatment of bronchospasm associated with acute exacerbations of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

- the treatment of bronchospasm associated with acute severe exacerbations of bronchial asthma when used in conjunction with a $beta_2$ adrenergic agonist such as salbutamol.

pms-IPRATROPIUM nebulizer solution must be administered by means of nebulizer using gas flow (oxygen or compressed air).

Pediatrics
The efficacy and safety of pms-IPRATROPIUM in children younger than 5 years have not been established.

CONTRAINDICATIONS

pms-IPRATROPIUM is contraindicated in:

- Patients with a history of hypersensitivity to any of its components or to atropine or its derivatives. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

WARNINGS AND PRECAUTIONS

General

Ipratropium bromide nebulizer solution is intended only for inhalation with suitable nebulizing devices and must not be taken orally or administered parenterally.

It is recommended that the nebulized ipratropium bromide solution be administered via a mouth piece. If this is not available and a nebulizer mask is used, it must fit properly.

Ipratropium bromide nebulizer solution in the 20 mL multidose bottle contains preservatives (Benzalkonium Chloride and disodium ethylenediamine tetraacetic acid- EDTA-disodium). It has been reported that these preservatives may cause bronchoconstriction in some patients with hyper reactive airways.

Ipratropium bromide nebulizer solution should not be used alone for the abatement of an acute asthmatic attack since the drug has a slower onset of effect than that of an adrenergic $beta_2$-agonist.

Patients should be instructed in the proper use of the nebulizer.

Caution is advised against accidental release of the solution into the eyes.

In patients with glaucoma, prostatic hyperplasia, urinary retention and bladder neck obstruction, ipratropium bromide nebulizer solution should be used with caution.

If a reduced response to ipratropium bromide nebulizer solution becomes apparent, the patient should seek medical advice.

Ipratropium bromide nebulizer solution, when administered to patients with acute severe asthma, should be used with concomitant $beta_2$ adrenergic agonist therapy.

Anticholinergic Effects

Like other anticholinergic drugs, ipratropium bromide nebulizer solution should be used with caution in patients with narrow-angle glaucoma or urinary retention.

Worsening of Narrow-Angle Glaucoma
Ipratropium bromide nebulizer solution should be used with caution in patients with narrow-angle glaucoma.

Care should be taken to ensure that the nebulizer mask fits the patient's face properly and that nebulized solution has not come in contact with the eyes. Patients should be advised that this may result in precipitation or worsening of narrow-angle glaucoma. There have been isolated cases of ocular complications (i.e., mydriasis, increased intraocular pressure, narrow angle closure glaucoma, eye pain) when nebulized ipratropium bromide either alone or in

combination with an adrenergic beta2-agonist solution has come in contact with the eyes.

In patients with glaucoma or narrow anterior chambers, the administration by nebulizer of a combined ipratropium/beta$_2$-agonist solution should be avoided unless measures (e.g., use of swimming goggles or use of a nebulizer with a mouthpiece) are taken to ensure that nebulized solution does not reach the eye. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. Miotic drops alone are not considered to be effective treatment.

Worsening of Urinary Retention
Ipratropium bromide nebulizer solution should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Carcinogenesis and Mutagenesis

Please see TOXICOLOGY section.

Gastrointestinal

Patients with cystic fibrosis may be more prone to gastrointestinal motility disturbances.

Immune

Hypersensitivity reactions including urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema may occur after administration of ipratropium bromide. In clinical trials and post-marketing experience with ipratropium containing products, hypersensitivity reactions such as skin rash, pruritus, angioedema of tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported (see ADVERSE REACTIONS). If such a reaction occurs, therapy with ipratropium bromide nebulizer solution should be stopped at once and alternative treatment should be considered (see CONTRAINDICATIONS).

Ophthalmologic

Worsening of Narrow-Angle Glaucoma (see WARNINGS AND PRECAUTIONS, Anticholinergic Effects).

Renal

Worsening of Urinary Retention (see WARNINGS AND PRECAUTIONS, Anticholinergic Effects).

Respiratory

Paradoxical Bronchospasm
Severe life threatening paradoxical bronchospasm has been reported in patients receiving $beta_2$-agonists. If it occurs, therapy with ipratropium bromide nebulizer solution should be discontinued immediately and alternative therapy instituted.

Dyspnea
The patient should be instructed to consult a doctor immediately in the event of acute, rapidly worsening dyspnea. In addition, the patient should be warned to seek medical advice should a reduced response become apparent.

Special Populations

Pregnant Women
The safety of ipratropium bromide nebulizer solution in pregnancy has not been established. There are no adequate and well-controlled studies of ipratropium bromide nebulizer solution in pregnant women.

Nonclinical studies have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man.

Because animal reproduction studies are not always predictive of human response, ipratropium bromide nebulizer solution should be used during pregnancy only if the potential benefit justifies the potential risk to the unborn child.

Nursing Women
No specific studies have been conducted on the excretion of ipratropium bromide in breast milk. It is considered unlikely that ipratropium bromide would reach the infant to an important extent, especially when administered by inhalation. However, caution should be exercised when ipratropium bromide nebulizer solution is administered to nursing mothers. The benefits of ipratropium bromide nebulizer solution use during lactation should therefore be weighed against possible effects on the infant.

Pediatrics
The efficacy and safety of ipratropium bromide in children younger than 5 years have not been established.

Effects on Ability to Drive and Use Machines
No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as dizziness, accommodation disorder, mydriasis and blurred vision during treatment with ipratropium bromide nebulizer solution. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Use of ipratropium bromide may result in:

- Ocular effects (see WARNINGS AND PRECAUTIONS, General and Ophthalmologic)

- Urinary retention (see WARNINGS AND PRECAUTIONS)

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Acute Administration

The frequency of adverse reactions recorded in 214 patients receiving ipratropium bromide nebulizer solution was as follows:

Adverse Reaction	% of Patients
Dry mouth or throat	9.3
Bad taste	5.1
Tremor	4.2
Exacerbation of symptoms	4.2
Burning eyes	0.9
Nausea	0.9
Sweating	0.9
Cough	0.9
Headache	0.5
Palpitations	0.5

The adverse reaction judged to be most severe was exacerbation of bronchospasm. This occurred in eight patients treated with ipratropium bromide nebulizer solution alone, six of whom withdrew from the clinical studies.
Bronchospasm occurred in 3 patients with acute severe asthma who received ipratropium bromide nebulizer solution alone. In two patients, this was reversed after therapy with a $beta_2$-sympathomimetic solution. The third patient received no other therapy.

The following table compares the incidence of adverse reactions of the combination of ipratropium bromide and a $beta_2$-agonist (either fenoterol or salbutamol) solution with that of the $beta_2$- agonist alone.

Adverse Reaction	Ipratropium Bromide+ $Beta_2$-Agonist (% of 94 patients)	$Beta_2$- Agonist (% of 96 patients)
Tremor	31.9	26.0
Dry mouth	16.0	28.1
Bad taste	16.0	13.5
Vomiting	2.1	2.1
Palpitations	2.1	1.0
Headache	1.1	2.1
Cough	1.1	0.0
Flushing	1.1	0.0
Dizziness	0.0	1.0
Numbness in leg	0.0	1.0

Chronic Administration

The frequency of adverse reactions reported as possibly related to ipratropium bromide treatment in 219 COPD patients participating in long-term (12-week) controlled clinical trials was as follows:

Adverse Reaction	% of Patients
Dry mouth	2.7
Coughing	1.8
Dyspnea	1.8
Headache	1.8
Urinary retention	1.4
Tremor	0.9
Nausea	0.9
Palpitation	0.9
Eye pain	0.9

Observed adverse events occurring in at least 1% of subjects include rhinitis (0.9%) and sputum increase (0.9%).

The following other adverse reactions were reported in one patient each: bronchospasm, tachycardia and urticaria.

In addition, the following adverse events were observed in one patient each: bronchitis, chest pain, depression, fatigue, flu-symptoms, hypoaesthesia, increased saliva, insomnia, nervousness, pain, paraesthesia, pharyngitis and somnolence.

The frequency of adverse reactions reported as possibly related to drug treatment in greater than 1% of COPD patients participating in long-term (12-week) controlled clinical trials that compared the efficacy and safety of ipratropium bromide + $beta_2$-agonists (metaproterenol or salbutamol) versus the $beta_2$-agonist alone, was as follows:

Adverse Effect	% of Patients	
	Ipratropium Bromide + Beta$_2$- Agonist (n = 208)	**Beta$_2$-Agonist (n = 417)**
Headache	4.3	1.7
Tremor	3.8	3.4
Nervousness	3.8	1.9
Dyspnea	2.4	3.4
Dry mouth	2.4	1.0
Bronchitis	2.9	2.9
Dizziness	1.4	1.9
Coughing	1.4	1.0
Taste perversion	1.9	1.2
Insomnia	1.9	0.2
Dysuria	1.0	0.2
Nausea	1.0	1.7
Abnormal vision	0.5	1.2
Chest pain	1.4	0.7
Constipation	1.4	0.0
Dysphonia	1.0	0.2
Dyspepsia	1.0	0.0
Bronchospasm aggravated	1.0	0.7
Micturition frequency	1.0	0.2

Less Common Clinical Trial Adverse Drug Reactions (<1%)

There have been isolated reports of ocular effects such as mydriasis, increased intraocular pressure, and acute glaucoma associated with the escape of nebulized ipratropium bromide, alone or in combination with a beta$_2$-agonist solution into the eyes.

Side effects such as tachycardia and palpitations, supraventricular tachycardia and atrial fibrillation, ocular accommodation disturbances, nausea and urinary retention have been reversible, although the risk of urinary retention may be increased in patients with pre-existing outflow tract obstruction.

Ocular side effects have been reported (see WARNINGS AND PRECAUTIONS).

Post-Market Adverse Drug Reactions

World-wide safety data, which includes post-marketing data, spontaneous reports and literature reports, indicates that the most frequent non-respiratory side effects of ipratropium bromide nebulizer solution are headache and dryness of mouth/throat.

Immediate hypersensitivity reactions may occur after administration of ipratropium bromide nebulizer solution. Allergic type reactions such as skin rash, pruritus, angioedema of the tongue, lips and face, urticaria (including giant urticaria), laryngospasm, oropharyngeal edema, bronchospasm, and anaphylactic reactions, may occur.

Dizziness has been reported.

DRUG INTERACTIONS

It is strongly recommended not to mix ipratropium bromide nebulizer solution with other drugs in the same nebulizer.

Overview

In patients receiving other anticholinergic drugs, ipratropium bromide nebulizer solution should be used with caution because of possible additive effects.

Ipratropium bromide nebulizer solution with preservatives (i.e., from the 20 mL multidose bottle) should not be mixed with sodium cromoglycate, as this produces a cloudy solution caused by complexation between the preservatives and sodium cromoglycate. If the patient's condition requires the administration of sodium cromoglycate, it should be given in combination with ipratropium bromide nebulizer solution without preservatives.

In acute and maintenance therapy of chronic reversible airways obstruction, ipratropium bromide has been shown to provide additive bronchodilating effects to theophylline and beta-adrenoceptor agonists (sympathomimetic amines). Repeated inhalation of ipratropium bromide has not been linked to tolerance towards bronchodilating effects.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Counselling by physicians on smoking cessation should be the first step in treating patients with chronic obstructive pulmonary disease (COPD), who smoke, independent of the clinical presentation i.e., chronic bronchitis (with or without airflow limitation) or emphysema. Cessation of smoking produces dramatic symptomatic benefits and has been shown to confer a survival advantage.

In adults, the average single dose of pms-IPRATROPIUM (ipratropium bromide) solution is 250 - 500 mcg of ipratropium bromide. In children, aged 5 - 12 years, the recommended dose is 125 - 250 mcg of ipratropium bromide. In most cases, dilution of the dose with sterile preservative-free saline is not necessary. However, volumes of pms-IPRATROPIUM solution less than 2 mL are not appropriate for nebulization and must be diluted with saline or another suitable nebulizer solution to make up a total fill volume of 2 - 5 mL (see PHARMACEUTICAL INFORMATION).

Nebulization should take place using a gas flow (oxygen or compressed air) of 6 - 10 L/minute and the solution nebulized to dryness over a 10 - 15 minute period. The Hudson Updraft™,

Bennett Twin Jet®, DeVilbiss, Pari Compressors and lnspiron Mini-Neb® nebulizers, with facemask or mouthpiece have been used. The manufacturers' instructions concerning cleaning and maintenance of the nebulizer should be strictly followed.

Treatment with pms-IPRATROPIUM solution may be repeated every 4 - 6 hours as necessary.

Daily doses exceeding 2 mg in adults should be given under medical supervision.

For the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, the recommended dose is 500 mcg of pms-IPRATROPIUM (ipratropium bromide) nebulizer solution given 3 - 4 times per day.

Missed Dose

If a dose is missed, the next scheduled dose should be taken. An extra dose must not be taken.

OVERDOSAGE

Doses of ipratropium bromide up to 1.2 mg (60 puffs) have been administered by nebulization without the appearance of serious systemic anticholinergic effects. Minor systemic manifestations of anticholinergic action, including dry mouth, visual accommodation disturbances and increase of heart rate may occur.

Should signs of serious anticholinergic toxicity appear, cholinesterase inhibitors may be considered.

For management of a suspected overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In nonclinical studies, it appears to inhibit vagally mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase in intracellular concentration of Ca^{++} which is caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. Ca^{++} release is mediated by the second messenger system consisting of IP3 (inositol triphosphate) and DAG (diacylglycerol).

The bronchodilation following inhalation of ipratropium bromide is primarily local and site specific to the lung and not systemic in nature.

On inhalation, the onset of action is noted within 5 to 15 minutes, with a peak response between 1 and 2 hours, lasting about 2 additional hours, with subsequent decline from the peak. Bronchodilation is still evident 8 hours after inhalation.

Pharmacodynamics

Large, single inhaled doses of ipratropium bromide have been given to man without any signs of toxicity. After the administration of 400 mcg to 10 healthy subjects, no changes were detected in pulse rate, blood pressure, intraocular pressure, salivary secretion, visual accommodation or electrocardiograms. Likewise, in a similar study no change in pulse rate or salivary secretion were seen when cumulative doses up to 1.2 mg were administered by inhalation to healthy volunteers.

Special studies utilizing normal therapeutic doses in asthmatic and chronic bronchitic patients have not revealed any systemic anticholinergic effects.

In one study, 14 patients were treated for 45 days with ipratropium bromide 40 mcg q.i.d. or ipratropium bromide 40 mcg q.i.d. plus oral fenoterol 5 mg q.i.d. No changes in visual acuity, intraocular pressure, pupil size or accommodation of vision occurred. Micturition function studies in 20 male patients showed no differences in urinary flow, total flow time and time until maximum flow between placebo and ipratropium bromide 40 mcg t.i.d. administered for 3 days.

A wide variety of challenge studies have been conducted using ipratropium bromide as a protective agent. In pharmacologically induced bronchospasm, ipratropium bromide, in clinical doses, was very effective against methacholine and acetylcholine, moderately effective against propranolol but had no effect against histamine or serotonin. Studies in exercise induced bronchospasm have yielded variable results. Some investigations have indicated that ipratropium bromide has little or no effect but other studies have shown that some patients, at least, were protected against bronchospasm induced by exercise. Likewise, the protection against cold air induced bronchospasm has been variable.

The Lung Health Study

The Lung Health Study was a randomized multi-centre clinical trial carried out from October 1986 to April 1994 in North America. It was designed to test the effectiveness of intervention-smoking cessation and bronchodilator administration in smokers aged 35 - 60 years who have mild obstructive pulmonary disease. The main outcome or end point was the rate of change and cumulative change in FEV_1 over a 5-year period.

A total of 5887 male and female smokers, aged 35 to 60 years, with spirometric signs of early chronic obstructive pulmonary disease were recruited. Participants were randomized to one of the following groups: (1) smoking intervention plus bronchodilator, (2) smoking intervention plus placebo, or (3) no intervention.

Smoking intervention consisted of an intensive 12-session smoking cessation program

combining behaviour modification and use of nicotine gum, with continuing 5-year maintenance program to minimize relapse. Two puffs ipratropium bromide was prescribed three times daily from a metered-dose-inhaler.

The results showed that participants in the two smoking intervention groups showed significantly smaller declines in FEV_1 than did those in the control group. Most of this difference occurred during the first year following entry into the study and was attributable to smoking cessation, with those who achieved sustained smoking cessation experiencing the largest benefit. The benefit associated with the use of the ipratropium bromide vanished after the ipratropium bromide was discontinued at the end of the study.

In summary, the results showed that smoking intervention reduced the rate of decline in FEV_1 in middle aged smokers with mild airways obstruction who remained non-smokers throughout the 5 years. The other intervention, administration of ipratropium bromide, did not alter the rate of decline in lung function. There was a small one time improvement in lung function associated with the onset of ipratropium use, but this disappeared rapidly when ipratropium use was discontinued at the end of the study. Otherwise, the regular use of ipratropium bromide had no effect on the rate of decline of lung function over 5 years in patients studied.

Pharmacokinetics

Absorption

Ipratropium bromide is absorbed quickly after oral inhalation of a nominal dose of 40 mcg administered from a pressurized metered dose inhaler. The peak plasma concentration (mean C_{max} = 32 pg/mL) is reached within 5 minutes after inhalation. The therapeutic effect of ipratropium bromide is produced by a local action in the airways. Therefore time courses of bronchodilation and systemic pharmacokinetics do not run in parallel. The plasma concentration-versus-time curve was similar to that seen after oral administration, likely reflecting the large fraction of inhaled dose which is deposited on the pharyngeal mucosa and swallowed.

Intravenous administration of 1.0 mg in man showed a rapid distribution into tissues (half-life of an alpha phase approximately five minutes), and a terminal half-life (beta phase) of 3 - 4 hours. Plasma concentrations after inhaled ipratropium bromide were about 1000 times lower than equipotent oral or intravenous doses (15 and 0.15 mg, respectively).

Cumulative renal excretion (0 - 24 hrs) of ipratropium (parent compound) is approximated to 46% of an intravenously administered dose, below 1% of an oral dose and approximately 3 to 13% of an inhaled dose. Based on these data, the apparent systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7 to 28%, respectively. Taking this into account, swallowed dose portions of ipratropium bromide do not relevantly contribute to systemic exposure.

Distribution

Kinetic parameters describing the disposition of ipratropium were calculated from plasma concentrations after IV administration. A rapid biphasic decline in plasma concentrations is

observed. The apparent volume of distribution at steady-state (Vdss) is approximately 176 L (≈ 2.4 L/kg).

The drug is minimally (less than 20%) bound to plasma proteins. Nonclinical data indicate that the quaternary amine ipratropium does not cross the placental or the blood-brain barrier.

Metabolism
The half-life of the terminal elimination phase is approximately 1.6 hours. Ipratropium has a total clearance of 2.3 L/min and a renal clearance of 0.9 L/min. After intravenous administration approximately 60% of a dose is metabolised, the major portion probably in the liver by oxidation.

Elimination
Up to 8 metabolites of ipratropium bromide have been detected in man, dog and rat. In an excretion balance study cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 72.1% after intravenous administration, 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was 6.3% following intravenous application, 88.5% following oral dosing and 69.4% after inhalation. Regarding the excretion of drug-related radioactivity after intravenous administration, the main excretion occurs via the kidneys. The half-life for elimination of drug-related radioactivity (parent compound and metabolites) is 3.6 hours. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

Thirty-nine percent of the active ingredient is excreted renally after intravenous administration, 4.4% - 13.1% after inhalation from a metered dose inhaler is excreted as unchanged compound in urine.

Special Populations and Conditions

Pediatrics: The efficacy and safety of ipratropium bromide in children younger than 5 years have not been established.

STORAGE AND STABILITY

Unopened bottles of pms-IPRATROPIUM solution should be stored at controlled room temperature (between 15°C and 30°C). Solutions diluted with preservative free sterile Sodium Chloride Inhalation Solution, USP 0.9% should be used within 24 hours from time of dilution when stored at room temperature and within 48 hours when stored in the refrigerator.

A controlled Preservative Challenge test, done in accordance with the current USP guideline for Preservative Efficacy Testing, indicated that bottles of ipratropium bromide nebulizer solution, opened and closed several times, simulating patient use, were stable for up to 28 days when stored at room temperature (15º - 30ºC).

Controlled laboratory experiments using mixtures of ipratropium bromide solution with ALUPENT® (orciprenaline sulfate), BEROTEC® (fenoterol hydrobromide) or salbutamol sulfate (6 mg/mL preserved with benzalkonium chloride) solutions and diluted with a sterile bacteriostatic sodium chloride solution 0.9% (i.e., normal saline), preserved with benzalkonium chloride, indicated that such mixtures were stable for 7 days at room temperature. For the preparation of such mixtures, it is recommended that only sterile solutions of bacteriostatic sodium chloride 0.9% preserved with 0.01% Benzalkonium Chloride be used to maintain the level of preservative in the mixture.

The safety of preservatives other than Benzalkonium Chloride has not been established.

SPECIAL HANDLING INSTRUCTIONS

Incompatibilities

pms-IPRATROPIUM solution with preservatives (i.e., from the 20 mL multidose bottle) should not be mixed with sodium cromoglycate solution, as this produces a cloudy solution caused by complexation between the preservatives and sodium cromoglycate. If the patient's condition requires the administration of sodium cromoglycate, it should be given in combination with ipratropium bromide solution without preservatives.

DOSAGE FORMS, COMPOSITION AND PACKAGING

pms-IPRATROPIUM solution is provided as 20 mL of clear, colourless or almost colourless solution containing 250 mcg/mL (0.025%) ipratropium bromide in isotonic solution. This solution is preserved with Benzalkonium Chloride (250 mcg/mL) and EDTA-disodium (500 mcg/mL) at a pH of 3.4, and is presented in an amber glass bottle with screwcap.

PART II: SCIENTIFIC INFORMATION

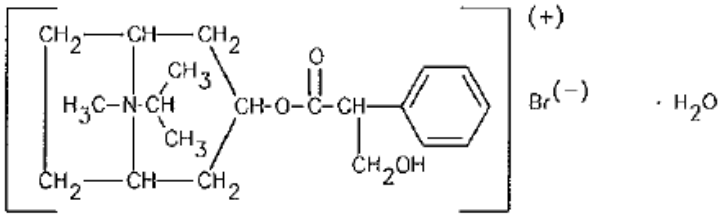
PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: Ipratropium bromide monohydrate

Chemical Name: (8r)-3α-hydroxy-8-isopropyl-1αH, 5αH-tropanium bromide (±)-tropate monohydrate

Structural Formula:



Molecular Formula: $C_{20}H_{30}NO_3Br \bullet H_2O$

Molecular Weight: 430.4 g/mol

Physicochemical Properties: White crystalline substance with a bitter taste. Freely soluble in water and alcohol; insoluble in chloroform and ether. In neutral and acid solutions the substance is rather stable; in alkaline solutions the ester bond is rapidly hydrolyzed. The melting point is 229 - 231°C with decomposition. [α] 20=0°

CLINICAL TRIALS

In controlled 12-week studies in patients with bronchospasm associated with chronic obstructive pulmonary disease (chronic bronchitis and emphysema), significant improvements in pulmonary function (FEV_1 and $FEF_{25-75\%}$ in increases of 15% or more) occurred within 15 minutes, reached a peak in 1 to 2 hours, and persisted for periods of 4 to 5 hours in the majority of patients, with 25 to 38% of the patients demonstrating increases of at least 15% at 7 to 8 hours. Continued effectiveness of ipratropium bromide nebulizer solution was demonstrated throughout the 12-week period. In addition, significant changes in forced vital capacity (FVC) have been demonstrated.

Additional controlled 12-week studies were conducted to evaluate the safety and efficacy of ipratropium bromide nebulizer solution administered concomitantly with bronchodilator solutions of orciprenaline or salbutamol, compared with the administration of each of the beta agonists alone.

Combined therapy produced significant additional responses in FEV_1, FVC and $FEF_{25-75\%}$. On combined therapy, the median duration of 15% improvement in FEV_1 was 5 to 7 hours, compared with 3 to 4 hours in patients receiving a beta agonist alone.

DETAILED PHARMACOLOGY

Mechanism of Action

Ipratropium bromide is an anticholinergic agent which, when delivered by aerosol, exerts its effects primarily in the bronchial tree. It abolishes acetylcholine-induced bronchospasm in the guinea pig and dog after intravenous administration of ED_{50} of 0.15 and 0.40 mcg/kg with a transient effect on blood pressure. By inhalation, approximately 25 mcg of ipratropium bromide produces a 50% inhibition of acetylcholine-induced bronchospasm in the dog with no detectable effect on blood pressure but with an increased duration of action compared to IV administration. Histological evaluation of human bronchial mucosae following chronic inhalation of ipratropium bromide showed no alterations of epithelial, ciliated or goblet cells. Short term mucociliary clearance in normal and bronchitic subjects was not adversely affected by 200 mcg of inhaled ipratropium bromide.

The anticholinergic effects of ipratropium bromide were evaluated in several other organ systems following oral, subcutaneous, intravenous and inhalation administration. In dogs, a 50% increase in heart rate resulted from a s.c. dose of about 0.011 mg/kg, equipotent to atropine, but the equi-effective oral dose of ipratropium was 58 times greater. By inhalation, no increase in heart rate or pathological changes in ECG pattern were recorded at doses up to 8 mg. In another study, blood pressure and heart rate in the dog could be modulated after intravenous (IV) administration of low doses of ipratropium but metered aerosol administration of 100 puffs (40 mcg/puff) was required to produce an 11% increase in heart rate.

Salivary secretion in rat, mouse and dog was effectively inhibited by low parenteral doses of ipratropium bromide (0.001 to 0.032 mg/kg) but when given by the oral route, the effective dose increased over 100-fold. Aerosol administration in dogs of about 65 puffs (0.04 mg/puff) produced a 50% decrease in salivary flow. Similarly, effects on gastric secretion in the rat showed at least a 100-fold difference between effective enteral and subcutaneous doses.

Mydriatic effects of ipratropium bromide in mice were approximately equipotent to atropine after s.c. doses but were 10 - 20 times less after oral administration. Tests in the rabbit indicated that doses up to 100 mg/kg had no effect on the central nervous system.

Ipratropium bromide administered s.c. inhibited the secretory effects of the cholinergic agonist, oxitropium, in mice. It also inhibited spasmolytic effects equivalent to or greater than atropine in isolated guinea pig gut. *In vitro* tests with isolated rectum of the guinea pig demonstrated the effectiveness of ipratropium bromide in suppressing the spasmogenic effects of acetylcholine and pilocarpine. It was ineffective against histamine or barium chloride induced spasm. Ipratropium bromide exerted anticholinergic effects on the *in situ* bladder and intestine preparations of the dog. Intravenous doses were 500 times more potent than oral or intraduodenal administration.

TOXICOLOGY

Single Dose Studies

Acute toxicity has been investigated with observation periods of 14 days in several rodent and non-rodent species.

Species	Sex	Route	LD_{50} (mg/kg)
Mouse		IV	13.5
Mouse	M	IV	12.3
Mouse	F	IV	15.0
Mouse		s.c.	322
Mouse		s.c.	300
Mouse		oral	2010
Mouse		oral	1038
Rat		IV	15.8
Rat		s.c.	1500
Rat		oral	> 4000
Rat		oral	1722

The signs of toxicity were apathy, reduced mobility, ataxia, paralysis of skeletal muscle, clonic convulsions and death from respiratory failure. Toxic signs persisted for 3 hours after IV and 8 days after oral administration.

Single dose tolerance studies were performed in dogs. No deaths occurred at doses of up to 400 mg/kg oral or 50 mg/kg s.c. Signs of toxicity were mydriasis, dryness of oral, nasal and optic mucosa, vomiting, ataxia, increased heart rate, decreased body temperature and death

from respiratory failure.

A single dose inhalation toxicity study of ipratropium bromide administered as a 4% and 8% solution to guinea pigs was performed. No toxic signs were observed with the 4% solution and death occurred after 5 hours of administration with the 8% solution (approximately 200 mg/kg).

A single dose inhalation tolerance study in rats with Benzalkonium Chloride (0.025%) or Benzalkonium Chloride (0.025%) plus ipratropium bromide (0.025%) administered over 8 hours was performed. No clinical signs of intolerance were observed. Necropsy and histological findings (16 hours and 14 days after administration) were also negative.

Anesthetized normal and hypoventilated dogs tolerated doses up to 200 puffs (4 mg) of ipratropium bromide without ECG changes or heart failure. Reductions in heart rate were observed. Similar findings were seen in dogs given IV infusions (10 mg/kg/min) up to 1550 mg/kg or 1000 mg/kg plus 200 puffs from a placebo inhaler. Blood pressure reductions were also seen in these experiments.

A single dose inhalation, dose tolerance study in rats using doses of up to 160 puffs (3.2 mg) from an ipratropium bromide inhaler was performed. No deaths occurred.

Multiple Dose Studies

Oral
A multiple dose toxicity study of nine weeks duration in rats, utilizing doses of 10, 100 and 500 mg/kg revealed no pathological findings apart from a dose related decrease in food consumption and growth rate.

A four week study in dogs using doses of 3, 30 and 150 (for three weeks) increased to 300 mg/kg showed mydriasis, inhibition of lacrimal and salivary secretion, tracheal and ocular inflammation, decreased food intake and weight loss at the medium and high doses. Three of six dogs died when the dose was increased from 150 to 300 mg/kg.

A supplementary study of 13 weeks using doses of 1.5, 3.0 and 15 mg/kg revealed no pathological changes apart from a dose related inhibition of lacrimal secretions and associated keratoconjunctivitis and dryness of the mouth.

Subcutaneous
Rats were treated with subcutaneous injections of 1, 10 and 100 mg/kg. One death occurred in the 10 mg/kg dose group from paralytic ileus. Inflammatory changes were noted at the injection site.

A four week study in dogs using doses of 10, 20 and 30 mg/kg (increased to 40 mg/kg on the last five days) was conducted. Dryness of the oral and nasal mucous membranes and mydriasis were noted along with conjunctivitis and keratitis associated with decreased lacrimal secretions. A decrease in food intake and body weight also occurred. One dog died

in the high dose group. Signs of liver damage were noted in two high dose dogs. Low testicular weights, which have not been observed in other subsequent studies, were also observed.

Inhalation
Twelve rats were exposed to aerosolized ipratropium bromide in a concentration of 11.5 mcg/L for 1 hour, 4 times per day for 7 days. No drug toxicity was found.

In another study, administration of ipratropium bromide at concentrations of 128, 256 and 384 mcg per rat per day for 30 days showed no signs of toxicity apart from a low grade inflammatory response and areas of fibrosis and hemorrhage in the parametrium of 2 of 9 females in the high dose group. This finding has not been observed in subsequent studies.

Four rhesus monkeys inhaled 500 mcg of ipratropium bromide twice a day (total dose 1 mg/day) for seven days without the appearance of any drug induced toxicity.

In another rhesus monkey study, the animals were given ipratropium bromide at doses of 200, 400 and 800 mcg/day by inhalation for six weeks. Included in the tests were measurements of mucociliary transport rate and ciliary beat frequency. No signs of drug toxicity were found.

Oral
A 6 month and a 1 year study in rats using doses of 6, 30 and 150 mg/kg were performed. The high dose was increased to 200 mg/kg after 14 weeks. Reductions in food consumption and growth rates were observed in the highest dose group. A dose dependent constipation which caused severe coprostasis and dilatation of the intestines was observed in the highest dose groups. A toxic hepatosis was observed in some animals of the highest dose group.

Ipratropium bromide was administered to dogs at doses of 1.5, 3.0, 15.0 and 75.0 mg/kg for 1 year. A decrease in body weight development was seen in the highest dose group and food consumption was reduced in the dogs receiving 3 mg/kg and above. Emesis was seen in all treated groups. A dose dependent decrease (3 mg/kg and above) in nasal, oral and lacrimal secretions, the latter leading to keratoconjunctivitis, was observed. Increases in SGPT and SGOT (15 and 75 mg/kg) and alkaline phosphatase (75 mg/kg) were noted. Localized gastric necrosis was found in two dogs at the highest dose and a non-dose-dependent fatty degeneration of the liver, which varied from animal to animal, was also seen.

Inhalation
A 6 month study in rats was performed using doses of 128, 256 and 384 mcg per rat per day. Measurements included ciliary beat frequency, lung mechanics and blood gas. The only finding was a dose related decrease in growth rate of the male animals.

A 6 month inhalation toxicity study was performed in rhesus monkeys utilizing daily doses of 20, 800 and 1600 mcg. All findings were negative including measurements of lung mechanics, ciliary beat frequency and blood gases.

Mutagenicity

Three Ames tests, a micronucleus test in mice, a cytogenetic study in Chinese hamsters, and a dominant lethal test in mice were performed to assess the mutagenic potential of ipratropium bromide. Two positive tests (one Ames and the micronucleus study) were apparently spurious as they could not be reproduced with subsequent exhaustive experimentation. In the cytogenetic study, a dose-related increase in the number of chromatid gaps, but not of other aberrations, was seen. The significance of this finding is not known. All other test results were negative.

Carcinogenicity

Ipratropium bromide was tested individually for neoplastic properties in several carcinogenicity studies. Carcinogenicity studies in mice (107 weeks duration) and rats (114 weeks duration) utilizing oral doses of up to 6 mg/kg were performed. Ipratropium bromide revealed no carcinogenic potential when tested orally in mice and rats.

Genotoxicity

Ipratropium bromide was tested in numerous *in-vivo* and *in-vitro* genotoxicity tests and showed no evidence of mutagenic properties.

Reproductive Studies

Three teratology studies, one in mice using oral doses of 2 and 10 mg/kg and two in rats have been conducted. The first rat study used the same dosages while the second employed 10 and 20 mg/kg. None of these studies revealed any drug induced fetal abnormalities.

A similar oral study in rabbits utilizing doses of 2 and 10 mg/kg again demonstrated no teratogenic or embryotoxic effects of ipratropium bromide.

An inhalation teratology study in rabbits using doses of 0.3, 0.9 and 1.8 mg/kg demonstrated no effect on litter parameters and no embryotoxic or teratogenic effects.

A fertility study in rats with oral doses of 5, 10 and 500 mg/kg given 60 days prior to and during early gestation was performed. Fertility was delayed in eight of 20 couples at 500 mg/kg dose and spurious pregnancy in five of 20 females occurred at this dose. In addition, the conception rate was decreased in 75% of females at this dose. No embryotoxic or teratogenic effects were observed.

Apart from these findings, the studies performed with ipratropium bromide revealed only marginal effects, if any, on embryos, foetuses and pups and these only in the range of maternal toxicity. Ipratropium bromide did not affect fertility of male or female rats at oral doses up to 50 mg/kg (approximately 3,400 times the MRHDD on a mg/m^2 basis).

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PART III: CONSUMER INFORMATION

pms-IPRATROPIUM
Ipratropium Bromide Nebulizer Solution
250 mcg/mL (0.025%) in 20 mL Bottles

Read this carefully before you start taking pms-IPRATROPIUM and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about pms-IPRATROPIUM.

ABOUT THIS MEDICATION

What the medication is used for:
pms-IPRATROPIUM is used to treat the wheezing or shortness of breath caused by COPD (chronic obstructive pulmonary disease which includes chronic bronchitis and emphysema). For the treatment of asthma, pms-IPRATROPIUM must be used in conjunction with some other bronchodilating medication. pms-IPRATROPIUM contains 250 mcg/mL (0.025%) ipratropium bromide and the preservatives Benzalkonium Chloride and disodium ethylene diamine tetraacetic acid (EDTA-disodium).

What it does:
pms-IPRATROPIUM belongs to a group of medicines known as "bronchodilators" which make breathing easier by opening your narrowed airways.

When it should not be used:
pms-IPRATROPIUM should not be used by patients with allergic reactions to ipratropium bromide, atropinics or any component of the drug.
If you do not get the expected relief from your treatment, you should contact your doctor.

What the medicinal ingredient is:
Ipratropium bromide
What the non-medicinal ingredients are:
Benzalkonium chloride solution (50% w/v), Edetate Disodium Dihydrate, Hydrochloric Acid, Purified Water and Sodium Chloride

What dosage forms it comes in:
Nebulizer Solution; 20 mL Bottle

WARNINGS AND PRECAUTIONS

The solution is intended for inhalation only. Do not inject or drink.

Do not let the nebulized mist get into your eyes as this may cause blindness known as acute angle glaucoma. This may present as eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes. If any combination of these symptoms occurs, seek immediate medical attention. Patients with glaucoma should use swimming goggles or a nebulizer with a mouthpiece to prevent nebulized solution getting into the eyes.

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

- are pregnant or intend to become pregnant;
- are breastfeeding;
- are having treatment for a thyroid or adrenal gland condition;
- are having treatment for high blood pressure, angina or a heart problem;
- have diabetes;
- have low levels of potassium in your blood (hypokalemia), especially if you are taking:
  - drugs known as xanthine derivatives (such as theophylline)
  - steroids to treat asthma
  - water pills (diuretics)
- have eye problems, such as glaucoma or eye pain;
- are taking any other medications, including eye drops or any medications you can buy without a prescription;
- have difficulty in urination;
- have enlarged prostate;
- have any allergies or reactions to foods or drugs;
- have a history of convulsions (uncontrolled shaking or seizures);
- have liver or kidney disease.

Contact your doctor immediately if:

- you require more than one dose to relieve your breathing problems;
- your shortness of breath becomes worse;
- you don't get the same benefit from your medicine as you did before;
- you have breathing difficulties and chest pain;
- you experience difficulty with urination.

pms-IPRATROPIUM may cause dizziness, difficulty in focusing the eye, dilated pupils, and blurred vision. You should not drive or operate machinery if this occurs.

INTERACTIONS WITH THIS MEDICATION

Do not mix pms-IPRATROPIUM with other drugs in the same nebulizer.

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.

The following may interact with pms-IPRATROPIUM:

- digitalis;
- other anticholinergic drugs, such as ipratropium bromide and beta$_2$-adrenergic agents such as salbutamol;
- beta blockers, such as propranolol;
- xanthine derivatives such as theophylline;
- monoamine oxidase inhibitors such as isocarboxazid;
- tricyclic antidepressants such as amitriptyline;
- epinephrine;
- certain diuretics or "water pills" such as furosemide, hydrochlorothiazide.

PROPER USE OF THIS MEDICATION

pms-IPRATROPIUM **should only be inhaled** from a nebulizer. It must not be injected or swallowed.

Do not let the pms-IPRATROPIUM or the mist produced by the nebulizer, get in your eyes.

Use your nebulizer in a well ventilated room. Some of the mist will be released into the air and may be breathed in by others.

Use pms-IPRATROPIUM only as directed by your doctor. During administration your doctor may want to monitor your blood.

pms-IPRATROPIUM has been prescribed to treat your current condition. DO NOT give it to other people. Always use pms-IPRATROPIUM exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

pms-IPRATROPIUM should be used only in a properly functioning and regularly maintained nebulizer or an intermittent positive pressure ventilator. Before starting treatment, be certain that you are completely familiar with the use and proper care of your nebulizer. The content of the bottle does not need to be diluted for nebulization.

Usage Instructions:

Your doctor or pharmacist will tell you how to prepare your pms-IPRATROPIUM nebulizer solution. Your doctor or pharmacist might instruct you to use sterile sodium chloride solution (0.9%) to dilute the pms-IPRATROPIUM solution. If you are told to dilute pms-IPRATROPIUM solution, you must do so immediately before you plan to use the solution. If necessary, doses may be diluted to a total nebulization volume of 3-5 mL with preservative free 0.9% sterile sodium chloride solution and used immediately. Discard any unused solution. Nebulize over 10-15 minutes at gas flow of 6-10L/min. Repeat every 4-6 hours as necessary.

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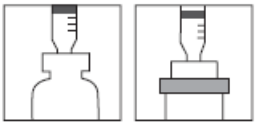
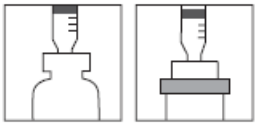
1) Immediately before you plan to use the nebulizer, using a syringe, withdraw the prescribed dose, usually ½ to 2 mL (cc), of pms-IPRATROPIUM from the bottle and add to the nebulizer chamber. Do not store the prescribed dose in the syringe for later use.



2) If your doctor has instructed you to use another inhalation solution in combination with pms-IPRATROPIUM, you should add the appropriate amount of that solution to the nebulizer chamber as well.

3) Add sodium chloride solution to the chamber, if you have been directed to do so by your physician or pharmacist.



4) Gently shake the nebulizer chamber and connect it to the mouthpiece or face mask. Then connect the nebulizer tube to the air or oxygen pump and begin therapy.

5) Breathe calmly and deeply through the mask or mouthpiece until no more mist is formed in the nebulizer chamber. This usually takes 10 - 15 minutes. It is very important to adjust the face mask, if required, to prevent the mist from getting in your eyes.

6) Store your re-capped bottle of pms-IPRATROPIUM and sodium chloride solution in the refrigerator until the next treatment.

7) Follow the instructions provided by the nebulizer and air pump manufacturers for the proper care and maintenance of the equipment. Keep the nebulizer, nebulizer tube and face mask clean to minimize microbial contamination.

Do not mix pms-IPRATROPIUM with other drugs in the same nebulizer.

Keep out of the reach of children.

Overdose:

If you think you have taken too much pms-IPRATROPIUM, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If a dose is missed and no symptoms occur, the regular next dose according to the dosing schedule should be taken. If a dose is missed and respiratory symptoms are experienced, the missing dose should be taken and the dosing schedule according to the recommended dosage should be resumed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- wheezing after inhalation;
- headache, dizziness;
- nausea (feeling sick), digestive problems like constipation, diarrhoea and vomiting;.
- muscle problems such as cramps weakness, pain, feeling weak, tremor (shaking);
- feeling nervous;
- mental disorder;
- impaired voice sounds;
- increased sweating;
- bronchitis and upper respiratory tract infection (a cold)
- throat irritation, cough, dry mouth or throat, bad taste- sucking on a sour candy or rinsing your mouth may help.

Check with your doctor if the dry mouth or bad taste persist or if you experience constipation for a prolonged period of time. Stop taking the medication and tell your doctor immediately if you notice any of the following:

- you are wheezy or have any other difficulties in breathing;
- you are having an allergic reaction – the signs may include skin rash, itching and nettle rash. In severe cases the signs include swelling of your tongue, lips and face, sudden difficulties in breathing and reduction of your blood pressure.

If you have any questions about pms-IPRATROPIUM or your nebulizer, contact your doctor or pharmacist.

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

	Symptom / effect	Talk to your healthcare professional		Stop taking drug and get imme-diate medi-cal help
		Only if severe	In all cases	
Uncommon	**Bronchospasm:** Increased wheezing or tightness in the chest, difficulty in breathing, coughing bouts			√
	Shortness of breath			√
	Hypotension or Hypertension, Changes in blood pressure: dizziness, fainting, light-headedness			√
	Skin rash			√
Rare	**Allergic Reaction:** Rash, hives, swelling of the face, lips, mouth, tongue or throat, difficulty swallowing or breathing, choking due to swelling of the muscles around the voice box			√
	Fast or irregular heart beat / chest pain			√
	Eye Disorders: new or worsened pressure in your eyes, eye pain or discomfort, blurred vision, seeing halos or rainbows around items or red eyes			√
	Urinary Retention: difficulty and pain when passing urine, urinating frequently, urination in a weak stream or drips			√
	Muscle pain, weakness or spasms; paralysis			√
	Myocardial Ischaemia:			√

	decreased blood flow to the heart leading to angina (chest pain), shortness of breath, or a heart attack			
	Angina: Chest pain			√
	Decreased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell			√

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

HOW TO STORE IT

Keep this medication out of the reach of children.

Unopened bottles of pms-IPRATROPIUM should be stored at controlled room temperature (between 15°C and 30°C). Solutions diluted with preservative free sterile Sodium Chloride Inhalation Solution, USP 0.9% should be used within 24 hours from time of dilution when stored at room temperature and within 48 hours when stored in the refrigerator.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada,
    Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Pharmascience Inc. at, 1-888-550-6060.

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