PRODUCT MONOGRAPH

[Pr] pms-IPRATROPIUM

(Ipratropium Bromide Nasal Spray, House Standard)

0.03% w/v

(21 μg/metered spray)

Topical Anticholinergic for Nasal Administration

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(Ipratropium Bromide Nasal Spray, House Standard)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
nasal	Solution, 0.03% w/v ipratropium bromide	Benzalkonium chloride, edetate disodium, hydrochloric acid, sodium chloride, sodium hydroxide and purified water.

INDICATIONS AND CLINICAL USE

pms-IPRATROPIUM (ipratropium bromide) nasal spray 0.03% is indicated for:

$ treatment of symptomatic relief of rhinorrhea associated with allergic or non-allergic perennial rhinitis.

CONTRAINDICATIONS

$ Known hypersensitivity to ipratropium bromide, atropinics or to any of the ingredients of pms-IPRATROPIUM nasal spray (see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph).

WARNINGS AND PRECAUTIONS

General

Immediate hypersensitivity reactions may occur after administration of ipratropium bromide, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal edema, and anaphylaxis.

Patients predisposed to narrow-angle glaucoma, or with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder neck obstruction) should use ipratropium bromide nasal spray with caution.

Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances.

Ipratropium bromide nasal spray contains the (antimicrobial) preservative benzalkonium chloride

which may cause irritation of the nasal mucosa.

Ocular complications
Care should be taken to ensure that ipratropium bromide nasal spray does not reach the eye. There have been isolated reports of ocular complications (i.e., mydriasis, increased intra ocular pressure, narrow angle glaucoma, and eye pain) when aerosolized ipratropium bromide either alone or in combination with an adrenergic beta2-agonist has been released into the eyes.

Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival and corneal congestion may be signs of acute angle-closure glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately.

Patients must be instructed in the correct administration of ipratropium bromide nasal spray. Care must be taken not to allow the aqueous spray into the eyes. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.

Caution should be taken to avoid accidental release of the nasal spray into the eyes.

Special Populations

Fertility: Preclinical studies performed with ipratropium bromide showed no adverse effect on fertility (see Toxicology Section). Clinical data on fertility are not available for ipratropium bromide.

Pregnant Women: The safety of ipratropium bromide nasal spray administration during pregnancy has not yet been established. The benefits of using ipratropium bromide when pregnancy is confirmed or suspected must be weighed against possible hazards to the fetus. Studies in rats, mice and rabbits showed nor embryotoxic effects or teratogenic effects.

Nursing Women: No specific studies have been conducted on excretion of ipratropium bromide in breast milk. Benefits of ipratropium bromide nasal spray use during lactation should therefore be weighed against possible effects on the infant.

Pediatrics: There is insufficient evidence available at present to recommend ipratropium bromide nasal spray for use in children under 12 years of age.

ADVERSE REACTIONS

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.

Many of the listed undesirable effects can be assigned to the anticholinergic properties of ipratropium bromide. As with all inhalation therapy ipratropium bromide may show symptoms of local irritation. Adverse drug reactions were identified from data obtained in clinical trials and pharmacovigilance during post approval use of the drug.

The most frequent side effects reported in clinical trials were epistaxis, nasal dryness, headache, nasal discomfort and throat irritation.

Ipratropium bromide Nasal Spray 0.03%
Adverse reaction information concerning ipratropium bromide nasal spray 0.03% in patients with perennial rhinitis is derived from five multicenter, placebo-controlled clinical trials involving 854 patients (454 patients on ipratropium bromide and 400 patients on placebo), and a one-year open-label, follow-up trial. In three of the placebo-controlled trials, patients received ipratropium bromide nasal spray, 42 mcg per nostril, or placebo three times daily, for eight weeks. In the other two placebo-controlled trials, ipratropium bromide nasal spray, 21 or 42 mcg per nostril, was administered to patients two or three times daily for four weeks. Of the 285 patients who entered the open- label, follow-up trial, 232 were treated for 3 months, 200 for 6 months, and 159 up to one year, with the majority (>86%) of patients going one year being maintained on 42 mcg per nostril, two or three times daily, of ipratropium bromide nasal spray.

Adverse reactions reported for patients who received ipratropium bromide nasal spray 0.03%, 42 mcg per nostril, or placebo two or three times daily where the prevalence in the ipratropium bromide group is 2.0% or greater and exceeds the prevalence in placebo group appear in the following table:

Table 1 - Percentage of Patients Reporting Reactions†

	Ipratropium bromide Nasal Spray 0.03% n= 356 (%)		Placebo Spray n= 347 (%)	
	Incidence	Discontinued	Incidence	Discontinued
Headache	9.8	0.6	9.2	0
Upper respiratory tract infection	9.8	1.4	7.2	1.4
Epistaxis	9.0	0.3	4.6	0.3
Rhinitis*				
Nasal dryness	5.1	0	0.9	0.3
Nasal irritation[1]	2.0	0	1.7	0.6
Other nasal symptoms[2]	3.1	1.1	1.7	0.3
Pharyngitis	8.1	0.3	4.6	0
Nausea	2.2	0.3	0.9	0

[1]Nasal irritation includes reports of nasal itching, nasal burning, nasal irritation and rhinitis ulcerative.

[2]Other nasal symptoms include reports of nasal congestion, increased rhinorrhea, increased rhinitis, posterior nasal drip, sneezing, nasal polyps and nasal edema.

†This table includes only adverse reactions for which the prevalence in the ipratropium bromide group was 2.0% or greater and exceeds the prevalence in the placebo group.

*All reactions are listed by their WHO term; rhinitis has been presented by descriptive terms for clarification.

Adverse reactions were usually mild to moderate and transient in the five placebo-controlled trials, resulting in discontinuation of treatment for 5.3% of the ipratropium bromide nasal spray 0.03% and 5.3% of the placebo-treated patients. There was no evidence of nasal rebound (i.e., a clinically significant increase in rhinorrhea, posterior nasal drip, sneezing or nasal congestion severity compared to baseline) upon discontinuation of double-blind therapy in these trials. There were no drug-related serious or anticholinergic adverse reactions (with the exception of dry mouth reported for 1% of the ipratropium bromide and 0.5% of the placebo-treated patients) during the placebo-controlled trials or the one-year open-label, follow-up trial in patients on ipratropium bromide nasal spray 0.03%.

Nasal adverse events and adverse reactions were reported for 84 (29.5%) of the 285 patients in the one-year open-label, follow-up trial. The incidence for the most frequently reported nasal adverse reactions were nasal congestion (1.4%), nasal dryness (9.5%), and epistaxis (4.2%).

Drug-related and non-drug related nasal dryness and/or epistaxis occurred in 45 patients. It resolved with continued treatment or dose reduction in 40 of these patients (89%), and required

discontinuation of treatment in 5 patients (11%).
Adverse reactions, which were found in less than 2% of perennial rhinitis patients receiving ipratropium bromide Nasal Spray 0.03% in the five multicenter, placebo-controlled clinical trials and one year open-label follow-up trial were; rash, urticaria, and conjunctivitis.

Adverse events, observed in perennial rhinitis patients receiving ipratropium bromide nasal spray 0.03% in the five multicenter, placebo-controlled clinical trials and one year open-label follow-up trials were: paraesthesia, fatigue, dizziness, insomnia, dysphonia, migraine, vertigo, furunculosis, generalized oedema, diarrhoea, abdominal pain, taste perversion and xerophthalmia.

There have been isolated reports of ocular events such as mydriasis, increased intra ocular pressure, glaucoma and eye pain associated with the release of aerosolized ipratropium bromide into the eyes. These ocular events have not been reported with the use of ipratropium bromide Nasal Spray.

Post-Market Adverse Drug Reactions

World-wide safety data, including post-marketing data, spontaneous reports, literature reports, and reports from clinical trials list below the most frequent undesirable effects of ipratropium bromide according to system organ class.

Immune system disorders
anaphylactic
reaction
hypersensitivity
angioedema

Nervous system disorders
headache
dizziness

Eye disorder
accommodation disorder
mydriasis
intraocular pressure increased
glaucoma
eye pain
vision blurred
halo vision
conjunctival hyperaemia
corneal oedema

Cardiac disorders
supraventricular tachycardia
atrial fibrillation

heart rate increased
palpitations

Respiratory, thoracic and mediastinal disorders
epistaxis
nasal dryness throat
irritation nasal
discomfort dry
throat
bronchospasm
laryngospasm
pharyngeal oedema

Gastrointestinal disorders
dry mouth
nausea
gastrointestinal motility disorder
oedema mouth
stomatitis

Skin and subcutaneous tissue disorders
rash
pruritus
urticaria

Renal and urinary disorders
urinary retention

DRUG INTERACTIONS

Overview

Ipratropium bromide nasal spray is minimally absorbed into the systemic circulation; nonetheless, if patients are receiving other anticholinergic drugs, including ipratropium bromide containing aerosols for oral inhalation**,** ipratropium bromide nasal spray should be used with caution because of possible additive effects.

Although the open-label, long-term studies to date have not shown a drug-drug interaction, ipratropium bromide nasal spray should be used with caution in patients concomitantly using intra nasal steroids because of the possible adverse local effects, (e.g., epistaxis, etc.). Any patient who experiences the above adverse effect should contact their doctor and a reduction in dose or frequency of ipratropium bromide nasal spray or the nasal steroid should be considered.

Ipratropium bromide nasal spray 0.03%
There is no evidence that the concomitant use of ipratropium bromide nasal spray with other drugs commonly prescribed for perennial rhinitis i.e. antihistamines, decongestants or nasal

steroids increases the incidence of side effects.

Drug-Lifestyle Interactions

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 nasal spray. 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.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
The dose of pms-IPRATROPIUM (ipratropium bromide) nasal spray 0.03% for symptomatic relief of rhinorrhea associated with allergic or non-allergic perennial rhinitis is two sprays (42 mcg) per nostril two or three times a day (total dose 168 to 252 mcg/day). Optimum dosage varies with the response of the individual patient.

Not recommended for use in children under 12 years of age.

Administration
pms-IPRATROPIUM nasal spray must be administered by means of nasal aerosol.

OVERDOSAGE

Acute overdosage by intra nasal administration is unlikely since ipratropium bromide is not well absorbed systemically after intra nasal or oral administration. Minor systemic manifestation of anticholinergic action, including dry mouth, visual accommodation disorder and increased heart rate may occur.

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

For management of a suspected drug overdose, contact your regional Poison Control Center immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ipratropium bromide, a quaternary ammonium derivative of atropine, is an anticholinergic drug. Ipratropium bromide administered intra nasally has a localized parasympathetic blocking action which reduces watery hyper secretion from mucosal glands in the nose.

Ipratropium bromide administration via nasal aerosol had no marked effect on sense of smell, nasal mucociliary transport, ciliary beat frequency, or the air-conditioning capacity of the nose.

Two nasal provocation trials in perennial rhinitis patients (n=44) using Ipratropium bromide nasal spray showed a dose-dependent increase in inhibition of methacholine-induced nasal secretion with an onset of action within 15 minutes. The duration of action of Ipratropium bromide nasal spray was also dose-dependent.

In an 8-week study in adults with allergic rhinitis doses up to 168 mcg/nostril 2 times a day were well tolerated and effective with a more rapid onset.

Ipratropium bromide is not readily absorbed into the systemic circulation from the nasal mucosa as confirmed by blood level measurements and renal excretion studies with ipratropium bromide nasal spray 0.03%, 0.06% and 0.12%. The plasma half-life in man is less than two hours after i.v. administration of ipratropium bromide. Serum protein binding is less than 20%. In placebo-controlled pharmacokinetic trials in a total of 17 volunteers, 0.03%, 0.06%, and 0.12% concentrations of ipratropium bromide nasal spray exhibited linear kinetics up to a total dose of 336 mcg. One clinical trial has shown that the rate of ipratropium absorption was accelerated in a limited number of perennial rhinitis patients (n=4) using ipratropium bromide nasal spray 0.06% chronically versus normal patients (cross trial comparison). This is presumably due to an inflamed nasal mucosa which is, therefore, more permeable. However, the extent of absorption was the same for patients and normal volunteer groups. Since there was no increase in the frequency of systemic adverse events, the clinical significance of this increased rate of absorption is not known.

Studies in rats have shown that ipratropium bromide does not cross the blood/brain barrier. In double-blind, placebo-controlled, crossover, single dose pharmacokinetic trials (n=17), ipratropium bromide nasal spray 0.03%, 0.06%, and 0.12% (84 mcg, 168 mcg and 336 mcg total nasal dose, respectively) did not significantly affect pupillary diameter, or have any systemic anticholinergic physiologic effect (i.e., changes in heart rate or systolic/diastolic blood pressure) or adverse events (e.g., dry mouth, blurred vision, constipation, difficulty urinating, etc.).

Pharmacodynamics

Methacholine Challenge: It has been established that the topical application of methacholine to the nasal mucosa under controlled clinical conditions can be used to conduct a simple and reproducible test for the measurement of nasal reactivity. Five pharmacodynamic studies on ipratropium bromide Nasal Aerosol were conducted using the methacholine test. These studies were designed to determine whether ipratropium bromide, a specific antagonist of methacholine, could effectively and consistently reduce nasal secretions in healthy subjects and in patients with

rhinitis. Results from these studies indicated that aerosolized intra nasal ipratropium bromide effectively reduces hyper secretion after methacholine challenge, in both healthy subjects and allergic/nonallergic patients. No significant change in the number of sneezes or nasal congestion was found. No local or systemic side effects were reported.

These results are supported by the evidence from a methacholine challenge study performed with ipratropium bromide nasal spray (aqueous) 0.03% and 0.12% (42 and 168 μg/nostril, respectively) in patients with perennial rhinitis. Dose-dependent inhibition of the nasal hyper secretion induced by methacholine was observed, with an onset of action within 15 minutes. Duration of action was also dose-dependent, with the lower dose no longer effective after 3 hours, and the higher dose effective for up to 6 hours. Placebo-controlled efficacy trials in patients with perennial rhinitis exhibited a much longer duration of action (up to 12 hours).

Tolerance Studies: The first tolerance study, a randomized, double-blind, three period crossover study, examined the effect of single high doses of aerosolized intra nasal ipratropium bromide on healthy subjects. Subjects received single doses of 200 or 400 μg (10 or 20 puffs altogether) ipratropium bromide or placebo on separate test days. Ten subjective symptoms (general malaise, palpitations, sensation of heat, thirst, speech impediment, blurred vision, dryness of nose, dryness of mouth, headache) were assessed by the individuals, using a visual analogue scale.

The objective measures (blood pressure, pulse rate, nearest reading distance, amount of saliva produced in a 3 minute period) did not reveal any significant differences. No statistically significant differences were found between the 3 treatment groups for any of the subjective parameters. The second tolerance study was designed to evaluate the effects of single and repeated administration of aerosolized ipratropium bromide to the nasal mucosa. Twelve healthy male subjects were entered into the study. Seven subjects were given a single administration of ipratropium bromide as follows:

2 subjects - 40 μg/nostril
2 subjects - 80 μg/nostril
3 subjects - 160 μg/nostril

Five subjects received multiple administrations as follows:

2 subjects - 40 μg/nostril qid for 7 days
(Total daily dose - 320 μg)

3 subjects - 80 μg/nostril qid for 7 days
(Total daily dose - 640 μg)

No substantial changes were seen in the results of the physical examination following single or repeated administration. No laboratory values were outside the normal range, with the exception of 1 subject whose WBC increased above the normal range 1 day after administration. Since this subject received the lowest dose (80 μg) and such an abnormal change was not observed in other subjects receiving higher doses, the change was not judged to be attributable to the drug.

There were no observable changes in the nasal mucosa or nasal secretions. One subject receiving a multiple dose (40 μg/nostril) reported nasal blockage and another subject, in the same group, a dry nose. Two subjects receiving a single dose of 40 μg per nostril reported nasal blockage.

A third tolerance study was designed to closely monitor changes in the structure and function of the nose during aerosolized intra nasal ipratropium bromide treatment for one year. Biopsy, microscopy and ciliary motility measurements were done at 6 month intervals (0, 6 and 12 months). Olfactory detection thresholds were determined at 0, 3, 6, 9, and 12 months.
Biopsy samples were studied to assess whether the histology of the mucosal layer, or the thickness of the basement membrane, could change during long-term use of ipratropium bromide. Although there are virtually no 'normal' baseline values in this area, it was assumed that any significant trauma could be assessed by studying nasal biopsy samples. Ciliary motility was measured using a sample of mucosal scraping, recorded under a light microscope by a slow motion version of a video.

Twenty patients and seven healthy controls (only 3 controls for the biopsies) were entered into the study. Twelve patients participated for the full year. None of the patients withdrew from the study because of adverse effects. Patients were instructed to use 40 μg per nostril 4 times a day initially, but were later permitted to tailor the dose to their individual needs.

With regard to most parameters (i.e. leukocytic infiltration, neutrophil polymorphs, lymphocytes, eosinophils, oncocytes, margination of leukocytes, mononuclear cells), between 50 and 100% of the patients' biopsy results remained virtually unchanged. Parameters such as edema and vascular dilatation showed an overall decrease from entry to final assessment. Minimum basement membrane thickness (0 versus 6 and 12 months) comparisons were not significantly different. There was a significant reduction in the maximum thickness at 6 and 12 months compared to baseline. However, according to the lab control data, the basement membrane thickness of the patients in the study was not outside the normal range at any time point.

No significant changes were seen in the structure or function of the nasal cilia, or the sense of smell.

Special Effects: In vitro and in vivo studies were conducted to assess the effect of aerosolized intra nasal ipratropium bromide on mucociliary transport in healthy subjects.

In vivo: Twelve healthy subjects participated in a randomized, double-blind, crossover trial involving the saccharin transport test. Nasal mucociliary transport time was measured by the saccharin transport time (ST) 15 minutes after each 80 μg ipratropium bromide or placebo administration. In the test, a 5 μg granule of saccharin was placed approximately 1 cm into the nostril and the time elapsed until the subject experienced a sweet taste was recorded. A baseline ST was performed prior to dosing on the first day. Each subject received active drug twice and placebo twice, with at least a 48 hour interval between tests.
There were no statistically significant differences between baseline, ipratropium bromide, and the placebo values for the mean saccharin transport time. No local or systemic side effects were reported.

In vitro: A study was conducted to examine the effect of ipratropium bromide on the ciliary beat frequency of the nasal mucosa. Specimens from nine healthy subjects were obtained from the inferior nasal concha with a bronchoscopy brush after thorough cleansing of the nose. Viable cells were perfused with solutions of ipratropium bromide in concentrations varying from 0 to 0.0001 mg/mL.

At baseline, before perfusion, the average ciliary beat frequency was 10.8 ± 1 Hz. There was no significant change in either the beat frequency for the samples perfused with ipratropium bromide, or for those samples with no perfusion.

Nasal Air Conditioning Capacity
The effect of aerosolized intra nasal ipratropium bromide on the air conditioning capacity of the nose was assessed in a study with 16 healthy subjects and 9 patients with vasomotor rhinitis.

Each subject received an assessment for a 10 minute period prior to, and 15 to 30 minutes after the administration of 60 µg ipratropium bromide to one nostril. The patients were measured twice on two different days. At each measurement, enthalpy (kJ) and the amount of water loss (g) over a 10 minute period were calculated.

There was no significant difference between the results obtained before and after treatment with ipratropium bromide in healthy subjects or in patients with vasomotor rhinitis. It was concluded that ipratropium bromide does not influence air conditioning capacity in patients with vasomotor rhinitis or in healthy volunteers during short-term treatment.

Pharmacokinetics

Absorption: Ipratropium bromide is a quarternary amine that is rapidly absorbed from the nasal mucosa, however to a low extent. In health volunteers less than 10% of a nasally given dose was excreted unchanged in the urine over 24 hours.

The systemic absorption of ipratropium across inflamed nasal mucosa was not altered due to experimentally induced cold, as estimated from the renal excretion of ipratropium over 24 hours. After a single dose or 4 times daily dosing 6-8% of ipratropium was excreted unchanged in healthy as well as in infected volunteers. Following chronic dosing in rhinitis patients the amount of unchanged ipratropium excreted in the urine over a 24-hour period at steady state was 4-6% of the dose. Assuming the literature value of 50% of the dose excreted into the urine following intravenous administration, the estimated bioavailability of ipratropium following nasal administration is less than 20%.

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 mucosae and swallowed.

Distribution: Kinetic parameters describing the disposition of ipratropium were calculated from plasma concentrations after i.v. administration.

A rapid biphasic decline in plasma concentrations is observed. The apparent volume of distribution at steady-state (Vdss) is approximately 176L (2.4L/kg). The drug is minimally (less than 20%) bound to plasma proteins. The quaternary amine ipratropium does not cross the blood-brain barrier. The half-life of the terminal elimination phase is approximately 1.6 hours

Metabolism: 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 metabolized, the major portion probably in the liver by oxidation.

Up to 8 metabolites of ipratropium bromide have been detected in man, rat and dog.

Excretion: 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. Therefore the dominant excretion of drug-related radioactivity occured via the kidneys. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

STORAGE AND STABILITY

Store tightly closed between 15°C and 30°C. The contents are stable up to the expiration date stamped on the label. Avoid excessive heat or freezing. Keep out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each spray is designed to deliver 0.07 mL which contains: ipratropium bromide 21µg. Available in HDPE bottles of 30 mL, fitted with a metered nasal spray pump, a safety clip to prevent accidental discharge of the spray and a clear plastic dust cap. The 30 mL bottle is designed to deliver 345 sprays of 0.07 mL each or 28 days of therapy at the maximum recommended dose (2 sprays per nostril 3 times a day).

Composition: Each spray of 0.03% contains 21 µg ipratropium bromide.
Nonmedicinal ingredients: benzalkonium chloride, edetate disodium, hydrochloric acid, sodium chloride, sodium hydroxide and purified water.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

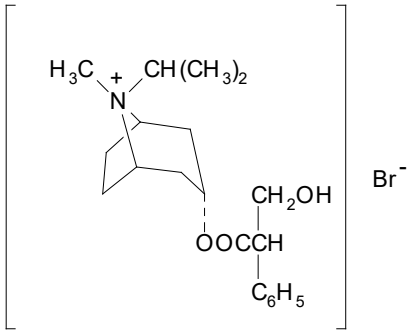
Proper name: Ipratropium bromide (BAN, USAN, rINN)

Chemical name: (8r)-3α hydroxy-8-Isopropyl-1αH, 5αH-tropanium bromide

Molecular formula: $C_{20}H_{30}NO_3Br$

Molecular weight: 412.37 g/mol

Structural formula:



Description: 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 stable; in alkaline solutions the ester bond is rapidly hydrolyzed.

Melting point: 230°C, with decomposition.

CLINICAL TRIALS

Ipratropium bromide nasal spray 0.03%

In patients with perennial rhinitis (allergic or nonallergic), use of ipratropium bromide nasal spray 0.03% (42 mcg per nostril, two or three times daily; n=343) resulted in a clinically significant decrease in the severity and duration of rhinorrhea compared to placebo (n=331) in four separate multicenter, parallel group trials. This decrease in rhinorrhea resulted in a substantial reduction in the degree of interference with patient daily activities and moods more consistently in the ipratropium bromide nasal spray than placebo treatment groups. A modest decrease in other nasal symptoms (i.e., posterior nasal drip, sneezing and congestion) was also observed in both the ipratropium bromide nasal spray and placebo treatment groups, and may represent the salutary effect of the nasal spray formulation excipients.

Results from three eight-week, double-blind, placebo-controlled clinical trials (n=580, 295 patients receiving ipratropium bromide nasal spray 0.03%) have shown that significant symptomatic relief of rhinorrhea was obtained on the first full day of treatment with ipratropium bromide nasal spray , with continued gradual improvement over the eight-week treatment period. Upon entry into these trials, 20% of patients (n=117) reported lack of control of rhinorrhea with prior use of antihistamines; there was a significant reduction in rhinorrhea in the patient group unresponsive to antihistamines assigned to ipratropium bromide nasal spray 0.03% (n=61), as well as in patients who had been responsive to antihistamines (n=430).

In a one-year, open-label follow-up trial involving 285 patients with nonallergic perennial rhinitis, daily use of ipratropium bromide nasal spray 0.03%, 21 or 42 mcg per nostril, two or three times daily, continued to control rhinorrhea and was well tolerated, with no evidence of tachyphylaxis. Patient and physician global assessments demonstrated that long-term treatment may also contribute to the control of posterior nasal drip, sneezing and nasal congestion. In addition, use of concomitant medications (antihistamines, decongestants, and intra-nasal steroids) for greater than 3 months to treat perennial rhinitis symptoms was decreased from 26% of patients (n=75) prior to the study to 13% (n=37) during long term treatment.

DETAILED PHARMACOLOGY

ANIMAL

In vivo: Ipratropium bromide is an anticholinergic agent which, when delivered by oral inhalation, exerts its effects primarily in the bronchial tree. It abolishes acetylcholine-induced bronchospasm in the guinea pig and dog after intravenous administration at an ED_{50} of 0.15-0.40 μg/kg with a transient effect on blood pressure. By oral inhalation, approximately 25 μg 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 i.v. administration.

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 subcutaneous dose of about 0.011 mg/kg (equipotent to atropine) but the equi-effective oral dose of ipratropium was 58 times greater. When given by oral inhalation, no increase in heart rate or pathological changes in ECG pattern were recorded at doses up to 8 mg. In another experiment, blood pressure and heart rate in the dog could be modulated after i.v. administration of low doses of ipratropium bromide, but metered aerosol administration of 100 puffs (40 μg/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% inhibition of 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 of doses of ipratropium bromide up to 100 mg/kg in the rabbit showed no effect on the central nervous system. Ipratropium bromide, subcutaneously, inhibited the secretory effects of the cholinergic agonist, oxtremorine, in mice. It also exhibited spasmolytic effects equivalent to, or greater than, atropine in isolated guinea pig gut.

In vitro and in situ: Tests with the isolated rectum of the guinea pig (in vitro) 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

Local and systemic tolerability of ipratropium bromide have comprehensively been investigated in several animal species using various administration routes.

Table 1: Acute Toxicity

SPECIES	SEX	ROUTE	LD_{50} (mg/kg)
Mouse		i.v.	13.5
Mouse	M	i.v.	12.3
Mouse	F	i.v.	15.0
Mouse		s.c.	322.0
Mouse		s.c.	300.0
Mouse		oral	2010.0
Mouse		oral	1038.0
Rat		i.v.	15.8
Rat		s.c.	1500.0
Rat		oral	4000.0
Rat		oral	1722.0

The acute inhalation, oral and intravenous toxicity has been assessed in several rodent and non-rodent species. When administered by inhalation, the minimum lethal dose in male Guinea pigs was 199 mg/kg. In rats, no mortality was observed up to the highest technically feasible dosages (.i.e. 0.05 mg/kg after 4 h of administration or 160 puffs of ipratropium bromide, 0.02 mg/puff).

The oral LD_{50} values for the mouse, rat and rabbit were 1585, 1925 and 1920 mg/kg, respectively. The intravenous LD_{50} for the mouse, rat and dog was, respectively, 13.6, 15.8 and about 18.2 mg/kg. Clinical signs included mydriasis, dry oral mucosa, dyspnoea, tremor, spasms and/or tachycardia.

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 i.v. administration and for 8 days after oral administration.

Acute dose tolerance studies were performed in dogs. No deaths occurred up to doses of 400 mg/kg oral or 50 mg/kg subcutaneous. 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.

An acute 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). 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 i.v. 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.

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

SUBACUTE

Oral

A subacute toxicity study of 9 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 4 week study in dogs using doses of 3, 30 and 150 (for 3 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 6 dogs died when the dose was increased from 150 to 300 mg/kg.

A supplementary study in dogs of 13 weeks duration, 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 4 week study in dogs using doses of 10, 20 and 30 mg/kg (increased to 40 mg/kg on the last 5 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 2 high dose dogs. Low testicular weights, which have not been observed in other subsequent studies, were also observed.

Inhalation (Oral)

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

In another study, administration of ipratropium bromide in doses of 128, 256 and 384 μg 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 2/9 females in the high dose group. This finding has not been observed in subsequent studies.

Four rhesus monkeys inhaled 500 μg of ipratropium bromide twice a day (total dose 1 mg/day) for 7 days without the appearance of any drug induced toxicity.

In another study rhesus monkeys were given ipratropium bromide in doses of 200, 400 and 800 μg/day by inhalation for 6 weeks. Included in the tests were measurements of mucociliary transport rate and ciliary beat frequency. No signs of drug toxicity were found.

CHRONIC

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 hepatotosis was observed in some animals of the highest dose group. Ipratropium bromide was administered to dogs in 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 2 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 (Oral)

A 6 month study in rats was performed using doses of 128, 256 and 384 μg 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. See below

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

Repeat-dose toxicity studies have been performed in rats, rabbits, dogs and Rhesus monkeys. In inhalation studies up to 6 months in rats, dogs and Rhesus monkeys, the No Observed Adverse Effect Level (NOAEL) was 0.38 mg/kg/day, 0.18 mg/kg/day and 0.8 mg/kg/day, respectively. Dry oral mucosa and tachycardia were noted in the dogs. No substance-related histopathological lesions were observed in the broncho-pulmonary system or in any other organs. In the rat, the NOAEL after 18 months of oral administration was 0.5 mg/kg/day. Repeat-dose inhalation toxicity studies in rats for up to 6 months and in dogs for up to 3 months with other formulations (intranasal formulation, alternative propellant HFA 134a and lactose powder formulation) revealed no additional information on the general toxicity profile of ipratropium bromide [86-93]. Intranasal administration for up to 6 months revealed a No Effect Level (NOEL) > 0.20 mg/kg/day in dogs and confirmed earlier studies with intranasal administration for up to 13 weeks.

Repeat-dose toxicity studies of ipratropium bromide have shown the toxicological profiles of the HFA formulation and the conventional CFC formulation to be similar.

Inhalation (aqueous nasal spray)
A 26-week nose-only inhalation study was performed in Sprague-Dawley rats (n=20/sex) using ipratropium bromide nasal spray 0.03, 0.06 or 0.12%. Daily exposure ranged from 126 µg/kg to 2016 µg/kg ipratropium bromide. There were 9 deaths in the highest dose group which were attributed to test substance administration. Reduced body weight gain, decreased food consumption and clinical signs of toxicity were also noted at this dose. Reduced body weight gain was also observed in males of the 504 µg/kg/day group. A dose of 252 µg/kg/day of ipratropium bromide was considered to be a "no toxic effect level" in this study, and a dose of 2016 µg/kg/day approximated a "maximum tolerated dose".

Thirteen week intra nasal studies were performed in dogs, with ipratropium bromide nasal spray 0.03, 0.06 and 0.12%. The dose schedules were equivalent to 168, 336, 504, 1008 and 2016 µg/day. There were no treatment-related effects on mortality, food consumption, body weight or clinical pathology. Microscopic evaluation of the nasal turbinates of the dogs treated at the higher dosages of ipratropium bromide nasal spray (504, 1008 and 2016 µg/day) revealed some inflammatory lesions. However, the increased observation of these findings at 13 weeks versus 4 weeks in each group supported the hypothesis that these lesions were probably caused by the frequency of test material instillation rather than by irritation due to the drug.

A 26-week intranasal toxicty study was performed in beagle dogs (n=48) to determine the potential for three different formulations of ipratropium bromide nasal spray (0.03, 0.06 and 0.12%) to cause local and systemic toxicity when administered subchronically. There were 5 test groups including a vehicle control group; an applicator control group; ipratropium bromide nasal spray 0.03%, 50.4 µg/kg/day; ipratropium bromide nasal spray 0.06%, 100.8 µg/kg/day; and ipratropium bromide nasal spray 0.12%, 201.6 µg/kg/day. There was no evidence of toxicological or histopathological effects in any treated animal in this study. There were also no treatment related effects on body weight gain, or ophthalmoscopic, electrocardiographic, nasal and clinical pathological examinations. Chronic inflammatory changes were noted in the nasal turbinates, larynx and lungs, but occurred with similar incidence and severity in all groups and were not considered to be drug related.

An aqueous solution of ipratropium bromide (0.05 mg/kg), was locally well tolerated when administered to rats by inhalation (single administration over 4 h). In ŕepeat-dose toxicity studies, ípratropium bromide was locally well tolerated.

Neither active anaphylaxis nor passive cutaneous anaphylactic reactions were demonstrated in Guinea pigs.

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.

There was no evidence of genotoxicity *in vitro* (Ames test) and *in vivo* (micronucleus test, dominant lethal test in mice, cytogenetic assay on bone marrow cells of Chinese hamsters).

CARCINOGENICITY

Carcinogenicity studies in mice (107 weeks duration) and rats (114 weeks duration) utilizing oral doses of up to 6 mg/kg were performed. These studies demonstrated that ipratropium bromide does not have a tumorigenic or carcinogenic effect.

REPRODUCTIVE STUDIES

Three teratological studies, one in mice using oral doses of 2 and 10 mg/kg, and two in rats, were performed. The first study used the same doses and the second employed 10 and 20 mg/kg and revealed no drug induced fetal abnormalities. A similar oral study in rabbits utilizing doses of 2 and 10 mg/kg again showed 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.

High oral dose levels, i.e. 1000 mg/kg/day in the rat [101] and 125 mg/kg/day in the rabbit [105] were maternotoxic for both species and embryo-/fetotoxic in the rat, where the fetal weight was reduced. Treatment-related malformations were not observed.

A fertility study in rats with oral doses of 5, 50 and 500 mg/kg being given 60 days prior to and during early gestation was performed. Fertility was delayed in 8 of 20 couples at 500 mg/kg and spurious pregnancy in 5 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.

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PART III: CONSUMER INFORMATION

Pr pms-IPRATROPIUM
(Ipratropium Bromide Nasal Spray, House Standard)

This leaflet is part III of a three-part "Product Monograph" published when pms-IPRATROPIUM was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-IPRATROPIUM Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
pms-IPRATROPIUM nasal spray 0.03% is used to treat the runny nose associated with perennial allergic or nonallergic rhinitis.

pms-IPRATROPIUM nasal spray is intended to relieve your rhinorrhea (runny nose) with regular use. It is therefore important that you use pms-IPRATROPIUM nasal spray as prescribed by your physician. Some improvement in rhinorrhea is usually apparent during the first full day of treatment with pms-IPRATROPIUM nasal spray.
However, maximum benefit may not occur for up to several weeks after treatment has started.

What it does:
pms-IPRATROPIUM nasal spray works to stop the glands in your nose from producing excessive nasal secretions. pms-IPRATROPIUM nasal spray must be prescribed by a doctor.

When it should not be used:
Nasal spray should not be used by patients with a history of allergy to ipratropium bromide, or to any component of this formulation.

pms-IPRATROPIUM nasal spray should not be used by patients with allergic reaction to ipratropium bromide, atropinics (atropine or atropine-like drugs) or to any component of the drug (See **What the nonmedicinal ingredients are**)

What the medicinal ingredient is:
Ipratropium bromide

What the nonmedicinal ingredients are:
Benzalkonium chloride, edetate disodium, hydrochloric acid, sodium chloride, sodium hydroxide and purified water.

What dosage forms it comes in:
Nasal Spray: 0.03% w/v

WARNINGS AND PRECAUTIONS

BEFORE you use pms-IPRATROPIUM talk to your doctor or pharmacist if:
- you are pregnant or intend to become pregnant;
- you are breast feeding;
- you have any other health problems, now or in the past;
- you have eye problems, such as predisposition to glaucoma;
- you have difficulty/trouble urinating or problems with your prostate;
- you are taking any other medications including eye drops or any medications you can buy without prescription;
- you have any allergies or reactions to foods or drugs.

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

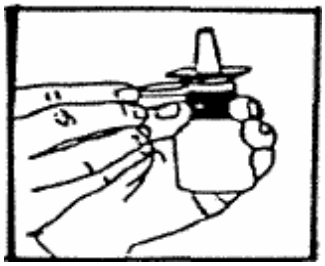
INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with pms-IPRATROPIUM nasal spray include: Other anticholinergic drugs.

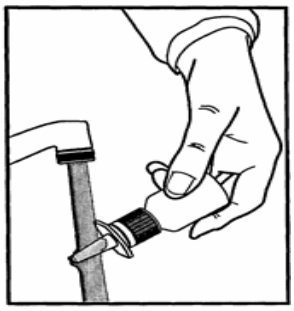
PROPER USE OF THIS MEDICATION

Usual dose:

1.



Remove the clear plastic dust cap and the safety clip from the nasal spray pump. The safety clip prevents the accidental discharge of the spray in your pocket or purse.



2.The nasal spray pump must be primed before pms-IPRATROPIUM nasal spray is used for the first time. To prime the pump, hold the bottle with your thumb at the base and your index and middle fingers on the white shoulder area. Make sure the bottle points upright and away from your eyes. Press your thumb firmly against the bottle seven times. Each time, maintain the pump in the closed position for at least one second before releasing

the pressure. The pump is now primed and can be used. Your pump should not have to be reprimed unless you have not used the medication for more than 24 hours; repriming the pump will only require one or two sprays.

3 Before using pms-IPRATROPIUM nasal spray, blow your nose gently to clear your nostrils if necessary.

4. Close one nostril by gently placing your finger against the side of your nose, tilt your head slightly forward and, keeping the bottle upright, insert the nasal tip into the other nostril. Point the tip toward the *back* and *outer* side of the nose.

5. Press firmly and quickly upwards with the thumb at the base while holding the white shoulder portion of the pump between your index and middle fingers. Following each spray, sniff deeply and breathe out through your mouth.

6. After spraying the nostril and removing the unit, tilt your head backwards for a few seconds to let the spray spread over the back of the nose.

7. Repeat steps 4 through 6 in the other nostril.

8. Replace the clear plastic dust cap and safety clip.

9. When the amount of pms-IPRATROPIUM nasal spray begins to run low, the amount of medication in each spray cannot be assured. Therefore, at some time before the medication is completely used up, you should consult your physician or pharmacist to determine whether a refill is needed. You should not take extra doses of pms-IPRATROPIUM nasal spray without consulting your physician.

To Clean:

If the nasal tip becomes clogged, remove the clear plastic dust cap and safety clip. Hold the nasal tip under running warm tap water for about a minute. Dry the nasal tip, reprime the nasal spray pump (step 2 above), and replace the plastic dust cap and safety clip.

Avoid spraying pms-IPRATROPIUM nasal spray in or around your eyes. Should this occur, immediately flush your eyes with cool tap water for several minutes. If you accidentally spray pms-IPRATROPIUM nasal spray in your eyes, you may experience a temporary blurring of vision and increased sensitivity to light, which may last a few hours.

Do not exceed the number of sprays, or the length of use, prescribed by your doctor.

pms-IPRATROPIUM nasal spray has been prescribed to treat your current condition. Do not give it to other people.

Do not take other medication without your doctor's advice.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Center immediately, even if there are no symptoms. Always take the labeled medicine container with you.

Missed Dose:
If you forget to take your dose, don't worry. Take your next dose as usual. Do not double your dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any other drug product, pms-IPRATROPIUM nasal spray may cause unwanted effects along with its good effects. If you do experience any of the unwanted effects listed below, you should contact your doctor. He/she may recommend that you lower your dose of pms-IPRATROPIUM nasal spray.

The most frequent side effects are headache, throat irritation, nasal discomfort, nasal dryness and nosebleeds.

Other side effects include: increased heart rate and a feeling that your heart is beating fast, heart problems such as fast or irregular heart beat ; eye disorders such as difficulty in focusing the eyes, seeing halos, swelling of the cornea, build up or increased pressure in the eye, dilated pupils, swelling of the blood vessels in the conjunctiva (outermost layer of the eye and inner surface of the eyelids), blurred vision, eye pain; difficulty in passing urine; swelling of the muscles around the voice box; dry throat, dry mouth, swelling of the mouth and throat, increased wheezing or tightness in the chest or difficulty in breathing (bronchospasm) ; digestive problems like constipation, diarrhoea and vomiting; dizziness.

Some people can be allergic to medicines. If you have any of the following symptoms soon after taking pms-IPRATROPIUM nasal spray, stop taking this medicine and tell your doctor immediately or go the nearest hospital:

- Sudden wheeziness and chest pain or tightness
- Sudden difficulty in breathing and reduction in your blood pressure

- Swelling of eyelids, face, tongue or throat
- Lumpy skin rash, or "hives" anywhere on the body.

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 emergency medical attention
		Only if severe	In all cases	
Uncommon	Blurred vision or pain in he eyes			T
	Fast or irregular heart beat			T
	Difficult or painful urination			T
	Rash			T
	Increased wheezing or tightness in the chest or difficulty in breathing (bronchospasm)			T
	Swelling of the tongue or lips			T
	Difficulty in swallowing			T

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

HOW TO STORE IT

Store tightly closed between 15°C and 30°C. Avoid excessive heat or freezing. Keep out of reach 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 product monograph, prepared for health professionals, can be obtained by contacting Pharmascience Inc. at 1-888-550-6060.

This leaflet was prepared by
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Montreal Quebec
H4P 2T4

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