PRODUCT MONOGRAPH

Pr ratio-IPRATROPIUM UDV

(Ipratropium Bromide)

1 mL and 2 mL inhalation solution unit dose vials

Each plastic unit dose vial (UDV) contains:
250 mcg of ipratropium bromide in 1 mL
250 mcg of ipratropium bromide in 2 mL
500 mcg of ipratropium bromide in 2 mL

BRONCHODILATOR

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[Pr] ratio-IPRATROPIUM Inhalation Solution
[Pr] ratio-IPRATROPIUM UDV

(Ipratropium Bromide)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Inhalation	Inhalation Solution 250 mcg/mL, 250 mcg/2 mL, 500 mcg/2 mL Unit Dose Vials	Sodium chloride, hydrochloride acid and purified water *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

ratio-IPRATROPIUM UDV (ipratropium bromide) Inhalation Solution administered either alone or with an adrenergic stimulant solution is indicated:

- As a bronchodilator for the maintenance treatment of bronchospasm associated with, or for the therapy of, acute exacerbations of chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. **ratio-IPRATROPIUM UDV** www.sylvainboudreau.comsolution, when used in conjunction with a β_2 adrenergic stimulant solution such as fenoterol or salbutamol, is indicated for acute asthmatic attacks. It is to be administered by compressed air or oxygen driven nebulizers.

Pediatrics:
The efficacy and safety of **ratio-IPRATROPIUM UDV** in children younger than 5 years has not been established.

CONTRAINDICATIONS

- Known hypersensitivity to **ratio-IPRATROPIUM UDV** (ipratropium bromide), to any of the product ingredients, or to atropinics.

WARNINGS AND PRECAUTIONS

General

ratio-IPRATROPIUM UDV 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 β_2 agonist.

Immediate hypersensitivity reactions may occur after administration of **ratio-IPRATROPIUM UDV**, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal edema and anaphylaxis.

ratio-IPRATROPIUM UDV (ipratropium bromide) solution (UDV's) is intended only for inhalation with suitable nebulizing devices and should not be taken orally or administered parenterally.

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, **ratio-IPRATROPIUM UDV** (ipratropium bromide) should be used with caution.

If a reduced response to **ratio-IPRATROPIUM UDV** becomes apparent, the patient should seek medical advice.

ratio-IPRATROPIUM UDV solution, when administered to patients with acute severe asthma, should be used with concomitant β_2 adrenergic stimulant therapy.

Carcinogenesis and Mutagenesis
Please see TOXICOLOGY section.

Ear/Nose/Throat
GLAUCOMA, ANGLE-CLOSURE

Care should be taken to ensure that the nebulizer mask fits the patient's face properly and that nebulized solution does not escape into the eyes. In patients with glaucoma or narrow anterior chambers, the administration by nebulizer of a combined ratio-IPRATROPIUM/β_2 agonist solution should be avoided unless measures (eg., use of swimming goggles or use of a nebulizer with a mouth piece) are taken to ensure that nebulized solution does not reach the eye. There have been isolated reports of ocular complications (i.e., mydriasis, increased intraocular pressure, angle closure glaucoma) when nebulized ipratropium bromide either alone or in combination with an adrenergic β_2 agonist solution has escaped into the eyes.

Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal edema may be signs of acute narrow-angle glaucoma. In the event that glaucoma is precipitated or worsened, treatment should include standard measures for this condition.

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

Special Populations

Pregnant Women:

The safety of **ratio-IPRATROPIUM UDV** in pregnancy has not been established. The benefits of using **ratio-IPRATROPIUM UDV** when pregnancy is present or suspected must be weighed against possible hazards caused to the fetus. Studies in rats, mice and rabbits showed no embryotoxic nor teratogenic effects.

Nursing Women:

No specific studies have been conducted on excretion of this drug in breast milk. Benefits of **ratio-IPRATROPIUM** use during lactation should therefore be weighed against possible effects on the infant.

Pediatrics:

The efficacy and safety of **ratio-IPRATROPIUM UDV** in children younger than 5 years has not been established.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Side effects noted as with the use of other inhalation therapy are cough, local irritation and inhalation induced bronchospasm, and in very rare instances exacerbation of symptoms has been observed.

The most frequent non-respiratory adverse events reported in clinical trials were headache, gastro-intestinal motility (constipation, diarrhoea and vomiting), dizziness and dryness of the mouth/throat.

The adverse event profile was examined in a total of 214 patients receiving ipratropium bromide solution, 94 patients receiving ipratropium bromide plus a β_2 agonist (either fenoterol or salbutamol) solution and in 96 patients receiving a β_2 agonist alone. Furthermore the frequency

of adverse reactions reported as possibly related to ipratropium bromide treatment was studied in a 12-week controlled clinical trial in 219 COPD patients.

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 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 8 patients treated with ipratropium bromide solution alone, 6 of whom withdrew from the clinical studies.

Bronchospasm occurred in 3 patients with acute severe asthma who received ipratropium bromide solution alone. In two patients, this was reversed after therapy with a β_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 β_2 agonist (either fenoterol or salbutamol) solution with that of the β_2 agonist alone.

ADVERSE REACTION	ipratropium bromide + β_2 AGONIST (% of 94 patients)	β_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 REACTIONS	% 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, 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 + β_2 agonists (metaproterenol or salbutamol) versus the β_2 agonist alone, was as follows:

ADVERSE EFFECT	% OF PATIENTS	
	ipratropium bromide + β2 AGONIST (n = 208)	β_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 β_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 are headache and dryness of mouth/throat.

Immediate hypersensitivity reactions may occur after administration of ipratropium bromide. 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

Overview

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

If the patient's condition requires the administration of sodium cromoglycate, it should be given in combination with **ratio-IPRATROPIUM** solution without preservatives (i.e., from the unit dose vial).

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 **ratio-IPRATROPIUM UDV** (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 **ratio-IPRATROPIUM UDV** solution less than 2 mLs 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 Inspiron 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 **ratio-IPRATROPIUM UDV** 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 **ratio-IPRATROPIUM UDV** (ipratropium bromide) 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 **ratio-IPRATROPIUM UDV** (ipratropium bromide) up to 1.2 mg (60 puffs) have been administered by inhalation 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 drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Ipratropium bromide, a quaternary ammonium derivative of atropine is an anticholinergic drug having bronchodilator properties. 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. 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 µg by inhaler (10 times the recommended single dose) to 10 normal subjects, no changes were detected in pulse rate, blood pressure, intraocular pressure, salivary secretion, visual accommodation or electrocardiograms. Likewise, in another

study, no changes in pulse rate or salivary secretion were seen when cumulative doses up to 1.2 mg were administered by inhaler to 12 normal volunteers.

Special studies utilizing normal therapeutic doses in asthmatic and chronic bronchitic patients again have not revealed any systemic anticholinergic effects. In one study, 14 patients were treated for 45 days with either ipratropium bromide inhaler 40 µg q.i.d. or ipratropium bromide inhaler 40 µg q.i.d. plus oral Berotec 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 inhaler 40 µg t.i.d administered for 3 days.

Deterioration in pulmonary function in patients treated in all clinical trials with therapeutic doses of ipratropium bromide solution was examined. The following table shows the number of patients who showed a 15% or greater fall in FEV_1 at any time within 2 hours following the administration of the drug. Also shown are the figures for comparative agents used.

Treatment	Incidence	
Normal saline	15/90	(16.7%)
Ipratropium bromide Solution	14/214	(6.5%)
Ipratropium bromide Inhaler	4/78	(5.1%)
Berotec Solution	4/83	(4.8%)
Ipratropium bromide Solution + Berotec Solution	1/81	(1.2%)

Dose titration studies in stable asthmatic patients with ipratropium bromide solution have indicated that maximal improvement in pulmonary function occurs at approximately 250 µg for adults and 125 µg for children over 5 years.

A clinical pharmacology study comparing single doses of ipratropium bromide inhaler (80 mg) and ipratropium bromide solution (250 mg) in 16 stable adult asthmatics was performed. No difference between the regimens was found, based on an improvement in pulmonary function over a 2 hour period.

A wide variety of challenge studies have been conducted utilizing 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 little or 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 are protected against bronchospasm induced by exercise. Likewise, the protective effects of ipratropium bromide against cold air induced bronchospasm have been variable.

Antigen challenge studies have demonstrated that ipratropium bromide offers some protection against the “early” allergic asthma response, but has no effect on the “late” response.

Pharmacokinetics

Absorption:

Ipratropium bromide is absorbed quickly after oral inhalation of a nominal dose of 40 µg administered from a pressurized metered dose inhaler. The peak plasma concentrations (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 systemic bioavailability after inhalation of 2 mg ipratropium bromide, via an ultrasonic Mizer inhaler, over 20 minutes is estimated to be 7% of the dose. The bioavailability of the swallowed portion of the dose is approximately 2%.

Distribution:

Intravenous administration of 1.0 mg in man showed a rapid distribution into tissues (half-life of an alpha phase approximately 5 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).

Parameters describing the disposition of ipratropium bromide were calculated from the plasma concentrations after i.v. administration. A rapid biphasic decline in plasma is noted for ipratropium. The half-life of the terminal elimination phase is about 1.6 hours. The total clearance of the active ingredient is 2.3 L/min. Approximately 40% of the clearance is renal (0.9 L/min) and 60% non-renal i.e. mainly hepato-metabolic. The volume of distribution is 338 L (corresponding to approximately 4.6 L/kg).

Radio-labelled technetium was administered with ipratropium bromide solution in an adult dose finding study. The following table outlines the doses reaching the patient. The figures for ipratropium bromide inhaler are published estimates.

Dose Available (µg)	Amount Reaching Patient (µg)	Lung Dose (µg)
500	53	17.0
250	27	8.5
125	13	4.3
40 (ipratropium bromide Inhaler)	40	4.4

The drug is minimally (less than 20%) bound to plasma proteins. The ipratropium ion does not cross the blood-brain barrier, consistent with the quaternary amine structure of the molecule.

Metabolism:

Up to 8 metabolites of ipratropium bromide have been detected in man, rat and dog. However, the main metabolites bind poorly to the muscarinic receptor.

Excretion:
In man, about 70% of the ^{14}C labelled drug is excreted unchanged after i.v. administration and only one metabolite exceeds 10% of the total radioactivity. The elimination of ipratropium and its metabolites occurs primarily via the kidney with less than 10% of the total intravenous dose excreted via the biliary or fecal route. After oral or inhaled doses, however, up to 90% of the radiolabelled dose is detectable in the feces, suggesting relatively low lung deposition and poor absorption of the swallowed portion.

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. Depending on the formulation and inhalation technique, renal excretion may increase up to 13% of the dose (40 or 80 µg dose), reflecting a higher deposition in the airways and a higher bioavailability.

Special Population and Conditions

Pediatrics: The efficacy and safety of **ratio-IPRATROPIUM** in children younger than 5 years has not been established.

STORAGE AND STABILITY

1 mL or 2mL Unit Dose Vials

1 mL Unit Dose Vials
Store at 15-25°C. Protect form heat and light.

2 mL Unit Dose Vials
Store at 15-30°C. Protect form heat and light.

The solution is physically compatible with Alupent® (orciprenaline sulphate), fenoterol hydrobromide or salbutamol sulfate (6 mg/mL) solutions. If such mixtures are prepared, they should be diluted with preservative-free sterile sodium chloride solution 0.9% and used immediately. Any unused portion of such combined solutions must be discarded.

DOSAGE FORMS, COMPOSITION AND PACKAGING

2 ML UNIT DOSE VIAL:

250 mcg/mL:

ratio-IPRATROPIUM UDV solution is also provided as 2 mL of clear, colourless solution containing 250 mcg/mL (0.025%) ipratropium bromide in isotonic solution, presented in a plastic single use vial. Each vial contains a total of 500 mcg of ipratropium bromide. Each UDV strip is packaged in an aluminum/low density polyethylene (LDPE) pouch.

Non-medicinal ingredients include sodium chloride, hydrochloric acid and purified water.

125 mcg/mL:

ratio-IPRATROPIUM UDV solution is also provided as 2 mL of clear, colourless solution containing 125 mcg/mL (0.0125%) ipratropium bromide in isotonic solution, presented in a plastic single use vial. Each vial contains a total of 250 mcg of ipratropium bromide. Each UDV strip is packaged in an aluminum/low density polyethylene (LDPE) pouch.

Non-medicinal ingredients include sodium chloride, hydrochloric acid and purified water.

1 ML UNIT DOSE VIAL:

ratio-IPRATROPIUM UDV solution is also provided as 1 mL of clear, colourless solution containing 250 mcg/mL (0.025%) ipratropium bromide in isotonic solution, presented in a plastic single use vial. Each vial contains a total of 250 mcg of ipratropium bromide. Each UDV strip is packaged in an aluminum/low density polyethylene (LDPE) pouch.

Non-medicinal ingredients include sodium chloride, hydrochloric acid and purified water.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

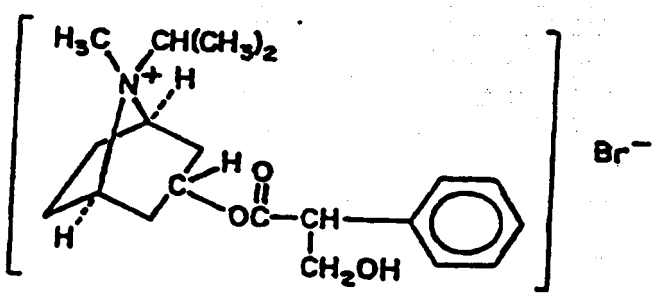
Drug Substance

Proper name: ipratropium bromide

Chemical name: (8r)-8-Isopropyl-3-(±)-tropoyloxylαH, 5αH-tropanium bromide

Molecular formula and molecular mass: $C_{20}H_{30}NO_3Br$
412.37

Structural formula:



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.

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 1-2 hours, and persisted for periods of 4-5 hours in the majority of patients, with 25-38% of the patients demonstrating increases of at least 15% at 7-8 hours. Continued effectiveness of ipratropium bromide 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 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 5-7 hours, compared with 3-4 hours in patients receiving a beta agonist alone.

DETAILED PHARMACOLOGY

Ipratropium bromide (**ratio-IPRATROPIUM UDV**) 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 at an ED_{50} of 0.15-0.40 µg/kg with a transient effect on blood pressure. By 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. 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 µg 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 an s.c. 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 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* tests with the 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. Ipratropium bromide was administered by inhalation in combination with a β_2 sympathomimetic agent (fenoterol hydrobromide). In both the dog and guinea pig, these agents were additive in antagonizing acetylcholine induced bronchospasm with ED_{50} being 19.8 µg (ipratropium), 49.25 µg (fenoterol) and 11.05 µg + 27.63 µg (ipratropium + fenoterol). In the dog, 50 µg of fenoterol by inhalation produced an 8% increase in heart rate and a 16% increase in left ventricular dp/dt. When 20 µg ipratropium was added to the above, the corresponding increases were 8% and 9%.

TOXICOLOGY

ACUTE

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		i.v.	13.5
Mouse	M	i.v.	12.3
Mouse	F	i.v.	15.0
Mouse		s.c.	322
Mouse		s.c.	300
Mouse		oral	2010
Mouse		oral	1038
Rat		i.v.	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 i.v. and for 8 days after oral administration.

IPRATROPIUM BROMIDE + FENOTEROL HYDROBROMIDE (RATIO 1:2.5)

SPECIES	SEX	ROUTE	LD_{50}(mg/kg)
Mouse	M	i.v.	23.6
Mouse	F	i.v.	26.2
Mouse	M	oral	630
Mouse	F	oral	650
Rat	M	i.v.	32.5
Rat	F	i.v.	32.5
Rat	M	oral	3200
Rat	F	oral	2450

The signs of toxicity were spasmodic breathing, tonic, clonic and saltatory convulsions, sedation, ataxia, spasms, exophthalmus, chromolacryorrhoea, reduced motility, tremor and positive sliding test. Late mortality occurred only 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 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.

An acute inhalation toxicity study of ipratropium bromide administered as 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).

An acute 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 EGG 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 was performed. No deaths occurred. A combination of ipratropium bromide (up to 3.2 mg/kg) with fenoterol hydrobromide (up to 8 mg/kg) was administered by inhaler (up to 320 puffs) to rats. There were no deaths or clinical signs observed.

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.

Intravenous:

A 32 day study in rats was conducted with the combination of ipratropium bromide and fenoterol hydrobromide at doses of 1.32 + 3.32 µg/kg (Group 1), 8 + 20 µg/kg (Group 2) and 24 + 60 µg/kg (Group 3) respectively. Fenoterol 60 µg/kg (Group 4) and ipratropium 24 µg/kg (Group 5) were also administered. Increases in heart rate (dose related in all treated animals) and dry mouth and nose (Groups 3 and 5) were seen. Increases in LDH (Groups 3 and 4), creatine kinase (all treated Groups), potassium (Groups 2, 3 and 4) and cholesterol (Groups 3 and 4) were observed. Myocardial scars were seen in one animal in Group 3 and fatty changes in the liver were noted in one animal in Group 4.

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:

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.

Rats were exposed to a combination of fenoterol and ipratropium twice, 4 times and 8 times per day. Metered dose inhalers containing 50 µg fenoterol and 20 µg ipratropium per actuation were discharged into the exposure chamber at a rate of 6 doses per minute for 25 minutes over a 7 day period. No changes apart from a reduction in food consumption in the first 2 days in the high dose group were noted.

A 28 day study in dogs was conducted using fenoterol and ipratropium in the following doses respectively: 350 + 140 µg (Group 3); 1050 + 420 µg (Group 4); 3150 + 1260 µg (Group 5). Vasodilation occurred in Groups 4 and 5 and heart rate was increased in the treated animals. Potassium levels were raised in Group 5. Liver glycogen content was raised in 4 (of 6) animals in Group 5 and 2 in Group 4.

A further 13 week combination study was done in dogs using doses of 23 + 9 µg (Group 1), 160 + 64 µg (Group 2) and 1100 + 440 (Group 3) fenoterol + ipratropium respectively. Peripheral hyperaemia and dry mucous membranes were observed in all treated animals. Increases in heart rate were seen in Groups 1 to 3, and 5 of 6 dogs in Group 3 had disturbances of impulse formation and conduction. Slight increases in GPT in Groups 2 and 3, as well as increases in AP in individual animals of Groups 1 to 3 were noted. Histological findings consisted of a scar in the papillary muscle of the left ventricle of one dog in Group 3 as well as centrolobular fatty infiltration of hepatocytes in dogs of Groups 2 and 3.

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 hepatosis 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:

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.

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.

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:

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.

Two inhalation teratology studies with the combination of fenoterol and ipratropium in rats (doses up to 8 x 25 minute exposures of 7.5 mg fenoterol + 3.0 mg ipratropium per day) and rabbits (doses up to 3.0 mg fenoterol + 1.2 mg ipratropium) revealed no embryotoxic or teratogenic effects.

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.

REFERENCES

1. Beasley GRW, Ratterty P, Holgate ST. Bronchoconstrictor properties of preservatives in ipratropium bromide (ATROVENT) nebuliser solutions. Br Med J 1987; 294:1197-8.

2. Beck R, Robertson C, Galdes-Sebaldt M, Levison H. Combined salbutamol and ipratropium bromide by inhalation in the treatment of severe acute asthma. J Pediatr 1985; 107:605-8.

3. Bryant DH. Nebulized ipratropium bromide in the treatment of acute asthma. Chest 1985;88:24-9.

4. Chan CS, Brown IG, Kelly GA, Dent AG, Zimmerman PV. Bronchodilator responses to nebulized ipratropium and salbutamol singly and in combination in chronic bronchitis. Br J Clin Pharmacol 1984; 17:103-5.

5. Chan-Yeung M. The effect of Sch 1000 and disodium cromoglycate on exercise-induced asthma. Chest 1977;71:320-3.

6. Cockroft DW, Ruffin RE, Hargreave FE. Effect of Sch 1000 in allergen-induced asthma, Clin Allergy 1978; 8:361-72.

7. Cockroft DW, Killian DN, Mellon JJA, Hargreave FE. Protective effect of drugs on histamine-induced asthma. Thorax 1977;32:429-37.

8. Davis A, Vickerson F, Worsley G, Mindorff G, Kazim F, Levison H. Determination of the dose response relationship for nebulized ipratropium in asthmatic children. J Pediatr 1984; 105:1002-5.

9. Douglas NJ, Davidson I, Sudlow MF, Flenley DC. Bronchodilation and the site of airway resistance in severe chronic bronchitis 1979;34:51-6.

10. Anonymous. Ipratropium (ATROVENT) for airway obstruction. Drug Ther Bull 1980; 18:59.

11. Engelhardt A. Pharmacology and toxicology of ATROVENT Scand J Respir Dis 1979;60 (Suppl 103):1l0-5.

12. Jenkins CR, Chow GM, Fisher BL, Martin GE. Comparison of ipratropium bromide and salbutamol by aerosolized solution. Aust NZ J Med 1981; 11:513-6.

13. Lenney W, Evans NAP. Nebulized salbutamol and ipratropium bromide in asthmatic children. Br J Dis Chest 1986;80:59-65.

14. McIntosh D. A comparison between fenoterol/ipratropium bromide combinations and salbutamol administered as nebulizer solutions assessing dose-response and duration of action. Pharmacothapeutica 1986;4:416-21.

15. Molkenboer JFWM, Lardenoye JG. The effect of ATROVENT in micturition function, double-blind cross-over study. Scand J Respir Dis 1979;60(Suppl 103) 154-8.

16. Pavia, Bateman JRM, Sheahan NF, Clarke SW. Effect of ipratropium bromide on mucociliary clearance and pulmonary function in reversible airways obstruction. Thorax 1979; 34:501-7.

17. Rebuck AS, Abboud R, Pare PD, et al. Nebulized anticholinergic and sympathomimetic treatment of obstructive airways disease in the emergency room. Am J Med 1987;82:59-64.

18. Rominger KL. Chemistry and pharmacokinetics of ipratropium bromide. Scand J Respir Dis l979;60(Suppl 103):116-126.

19. Ruffin RE, Cockcroft DW, Hargreave FE.A comparison of the protective effect of fenoterol and Sch 1000 on allergen-induced asthma. J Allergy Clin Immunol 1978;61:42-7.

20. Ruffin RE, Wolff RD, Dolovich MB, Rossman CM, Fitzgerald MB, Newhouse MT. Aerosol therapy with Sch 1000: Short-term mucociliary clearance in normal and bronchitic subjects and toxicology in normal subjects. Chest 1978; 73:501-6.

21. Sackner MA, Friedman M, Silva G, Fernandez R. The pulmonary hemodynamic effects of aerosols of isoproterenol and ipratropium in normal subjects and patients with reversible airway obstruction. Am Rev Respir Dis 1977; 116:1013-22.

22. Ward MJ, Macfarlane JH, Davies D. A place for ipratropium bromide in the treatment of severe asthma, Br J Dis Chest 1985; 79:374-8.

23. Ward MJ, Fentem PH, Roderick-Smith WH, Davies D. Ipratropium bromide in acute asthma. Br Med J 1981;282:598-600.

24. Proceedings from the Canadian Bronchitis Symposium. February 18-19, 1994. Recommendations on the Management of Chronic Bronchitis. CMAJ, suppl. Nov. 15, 1994. Vol. 151(10).

25. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of Smoking Intervention and the use of an Inhaled Anticholinergic Bronchodilator on the Rate of Decline of FEV_1: The Lung Health Study. JAMA. Nov. 16, 1994, Vol. 272. No. 19: 1471-1556.

26. Product Monograph for [Pr]Atrovent® manufactured by Boehringer Ingelheim (Canada) Ltd., dated August 26, 2009

PART III: CONSUMER INFORMATION

ratio-IPRATROPIUM UDV
(Ipratropium Bromide)

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

ABOUT THIS MEDICATION

What the medication is used for:
ratio-IPRATROPIUM UDV solution is a bronchodilator which relieves the wheezing and shortness of breath caused by chronic bronchitis or by asthma. For the treatment of asthma, ratio-IPRATROPIUM UDV solution must be used in conjunction with some other bronchodilating medication. ratio-IPRATROPIUM UDV solution is available only on prescription.

Before starting treatment with ratio-IPRATROPIUM UDV solution, be certain that you are completely familiar with the use and proper care of your nebulizer.

What is COPD?
COPD (Chronic Obstructive Pulmonary Disease) is a type of lung disease in which there is a permanent narrowing of the airways, leading to breathing difficulties. In many patients, this narrowing of the airways is a result of many years of cigarette smoking. Smoking cessation produces symptomatic benefits and will slow the progression of chronic bronchitis (which is a form of COPD). COPD can be helped by medication as well.

What is Asthma?
Asthma is a disease in which the airways can become temporarily narrowed, leading to breathing difficulties. This narrowing of the airways is due to inflammation, which causes swelling and irritation of the airways and tightening of the muscles around the airways. The narrowed airway can be relieved with the help of medication.

It is important to know that the treatment of COPD and Asthma may be different for each patient. Your doctor will most likely discuss with you the best plan for the treatment of your particular condition. This plan may include taking other medication(s) in addition to ratio-IPRATROPIUM UDV. It is necessary that you follow your physician's directions for the treatment of your condition. If you have any questions about how you should treat your condition at home, you should consult your doctor.

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

When it should not be used:
ratio-IPRATROPIUM UDV 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 important nonmedicinal ingredients are:
Non-medicinal ingredients include hydrochloric acid, purified water and sodium chloride

What dosage forms it comes in:
Inhalation Solution; 250 mcg of ipratropium bromide in 1 mL, 250 mcg of ipratropium bromide in 2 mL or 500 mcg of ipratropium bromide in 2 mL

WARNINGS AND PRECAUTIONS

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

- **if you are pregnant or intend to become pregnant;**
- **if your are breast feeding;**
- **if you have any other health problems;**
- **if you are taking any other medications including those you can buy without a prescription and including eye drops;**
- **if you have any other medical problems such as difficult urination or enlarged prostate;**
- **if you have eye problems, such as glaucoma or eye pain;**
- **if you have any allergies or reactions to foods or drugs.**

INTERACTIONS WITH THIS MEDICATION

Other medications may be affected by ratio-IPRATROPIUM UDV solution or may affect how ratio-IPRATROPIUM UDV solution works. Do not take any other medication, including over-the-counter medications or herbal products unless your doctor tells you to. Tell any other doctor, dentist or pharmacist that you talk to that you are taking ratio-IPRATROPIUM UDV solution.

PROPER USE OF THIS MEDICATION

- **DO NOT exceed the prescribed dose or frequency of treatments.**
- **Before you start to use ratio-IPRATROPIUM UDV solution, read the following instructions carefully. Care should be taken to ensure that the nebulizer mask fits the face properly and that nebulized solution does not escape into the eyes. If you have any questions about using the nebulizer, check with your doctor or pharmacist.**

ratio-IPRATROPIUM UDV (Ipratropium Bromide) Solution

2 mL Unit Dose Vial

250 mcg/mL

Each plastic vial contains 2 mL of ratio-IPRATROPIUM UDV solution. Each millilitre (mL) of solution contains 250 mcg (0.025%) ipratropium bromide in a isotonic solution.

125 mcg/mL

Each plastic vial contains 2 mL of ratio-IPRATROPIUM UDV solution. Each millilitre (mL) of solution contains 125 mcg (0.0125%) ipratropium bromide in a isotonic solution.

1 mL Unit Dose Vial

250 mcg/mL

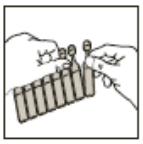
Each plastic vial contains 1 mL of ratio-IPRATROPIUM UDV solution. Each millilitre (mL) of solution contains 250 mcg (0.025%) ipratropium bromide in a isotonic solution.

Before starting treatment with ratio-IPRATROPIUM UDV solution, be certain that you are completely familiar with the use and proper care of your nebulizer.

Usage Instructions:
Your doctor or pharmacist will tell you how to prepare your ratio-IPRATROPIUM UDV solution for inhalation. If you are told to dilute ratio-IPRATROPIUM UDV solution, you must do so immediately before you plan to use the solution.

In most cases, dilution of the dose with sterile preservative-free saline is not necessary. However, volumes of ratio-IPRATROPIUM UDV solution less than 2 mL are not appropriate for nebulization and must be diluted with saline or another suitable nebulizer solution to make up for a total fill volume of 2-5 mL.

1) Detach one plastic vial by pulling it firmly from the strip.

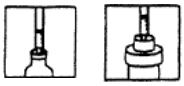


2) Open the vial by twisting off the top. It is important that you use the contents of the vial as soon as possible after opening it.

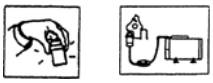
3) Squeeze the contents of the plastic vial into your nebulizer chamber. If your doctor has instructed you to use less than one complete vial, use a syringe to withdraw the prescribed dose. Any solution left in the plastic vial must be thrown away.

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

5) Using a syringe, add sodium chloride solution to the chamber if you have been directed to do so by your pharmacist or physician.



6) 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.



7) 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.

8) 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.

9) The unit dose vials should be stored at room

temperature. The vials should be protected from heat and light.

Please remember:

- **Do not exceed the prescribed dose or frequency of treatments.**
- **Do not mix this medication with any other medication in the nebulizer unless instructed to do so by your doctor or pharmacist.**
- **This medication has been prescribed for you and should not be given to other people.**
- **Keep out of the reach of children.**
- **The solution is intended for inhalation only. Do not inject or drink it.**
- **Do not let the nebulized mist get into your eyes. Patients with glaucoma should use swimming goggles or a nebulizer with a mouthpiece to prevent nebulized solution getting into the eyes.**

Overdose:

If you accidentally take too many puffs, you should get medical help immediately; either by calling the Regional Poison Control Centre, your doctor or by going to the nearest hospital (do not drive yourself). Always take the labelled medicine container with you.

Missed dose:

If a dose of this medication is missed, it is not necessary to make up the missed dose. Skip the missed dose and continue with the next scheduled dose. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any drug product, ratio-IPRATROPIUM UDV solution may cause unwanted effects. Do not be alarmed by this list of possible side effects. You may not experience any of them. If you do experience any unusual or unwanted effects while you are using ratio-IPRATROPIUM UDV solution you should contact your doctor or pharmacist immediately.

Undesirable effects include: Headache, dizziness, constipation, vomiting, diarrhea, nausea, cough, dry mouth, irritation of mouth and/or throat, hoarseness, increased wheezing or tightness in the chest or sudden difficulties in breathing (bronchospasm), rapid or irregular heart beat, sensation of rapid or irregular heart beat, difficult urination, retention of urine, pain in the eyes, blurred vision, skin rash/hives, itchiness, difficulty in swallowing, swelling of the mouth, lips or face, hypersensitivity reaction.

If you experience a dry mouth or 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.

Remember to tell any other doctor, dentist or pharmacist you consult that you are taking this medication.

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

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigiliance Program does not provide medical advice.

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 call your doctor or pharmacist
		Only if severe	In all cases	
Common	Increased wheezing or tightness in the chest or difficulty in breathing (bronchospasm)		✓	
Uncommon	Swelling of the tongue, lips or face		✓	
	Difficulty in swallowing		✓	
	Fast or irregular heart beat		✓	
	Blurred vision or pain in the eyes		✓	

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

		Talk with your doctor or pharmacist		
	Difficult or painful urination		✓	
	Skin rash		✓	

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

HOW TO STORE IT

Keep this medication out of the reach of children.

1 mL Unit Dose Vials
Store at 15-25°C. Protect from heat and light.

2 mL Unit Dose Vials
Store at 15-30°C. Protect from heat and light.

If required, the solution should be diluted with a preservative free sterile sodium chloride solution 0.9% and used immediately. Any solution remaining in the vial must be discarded.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor: ratiopharm inc., at :
17 800 Lapointe, Mirabel
Quebec, Canada, J7J 1P3
1-800-337-2584

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