PRODUCT MONOGRAPH

PrAtrovent® HFA
(Ipratropium Bromide)

Pressurized Inhalation Solution

20 mcg/metered dose

BRONCHODILATOR

Boehringer Ingelheim (Canada) Ltd.
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PrAtrovent® HFA

(Ipratropium Bromide)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral inhalation	Pressurized Inhalation Solution 20 mcg of ipratropium bromide/metered dose	Citric acid, ethanol, propellant HFA 134a (1,1,1,2-tetrafluorethane), nitrogen and water.

INDICATIONS AND CLINICAL USE

ATROVENT HFA (ipratropium bromide) pressurized inhalation solution is indicated as bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Pediatrics:
The efficacy and safety in children and adolescents under 18 years has not been established. ATROVENT HFA is not indicated in this patient population.

Geriatrics:
Elderly patients can use ATROVENT HFA at the recommended dose.

CONTRAINDICATIONS

- ATROVENT HFA (ipratropium bromide) pressurized inhalation solution is contraindicated in patients with known hypersensitivity to ipratropium bromide, atropine or its derivatives (such as the active substance ipratropium bromide) or any other aerosol components. For a complete listing see the DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

General

ATROVENT HFA is a bronchodilator for the maintenance treatment of bronchospasm associated with COPD and since the drug has a slower onset of action than that of an adrenergic β_2 agonist aerosol, it is not indicated for the initial treatment of acute episodes of bronchospasm where rescue therapy is required for rapid response.

Excessive Use and Use with other Muscarinic Antagonists

ATROVENT HFA should not be used more frequently or at higher doses than recommended (maximum recommended daily dose is 12 actuations = 240 mcg; minimum dosing interval is 4 hours).

ATROVENT HFA should not be administered concomitantly with other medications that contain a short- or long-acting muscarinic antagonist (e.g. ipratropium, tiotropium, glycopyrronium, aclidinium, umeclidinium).

Anticholinergic Effects

Like other anticholinergic drugs, ATROVENT HFA should be used with caution in patients with narrow-angle glaucoma or urinary retention.

Worsening of Narrow-Angle Glaucoma:
ATROVENT HFA should be used with caution in patients with narrow-angle glaucoma. Care should be taken to avoid spraying the mist into the eyes. Since the pressurized inhalation solution is applied via mouth piece and manually controlled, the risk for the mist entering the eyes is limited. There have been isolated cases of ocular complications (ie., mydriasis, increased intraocular pressure, narrow angle closure glaucoma, eye pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic beta2-agonist solution has come in contact with the eyes. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. Miotic drops alone are not considered to be effective treatment.

To ensure optimal delivery of ATROVENT (ipratropium bromide) pressurized inhalation solution to the bronchial tree, the patient should be properly instructed by the physician or other health professional in the use of the inhaler.

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

Carcinogenesis and Mutagenesis

Please see TOXICOLOGY section.

Cardiovascular

Cardiovascular effects, such as cardiac arrhythmias (e.g. atrial fibrillation and tachycardia), may be seen after the administration of muscarinic receptor antagonists (see ADVERSE REACTIONS).

Gastrointestinal

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

Immune

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

Ophthalmologic

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

Renal

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

Respiratory

Paradoxical bronchospasm:
As with other inhaled medicines ATROVENT may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs ATROVENT should be discontinued immediately and substituted with an alternative therapy.

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

Special Populations

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

Pregnant Women
The safety of ATROVENT pressurized inhalation solution in pregnancy has not been established. Nonclinical studies with ipratropium bromide have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man. Because animal reproduction studies are not always predictive of human response, ATROVENT HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the unborn child.

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

Pediatrics
The efficacy and safety in children and adolescents under 18 years has not been established. ATROVENT HFA is not indicated for pediatric patients.

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 ATROVENT HFA. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The following adverse reactions have been reported during use of ATROVENT in clinical trials and during the post-marketing experience.

The adverse event profile was examined in a total of 3250 patients that were treated in clinical trials with formulations of ATROVENT other than HFA (e.g. CFC, unit dose vials, capsules and solution for inhalation). The nature and frequency of adverse events in this extended population were similar to ATROVENT HFA.

Adverse reactions to ATROVENT HFA are similar in nature to reactions to other anticholinergic bronchodilators and may include cardiovascular effects (atrial arrhythmias and tachycardia),

ocular disorders (e.g. blurred vision), dysuria, urinary retention, gastrointestinal disorders (e.g., constipation and dry mouth), paradoxical bronchospasm, cough and immediate hypersensitivity reactions, including anaphylaxis (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS).

Clinical Trial Adverse Drug Reactions

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

Table 1 below summarizes the adverse events reported with a frequency of at least 1% in the ATROVENT HFA clinical trial safety data set, which includes a total of 1231 patients, of which 787 were treated with ATROVENT HFA at total daily doses of 20 µg to 320 µg for up to 4 months. Figures for ATROVENT CFC from the same data set are given for comparison. The adverse events reported are on the whole those that might be expected in a population of patients with COPD or asthma that is being treated with an inhaled anticholinergic. The only significant difference between the two placebo formulations is in the reporting frequency for "taste perversion", which was higher for placebo HFA than placebo CFC.

TABLE 1: COMMONLY REPORTED* ADVERSE EVENTS

	Atrovent				Placebo			
Formulation	**CFC**		**HFA**		**CFC**		**HFA**	
No. of Patients Exposed	**N=431**		**N=787**		**N=106**		**N=126**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
RESPIRATORY SYSTEM DISORDERS								
Any AE Within the Body System	165	38	305	39	34	32	38	30
Rhinitis	40	9	59	7	7	7	5	4
Bronchitis	33	8	67	9	5	5	32	
Dyspnoea	34	8	57	7	5	5	4	3
Coughing	25	6	46	6	4	4	7	6
Chronic obstructive airways disease	26	6	37	5	9	8	8	6
Upper Respiratory Tract Infection	17	4	44	6	8	8	8	6
Pharyngitis	23	5	38	5	1	<1	4	3
Asthma	14	3	36	5	0	0	0	0
Sinusitis	8	2	10	1	2	2	3	2
BODY AS A WHOLE - GENERAL DISORDERS								
Any AE Within the Body System	62	14	134	17	11	10	16	13
Headache	32	7	59	7	7	7	7	6
Pain	8	2	24	3	0	0	4	3
Influenza-like symptoms	6	1	24	3	0	0	3	2
Back pain	7	2	8	1	1	<1	1	<1
Chest pain	6	1	10	1	0	0	0	0
Fatigue	3	<1	9	1	1	<1	1	<1
GASTRO-INTESTINAL SYSTEM DISORDERS								
Any AE Within the Body System	47	11	97	12	6	6	6	5
Nausea	7	2	23	3	2	2	1	<1
Mouth dry	7	2	18	2	0	0	2	2
Diarrhoea	6	1	15	2	0	0	0	0
Abdominal pain	7	2	13	2	1	<1	0	0
Vomiting	5	1	15	2	0	0	0	0
Constipation	6	1	7	<1	1	<1	1	<1
Dyspepsia	6	1	7	<1	1	<1	0	0
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS								
Any AE Within the Body System	24	6	34	4	4	4	5	4
Dizziness	6	1	15	2	1	<1	2	2
Dysphonia	8	2	7	<1	0	0	1	<1
SPECIAL SENSES OTHER, DISORDERS								
Any AE Within the Body System	18	4	28	4	0	0	8	6
Taste Perversion	18	4	28	4	0	0	8	6
URINARY SYSTEM DISORDERS								
Any AE Within the Body System	10	2	15	2	5	5	4	3
Urinary tract infection	8	2	7	<1	2	2	1	<1
MUSCULO-SKELETAL SYSTEM DISORDERS								
Any AE Within the Body System	14	3	13	2	2	2	2	2
Myalgia	7	2	4	<1	2	2	1	<1
VISION DISORDERS								
Any AE Within the Body System	6	1	20	3	3	3	0	0
Conjunctivitis	3	<1	11	1	0	0	0	0

* Commonly reported adverse events are those that were reported with a frequency of at least 1% in the global safety data set regardless of relationship to treatment.
AE: Adverse event
n = No. of patients reporting AE. % = Percentage of patients reporting AE.
CFC: Chlorofluorocarbon formulation. HFA: Alternative Propellant, hydrofluoroalkane formulation.
Adverse events occurring prior to the first intake of test treatment are not included.
Treatment was the last treatment the patient received prior to the onset or worsening of the adverse event.

Many of the listed undesirable effects can be assigned to the anticholinergic properties of ATROVENT. As with all inhalation therapy ATROVENT 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 adverse events reported in clinical trials were headache, throat irritation, cough, dry mouth, gastrointestinal motility disorders (constipation, diarrhea, vomiting), dizziness and nausea.

As with other inhaled therapy including bronchodilators, cough, local irritation, paradoxical bronchospasm and in very rare instances, exacerbation of symptoms have been observed.

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 ATROVENT according to system organ class.

Immune system disorders
- hypersensitivity
- anaphylactic reaction

Nervous system disorders
- headache
- dizziness

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

Cardiac disorders
- palpitations
- supraventricular tachycardia
- atrial fibrillation
- heart rate increased

Respiratory, thoracic and mediastinal disorders
- throat irritation
- cough
- bronchospasm
- bronchospasm paradoxical

- laryngospasm
- pharyngeal oedema
- dry throat

Gastrointestinal disorders
- dry mouth
- nausea
- gastrointestinal motility disorder
- diarrhoea
- constipation
- vomiting
- stomatitis
- oedema mouth

Skin and subcutaneous tissue disorders
- rash
- pruritus
- angioedema
- urticaria

Renal and urinary disorders
- urinary retention

Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS

Drug-Drug Interactions

Anticholinergics

The chronic co-administration of ATROVENT inhalation with other anticholinergic drugs has not been studied. Therefore, ATROVENT HFA should not be administered concomitantly with other medications that contain a short- or long-acting muscarinic antagonist (e.g. ipratropium, tiotropium, glycopyrronium, aclidinium, umeclidinium).

Xanthine derivatives and $beta_2$ adrenergic agents may enhance the effect of ATROVENT pressurized inhalation solution.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Counselling by doctors on smoking cessation should be the first step in treating patients with 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.
- Spacer device is not required
- The safety and efficacy of ATROVENT HFA in pediatric patients under 18 years of age have not been established.

Recommended Dose and Dosage Adjustment

The optimal maintenance dosage must be individually determined and patients should be kept under medical supervision during treatment.

Recommended dose: The recommended dosage is 2 metered doses (actuations) (40 mcg) 3 or 4 times daily. Some patients may need up to 4 metered doses (actuations) (80 mcg) at a time to obtain maximum benefit during early treatment.

Maximum daily dose: The maximum daily dose should not exceed 12 metered doses (actuations) (240 mcg) and the minimum interval between doses should not be less than 4 hours.

If therapy does not produce a significant improvement or if the patient's condition gets worse, medical advice must be sought in order to determine a new plan of treatment. The patient should be instructed that in the case of acute or rapidly worsening dyspnoea a physician should be consulted immediately.

Missed Dose

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

OVERDOSAGE

Doses of ATROVENT (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 disorder 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

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

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

On inhalation the onset of action is noted within 5 to 15 minutes with a peak response between 1 and 2 hours, lasting about 2 additional hours with subsequent decline. An inhaled dose of 40 mcg induces bronchodilator effect lasting for some 6 hours.

In controlled 90 day studies in patients with bronchospasm associated with chronic obstructive pulmonary disease (COPD, chronic bronchitis and emphysema) significant improvements in pulmonary function occurred within 15 minutes, reached a peak in 1-2 hours, and persisted up to 4- 6 hours.

Pharmacodynamics

Large, single inhaled doses of ATROVENT have been given to man without any signs of toxicity. After the administration of 400 mcg 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 inhalation to 12 normal volunteers.

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

In one study, 14 patients were treated for 45 days with either ATROVENT 40 mcg q.i.d. or ATROVENT 40 mcg 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 ATROVENT 40 mcg t.i.d administered for 3 days.

A wide variety of challenge studies have been conducted utilizing ATROVENT as a protective agent. In pharmacologically induced bronchospasm, ATROVENT, 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 ATROVENT has little or no effect but other studies have shown that some patients, at least, are protected against bronchospasm induced by exercise. Likewise, the protective effects of ATROVENT against cold air induced bronchospasm have been variable.

Antigen challenge studies have demonstrated that ATROVENT offers some protection against the "early" allergic asthma response, but has no effect on the "late" response.

The Lung Health Study

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

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

Smoking intervention consisted of an intensive 12-session smoking cessation program combining behaviour modification and use of nicotine gum, with continuing 5-year maintenance program to minimize relapse. Two puffs ipratropium bromide was prescribed three times daily from a metered-dose-inhaler.

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

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

Pharmacokinetics

Absorption:

Ipratropium bromide is absorbed quickly after oral inhalation of a nominal dose of 40 mcg administered from a pressurized metered dose inhaler. The peak plasma concentration (mean C_{max} = 32 pg/mL) is reached within 5 minutes after inhalation. The therapeutic effect of ipratropium bromide is produced by a local action in the airways. Time courses of bronchodilation and systemic pharmacokinetics do not run in parallel. The plasma concentration-

versus-time curve was similar to that seen after oral administration, likely reflecting the large fraction of inhaled dose which is deposited on the pharyngeal mucosa and swallowed.

Following inhalation 10 to 30% of a dose is generally deposited in the lungs, depending on the formulation and inhalation technique. The major part of the dose is swallowed and passes the gastro-intestinal tract.

The portion of the dose deposited in the lungs reaches the circulation rapidly (within minutes).

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

Cumulative renal excretion (0-24 hrs) of the parent compound is approximated to 46% of an intravenously administered dose, below 1% of an oral dose and approximately 3 to 13% of an inhaled dose. Based on these data the total systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7 to 28% respectively.

Taking this into account, swallowed dose portions of ipratropium bromide do not relevantly contribute to systemic exposure.

Distribution:
The basic pharmacokinetic parameters describing the disposition of ipratropium were calculated from the plasma level data after i.v. administration. A rapid biphasic decline in plasma was noted for ipratropium. The main metabolites found in urine bind poorly to the muscarinic receptor. The apparent volume of distribution at steady-state (Vdss) is approximately 176 L (≈2.4 L/kg).

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

The known metabolites show very little or no affinity for the muscarinic receptor and have to be regarded as ineffective.

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

After intravenous administration approximately 60% of a dose is metabolized, the major portion probably in the liver by oxidation.

The known metabolites are formed by hydrolysis, dehydration or elimination of the hydroxy-methyl group in the tropic acid moiety.

Excretion:
The half-life of the terminal elimination phase was approximately 1.6 hours.

The total clearance of ipratropium is 2.3 L/minute with a renal clearance of 0.9 L/min.

In an excretion balance study cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 72.1% after intravenous administration, 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was 6.3% following intravenous application, 88.5% following oral dosing and 69.4% after inhalation.

Regarding the excretion of drug-related radioactivity after intravenous administration, the main excretion occurs via the kidneys. The half-life for elimination of drug-related radioactivity (parent compound and metabolites) is 3.6 hours.

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

Special Populations and Conditions

Pediatrics
ATROVENT HFA is recommended for the use in patients 18 years and older.

Hepatic Insufficiency
ATROVENT HFA has not been studied in patients with hepatic insufficiency.

Renal Insufficiency
ATROVENT HFA has not been studied in patients with renal insufficiency.

STORAGE AND STABILITY

The aerosol canister should be stored at room temperature (15-30ºC); the contents are stable up to the expiration date stamped on the label.

SPECIAL HANDLING INSTRUCTIONS

The product should be dispensed in the original container.

Caution: Contents under pressure. Container may explode if heated. Do not place in hot water or near radiators, stoves or other sources of heat. Do not puncture or incinerate container or store at temperatures over 30ºC.

Keep out of reach and sight of children. Avoid spraying in eyes.The product should be kept from freezing.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ATROVENT HFA (ipratropium bromide) pressurized inhalation solution is a metered dose aerosol system which contains a solution of ipratropium bromide and the propellant (1,1,1,2 - Tetrafluoroethane (HFA 134a)), citric acid, ethanol, nitrogen and water. It is supplied as a metal canister containing 200 actuations of ATROVENT with mouthpiece (oral adaptor). Each valve depression delivers 20 mcg ipratropium bromide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

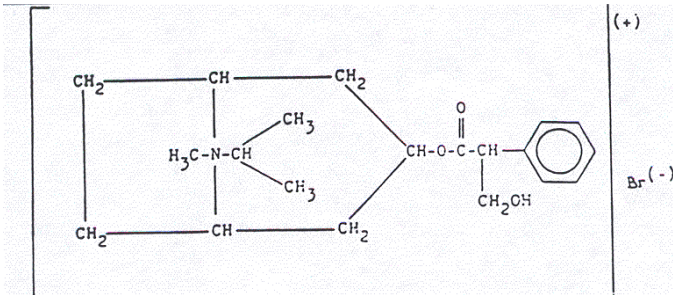
Drug Substance

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

Study demographics and trial design

The efficacy of ATROVENT HFA (ipratropium bromide HFA) pressurized inhalation solution were derived from two randomized, double-blind, controlled clinical studies. These studies enrolled males and females ages 40 years and older, with a history of COPD, a smoking history of > 10 pack-years, and FEV_1<65% and FEV_1/FVC < 70%.

Table 2- Summary of patient demographics for clinical trials in specific indication

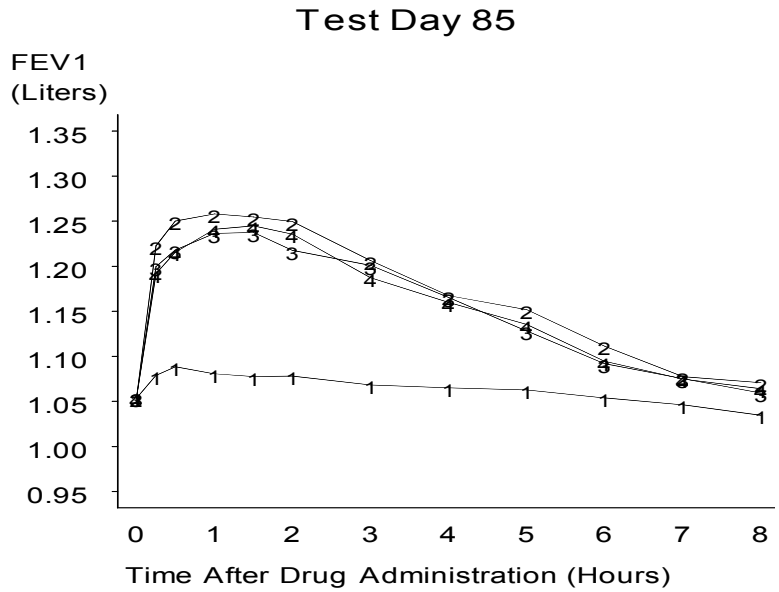
Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
244.1405	Double blind, parallel group	Ipratropium HFA 20 mcg 40 mcg Ipratropium CFC 20 mcg 2 oral inhalations, 4 times daily, 12 weeks	Ipratropium HFA n = 125 n = 127 Ipratropium CFC n = 127 Placebo n = 128	65.5 (41-87)	313 Males 194 Females
244.1408	Double blind, parallel group	Ipratropium HFA 20 mcg Ipratropium CFC 20 mcg 2 oral inhalations, 4 times daily, 12 weeks	Ipratropium HFA n = 118 Ipratropium CFC n = 56	66 (40-83)	123 Males 51 Females

Study results

In a 12-week randomized, double-blind active and placebo controlled trial, 507 patients with COPD were evaluated for bronchodilator efficacy of 40 mcg q.i.d. (n=125) and 80 mcg q.i.d. (n=127) ATROVENT HFA pressurized inhalation solution in comparison to 40 mcg q.i.d (n=127) ATROVENT CFC pressurized inhalation solution and their respective placebos (HFA n=62, CFC n=66).

Serial FEV_1 measurements (shown below as mean FEV_1 changes from test day baseline) on day 85 demonstrated that 2 inhalations of ATROVENT HFA pressurized inhalation solution produced significantly greater improvement in pulmonary function than placebo. ATROVENT HFA pressurized inhalation solution was shown to be clinically comparable to Atrovent CFC pressurized inhalation solution.

Adjusted Mean FEV_1 Over Time on day 85 Using Test Day Baseline as Covariate



1_____1 Placebo(N=128) 2_____2 IB HFA 40 mcg(N=124)
3_____3 IB HFA 80 mcg(N-126) 4_____4 IB CFC 40 mcg(N=127)

Note: IB = Ipratropium Bromide; means are adjusted for center effects and test day baseline FEV1; placebo HFA and CFC groups were combined.

The median time to onset of a 15% increase in FEV1 was between 14 and 17.5 minutes. The median time to peak effect was 90 minutes.

Both the HFA and CFC 40 mcg doses of Ipratropium bromide were equally efficacious as confirmed further by similar confidence intervals around differences in adjusted mean FEV_1AUC_{0-6} (±90mL) on all test days. Table 3 summarizes these equivalence tests.

TABLE 3: SUMMARY OF THE TESTS FOR THERAPEUTIC EQUIVALENCE BETWEEN IPRATROPIUM BROMIDE CFC 40 mcg AND IPRATROPIUM BROMIDE HFA 40 AND 80 mcg – ENDPOINT ANALYSES OF THE INTENT-TO-TREAT DATASET 12-WEEK US COPD TRIAL (244.1405)

	COMPARISON OF IPRATROPIUM BROMIDE CFC 40 mcg TO:					
	Ipratropium bromide HFA, 40 mcg			Ipratropium bromide HFA, 80 mcg		
	Difference	Std Error	90% Confidence Interval	Difference	Std Error	90% Confidence Interval
FEV_1AUC_{0-6}						
Day 1	0.024	0.020	(-0.009, 0.056)	0.045	0.020	(0.013,0.077)
Day 29	-0.012	0.020	(-0.045,0.022)	-0.006	0.020	(-0.039,0.028)
Day 57	-0.015	0.020	(-0.047,0.018)	-0.007	0.020	(-0.039,0.025)
Day 85	0.014	0.020	(-0.019,0.047)	0.002	0.020	(-0.031,0.034)
FEV_1Peak						
Day 1	0.040	0.023	(0.003,0.078)	0.052	0.023	(0.015,0.090)
Day 29	0.000	0.024	(-0.038,0.039)	-0.004	0.023	(-0.043,0.035)
Day 57	-0.001	0.022	(-0.037,0.034)	0.005	0.021	(-0.031,0.040)
Day 85	0.033	0.023	(-0.005,0.072)	0.004	0.023	(-0.034,0.042)

In another 12-week, double-blind clinical study in 174 adults with COPD, ATROVENT HFA pressurized inhalation solution 40 mcg q.i.d. (n=118) was compared to ATROVENT pressurized inhalation solution CFC 40 mcg q.i.d. (n=56). Safety and efficacy of HFA and CFC formulations were shown to be comparable. No significant differences were seen with respect to peak response or onset and duration of therapeutic response.

Therapeutic equivalence was demonstrated when the one-sided confidence interval for the adjusted mean treatment differences for both FEV_1 max and FEV1 AUC_{0-6} was contained within the equivalence region defined as greater than -0.120 L (Table 4). Similar results were found for FVCmax and $FVCAUC_{0-6}$.

TABLE 4: EVALUATION OF THE DIFFERENCE BETWEEN TREATMENT GROUPS WITH RESPECT TO FEV1 MAX AND FEV1 AUC_{0-6}, (INTENT-TO-TREAT DATA SET) 12-WEEK UK COPD TRIAL (244.1408)

Treatment Contrast: HFA-CFC	Difference in Adjusted* Mean (se)	90% Confidence Interval for Difference
FEV_1 max		
Visit 2 (Day 0)	0.0034 (0.0252 L)	-0.0383 L to 0.0451 L
Visit 4 (Day 42)	0.0227 (0.0245 L)	-0.0179 L to 0.0634 L
Visit 6(Day 84)	0.0085 (0.0268 L)	-0.0359 L to 0.0529 L
FEV_1 AUC_{0-6}		
Visit 2 (Day 0)	0.0066 (0.0204 L)	-0.0272 L to 0.0403 L
Visit 4 (Day 42)	0.0452 (0.0211 L)	0.0101 L to 0.0802 L
Visit 6 (Day 84)	0.0096 (0.0236 L)	-0.0295L to 0.0487 L

* Adjusted for test day baseline FEV_1 and center

The bronchodilator efficacy and comparability of ATROVENT HFA vs. ATROVENT CFC were also shown in the one-year safety and efficacy study in 456 COPD patients. Results of this study were similar to the 12-week study mentioned above.

DETAILED PHARMACOLOGY

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

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

When administered to the guinea pig and dog intravenously at an ED_{50} of 0.15-0.40 mcg/kg, ATROVENT abolishes acetylcholine induced bronchospasm with a transient effect on blood pressure. By inhalation, approximately 25 mcg of ipratropium bromide produces a 50% inhibition of acetylcholine induced bronchospasm in the dog with no detectable effect on blood

pressure but with an increased duration of action compared to i.v. administration. Histological evaluation of human bronchial mucosa following chronic inhalation of ipratropium bromide showed no alterations of epithelial, ciliated or goblet cells. Short term mucociliary clearance in normal and bronchitic subjects was not adversely affected by 200 mcg of inhaled ipratropium bromide.

The anticholinergic effects of ipratropium bromide were evaluated in several other organ systems following oral, subcutaneous, intravenous and inhalation administration. In dogs, a 50% increase in heart rate resulted from 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. 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 mcg/puff) was required to produce an 11% increase in heart rate.

Salivary secretion in rat, mouse and dog was effectively inhibited by low parenteral doses of ipratropium bromide (0.001 to 0.032 mg/kg) but when given by the oral route, the effective dose increased over 100-fold. Aerosol administration in dogs of about 65 puffs (0.04 mg/puff) produced a 50% 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.

TOXICOLOGY

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

ACUTE

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.

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 8 days after oral administration. The rather low oral toxicity compared to the higher intravenous toxicity reflects the poor gastro-intestinal absorption.

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.

When administered by inhalation, the minimum lethal dose in the guinea pig was 199 mg/kg and in rats dosed of 11.5 mcg/L/hr q.i.d. or 48 mcg/kg/4 hours did not cause mortality. The oral and intravenous LD_{50} were considerably higher than the minimum lethal dose by inhalation.

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.

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 of 13 weeks using doses of 1.5, 3.0 and 15 mg/kg revealed no pathological changes apart from a dose related inhibition of lacrimation 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

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

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

Four rhesus monkeys inhaled 500 mcg of ipratropium bromide twice a day (total dose 1 mg/day) for 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 mcg/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 l4 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

In inhalation studies up to 6 months in rats, dogs and Rhesus monkeys, the no-observed adverse effect level (NOAEL) was 0.384 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.

Repeated-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.

Intranasal administration for up to 6 months revealed 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.

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 the repeated dose toxicity studies, ipratropium bromide, was locally well tolerated.

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

MUTAGENICITY

In vitro mutagenicity on bacteria (Ames test) did not indicate a mutagenic potential. The results of in vivo assays (micronucleus test, dominant lethal test in mice, cytogenic assay on bone marrow cells of Chinese hamsters), did not demonstrate an increase in rate of chromosomal aberrations.

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 up to 6 mg/kg were performed. These studies demonstrated that ipratropium bromide does not have a tumorgenic or carcinogenic effects.

REPRODUCTIVE STUDIES

Studies to investigate the possible influence of ipratropium bromide on fertility, embryo-fetotoxicity, and peri/postnatal development have been performed on mice, rats and rabbits.

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

In an inhalation teratology study the highest, technically feasible doses for inhalation of the metered aerosol, 1.5 mg/kg/day in rats and 1.8 mg/dg/day in rabbits, showed no adverse effects on litter parameters, and 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.

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PART III: CONSUMER INFORMATION

PrAtrovent® HFA
(Ipratropium Bromide)
Pressurized Inhalation Solution

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

ABOUT THIS MEDICATION

What the medication is used for:
ATROVENT HFA is used to treat the wheezing or shortness of breath caused by COPD (chronic obstructive pulmonary disease which includes chronic bronchitis and emphysema).

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

When it should not be used:
Do not use ATROVENT HFA if you:
- are allergic to ipratropium bromide or other drugs which are anticholinergic (contain atropine or its derivatives), or to any component of ATROVENT HFA (see "**What the non-medicinal ingredients are**").
- are under 18 years of age.

ATROVENT HFA should not be used for the treatment of acute episodes of bronchospasm where rapid response is required. If you get a sudden attack of breathlessness, then you should use an additional fast-acting relief medication which has been provided to you by your doctor.

What the medicinal ingredient is:
Ipratropium bromide

What the non-medicinal ingredients are:
Citric acid, ethanol, propellant (1,1,1,2 - Tetrafluoroethane (HFA 134a)), nitrogen and water.

What dosage forms it comes in:
Pressurized Inhalation Solution 20 mcg/metered dose

WARNINGS AND PRECAUTIONS

BEFORE you use ATROVENT HFA talk to your doctor or pharmacist if you:
- are pregnant or intend to become pregnant;
- are breast feeding;
- have any other health problems;
- have eye problems, such as glaucoma, or eye pain;
- are taking any other medications including eye drops or those you can buy without a prescription;
- have difficulty urinating;
- have cystic fibrosis;
- have any allergies or reactions to foods, drugs or aerosols.

ATROVENT HFA is not recommended for use in children and adolescents under 18 years of age.

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

ATROVENT HFA 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

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

The following may interact with ATROVENT HFA:
- other anticholinergic drugs, such as ipratropium bromide, tiotropium, glycopyrronium, aclidinium, umeclidinium;
- xanthine derivatives such as theophylline;
- $beta_2$-adrenergic agents such as salbutamol.

PROPER USE OF THIS MEDICATION

- **ATROVENT HFA pressurized inhalation solution has been prescribed to treat your current condition. DO NOT give it to other people.**
- **DO NOT exceed the number of puffs prescribed by your doctor.**
- **DO NOT use the inhaler more often than your doctor recommends.**
- **DO NOT take any other medication without your doctor's advice. Tell any *other* doctor, dentist, or pharmacist with whom you consult that you are using ATROVENT HFA pressurized inhalation solution.**

- **When using your ATROVENT HFA pressurized inhalation solution with the standard mouthpiece, make sure you do not spray the aerosol into your eyes.**
- **The container is under pressure and should not be opened by force or exposed to temperatures above 50ºC.**

Usual adult dose:

The usual dose is 2 puffs taken up to 3 or 4 times daily. Doses must be taken at least 4 hours apart. Some people may need up to 4 puffs at a time during early treatment. Do not use more than 12 puffs per day.

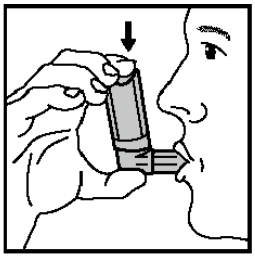
How to Use Your ATROVENT HFA Pressurized Inhalation Solution:

The plastic mouthpiece has been especially designed for use with ATROVENT HFA pressurized inhalation solution to ensure that you always get the right amount of the medicine. The mouthpiece must never be used with any other pressurized inhalation solution nor must the ATROVENT HFA pressurized inhalation solution be used with any mouthpiece other than the one supplied with the product.

If you are troubled with mucus try to clear your chest as completely as possible by coughing before you use ATROVENT HFA pressurized inhalation solution. This will allow the ATROVENT HFA pressurized inhalation solution to pass more deeply into your lungs.

1. Remove the protective cap from the inhaler.

2. Press down on the top of the inhaler twice to release 2 puffs into the air before the inhaler is used for the first time. If you have not used the inhaler for more than 3 days then only one puff needs to be released before the inhaler is ready to use.

3. 

Breathe out as completely as possible.
a) Place the mouthpiece into your mouth and close your lips around it. Keep your teeth apart and your tongue flat to allow free flow the medication into your lungs. The arrow and the base of the container should be pointing upwards.

b) Press down on the top of the inhaler and breathe in deeply through your mouth at the same time.

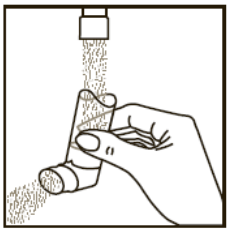
4. Hold your breath for a few seconds, then breathe out slowly.

5. If your doctor has recommended a second puff, wait about one minute and then repeat steps 3 and 4.

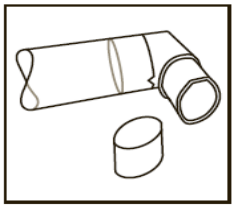
6. Replace the protective plastic cap.

Care of the Mouthpiece/Canister:

The container is not transparent. It is therefore not possible to see when it is empty. The inhaler will deliver **200** doses. When the labelled number of doses have been used (usually after 3 weeks when used as recommended) the inhaler may still appear to contain a small amount of fluid. The inhaler should, however, be replaced so that you can be certain that you are getting the right amount of your medicine in each actuation.



Clean your mouthpiece at least once a week.
It is important to keep the mouthpiece of your inhaler clean to ensure that medicine does not build up and block the spray.
For cleaning, first take off the dust cap and remove the canister from the mouthpiece. Rinse warm water through the mouthpiece until no medication build-up and/or dirt is visible.



After cleaning shake out the mouthpiece and let it air-dry **without** using any heating system. Once the inhaler is dry, replace the canister and the dust cap.

Overdose:

If you think you have taken too much ATROVENT HFA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

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

Side effects may include:
- Headache, dizziness;
- Nausea (feeling sick), digestive problems like constipation, diarrhea, vomiting;
- Impaired voice sounds;
- Throat irritation, cough, dry mouth or throat, bad taste – sucking on a sour candy or rinsing your mouth may help.

If any of these affects you severely, tell your doctor, nurse or pharmacist.

Check with your doctor if the dry mouth or bad taste persist or if you experience constipation for a prolonged period of time.

Stop taking the medication and tell your doctor immediately if you notice any of the following:

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

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

Symptom / effect		Talk with your doctor or pharmacist immediately		Stop taking drug and and seek immediate medical help
		Only if severe	In all cases	
Uncommon	**Bronchospasm:** increased wheezing or tightness in the chest, difficulty in breathing, coughing bouts			✓
	Shortness of breath			✓
	Skin rash			✓
	Allergic reaction: rash, hives, swelling of the face, lips, mouth, tongue or throat, difficulty swallowing or breathing, choking due to swelling of the muscles around the voice box			✓
	Fast or irregular heart beat: a feeling that your heart is beating fast, or skipping a heartbeat			✓

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

Symptom / effect		Talk with your doctor or pharmacist immediately		Stop taking drug and and seek immediate medical help
		Only if severe	In all cases	
	Eye Disorders: new or worsened pressure in your eyes, eye pain or discomfort, blurred vision, seeing halos or rainbows around items or red eyes			✓
	Urinary Retention: difficulty and pain when passing urine, urinating frequently, urination in a weak stream or drips			✓

This is not a complete list of side effects. For any unexpected effects while taking* ATROVENT HFA *contact your doctor or pharmacist.

HOW TO STORE IT

- **Keep this medication out of the reach and sight of children.**
- Store at room temperature (15-30ºC). Keep from freezing.
- Container may explode if heated. Contents under pressure. Do not place in hot water or near radiators, stoves, or other sources of heat. Do not puncture or incinerate container or store at temperatures over 30ºC.
- The expiry date of this medicine is printed on the label. Do not use the medicine after this date.

Reporting Side Effects

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

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

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

MORE INFORMATION

If you want more information about Atrovent HFA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp), the manufacturer's website (https://www.boehringer-ingelheim.ca), or by calling the manufacturer, Boehringer Ingelheim (Canada) Ltd., at: 1-800-263-5103, extension 84633.

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd. The information in this leaflet is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

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