

AUSTRALIAN PRODUCT INFORMATION – ATROVENT® (ipratropium bromide monohydrate) pressurised inhalation aerosol

1 NAME OF THE MEDICINE

ipratropium bromide monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ATROVENT contains ipratropium bromide monohydrate 21 micrograms [equivalent to 20 micrograms of ipratropium bromide] per actuation.

Excipients with known effect

Contains 8.415 mg ethanol absolute per actuation.

For full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ATROVENT is a pressurised inhalation solution.

Each ATROVENT metered dose aerosol can is filled with a clear, colourless liquid, free from suspended particles.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ATROVENT metered aerosol is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with asthma and chronic obstructive pulmonary disease (COPD).

4.2 DOSE AND METHOD OF ADMINISTRATION

Note: One puff (metered dose) of ATROVENT contains 21 micrograms of ipratropium bromide monohydrate [equivalent to 20 micrograms of ipratropium bromide].

If the response to the treatment is inadequate, medical advice should be sought so that appropriate measures can be taken. It is advisable not to greatly exceed the recommended daily dose as this suggests additional therapeutic modalities may be needed.

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. In the case of acute or rapidly worsening dyspnoea, a doctor should be consulted immediately.

Adults

Two puffs 3 to 4 times daily, although some patients may need up to 4 puffs at a time to obtain maximum benefit during early treatment.

Children

Administration to children should be supervised by an adult.

6-12 years: One or two puffs 3 to 4 times daily

Under 6 years: One puff 3 times daily

Patients with poor inhaler technique will benefit from the consistent use of a spacer device with their metered aerosol. Use of a spacer will also decrease the amount of drug deposited in the mouth and back of the throat, and therefore reduce the incidence of local irritation in susceptible patients.

In those people using a spacer, a change in formulation of the drug used, or a change in the make of the spacer may be associated with alterations in the amount of drug delivered to the lungs. The clinical significance of these alterations is uncertain. However, in these situations, the person should be monitored for any change in their condition.

If using a spacer, the patient should be instructed to breathe in and out after each actuation of the drug into the spacer. Any delay should be kept to a minimum.

Static on the walls of the spacer may cause variability in drug delivery. Patients should be instructed to wash the spacer in warm water and detergent and allow it to dry without rinsing or drying with a cloth. This should be performed before initial use of the spacer and at least monthly thereafter.

The ATROVENT metered aerosol can must only be used with the mouthpiece supplied with the product.

4.3 CONTRAINDICATIONS

Known hypersensitivity to atropine or its derivatives (such as the active substance ipratropium bromide), or to any of the other ingredients of ATROVENT.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity

Immediate hypersensitivity reactions may occur after administration of ATROVENT, as demonstrated by rare cases of urticaria, angio-oedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

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.

Anticholinergic effects

Like other drugs with anticholinergic activity, ipratropium bromide should be avoided or used with caution in patients where atropine-like effects may precipitate or exacerbate a pre-existing clinical condition. Patients at particular risk are those with eyes with narrow iridocorneal angles as acute angle-closure glaucoma may be precipitated, or patients with a tendency towards urinary retention or constipation.

Ocular complications

ATROVENT should be used with caution in patients predisposed to narrow-angle glaucoma.

There have been isolated reports of ocular complications (mydriasis, increased intraocular pressure, acute angle glaucoma, eye pain) as a result of direct eye contact of ipratropium bromide formulations. Thus, patients must be instructed in the correct administration of ATROVENT and warned not to allow the aerosol to enter the eyes.

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

Renal and urinary effects

ATROVENT should be used with caution in patients with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder-neck obstruction).

Gastro-intestinal motility disturbances

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

Propellants

ATROVENT CFC-free metered aerosol contains the hydrofluoroalkane propellant norflurane. In animal studies, norflurane has been shown to have no significant pharmacological effects, except at very high exposure concentrations when narcosis and a relatively weak sensitisation to the arrhythmogenic effects of catecholamines were found. The potency of the cardiac sensation was less than that of trichloromethane.

Excessive inhalation of the aerosol should, however, be avoided as this carries a potential hazard, both from the propellant as well as from overdosage of the active therapeutic agent contained in the formulation. The recommended dose should not be exceeded and the patients should be so informed.

Use in the elderly

No data available

Paediatric use

Paediatric patients can use ATROVENT metered aerosol at the recommended dose.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The chronic co-administration of ATROVENT inhalation with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of ATROVENT with other anticholinergic drugs is not recommended.

Beta-adrenergics and xanthine preparations may intensify the bronchodilatory effect of ATROVENT.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Clinical data on fertility are not available for ipratropium bromide.

Use in Pregnancy (Category B1)

Care is recommended during pregnancy, particularly in the first trimester. The safety of ATROVENT during pregnancy has not been established. The benefits of using ATROVENT when pregnancy is confirmed or suspected must be weighed against possible hazards to the fetus. Studies in rats, mice and rabbits showed no embryo-toxic nor teratogenic effects.

Use in Lactation

No specific studies are available to determine the excretion of ipratropium bromide in human breast milk. Although lipid-insoluble quaternary cations pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to an important extent, especially when administered by inhalation. However, as many drugs are excreted into breast milk, caution should be exercised when ATROVENT is administered to breastfeeding mothers.

4.7 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. 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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. The most frequent side effects reported in clinical trials were headache, dizziness, throat irritation, cough, gastrointestinal disorders (including constipation, diarrhoea, gastrointestinal motility disorder, dry mouth, nausea, stomatitis, oedema mouth and vomiting).

If the substance enters the eyes by inappropriate handling, mild and reversible disturbance of accommodation may occur. Other ocular complications have also been reported (see section 4.4 Special warning and precautions for use). However, acute angle-closure glaucoma has been reported following direct eye contact.

Allergic-type reactions such as angio-oedema of the tongue, lips and face may also occur.

The following adverse reactions have been reported during use of ATROVENT in clinical trials and during the post-marketing experience at the following frequency: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$).

System Organ Class	Common	Uncommon	Rare
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 (including reports of change in bowel motions and habits, dyspepsia, gastrointestinal reflux and flatulence) ¹	diarrhoea, constipation, vomiting, stomatitis, oedema mouth	
Skin and subcutaneous tissue disorders		rash, pruritus, angioedema	urticaria
Renal and urinary disorders		urinary retention	

¹ The definition is based on a post-hoc review of all ADR terms reported in the defined study dataset. Terms that report a clinically related term with greater medical specificity were excluded and added to the more specific term (e.g. "nausea", "vomiting").

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

No symptoms specific to over-dosage have been encountered. In view of the wide therapeutic range and topical administration of ATROVENT inhalation solutions, no serious anticholinergic symptoms are to be expected. Minor systemic manifestations of anticholinergic action, including dry mouth, visual accommodation disorder and tachycardia may occur.

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Anticholinergics. ATC Code: R03BB01

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

ATROVENT is an anticholinergic bronchodilator. It appears to inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagal nerve. Anticholinergics prevent the increase in intracellular calcium concentration caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. Bronchodilation following inhalation of ATROVENT is a local, site specific effect at the bronchial smooth muscle. ATROVENT has no deleterious effect on airway mucous secretion or mucociliary clearance.

The time course of action of ATROVENT also differs from the β_2 agonists in that although the onset of bronchodilator response is seen within 3-5 minutes of administration, peak response is not reached until 1.5-2 hours after inhalation. The duration of significant bronchodilator action is up to 6 hours.

ATROVENT may be used in combination with β_2 agonists. There is evidence that in patients who respond to ATROVENT, the concurrent administration of ATROVENT and β_2 agonists produces a greater relief of bronchospasm than either drug given alone.

Clinical Trials

The use of ATROVENT metered aerosol, delivered using CFC-containing propellants, is well established in clinical practice. A clinical programme has been conducted to demonstrate the therapeutic equivalence of ATROVENT CFC-free and CFC-containing metered aerosols. The safety and efficacy of ATROVENT CFC-free metered aerosol, in chronic obstructive pulmonary disease (COPD) and asthma, was established from the results of one 12-month and two 12-week safety and efficacy trials conducted in COPD, a 12-week study in asthmatic adults and a 12-week safety study in asthmatic children.

A randomised, open-label, parallel design 12-month study in COPD patients, compared the safety and efficacy of ATROVENT metered aerosols containing either CFCs (n=151) or norflurane (n=305). Time profiles of forced expiratory volume in one second (FEV₁) mean changes from baseline on all test days demonstrated the efficacy and overall comparability of the ATROVENT CFC-free and CFC-containing aerosols. The two formulations were generally comparable throughout the trial with respect FEV₁ area under the curve for 0 to 6 hours (AUC₀₋₆). The overall safety profile indicated that both treatments were well tolerated.

A 12-week, double-blind, randomised trial in COPD patients, comparing safety and efficacy of ATROVENT CFC-free and CFC-containing metered aerosols (n= 118 and 56 respectively), concluded there were no differences in respect of changes in morning and evening peak expiratory flow rates. In addition, a randomised, double-blind, placebo and active controlled study of 12-weeks duration in COPD patients, concluded that ATROVENT CFC-free 42 μ g (n=125) and 84 μ g (n=127) were significantly more effective than placebo in terms of adjusted mean FEV₁ AUC₀₋₆ and peak response. For each trial, the safety profiles of both formulations were found to be comparable.

A multi-dose comparison of ATROVENT CFC-free with CFC-containing metered aerosol in a 12-week, double-blind, parallel group study of adult patients with bronchial asthma, demonstrated that patients who switched to the CFC-free aerosol (n=159) from the CFC-containing aerosol (n=75), had no change in daily peak expiratory flow rate values and usage of rescue medication. Similar results were observed in paediatric patients with bronchial asthma in a 12-week, double-blind, parallel group study comparing ATROVENT CFC-free (n=133) with the ATROVENT CFC-containing aerosol (n=58). For both studies, the adverse event profile of both formulations was very similar for all events reported.

In summary the data shows that ATROVENT CFC-free metered aerosol is comparable in terms of efficacy and safety to the CFC-containing formulation.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following inhalation, 10 to 30% of the dose (depending on the formulation and inhalation technique) is generally deposited in the lungs. The major part of the dose is swallowed and passes into the gastrointestinal tract. Due to the low gastrointestinal absorption of ipratropium bromide, the bioavailability of the portion of the dose swallowed, accounts for approximately 2% of the dose. This fraction of the dose does not make a relevant contribution to the plasma concentrations of the active ingredient. The portion of the dose deposited in the lungs reaches the circulation rapidly (within minutes) and has nearly complete systemic availability.

From renal excretion data (0-24 hours), the total systemic bioavailability (pulmonary and gastrointestinal portions) of inhaled doses of ipratropium bromide was estimated to be in the range 7 to 28%. This is also a valid range for inhalation from ATROVENT CFC-free because the kinetic results (renal excretion, AUC and C_{max}) from the CFC-free and the CFC-containing formulations are approximately comparable.

Distribution

Kinetic parameters describing the disposition of ipratropium bromide were calculated from plasma concentrations after intravenous administration. A rapid biphasic decline in plasma concentrations is observed. The volume of distribution (V_z) is 338 L (approximately 4.6 L/kg). The half-life of the terminal elimination phase is about 1.6 hours. The drug is less than 20% bound to plasma proteins. The ipratropium ion does not cross the blood-brain barrier, consistent with the ammonium structure of the molecule. The main urinary metabolites bind poorly to the muscarinic receptor and have no activity.

Metabolism

The mean total clearance of the drug is 2.3 L/min. The major portion, approximately 60% of the systemically available dose, is eliminated by metabolic degradation, probably in the liver.

Excretion

Approximately 40% of the systemically available dose is cleared via urinary excretion, corresponding to an experimental renal clearance of 0.9 L/min. After oral dosing less than 1% of the dose is renally excreted, indicating an insignificant absorption of ipratropium bromide from the gastrointestinal tract.

In excretion balance studies, after intravenous administration of a radioactive dose, less than 10% of the drug-related radioactivity (including parent compound and all metabolites), are excreted via the biliary-faecal route. The dominant excretion of drug-related radioactivity occurs via the kidneys.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Carcinogenicity

Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic potential at dietary doses up to 6 mg/kg/day for ATROVENT.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

In addition to ipratropium bromide, ATROVENT metered aerosol contains citric acid, purified water, ethanol absolute and the non-chlorofluorocarbon (CFC-free) propellant norflurane (also known as HFA [hydrofluoroalkane] 134a).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

Avoid storage in direct sunlight or heat. Do not puncture or incinerate, as canister may explode.

6.5 NATURE AND CONTENTS OF CONTAINER

ATROVENT is contained in a 17 mL stainless steel metered dose aerosol can complete with mouthpiece, containing 200 metered doses.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

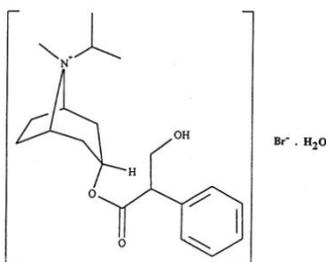
Ipratropium bromide is a synthetic quaternary ammonium compound, chemically related to atropine. The addition of an N-isopropyl group distinguishes the molecule from atropine and is responsible for a lower lipid solubility.

Ipratropium bromide is a white or off-white crystalline substance. It is freely soluble in methanol, soluble in water and sparingly soluble in ethanol 96% (v/v).

The chemical name for ipratropium bromide (as monohydrate) is (1R,3r,5S,8r)-3-[(RS)-(3-hydroxy-2-phenyl-propanoyl)-oxy]-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane bromide monohydrate.

The molecular formula is C₂₀H₃₀NO₃Br.H₂O and the molecular weight is 430.4.

Ipratropium bromide has the following structural formula:



CAS number

66985-17-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

5 May 2003

10 DATE OF REVISION

28 November 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatting based on new Form for PI
2, 3, 4.2	'ipratropium bromide' updated to its AAN 'ipratropium bromide monohydrate' 'ipratropium bromide (anhydrous)' updated to its AAN 'ipratropium bromide'
6.1	'citric acid-anhydrous' updated to its AAN 'citric acid' 'water-purified' updated to its AAN 'purified water' 'ethanol-absolute' updated to its AAN 'ethanol absolute'
8	Inclusion of company website address
9	Amended as per ARTG entry