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

1. NAME OF THE MEDICINE

ipratropium bromide monohydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of ATROVENT Inhalation Solution contains ipratropium bromide monohydrate 261 micrograms (equivalent to 250 micrograms ipratropium bromide).

Each 1 mL of ATROVENT UNIT DOSE VIAL (UDV) contains ipratropium bromide monohydrate 261 micrograms (equivalent to 250 micrograms ipratropium bromide).

Each 1 mL of ATROVENT ADULT UNIT DOSE VIALS (UDV) contains ipratropium bromide monohydrate 522 micrograms (equivalent to 500 micrograms ipratropium bromide).

Excipients with known effect:

ATROVENT Inhalation Solution contains 0.1 mg benzalkonium chloride in each mL and disodium edetate.

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

3. PHARMACEUTICAL FORM

ATROVENT is an inhalation solution.

ATROVENT Inhalation Solution - clear, colourless or almost colourless liquid, free from suspended particles in multidose bottle. Contains benzalkonium chloride as the preservative.

ATROVENT UDV - preservative free, clear, colourless or almost colourless liquid, free from suspended particles.

ATROVENT ADULT UDV - preservative free, clear, colourless or almost colourless liquid, free from suspended particles.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Moderate asthmatic attacks; chronic forms of asthma; asthma in patients with diminished cardiac reserve; chronic obstructive bronchitis with bronchospasm; bronchospasm during or after surgery, use during assisted ventilation with a respirator.

Administration of ATROVENT via a nebuliser is intended for those patients who cannot use a metered dose aerosol.

4.2 DOSE AND METHOD OF ADMINISTRATION

ATROVENT solution can be administered via a range of commercially available nebulising devices. Where wall oxygen is available, solutions are best administered at a flow rate of 6-8 litres per minute.

Dosage is dependent on the mode of inhalation and the quality of nebulisation. The duration of inhalation can be controlled by the dilution volume. It is advisable not to greatly exceed the recommended daily dose as this suggests additional therapeutic modalities may be needed.

Note

20 drops from the dropper insert in the multidose bottle equal approximately 261 micrograms of ipratropium bromide monohydrate (equivalent to 250 micrograms ipratropium bromide).

The dosage should be adapted to the individual requirements of the patient; patients should also be kept under medical supervision during treatment. Unless otherwise prescribed, the following doses are recommended:

Adults

The recommended dose is 261-522 micrograms [equivalent to 250-500 micrograms ipratropium bromide], 4 times daily, diluted to 2-3 mL with normal saline, and nebulised until the entire volume of solution is consumed. Daily dose exceeding 2.088 mg (equivalent to 2 mg ipratropium bromide) in adults should be given under medical supervision.

In cases of moderate bronchospasm or with assisted ventilation, a dose in the lower range of 261 micrograms (equivalent to 250 micrograms ipratropium bromide) is recommended. In more severely distressed patients, 522 micrograms ipratropium bromide monohydrate (equivalent to 500 micrograms ipratropium bromide) has been shown to produce optimal bronchodilation.

ATROVENT can be administered combined with an inhaled β_2-agonist.

Children

The recommended dose is 261 micrograms (equivalent to 250 micrograms ipratropium bromide), 4 times daily, diluted to 2-3 mL with normal saline and nebulised until the entire volume of solution is consumed. Daily dose exceeding 1.044 mg (equivalent to 1 mg ipratropium bromide) in children ≤12 years of age should be given under medical supervision.

ATROVENT can be administered combined with an inhaled β_2 agonist.

It is advisable not to greatly exceed the recommended daily dose.

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 (difficulty in breathing) a doctor should be consulted immediately.

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 (excipients are listed in section 6.1 List of excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

ATROVENT Inhalation Solution contains 0.1 mg benzalkonium chloride in each mL.

Benzalkonium chloride may cause wheezing and breathing difficulties. Patients with asthma are at an increased risk for these adverse events.

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 monohydrate 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 aerolised ipratropium bromide monohydrate either alone or in combination with an adrenergic β_2 agonist. Thus, patients must be instructed in the correct administration of ATROVENT and warned not to allow the solution or mist to enter the eyes. A nebuliser mask must be fitted properly during inhalation.

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.

Local effects

ATROVENT Inhalation Solution in the multidose bottle contains benzalkonium chloride and disodium edetate. When inhaled these agents may cause bronchospasm in sensitive patients with hyper reactive airways. If the multidose nebulising solution is prescribed, it is suggested that patients be monitored for their FEV1, and if the FEV1 falls, therapy with the preservative free Unit Dose Vials or Metered Dose Aerosol should be used.

Use in the elderly

No data available

Paediatric use

Paediatric patients can use ATROVENT inhalation 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.

The risk of acute glaucoma in patients with a history of narrow-angle glaucoma (see section 4.4 Special warnings and precautions for use) may be increased when nebulised ipratropium bromide monohydrate and beta-mimetics are administered simultaneously.

Physical Compatibility

ATROVENT Inhalation Solutions and disodium cromoglycate inhalation solutions that contain the preservative benzalkonium chloride should not be administered simultaneously in the same nebuliser as precipitation may occur.

ATROVENT UDVs and disodium cromoglycate inhalation solutions should not be administered simultaneously in the same nebuliser.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Clinical data on fertility are not available for ipratropium bromide monohydrate.

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 foetus. 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 warnings 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 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 (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥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 overdosage 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 disturbances and tachycardia may occur.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacotherapeutic group: Anticholinergics
ATC Code: R03BB01

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 primarily 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 $ß_2$ agonists produces a greater relief of bronchospasm than either drug given alone.

ATROVENT inhibits acetylcholine-induced bronchospasm and provides partial protection against histamine and allergen-induced bronchospasm.

Clinical trials

No data available

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

ATROVENT Inhalation Solution - multidose bottles and ATROVENT UDVs contain sodium chloride, hydrochloric acid and purified water. The multidose solution also contains benzalkonium chloride as preservative and disodium edetate as stabiliser.

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 the bottles at below 30ºC. After opening the multidose bottle, the solution should be used as soon as possible and any unused solution should be discarded after 28 days.

Store the unopened Unit Dose Vials (UDV) at below 25ºC. Protect from light. Diluted solutions should be freshly prepared before use and any solution remaining in the nebuliser, on completion of inhalation, should be discarded.

6.5 NATURE AND CONTENTS OF CONTAINER

ATROVENT Inhalation Solution are available in glass bottles of 20 mL.

ATROVENT UDV are available in LDPE vials; packs of 10* or 30 vials of 1 mL.

ATROVENT Adult UDV are available in PE vials; packs of 10* or 30 vials of 1 mL.

*Not currently distributed in Australia.

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

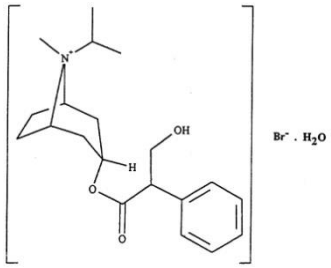
Ipratropium bromide monohydrate is a synthetic quaternary ammonium compound, chemically related to atropine. The addition of an N-isopropyl group distinguishes the molecule from atropine and is responsible for a lower lipid solubility.

Ipratropium bromide monohydrate 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 $C_{20}H_{30}NO_3Br.H_2O$ and the molecular weight is 430.4.

Ipratropium bromide monohydrate 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

ATROVENT Inhalation Solution: 18 November 1992

ATROVENT UDV: 26 September 1991

ATROVENT Adult UDV: 16 December 1996

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
All	IHIN update: ipratropium bromide to ipratropium bromide monohydrate; ipratropium bromide anhydrous to ipratropium bromide
2	Benzalkonium chloride added as an excipient with known effect
4.4	Revision of benzalkonium chloride warning
6.1	AAN update: water-purified to purified water
8	Inclusion of company website address
9	Amended as per ARTG entry