# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

ATROVENT aerosol inhaler 20 micrograms/metered dose.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ATROVENT CFC free pressurised inhalation solution: each actuation contains 0.021 mg ipratropium bromide monohydrate corresponding to 0.020 mg ipratropium bromide anhydrous.

Excipient with known effect:

Contains 8.415 mg of ethanol (anhydrous) in each actuation.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Aerosol inhaler, metered dose

ATROVENT is a solution type formulation with the active ingredient, ipratropium bromide, completely dissolved in a blend of the propellant, ethanol and water. It is a clear, colourless liquid, free from suspended particles filled in a metal container with a metering valve.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ATROVENT is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis, emphysema and asthma.

### 4.2 Dose and method of administration

The dosage should be adapted to the individual requirements and the patients should be kept under medical supervision during treatment. Unless otherwise prescribed, the following dosages are recommended for adults and children over 12 years of age:

| | |
|---|---|
| Adults: | Usually 2 metered doses 4 times daily.<br>Some patients may need up to 4 puffs at a time to obtain maximal benefit during early treatment. Since a requirement for increasing doses suggests that additional therapeutic modalities may be needed, a total daily dose of 12 puffs should generally not be exceeded. |
| Children 6-12 years: | Usually 1 or 2 puffs, 3 times daily. |
| Children under 6 years: | Usually 1 puff, 3 times daily. |

In order to ensure that the inhaler is used correctly, administration should be supervised by an adult.

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 dyspnea a physician should be consulted immediately. It is advisable not to exceed the recommended daily dose during either acute or maintenance treatment.

For acute exacerbations of chronic obstructive pulmonary disease treatment with ipratropium bromide inhalation solution may be indicated.

Because of insufficient information in children ATROVENT pressurised inhalation solution should only be used on medical advice and under the supervision of an adult.

## 4.3 Contraindications

ATROVENT is contraindicated in patients with known hypersensitivity to atropine or its derivatives (such as the active substance ipratropium bromide) or to any other component of the product.

## 4.4 Special warnings and precautions for use

Hypersensitivity
Immediate hypersensitivity reactions may occur after administration of ATROVENT pressurised inhalation solution, as demonstrated by rare cases of rash, urticaria, angio-oedema, oropharyngeal oedema, bronchospasm 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.

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

There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic beta2-agonist, has come in contact with the 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 narrow-angle glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately.

Patients must be instructed in the correct administration of ATROVENT pressurised inhalation solution.

Care must be taken not to allow the mist to enter into the eyes. Since the pressurised inhalation solution is applied via mouth piece and manually controlled, the risk for the mist entering the eyes is limited.

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 gastro-intestinal motility disturbances.

Alcohol content
ATROVENT contains about 8 mg of alcohol (ethanol) in each actuation. The amount in each actuation of this medicine is equivalent to less than 1 ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

## 4.5 Interaction with other medicines and other forms of interaction

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.

ATROVENT has been concomitantly used with other drugs commonly used in the treatment of chronic obstructive pulmonary disease, including sympathomimetic bronchodilators, methylxanthines, steroids and disodium cromoglycate without evidence of deleterious medical interactions.

The risk of acute glaucoma in patients with a history of narrow-angle glaucoma (see Warnings and Precautions) may be increased when nebulised ipratropium bromide and beta-mimetics are administered simultaneously.

## 4.6 Fertility, pregnancy and lactation

Pregnancy (Category B1)
The safety of ATROVENT during human pregnancy has not been established. The benefits of using ATROVENT during a confirmed or suspected pregnancy must be weighed against possible hazards to the unborn child. Nonclinical studies have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man.

Breast-feeding
It is not known whether ipratropium bromide is excreted into breast milk. But it is unlikely that ipratropium bromide would reach the infant to an important extent, especially when administered by inhalation. However, caution should be exercised when ATROVENT is administered to nursing mothers.

Fertility
Clinical data on fertility are not available for ipratropium bromide. Nonclinical studies performed with ipratropium bromide showed no adverse effect on fertility (Further Information see Section 5.3 Preclinical safety data).

## 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.

## 4.8 Undesirable effects

Summary of the safety profile
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, throat irritation, cough, dry mouth, gastro-intestinal motility disorders (including constipation, diarrhoea and vomiting), nausea, and dizziness.

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/}

### 4.9 Overdose

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

No symptoms specific to overdosage have been encountered. In view of the wide therapeutic range and topical administration of ATROVENT pressurised inhalation solution, no serious anticholinergic symptoms are to be expected. Minor systemic manifestations of anticholinergic action, including dry mouth, visual accommodation disorder and increase of heart rate may occur.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anticholinergics
ATC Code: R03BB01

Trials with a treatment duration of up to three months involving adult asthmatics and COPD patients, and asthmatic children, in which the HFA formulation and the CFC formulation have been compared have shown the two formulations to be therapeutically equivalent.

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.

In controlled 90 day studies in patients with bronchospasm associated with chronic obstructive pulmonary disease (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.

In controlled 90 day studies in patients with bronchospasm associated with asthma, significant improvements in pulmonary function (FEV1 increases of 15%) occurred in 51% of the patients.

Non-clinical and clinical evidence suggest no deleterious effect of ATROVENT on airway mucous secretion, mucociliary clearance or gas exchange.

## 5.2 Pharmacokinetic properties

Absorption

The therapeutic effect of ATROVENT is produced by a local action in the airways. Time courses of bronchodilation and systemic pharmacokinetics do not run in parallel.

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).

Cumulative renal excretion (0-24 hrs) of the parent compound is 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

Kinetic parameters describing the disposition of ipratropium were calculated from plasma concentrations after i.v. administration. A rapid biphasic decline in plasma concentrations is observed. The apparent volume of distribution at steady-state (Vdss) is approximately 176 L (≈ 2.4 L/kg). The drug is minimally (less then 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.

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

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

Elimination
The half-life of the terminal elimination phase is approximately 1.6 hours.

Ipratropium has a mean total clearance of 2.3 L/min and 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 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was 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.

## 5.3 Preclinical safety data

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

Single-dose toxicity
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 LD50 values for the mouse, rat and rabbit were 1585, 1925 and 1920 mg/kg, respectively. The intravenous LD50 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.

Repeat-dose toxicity
Repeat-dose toxicity studies have been performed in rats, rabbits, dogs and Rhesus monkeys.

In inhalation studies up to 6 months in rats, dogs and Rhesus monkeys, the No Observed Adverse Effect Level (NOAEL) was 0.38 mg/kg/day, 0.18 mg/kg/day and 0.8 mg/kg/day, respectively. Dry oral mucosa and tachycardia were noted in the dogs. No substance-related histopathological lesions were observed in the broncho-pulmonary system or in any other organs. In the rat, the NOAEL after 18 months of oral administration was 0.5 mg/kg/day.

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.

Local tolerance
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.

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

Genotoxicity and carcinogenicity
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).

No tumorigenic or carcinogenic effects were demonstrated in long term studies in mice and rats.

Reproductive and developmental toxicity
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.

The highest, technically feasible doses for inhalation of the pressurised inhalation solution, 1.5 mg/kg/day in rats and 1.8 mg/kg/day in rabbits, showed no adverse effects on reproduction.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Norflurane
Ethanol
Purified Water
Citric acid
Nitrogen

## 6.2 Incompatibilities

None known.

## 6.3 Shelf life

36 months unopened stored at or below 25°C.

## 6.4 Special precautions for storage

Stored at or below 25ºC. Protect from direct sunlight, heat and frost.

## 6.5 Nature and contents of container

17 mL stainless steel pressurised container with a 50 µL metering valve and oral adaptor. Each canister contains 200 actuations.

## 6.6 Special precautions for disposal and other handling

Only emptied containers should be disposed.

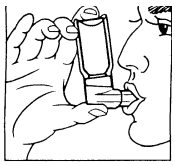
Instructions for Use/Handling

The correct administration is essential for successful therapy.

Before first time use: Depress the valve twice before the inhaler is used.

Before each use the following rules should be observed:

1. Remove protective cap.
2. Breathe out deeply.
3. Hold the inhaler as shown in Figure 1, and close lips over the mouthpiece.
   The arrow and the base of the container should be pointing upwards.



(Figure 1)

4. Breathe in as deeply as possible, pressing the base of the canister firmly at the same time, this releases one metered dose. Hold the breath for a few seconds, then remove the mouthpiece from the mouth and breath out.
   The same action should be repeated for a second inhalation.
5. Replace the protective cap after use.
6. After not using the inhaler for three days the valve has to be actuated once.

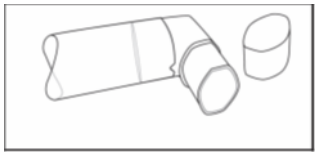
The container is not transparent. It is therefore not possible to see when it is empty. The inhaler will deliver 200 puffs. When the labelled number of doses have been used (usually after 3 weeks when used as recommended) the canister may still appear to contain a small amount of fluid. The inhaler should, 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 (see Figure 2).

(Figure 2)

After cleaning shake out the mouthpiece and let it air-dry without using any heating system. Once the mouthpiece is dry, replace the canister and the dust cap (see Figure 3).



(Figure 3)

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

The container is under pressure and should by no account be opened by force or exposed to temperatures above 50ºC.

## 7. MEDICINE SCHEDULE

Prescription Medicine

## 8. SPONSOR

Boehringer Ingelheim (N.Z.) Limited
PO Box 76-216
Manukau City
Auckland
NEW ZEALAND

Ph: 0800 802 461

## 9. DATE OF FIRST APPROVAL

24 October 2002

## 10. DATE OF REVISION OF THE TEXT

8 June 2022

## SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|---|---|
| 4.4 | Addition of alcohol content warning statements |
| 5.3 | Minor editorial changes to correct spelling |