

# New Zealand Datasheet

## Name of Medicine

ATROVENT<sup>®</sup> NASAL AQUEOUS

Ipratropium bromide 0.03%

## Presentation

ATROVENT NASAL AQUEOUS is an aqueous isotonic, pH-adjusted (pH 4.0 - 5.0) solution for nasal administration. It contains 0.03% (300 mcg/ml) ipratropium bromide.

ATROVENT NASAL AQUEOUS is supplied in pump-activated, metered dose containers of 15 ml (180 metered doses) and 30 ml (380 metered doses). Each valve actuation delivers 70 microlitres of the solution, equivalent to 21 mcg ipratropium bromide.

## Uses

### Actions

ATROVENT NASAL AQUEOUS is a topical anticholinergic preparation. It contains ipratropium bromide, a synthetic quaternary ammonium derivative of atropine. Ipratropium bromide administered intranasally has a localised parasympathetic blocking action, which reduces watery hypersecretion from mucosal glands in the nose.

Ipratropium bromide administration via nasal aerosol had no marked effect on sense of smell, nasal mucociliary transport, ciliary beat frequency, or the air-conditioning capacity of the nose.

Nasal provocation trials in perennial rhinitis patients (n=44) using ATROVENT NASAL AQUEOUS showed a dose-dependent increase in inhibition of methacholine-induced nasal secretion with an onset of action within 15 minutes. The duration of action of ATROVENT NASAL AQUEOUS was also dose-dependent.

In an 8-week study in adults with allergic rhinitis doses up to 168 mcg/nostril 2 times a day were well tolerated and effective with a more rapid onset.

Controlled clinical trials showed that intranasal ipratropium bromide is effective for controlling the severity and duration of rhinorrhoea in patients with allergic and non-allergic perennial rhinitis or the common cold.

Two placebo controlled studies of ATROVENT NASAL AQUEOUS 0.03% administered twice a day in adults and children, allergic and non allergic perennial rhinitis patients showed that ATROVENT NASAL AQUEOUS 0.03% 42 mcg per nostril was more effective in non-allergic than in allergic perennial rhinitis patients.

### Pharmacokinetics

Ipratropium is a quaternary amine that is rapidly absorbed from the nasal mucosa, however to a low extent. In healthy volunteers less than 10% of a nasally given dose was excreted unchanged in the urine over 24 hours. .

The systemic absorption of ipratropium across inflamed nasal mucosa was not altered due to experimentally-induced cold, as estimated from the renal excretion of ipratropium over 24 hours. After a single dose or 4 times daily dosing 6-8% of ipratropium was excreted unchanged in healthy as well

as in infected volunteers. Following chronic dosing in rhinitis patients the amount of unchanged ipratropium excreted in the urine over a 24-hour period at steady state was 4-6% of the dose. Assuming the literature value of 50% of the dose excreted into the urine following intravenous administration, the estimated bioavailability of ipratropium following nasal administration is less than 20%.

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 ( $V_{dss}$ ) is approximately 176L (2.4L/kg). The drug is minimally (less than 20%) bound to plasma proteins. The quaternary amine ipratropium does not cross the blood-brain barrier.

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

Ipratropium has a total clearance of 2.3 L/min and a renal clearance of 0.9 L/min. After intravenous administration approximately 60% of a dose is metabolised, probably the major portion in the liver by oxidation.

In an excretion balance study cumulative renal excretion (6 days) of intravenous administration of a radioactive dose, less than 10% of the drug-related radioactivity (including parent compound and all metabolites)

In an excretion balance study cumulative renal excretion (6 days) of after intravenous administration of a radioactive dose less than 10% of the 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.. Therefore the dominant excretion of drug-related radioactivity occurred via the kidneys. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective

## **Indications**

ATROVENT NASAL AQUEOUS is indicated for the treatment and management of perennial rhinitis, allergic rhinitis and vasomotor rhinitis when characterised by watery rhinorrhoea.

ATROVENT NASAL AQUEOUS is also indicated for the symptomatic relief of rhinorrhoea associated with the common cold.

## **Dosage and Administration**

Priming of pump is required before first use.

**For the treatment and management of perennial rhinitis, allergic rhinitis and vasomotor rhinitis when characterised by watery rhinorrhoea:**

### *Regular Therapy*

Adults: Two puffs doses up each nostril 2 - 3 times a day. Some patients may need 3 - 4 puffs up each nostril during early therapy to obtain maximum benefit during early treatment.

Children: 2 puffs up each nostril 2 times a day.

### *Intermittent Therapy*

Patients with occasional episodes of watery rhinorrhoea triggered by provoking factors, e.g. temperature changes, food and exercise, should administer 2 - 4 puffs up each nostril prior to exposure.

## **For the symptomatic relief of rhinorrhoea associated with the common cold**

Adults: Initially: Two puffs into each nostril 3 - 4 times a day, followed by TWO further puffs five minutes after the first puffs.

## **Contraindications**

Known hypersensitivity to atropine or its derivatives, or to any of the ingredients of ATROVENT NASAL AQUEOUS (sodium chloride, benzalkonium chloride, disodium edetate dihydrate).

## **Warnings and Precautions**

ATROVENT NASAL AQUEOUS should be used with caution in patients predisposed to narrow-angle glaucoma, or with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder neck obstruction).

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

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

ATROVENT NASAL AQUEOUS contains the (antimicrobial) preservative benzalkonium chloride which may cause irritation of the nasal mucosa.

## **Ocular complications**

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 beta<sub>2</sub>-agonist, has come into contact with the eyes. Thus patients must be instructed in the correct administration of ATROVENT NASAL AQUEOUS.

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 should be sought immediately.

## **Use in Pregnancy**

The safety of ATROVENT NASAL AQUEOUS during pregnancy has not been established. The benefits of using ATROVENT NASAL AQUEOUS during a confirmed or suspected pregnancy must be weighed against possible hazards to the unborn child. Preclinical studies showed no embryotoxic or teratogenic effects following inhalation at doses considerably higher than those recommended in man.

## **Use in Lactation**

It is not known whether ipratropium bromide is excreted into human milk. Although lipid-insoluble quaternary cations pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to an important extent, when taken intranasally. However, because many drugs are excreted into human milk, caution should be exercised when ATROVENT NASAL AQUEOUS is administered to nursing mothers.

## **Fertility**

Preclinical studies performed with ipratropium bromide showed no adverse effect on fertility. Clinical data on fertility are not available for ipratropium bromide.

## **Effect on driving or operating machinery**

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 NASAL

AQUEOUS. 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 Effects**

Many of the listed undesirable effects can be assigned to the anticholinergic properties of ATROVENT NASAL AQUEOUS. As with all topical therapy ATROVENT NASAL AQUEOUS 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 side effects reported in clinical trials were epistaxis, nasal dryness, headache, nasal discomfort and throat irritation.

### Immune system disorders

- anaphylactic reaction
- hypersensitivity

### Nervous system disorders

- headache
- dizziness

### Eye disorder

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

### Cardiac disorders

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

### Respiratory, thoracic and mediastinal disorders

- epistaxis
- nasal dryness
- throat irritation
- nasal discomfort
- dry throat
- bronchospasm
- laryngospasm
- pharyngeal oedema

### Gastrointestinal disorders

- dry mouth
- nausea

- gastrointestinal motility disorder
- oedema mouth
- stomatitis

#### Skin and subcutaneous tissue disorders

- rash
- angioedema
- pruritus
- urticaria

#### Renal and urinary disorders

- urinary retention

### **Interactions**

There is no evidence that the concomitant use of ATROVENT NASAL AQUEOUS with other drugs commonly prescribed for perennial rhinitis, i.e. antihistamines, decongestants or nasal steroids, or the common cold, i.e. decongestants, increases the incidence of side effects.

ATROVENT NASAL AQUEOUS is minimally absorbed into the systemic circulation; nonetheless, there is some potential for additive interaction with other concomitantly administered anti-cholinergic medications, including ipratropium bromide containing aerosols for oral inhalation.

### **Overdosage**

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

### **Pharmaceutical Precautions**

Store in a safe place out of the reach of children.

Store below 25°C. Avoid freezing.

### **Medicine Classification**

Pharmacy Medicine

### **Package Quantities**

15ml pump-activated, metered dose container.

### **Further Information**

Priming of pump is required before first use.

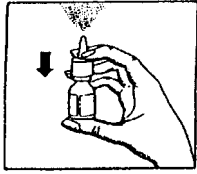
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### **Excipients**

Sodium chloride, benzalkonium chloride, disodium edetate dihydrate.

### **Instructions for use**

1. Remove the protective cap.
2. Before using the spray pump for the first time, activate repeatedly (about seven times) until an even spray mist is released (see fig.1). To activate the pump, hold the bottle between the thumb and index and middle fingers. Make sure the bottle points upright and away from the eyes. Press thumb firmly and quickly against the bottle (fig. 1). The pump is now ready for use.



(fig. 1)

3. If the pump has not been used for more than 24 hours, you will have to activate the bottle again by one or two sprays.
4. Before using the nasal spray, blow your nose to clear nostrils.
5. Close one nostril by gently placing a finger against the side of the nose, tilt the head slightly forward. While holding the bottle as shown in figure 1, insert the tip into the other nostril (see fig. 2). Point the tip toward the back and outer side of the nose.



(fig. 2)

6. Activate once the pump by pressing firmly and quickly upwards with the thumb. Following each spray, sniff deeply and breathe out through the mouth.
7. After spraying the nostril and removing the tip, tilt the head backwards for a few seconds to let the spray spread over the back of the nose.
8. Repeat steps 4 through 6 in the same nostril.
9. Repeat steps 4 to 7 in the other nostril.
10. Replace protective cap after use.

If ATROVENT NASAL AQUEOUS is accidentally sprayed into the eyes, immediately flush the eyes with cool tap water.

If the nasal tip becomes clogged, remove the protective cap. Hold the nasal tip under running, warm tap water for about a minute. Dry the nasal tip, activate the nasal spray pump and replace the protective cap.

### **Pre-clinical Information**

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

Acute toxicity has been investigated with observation periods of 14 days. 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 (e.g. i.e. 0.05 mg/kg after 4 h

hours of administration or 160 puffs of ATROVENT ipratropium bromide, 0.02 mg/puff). The oral and intravenous LD50, respectively, ranged from 17.5 mg/kg in dogs (i.v.) to 2050 mg/kg in mice (oral).

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.

The rather low oral toxicity compared to the higher intravenous toxicity reflects the poor gastrointestinal absorption.

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. Repeat-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 [86-93]. Intranasal administration for up to 6 months revealed a 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 repeat-dose toxicity studies, ipratropium bromide was locally well tolerated.

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

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.

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 metered dose aerosol, 1.5 mg/kg/day in rats and 1.8 mg/kg/day in rabbits, showed no adverse effects on reproduction.

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