Atrovent®

Boehringer Ingelheim

Composition

For ATROVENT® 20 mcg/puff Metered Dose Inhaler

1 metered dose (puff) contains 21 mcg (8r)-3α-hydroxy-8-isopropyl-1αH,5αH-tropanium bromide (±)-tropate monohydrate (= ipratropium bromide monohydrate) corresponding to 20mcg ipratropium bromide anhydrous.

Excipients

Propellant: 1,1,1,2-Tetrafluoroethane (HFA [hydrofluoralkane] 134a)

Other excipients: citric acid anhydrous, water purified, ethanol anhydrous, nitrogen (inert gas)

For ATROVENT® 0.025 % Nebuliser Solution

1 mL (20 drops) nebuliser solution contains 261mcg (8r)-3α-hydroxy-8-isopropyl-1αH,5αH-tropanium bromide (±)-tropate monohydrate (= ipratropium bromide monohydrate) corresponding to 250 mcg ipratropium bromide anhydrous

Excipients: benzalkonium chloride, disodium edetate dihydrate, sodium chloride, hydrochloric acid, purified water

Description

For ATROVENT® 20 mcg/puff Metered Dose Inhaler

Clear, colourless liquid, free from suspended particles

For ATROVENT® 0.025 % Nebuliser Solution

Clear, colourless or almost colourless liquid, free from suspended particles

Pharmacological Properties

Pharmacotherapeutic group: Anticholinergics

ATC Code : R03BB01

Mode of action

ATROVENT® (ipratropium bromide) is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In non-clinical 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 ATROVENT® (ipratropium bromide) is primarily local and site specific to the lung and not systemic in nature.

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

Clinical trials

For ATROVENT® 20 mcg/puff Metered Dose Inhaler

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.

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 for up to 4 - 6 hours.

In controlled 90 day studies in patients with bronchospasm associated with asthma, significant improvements in pulmonary function (FEV_1 increases of 15%) occurred in 54% of the patients.

For ATROVENT® 0.025% Nebuliser Solution

In controlled 85 - 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.

The bronchodilator effect of ATROVENT® in the treatment of acute bronchospasm associated with asthma has been shown in studies in adults and children over 6 years of age. In most of these studies ATROVENT® was administered in combination with an inhaled beta-agonist.

Although the data are limited, ATROVENT® has been shown to have a therapeutic effect in the treatment of bronchospasm associated with viral bronchiolitis and bronchopulmonary dysplasia in infants and very small children.

Pharmacokinetics

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 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

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 ($\approx$ 2.4 L/kg). The drug is minimally (less than 20%) bound to plasma proteins. Non-clinical 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, mainly by conjugation (40%), whereas after inhalation about 70% of the systemically available dose is metabolised by ester hydrolysis (41%) and conjugation (36%).

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

Elimination

Ipratropium has a 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 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.

Indications

For ATROVENT® 20 mcg/puff Metered Dose Inhaler

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

For ATROVENT® 0.025% Nebuliser Solution

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

ATROVENT® is indicated, when used concomitantly with inhaled beta-agonists in the treatment of acute bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and asthma.

Dosage & Administration

The dosage should be adapted to the individual requirements and the patients should be kept under medical supervision during treatment. It is advisable not to exceed the recommended daily dose during either acute or maintenance treatment.

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 physician should be consulted immediately.
The following dosages are recommended:

For ATROVENT® 20 mcg/puff Metered Dose Inhaler

Maintenance treatment

Adults and children > 6 years of age:
2 metered doses (puffs) 4 times daily.

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.

For acute exacerbations of chronic obstructive pulmonary disease treatment with ATROVENT® nebuliser solution may be indicated.

Because of insufficient information in children ATROVENT® metered dose aerosol should only be used on medical advice and under the supervision of an adult.

For ATROVENT® 0.025% Nebuliser Solution

(20 drops = about 1 mL; 1 drop = 0.0125 mg ipratropium bromide anhydrous)

Maintenance treatment:

Adults (including elderly) and adolescents over 12 years of age:
2.0 mL (40 drops = 0.5 mg ipratropium bromide anhydrous) 3 to 4 times daily

Children 6 - 12 years:
Because there is limited information in this age group, the following dose recommendation should be given under medical supervision:
1.0 mL (20 drops = 0.25 mg ipratropium bromide anhydrous) 3 to 4 times daily

Children < 6 years of age:
Because there is limited information in this age group the following dose recommendation should be given under medical supervision:
0.4 - 1.0 mL (8 - 20 drops = 0.1 - 0.25 mg ipratropium bromide anhydrous) 3 to 4 times daily

Acute attacks:

Adults (including elderly) and adolescents > 12 years of age:

2.0 mL (40 drops = 0.5 mg ipratropium bromide anhydrous); repeated doses can be administered until the patient is stable. The time interval between the doses may be determined by the physician.

ATROVENT® can be administered combined with an inhaled beta-agonist.

Children 6 - 12 years of age:
Because there is limited information in this age group, the following dose recommendation should be given under medical supervision:
1.0 mL (20 drops = 0.25 mg ipratropium bromide anhydrous); repeated doses can be administered until the patient is stable. The time interval between the doses may be determined by the physician.

ATROVENT® can be administered combined with an inhaled beta-agonist.

Children < 6 years of age:
Because there is limited information in this age group the following dose recommendation should be given under medical supervision:
0.4 - 1.0 mL (8 - 20 drops = 0.1 - 0.25 mg ipratropium bromide anhydrous); repeated doses can be administered until the patient is stable. The time interval between the doses may be determined by the physician.

ATROVENT® can be administered combined with an inhaled beta-agonist.

Daily doses exceeding 2 mg ipratropium bromide anhydrous in adults and adolescents >12 years of age and 1 mg in children ≤ 12 years of age should be given under medical supervision.

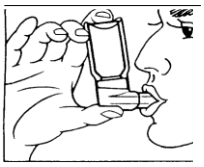
Instructions for use
Please read the instructions for use carefully, to ensure correct administration.

For ATROVENT® 20 mcg/puff Metered Dose Inhaler
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 fig. 1, and close lips over the mouthpiece. The arrow and the base of the container should be pointing upwards

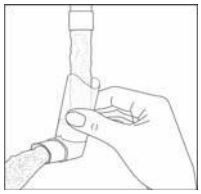


(fig. 1)

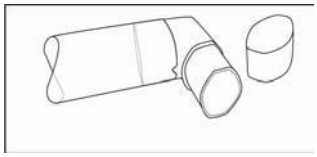
4. Breathe in as deeply as possible, pressing the base of the canister firmly at the same time, this releases one metered dose. Hold the breath for a few seconds, then remove the mouthpiece and breathe out. The same action should be repeated for a second inhalation.
5. Replace the protective cap after 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.


(fig. 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.


(fig. 3)

WARNING:
The plastic mouthpiece has been specially designed for use with ATROVENT® metered dose inhaler to ensure that you always get the right amount of the medicine. The mouthpiece must never be used with any other metered dose inhaler nor must the ATROVENT® metered dose inhaler 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 50°C.

For ATROVENT® 0.025 % Nebuliser Solution
The recommended dose is to be diluted with physiological saline to a final volume of 3 - 4 mL and nebulised and inhaled until the solution is consumed. The solution should be rediluted each time before use; any residual diluted solution should be discarded.

Dosage may be dependent upon the mode of inhalation and the quality of nebulisation. The duration of inhalation can be controlled by the dilution volume.

ATROVENT® Nebuliser Solution can be administered using a range of commercially available nebulising devices. Where wall oxygen is available the solution is best administered at a flow rate of 6 - 8 litres per minute.

ATROVENT® Nebuliser Solution is suitable for concurrent inhalation with the Nebuliser Solution of the secretomucolytics ambroxol hydrochloride and bromhexine hydrochloride, or fenoterol hydrobromide.

ATROVENT® Nebuliser Solution and disodium cromoglycate Nebuliser Solution should not be administered simultaneously in the same nebuliser as precipitation may occur.

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.

Special warnings and precautions
Hypersensitivity
Immediate hypersensitivity reactions may occur after administration of ATROVENT®, as demonstrated by rare cases of rash, urticaria, angioedema, 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 $beta_2$-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®.

For ATROVENT® 20 mcg/puff Metered Dose Inhaler
Care must be taken not to allow the mist to enter into the eyes. Since the metered dose inhaleris applied via mouth piece and manually controlled, the risk for the mist entering the eyes is limited.

For ATROVENT® 0.025% Nebuliser Solution
Care must be taken not to allow the solution or mist to enter into the eyes. It is recommended that the nebulised solution is administered via a mouth piece. If this is not available and a nebuliser mask is used, it must fit properly. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.

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.

Excipient(s)
ATROVENT® 0.025% Nebuliser Solution contains benzalkonium chloride:
This medicine 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.

ATROVENT® 20 mcg/puff Metered Dose Inhaler contains ethanol:
This medicine 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.

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.

For ATROVENT® 0.025% Nebuliser Solution
The risk of acute glaucoma in patients with a history of narrow-angle glaucoma (see section Special warnings and precautions) may be increased when nebulised ipratropium bromide and beta-mimetics are administered simultaneously.

Fertility, pregnancy and lactation

Pregnancy
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.

Lactation
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. Non-clinical studies performed with ipratropium bromide showed no adverse effect on fertility.

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.

Side effects
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.

Summary of the safety profile
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.

List of adverse reactions
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

Overdose

No symptoms specific to overdose have been encountered. In view of the wide therapeutic range and topical administration of ATROVENT®, 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.

Availability

For ATROVENT® 20 mcg/puff Metered Dose Inhaler
200 metered doses (10ml)

For ATROVENT® 0.025% Nebuliser Solution
Bottle of 20ml

Not all presentations may be available locally.

Store below 30°C.
Please refer to packaging material for information on shelf-life.

Manufactured by

For ATROVENT® 20 mcg/puff Metered Dose Inhaler
Manufactured by
Boehringer Ingelheim Pharma GmbH & Co. KG

Ingelheim am Rhein, Germany

For
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

For ATROVENT® 0.025% Nebuliser Solution
Manufactured by
Istituto De Angeli S.r.L.
Florence, Italy
for
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

Date of Revision: 18 April 2023