Atrovent® 500 mcg

Unit Dose Vials

Boehringer Ingelheim

Composition

1 unit dose vial (2 ml) solution for inhalation contains 522 mcg
(8r)-3α-hydroxy-8-isopropyl-1αH,5αH-tropanium bromide (±)-tropate monohydrate (= ipratropium bromide) corresponding to 500 mcg ipratropium bromide anhydrous
excipients: sodiumchloride, hydrochloric acid

Pharmacological Properties

ATROVENT is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In preclinical 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 cyclic guanosine monophosphate (cyclic GMP) caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. The bronchodilation following inhalation of ATROVENT is induced by local drug concentrations sufficient for anticholinergic efficacy at the bronchial smooth muscle and not by systemic drug concentrations.
In controlled 90 day studies in patients with bronchospasm associated with chronic obstructive pulmonary disease (chronic bronchitis and emphysema) significant improvements in pulmonary function (FEV_1 and $FEF_{25-75\%}$ increases of 15% or more) occurred within 15 minutes, reached a peak in 1–2 hours, and persisted in the majority of patients up to 6 hours. Preclinical and clinical evidence suggest no deleterious effect of ATROVENT on airway mucous secretion, mucociliary clearance or gas exchange.
The bronchodilator effect of ATROVENT in the treatment of acute bronchospasm associated with asthma has been shown in studies in adults. In most of these studies ATROVENT was administered in combination with an inhaled beta-agonist.

Pharmacokinetics

The therapeutic effect of ATROVENT is produced by a local action in the airways Therefore time courses of bronchodilation and systemic pharmacokinetics do not run in parallel.
Following inhalation dose portions from 10 to 30%, depending on the formulation and inhalation technique, are generally deposited in the lungs. The major part of the dose is swallowed and passes the gastro-intestinal tract.
Due to the negligible gastro-intestinal absorption of ipratropium bromide the bioavailability of the swallowed dose portion accounts for only ~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 a nearly complete systemic availability. From data of renal excretion (0–24 hrs) the total systemic bioavailability (pulmonary and gastro-intestinal portions) of inhaled doses of ipratropium bromide was estimated to be in the range 7 to 28%. It is assumed that this is also a valid range for the inhalation from the solution for inhalation preparation.
Kinetic parameters describing the disposition of ipratropium bromide were calculated from plasma concentrations after i.v. administration.

A rapid biphasic decline in plasma concentrations is observed. The volume of distribution (Vz) is 338 l (≙ 4.6 l/kg). The drug is minimally (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 half-life of the terminal elimination phase is about 1.6 hours. The mean total clearance of the drug is determined to be 2.3 L/min. The major portion of approximately 60% of the systemic available dose is eliminated by metabolic degradation, probably in the liver. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

A portion of approximately 40% of the systemic 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 gastro-intestinal 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.

Indications

ATROVENT 500 mcg unit dose vials are indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.
ATROVENT 500 mcg unit dose vials are 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.

Contraindications

ATROVENT is contraindicated in patients with known hypersensitivity to atropine or its derivatives or to any other component of the product.

Special Warnings and Precautions

Use of the nebuliser solution should be subject to close medical supervision during initial dosing.
ATROVENT should be used with caution in patients predisposed to narrow-angle glaucoma, or with 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, as demonstrated by rare cases of urticaria, angio-oedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.
Ocular complications
There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolized ipratropium bromide either alone or in combination with an adrenergic $beta_2$-agonist, has come into contact with the eyes. Eye pain or discomfort, blurred vision, visual halos or colored 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 solution for inhalation. Care must be taken not to allow the solution or mist into the eyes. It is recommended that the nebulized solution is administered via a mouth piece. If this is not available and a nebulizer mask is used, it must fit properly.
Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.

Drug Interactions

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 Special warnings and precautions) may be increased when nebulised ipratropium bromide and beta-mimetics are administered simultaneously.

Pregnancy and Lactation

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. Preclinical studies have shown no embryotoxic or

teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man. It is not known whether ATROVENT is excreted into breast milk. Although lipid-insoluble quaternary cations pass into breast milk, it is unlikely that ATROVENT would reach the infant to an important extent, when administered by inhalation. However, because many drugs are excreted in breast milk, caution should be exercised when ATROVENT is administered to nursing mothers.

Side Effects

The following side effects have been reported. The frequencies given below are based on clinical trials involving 3250 patients who have been treated with ATROVENT.

Frequencies: 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

Immune system disorders:

Uncommon: Urticaria (including giant urticaria)

Rare: Anaphylactic reaction, Angio-oedema of tongue, lips, face

Nervous system disorders:

Common: Headache, Dizziness

Eye Disorders:

Uncommon: Ocular accommodation disturbances, Angle closure glaucoma (See Special Warnings and Precautions)

Rare: Intraocular pressure increased, eye pain, mydriasis (See Special Warnings and Precautions)

Cardiac Disorders:

Uncommon: Tachycardia

Rare: Palpitations, Supraventricular tachycardia, Atrial fibrillation

Respiratory, Thoracic and mediastinal Disorders:

Common: Cough, local irritation, Inhalation induced bronchospasm

Rare: laryngospasm

Gastro-intestinal Disorders:

Common: Drynessofmouth, Vomiting, Gastrointestinal motility disorder (constipation, Diarrhea)

Rare: Nausea

Skin and Subcutaneous Disorders:

Uncommon: Skin rash, pruritis

Renal and urinary Disorders:

Rare: Urinary retention (the risk maybe increased in patients with pre-existing unrinary outfolow tract obstruction)

Dosage and Administration

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:

Maintenance treatment:

Adults (including elderly) and adolescents over 12 years of age:
1 unit dose vial (UDV) 3 to 4 times daily

Acute attacks:

Adults (including elderly) and adolescents over 12 years of age:
1 unit dose vial (UDV); 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.

The unit dose vials of 1ml are to be diluted with physiological saline up to a final volume of 2 – 4 ml or may be combined with Berotec* solution for inhalation.

Daily doses exceeding 2 mg in adults and children over 12 years of age should be given under medical supervision. It is advisable not to greatly 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. In the case of acute or rapidly worsening dyspnea (difficulty in breathing) a doctor should be consulted immediately.

ATROVENT solution for inhalation can be administered using a range of commercially available nebulising devices. Where wall oxygen is available the solution is best admininistered at a flow rate of 6 – 8 litres per minute. ATROVENT solution for inhalation is suitable for concurrent inhalation with the secretomucolytics Mucosolvan* solution for inhalation and Bisolvon* solution for inhalation, and Berotec* solution for inhalation.

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

Administration

The unit dose vials are intended only for inhalation with suitable nebulising devices and should not be taken orally or administered parenterally.

1. Prepare the nebuliser for filling, according to the instructions provided by the manufacturer or doctor.

2. Tear one unit dose vial from the strip.
3. Open the unit dose vial by firmly twisting the top.
4. Squeeze the content of the unit dose vial into the nebuliser reservoir.
5. Assemble the nebuliser and use as directed.

6. After use throw away any solution left in the reservoir and clean the nebuliser, following the manufacturer's instructions.

Since the unit dose vials contain no preservative, it is important that the contents are used soon after opening and that a fresh vial is used for each administration to avoid microbial contamination. Partly used, opened or damaged unit dose vials should be discarded.

Overdosage

No symptoms specific to overdosage 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 disturbances and increase of heart rate may occur.

Availability

Solution for inhalation in unit dose vials

Date of Package insert: *March 2007 (SPC)*

Storage instructions

Store in a safe place below 30°C and keep in original carton.

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

Do not take the medicine after the expiry date printed on the pack.

Manufactured by
Laboratoire Unither, Amiens, France,
for Boehringer Ingelheim International GmbH

This is medicament

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament
- The doctors and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children!

Council of Arab Health Ministers – Union of Arab Pharmacists

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