Atrovent®

Boehringer Ingelheim

1. NAME OF THE MEDICINAL PRODUCT

Atrovent Solution for Inhalation (UDVS) 500mcg/2ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for inhalation

3.1 Product description

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

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 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.

4.2 Posology and method of 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 a physician should be consulted immediately.

The following dosages are recommended:

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

Acute attacks:
Adults (including elderly) and adolescents > 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.

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

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

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

The unit dose vials of 1 mL are to be diluted with physiological saline up to a final volume of 2 - 4 mL or may be combined with fenoterol hydrobromide solution for inhalation.

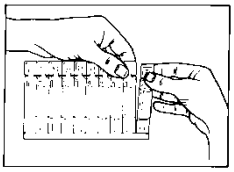
ATROVENT® solution for inhalation can be administered using a range of commercially available nebulising devices. Where wall oxygen is available the solution is best administered at a flow rate of 6 - 8 litres per minute.

ATROVENT® solution for inhalation is suitable for concurrent inhalation with the secretomucolytics ambroxol hydrochloride solution for inhalation and bromhexine hydrochloride or fenoterol hydrobromide.

ATROVENT® solution for inhalation in unit dose vials and disodium cromoglycate inhalation solutions should not be administered simultaneously in the same nebuliser.

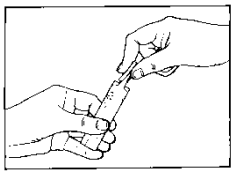
1. Prepare the nebuliser for filling, according to the instructions provided by the manufacturer or physician.

2. Tear one unit dose vial from the strip.



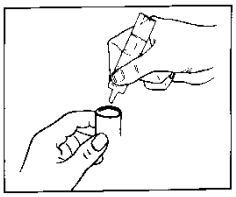
(fig. 1)

3. Open the unit dose vial by firmly twisting the top.



(fig. 2)

4. Squeeze the content of the unit dose vial into the nebuliser reservoir.



(fig. 3)

5. Dilute with saline up to a final volume of 2-4mL.
6. Assemble the nebuliser and use as directed.
7. 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.

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®, 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®.

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.

4.5 Interaction with other medicinal products 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.

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

4.6 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. Non-clinical 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.

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

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

4.9 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.

5. Pharmacological Properties

5.1 Pharmacodynamic 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

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. In most of these studies ATROVENT® was administered in combination with an inhaled beta-agonist.

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 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

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.
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

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, hydrochloric acid, purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to packaging material for information on shelf-life.

6.4 Special precautions for storage

Store below 30ºC

6.5 Nature and contents of container

Clear, colourless solution for inhalation in a colourless, transparent PE unit-dose vial. The unit-dose vials are packed in 10s in hermetically sealed white aluminium pouches.

Box of 60’s

6.6 Special precautions for disposal and other handling

For handling instructions, see section 4.2.

7. MANUFACTURER

Manufactured by
Laboratoire Unither
Amiens Cedex 2, France
for
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER

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9. DATE OF REVISION OF THE TEXT

04 September 2023

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