Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Atrovent 500 UDVs, 500 micrograms/ 2ml Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single dose unit contains 500 micrograms ipratropium bromide (as ipratropium bromide monohydrate) in 2 ml of solution (0.025% w/v)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser Solution (nebuliser liquid)
A clear, colourless aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

ATROVENT 500 UDVs, 2ml are indicated for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease and, when used concomitantly with inhaled $beta_2$-agonists, for treatment of acute and chronic asthma and acute bronchospasm associated with chronic obstructive pulmonary disease.

4.2 Posology and method of administration

The dosage should be adapted to the individual needs of the patient. The following doses are recommended:

Adults (including the elderly) and adolescents > 12 years of age:
500 micrograms 3 to 4 times daily.

For treatment of acute bronchospasm, 500 micrograms.
Repeated doses can be administered until the patient is stable. The time interval between the doses may be determined by the physician.

It is advisable not to exceed the recommended daily dose during either acute or maintenance treatment. Daily doses exceeding 2 mg in adults and adolescents > 12 years of age should only be given under medical supervision.

Children < 12 years of age:
250 micrograms up to a total daily dose of 1mg.
The time interval between doses may be determined by the physician.

For acute bronchospasm, repeated doses may be administered until the patient is stable. The time interval between doses may be determined by the physician.

It is advisable not to exceed the recommended daily dose. Daily doses exceeding 1mg in this age group should be given under medical supervision.

There is limited information for children < 6 years of age, therefore the recommended dose should only be given under medical supervision.

ATROVENT UDVs can be administered combined with an inhaled $beta_2$-agonist.

The dose of nebuliser solution may need to be diluted in order to obtain a final volume suitable for the particular nebuliser being used; if dilution is necessary use only sterile sodium chloride 0.9% solution.

If therapy does not produce a significant improvement or if the patient's condition gets worse, medical advice must be sought. The patient should be instructed that in the case of acute or rapidly worsening dyspnoea a physician should be consulted immediately.

ATROVENT UDVs can be administered using a range of commercially available nebulising devices.

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.

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

Please refer to the patient information leaflet for instructions on use with a nebuliser.

4.3 Contraindications

ATROVENT UDVs are 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 following the use of ATROVENT have been demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema 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
Caution is advocated in the use of anticholinergic agents in patients predisposed to narrow-angle glaucoma.

There have been isolated reports of ocular complications (i.e. mydriasis, increased intra-ocular pressure, narrow-angle glaucoma, eye pain) when aerosolised 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 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 UDVs. Care must be taken not to allow the solution or mist to enter the eyes. It is recommended that the nebulised solution is administered via a mouthpiece. 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-outflow obstruction).

Gastro-intestinal motility disturbances
As patients with cystic fibrosis may be prone to gastro-intestinal motility disturbances, ATROVENT, as with other anticholinergics, should be used with caution in these patients.

4.5 Interaction with other medicinal products and other forms of 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.

There is evidence that the administration of ATROVENT with beta-adrenergic drugs and xanthine preparations may intensify the bronchodilator effect of ATROVENT.

The risk of acute glaucoma in patients with a history of narrow-angle glaucoma (see section Special warnings and precautions for use) may be increased when nebulised ipratropium bromide and $beta_2$-agonists 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 the 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. It is unlikely that ipratropium bromide would reach the infant to an important extent, 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.

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.

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

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

MedDRA System Organ Class Adverse reaction	**Frequency**
Immune system disorders	

Hypersensitivity	Uncommon
Anaphylactic reaction	Uncommon
Nervous system disorders	
Headache	Common
Dizziness	Common
Eye disorders	
Vision blurred	Uncommon
Mydriasis [(1)]	Uncommon
Intraocular pressure increased [(1)]	Uncommon
Glaucoma [(1)]	Uncommon
Eye pain [(1)]	Uncommon
Halo vision	Uncommon
Conjunctival hyperaemia	Uncommon
Corneal oedema	Uncommon
Accommodation disorder	Rare
Cardiac disorders	
Palpitations	Uncommon
Supraventricular tachycardia	Uncommon
Atrial fibrillation	Rare
Heart rate increased	Rare
Respiratory, thoracic and mediastinal disorders	
Throat irritation	Common
Cough	Common
Bronchospasm	Uncommon
Bronchospasm paradoxical	Uncommon
Laryngospasm	Uncommon
Pharyngeal oedema	Uncommon
Dry throat	Uncommon
Gastro-intestinal disorders	
Dry mouth	Common
Nausea	Common
Gastrointestinal motility disorder	Common
Diarrhoea	Uncommon
Constipation	Uncommon
Vomiting	Uncommon
Stomatitis	Uncommon
Oedema mouth	Uncommon
Skin and subcutaneous tissue disorders	
Rash	Uncommon
Pruritus	Uncommon
Angioedema	Uncommon
Urticaria	Rare
Renal and urinary disorders	
Urinary retention[(2)]	Uncommon

[(1)] ocular complications have been reported when aerolised ipratropium bromide, either alone or in combination with an adrenergic beta$_2$-agonist, has come into contact with the eyes during nebuliser therapy – see section 4.4.

[(2)] the risk of urinary retention may be increased in patients with pre-existing urinary outflow tract obstruction.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

No symptoms specific to overdosage have been encountered. In view of the wide therapeutic window and topical administration of ATROVENT, no serious anticholinergic symptoms are to be expected. As with other anticholinergics, dry mouth, visual accommodation disorder and tachycardia would be the expected symptoms and signs of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anticholinergics
ATC Code: R03BB01

ATROVENT is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In non-clinical 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 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 on airway mucous secretion, mucociliary clearance or gas exchange.

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

The bronchodilator effect of ATROVENT in the treatment of acute bronchospasm associated with asthma has been shown in studies in adults and children ≥ 6 years of age. In most of these studies ATROVENT was administered in combination with an inhaled $beta_2$-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.

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, device and inhalation technique. The major part of the dose is swallowed and passes through 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 distribution of ipratropium bromide 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 the 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 probably the major portion in the liver by oxidation.

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 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

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Hydrochloric Acid (for pH adjustment)
Purified Water

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 2 years
Following removal from foil overwrap: 3 months
Once vial opened: Use immediately. Discard any unused portion.

Diluted Product:
From a microbiological point of view, unless the method of dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25°C. Keep vials in the outer carton in order to protect from light.

6.5 Nature and contents of container

Low-density polyethylene (LDPE) single dose units formed in strips of 10, in pack sizes of 20 and 60. Each single dose unit contains 2 ml of solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The dose of nebuliser solution may need to be diluted. If dilution is necessary use only sterile sodium chloride 0.9% solution.

7 MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

8 MARKETING AUTHORISATION NUMBER

PA0775/012/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 1985

Date of last renewal: 21 May 2005

10 DATE OF REVISION OF THE TEXT

January 2021