Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Atrovent Inhaler CFC-Free 20 micrograms per metered dose pressurised inhalation solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One metered dose (ex-valve) contains 20 micrograms ipratropium bromide (as the monohydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation, solution.
A clear, colourless liquid, free from suspended particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

ATROVENT Inhaler CFC-Free is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (including chronic bronchitis and emphysema) and asthma.

4.2 Posology and method of administration

Adults (including the elderly):
Usually 1 or 2 puffs three or four times daily, although some patients may need up to 4 puffs at a time to obtain maximum benefit during early treatment.

Children:
6-12 years: Usually 1 or 2 puffs three times daily.
< 6 years: Usually 1 puff three times daily.
In order to ensure that the inhaler is used correctly, administration should be supervised by an adult.

The recommended dose should not be exceeded.

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.

Administration:

The canister should be pressed twice to release two metered doses into the air before the inhaler is used for the first time, or when the inhaler has not been used for 3 days or more, to ensure that the inhaler is working properly and that it is ready for use.

Before each occasion on which the inhaler is used the following should be observed:
1. Remove the dustcap from the mouthpiece.

2. Holding the inhaler upright, breathe out gently and then immediately…

3. ...place the mouthpiece in the mouth and close the lips around it. After starting to breathe in slowly and deeply through the mouth, press the inhaler firmly to release the ATROVENT. Continue to breathe in as deeply as you can.

4. Hold the breath for 10 seconds, or as long as is comfortable, before breathing out slowly.

5. If a second inhalation is required you should wait at least one minute before repeating steps 2, 3 and 4.

6. After use, replace the dustcap on the mouthpiece.

The inhaler can be used with the Aerochamber Plus™ spacer device. This may be useful for patients, e.g. children, who find it difficult to synchronise breathing in and inhaler actuation.

The container is not transparent. It is therefore not possible to see when it is empty. The inhaler will deliver 200puffs. When these have all been used the inhaler may still appear to contain a small amount of fluid. The inhaler should, however, be replaced in order to ensure that each metered dose contains the correct amount of medicine.

The amount of treatment in the inhaler can be checked by observing its position in a container of water. Please refer to the Patient Information Leaflet for detailed instructions.

WARNING:
The plastic mouthpiece has been specially designed for use with ATROVENT Inhaler CFC-Free to ensure that you always get the right amount of the medicine. The mouthpiece must never be used with any other pressurised inhalation, solution nor must ATROVENT Inhaler CFC-Free be used with any mouthpiece other than the one supplied with the product.

The mouthpiece should be cleaned once a week. To clean the mouthpiece, the canister and dustcap must be removed. The mouthpiece should then be washed in warm soapy water, rinsed and allowed to air-dry without using any heating system. Care should be taken to ensure that the small hole in the mouthpiece is flushed through thoroughly. The canister and dustcap should be replaced once the mouthpiece is dry.

4.3 Contraindications

ATROVENT Inhaler CFC-Free 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 following the use of ATROVENT Inhaler CFC-Free 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 intraocular 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. Thus patients must be instructed in the correct administration of ATROVENT Inhaler CFC-Free and warned against the accidental release of the contents into the eye. Since the inhaler is applied via mouth piece and manually controlled, the risk for the mist entering the eyes is limited.

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.

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.

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 whetheripratropium 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. 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 headache, throat irritation, cough, dry mouth, gastro-intestinal motility disorders (including constipation, diarrhoea and vomiting), nausea, and dizziness.

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

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– see section 4.4 special warnings and precautions for use.

[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, Earlsfort Terrace, IRL – Dublin 2;
Tel: +353 1 6764971; Fax: +353 1 6762517.
Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

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. 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

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.

ATROVENT is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In nonclinical 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.

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.

In controlled 90 day studies in patients with bronchospasm associated with asthma, significant improvements in pulmonary function (FEV_1 increases of 15% or more) occurred in 40% of the patients.

Preclinical and clinical evidence suggest no deleterious effect of ATROVENT on airway mucous secretion, mucociliary clearance or gas exchange.

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 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 when delivery is via a nebuliser or a MDI product.

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 distributionat steady-state (Vdss) is approximately 176 L (≈ 2.4 L/kg). The drug is minimally (less than 20%) bound to plasma proteins. Nonclinical data indicate that the quaternary amine ipratropium does not cross the placental or the blood-brain barrier.

Biotransformation
After intravenous administration approximately 60% of a dose is metabolised, probably the major portion in the liver by oxidation.

The known metabolites, which are formed by hydrolysis, dehydration or elimination of the hydroxy-methyl group in the tropic acid moiety, show very little or no affinity for the muscarinic receptor and have to be regarded as ineffective.

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 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.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA 134a)
Ethanol anhydrous
Purified water
Citric acid anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Keep the inhaler in the outer carton.

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.

6.5 Nature and contents of container

17 ml stainless steel pressurised container (containing 10ml of solution) with a 50 µl metering valve and oral adaptor. Each canister contains a minimum of 200 actuations.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA0775/012/001

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Date of last renewal: 21 May 2005

10 DATE OF REVISION OF THE TEXT

March 2019