Atrovent
Ipratropium Bromide 0.02 mg

Metered Dose Inhaler

1. NAME OF THE MEDICINAL PRODUCT

Atrovent®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each actuation delivers 0.02 mg Ipratropium bromide.
Excipient with known effect: Ethanol. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Metered dose inhaler

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atrovent is indicated for the relief of symptoms of reversible bronchospasm associated with asthma, chronic bronchitis and emphysema.

4.2 Posology and method of administration

Posology

The dosage should be adapted to the individual requirements of the patient; patients should also be kept under medical supervision during treatment. It is advisable not to greatly exceed the recommended daily dose during both acute and maintenance treatment.
If therapy does not produce a significant improvement or if the patient's condition worsens, medical advice must be sought in order to determine a new regimen of therapy. In the case of acute or rapidly worsening dyspnea, a doctor should be consulted immediately.
The recommended dosage is as follows:

Adults
Usually 1 or 2 puffs four times daily, although some patients may need up to 4 puffs at a time to obtain maximum benefit during early treatment. However, the total number of inhalations should not exceed 12 in 24 hours.

Children
6-12 years: Usually 1 or 2 puffs three times daily.
In order to ensure that the inhaler is used correctly, administration should be supervised by an adult.
The dose recommendations are the same for children < 6 years of age. As there is insufficient experience in this age group, inhalation of the product should be medically supervised.

4.3 Contraindications

Atrovent is contraindicated in patients with hypersensitivity to the active substance, to atropine or atropine derivatives (such as ipratropium bromide) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity
Immediate hypersensitivity reactions may occur following the use of Atrovent, as demonstrated, for example, by rare cases of rash, urticaria, angioedema, oropharyngeal oedema, bronchospasm and anaphylaxis.

Paradoxical bronchospasm
As with other inhaled medications, Atrovent may cause paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, Atrovent must be discontinued immediately and replaced with an alternative therapy.

Special populations

Ocular complications
Atrovent should be used with caution in patients with a predisposition for narrow-angle glaucoma.
If the product accidentally comes into contact with the eyes during use, mild, reversible ocular complications may occur. There is a risk of an acute glaucoma attack, particularly in patients with narrow-angle glaucoma; the characteristic symptoms are eye pain, blurred vision, visual halos or coloured images, red eyes and corneal oedema.
If mydriasis and mild accommodation disturbances occur, treatment with miotic drops may be given.
In the event of severe ocular complications, an ophthalmologist should also be consulted.
As the inhaler is used in conjunction with a mouthpiece and is operated manually, the risk of the mist getting into the eyes is low.

Effect on the kidneys and urinary tract
In patients with micturition disorders (such as in prostatic hypertrophy or bladder neck obstruction), the benefit of treatment with ipratropium bromide must be carefully weighed against the potential risk of aggravating urinary retention.

Gastrointestinal motility disorders
Patients with cystic fibrosis are more likely to develop gastrointestinal motility disorders.

Contains alcohol (less than 100 mg per dose).

4.5 Interaction with other medicinal products and other forms of interaction

Chronic use of inhaled Atrovent together with other anticholinergic drugs has not been studied and is therefore not recommended.

β-Adrenergic agents and xanthine derivatives (such as theophylline) may enhance the therapeutic effect.

Other anticholinergic medications, such as those containing pirenzepine, may increase both the therapeutic and undesirable effects.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding
There are no data from use in pregnant or breast-feeding women.
Although no teratogenic effects have been identified to date, Atrovent should not be used during pregnancy (especially the first trimester) or while breast-feeding unless considered necessary by the treating physician after careful benefit/risk assessment.
The risks of inadequate treatment should be given due weight in this assessment.

Fertility
Clinical data on fertility are not available for ipratropium bromide. Non-clinical studies performed with ipratropium bromide showed no adverse effect on fertility (see section 5.3).

4.7 Effects on ability 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 undesirable effects such as dizziness, accommodation disturbances, mydriasis and blurred vision may occur during treatment with Atrovent. Caution is therefore required when driving or using machines.

4.8 Undesirable effects

Like all medicines, Atrovent can cause side effects.

a) Summary of the safety profile
Many of the undesirable effects listed can be attributed to the anticholinergic properties of Atrovent.

b) Tabulated summary of undesirable effects
The undesirable effects listed were identified from clinical trial data and post-marketing surveillance. Their frequency is defined using the following convention:

Very common	(≥ 1/10)
Common	(≥ 1/100 - < 1/10)
Uncommon	(≥ 1/1000 - < 1/100)
Rare	(≥ 1/10,000 - < 1/1000)
Very rare	(< 1/10,000)
Not known	(Frequency cannot be estimated from the available data)

Immune system disorders
Uncommon: Anaphylactic reactions, hypersensitivity

Nervous system disorders
Common: Headache, dizziness

Eye disorders
Uncommon: Blurred vision, mydriasis, increased intraocular pressure (sometimes with eye pain), halo or rainbow vision, conjunctival hyperaemia and corneal oedema, glaucoma
Rare: Accommodation disturbances

Cardiac disorders	
Uncommon	Palpitations, (supraventricular) tachycardia
Rare:	Atrial fibrillation,
Respiratory, thoracic and mediastinal disorders	
Common:	Cough, throat irritation
Uncommon:	(Paradoxical) bronchospasm, laryngospasm, pharyngeal oedema, dry throat
Gastrointestinal disorders	
Common:	Dry mouth, taste disturbance, gastrointestinal motility disorders, nausea
Uncommon:	Constipation, diarrhoea, abdominal pain, vomiting, stomatitis, oral oedema
Skin and subcutaneous tissue disorders	
Uncommon:	Rash, pruritus, angioedema
Rare:	Urticaria
Renal and urinary disorders	
Uncommon:	Urinary retention

c) Common undesirable effects

As with any other inhaled medication, Atrovent may also be associated with local irritation in the throat. The most common undesirable effects reported in clinical trials were headache, throat irritation, cough, dry mouth, gastrointestinal motility disorders (including constipation, diarrhoea and vomiting), nausea and dizziness.

Reporting of suspected adverse reactions

You can report side effects to the Ministry of Health by following the link ‘Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link:
https://sideeffects.health.gov.il

4.9 Overdose

No specific signs of overdose have been encountered to date.

However, in view of the wide therapeutic window and the fact that the product is administered topically, no serious anticholinergic symptoms are to be expected. Mild systemic anticholinergic side effects such as dry mouth, accommodation disturbances and increased heart rate may occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bronchodilators / antiasthmatic agents/anticholinergics
ATC code: R03BB01

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In non-clinical studies, it inhibits 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 (ipratropium) is primarily local and specific to the lung and is not systemic in nature.

Preclinical and clinical evidence suggests that Atrovent (ipratropium) has no adverse effect on airway mucus secretion, mucociliary clearance or gas exchange.

Clinical trials
Clinical trials with a treatment duration of up to 3 months in which the CFC formulation (Atrovent metered dose inhaler) and the CFC-free formulation (Atrovent metered dose inhaler) were compared in adult asthma and COPD patients and paediatric asthma patients 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 lung function occurred within 15 min. These improvements reached a peak in 1 - 2 hours and persisted for 4 - 6 hours.

In controlled 90-day studies in patients with bronchospasm associated with asthma, significant improvements in lung function (an increase of 15% in FEV_1) occurred in 51% of the patients.

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 - 30% of a dose is generally deposited in the lungs, depending on the formulation and inhalation technique. The majority of the dose is swallowed and passes through the gastrointestinal tract.

The portion of the dose deposited in the lungs reaches the circulation rapidly (within minutes).

Cumulative renal excretion (0 - 24 hours) of parent compound is approx. 46% of an intravenously administered dose, below 1% of an oral dose and approx. 3 - 13% of an inhaled dose. On the basis of these data, the total systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7 - 28% respectively.
Taking this into account, swallowed portions of ipratropium bromide doses do not contribute significantly to systemic exposure.

Distribution
Kinetic parameters describing the disposition of ipratropium were calculated from plasma concentrations after intravenous administration. A rapid biphasic decline in plasma concentrations was observed. The apparent volume of distribution at steady state (Vd_{ss}) is approx. 176 l (equivalent to 2.4 l/kg). The drug is minimally (less than 20%) bound to plasma proteins. Non-clinical data indicate that the quaternary ammonium compound ipratropium does not cross placenta or the blood-brain barrier.

Biotransformation

After intravenous administration, approx. 60% of the dose is metabolised, probably to a large extent by oxidation in the liver.

The known metabolites, which are formed by hydrolysis, dehydration or elimination of the hydroxymethyl group in the tropic acid moiety, bind poorly to the muscarinic receptor and must be regarded as ineffective.

Elimination
The terminal elimination half-life is approx. 1.6 hours.

Ipratropium has a total clearance of 2.3 l/min and a renal clearance of 0.9 l/min.

After inhalation of ipratropium bromide with HFA 134a as the propellant, cumulative renal excretion over 24 hours was approx. 12%.
In an excretion balance study, cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) was 72.1% after intravenous administration, 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was 6.3% after intravenous administration, 88.5% after oral administration and 69.4% after inhalation. Drug-related radioactivity after intravenous administration is excreted mainly via the kidneys. The elimination half-life of drug-related radioactivity (parent compound and metabolites) is 3.6 hours.

5.3 Preclinical safety data

Local and systemic tolerability of ipratropium bromide has been comprehensively investigated in several animal species using various administration routes.

Single dose toxicity
Acute inhalational, oral and intravenous toxicity has been assessed in several rodent and non-rodent species.
When administered by inhalation, the minimum lethal dose in male guinea pigs was 199 mg/kg. In rats, no mortality was observed up to the highest technically feasible doses (0.05 mg/kg after 4 hours of administration or 160 puffs of ipratropium bromide at a dose of 0.02 mg/puff).
The oral LD_{50} values for mice, rats and rabbits were 1585, 1925 and 1920 mg/kg respectively. The intravenous LD_{50} values for mice, rats and dogs were 13.6, 15.8 and approx. 18.2 mg/kg respectively. Clinical symptoms included mydriasis, dry oral mucosa, dyspnoea, tremor, spasms and/or tachycardia.

Repeated dose toxicity
Repeated dose toxicity studies have been performed in rats, rabbits, dogs and rhesus monkeys.
In inhalation studies up to 6 months in rats, dogs and rhesus monkeys, the no observed adverse effect levels (NOAELs) were 0.38 mg/kg/day, 0.18 mg/kg/day and 0.8 mg/kg/day respectively. Dryness of the oral mucosa and tachycardia were noted in dogs. No histopathological lesions related to ipratropium bromide were observed in the bronchopulmonary system or in any other organs. In rats, the NOAEL after 18 months of oral administration was 0.5 mg/kg/day.
Repeated dose inhalation toxicity studies in rats for up to 6 months and in dogs for up to 3 months with other formulations (intranasal formulation, alternative propellant HFA 134a and lactose powder formulations) revealed no additional information on the general toxicity profile of ipratropium bromide.
Intranasal administration for up to 6 months revealed a no effect level (NOEL) of > 0.20 mg/kg/day in dogs and confirmed the results of earlier studies with intranasal administration for up to 13 weeks. Repeated dose toxicity studies of ipratropium bromide have shown the toxicological profiles of the HFA formulation and the conventional CFC formulation to be similar.

Local tolerability

An aqueous solution of ipratropium bromide (0.05 mg/kg) was locally well tolerated when administered to rats by inhalation (single administration over 4 hours). In the repeated dose toxicity study, ipratropium bromide was locally well tolerated.

Immunogenicity
Neither active anaphylaxis nor passive cutaneous anaphylactic reactions occurred in guinea pigs.

Genotoxicity and carcinogenicity
There was no evidence of genotoxicity *in vitro* (Ames test) or *in vivo* (micronucleus test, dominant lethal test in mice, cytogenetic assay in Chinese hamster bone marrow cells).
No tumorigenic or carcinogenic effects were demonstrated in long-term studies in mice and rats.

Reproductive and developmental toxicity
Studies to investigate the possible influence of ipratropium bromide on fertility, embryo-/foetotoxicity and peri-/postnatal development have been performed in mice, rats and rabbits.
High oral doses (1000 mg/kg/day in rats and 125 mg/kg/day in rabbits) were maternotoxic for both species and embryo-/foetotoxic in rats and resulted in lower foetal weight. Malformations related to ipra-tropium bromide were not observed. The highest technically feasible doses for inhalation of the metered dose aerosol (1.5 mg/kg/day in rats and 1.8 mg/kg/day in rabbits) had no adverse effects on reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous, purified water, ethanol (absolute 99%), Propellant HFA 134A (1,1,1,2-Tetrafluoro-ethane)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C and protect from direct sunlight. The canister contains a pressurised liquid. Do not expose to temperature higher than 50°C. Do not pierce the canister.

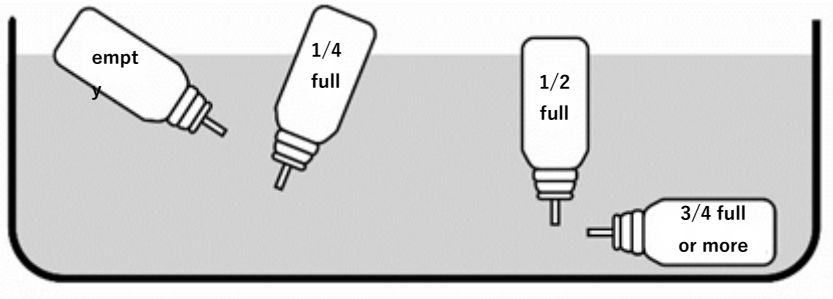
6.5 Nature and contents of container

Pressurised solution (10 ml = 200 metered doses) in a stainless steel canister with a metering valve, fitted with a removable plastic (PP) mouthpiece and a green plastic cap.

Pack sizes:
Original pack containing 10 ml solution.

6.6 Special precautions for disposal and other handling

Shaking the canister will show whether there is any liquid remaining in it. The approximate quantity of liquid in the canister can be estimated by removing the mouthpiece, placing the canister in a container filled with water and observing its position (see Figure below).



The approximate quantity of liquid in the canister is indicated by the position of the canister in the water.

7. MANUFACTURER

Boeringer Ingelheim Pharma GmbH & Co. KG, Binger Str. 173 D-55216
Ingelheim am Rhein, Germany

8. MARKETING AUTHORISATION HOLDER

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9. MARKETING AUTHORISATION NUMBER

130-01-30934-00

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