

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ipravent 20 micrograms per actuation pressurised inhalation, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One metered dose (ex-valve) contains 20 micrograms of ipratropium bromide (as the monohydrate). This is equivalent to a delivered dose (ex-actuator) of 17 micrograms ipratropium bromide (as the monohydrate).

Each metered dose (ex-valve) contains 8.4 mg of ethanol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation, solution

Ipravent is a colourless solution, filled in an aluminum container fitted with a suitable metering valve and a plastic actuator.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ipravent is indicated for the regular treatment of reversible bronchoconstriction associated with chronic obstructive pulmonary disease (COPD) and chronic asthma in adults.

4.2 Posology and method of administration

Dosage should be adjusted according to each individual's needs. It is not advisable to exceed the recommended daily dose for either acute or maintenance therapy.

Posology

For inhalation use.

The following dosage is recommended for the treatment of adults:

- 1-2 inhalations four times daily, Maximum of 12 inhalations per day
- For elderly patients give the same dose as in adults.

Treatment Control: The inhalation technique of revisiting patient's should be checked.

The recommended dose should not be exceeded.

Paediatric population

This medicinal product is not intended for the use in children and adolescents.

Method of administration

If the Inhaler has been exposed to low temperatures, the patient should take the metal canister out of the plastic case and warm it in their hands for a minimum of two minutes

The correct administration of ipratropium bromide from the inhaler is essential for successful therapy. It is imperative that patient's inhaler technique should be checked to ensure optimum drug delivery of ipratropium bromide to the lungs from time to time. For detailed information on instructions for use please refer to the Patient Information Leaflet.

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.

On each occasion on which the inhaler is used the following instructions should be followed:

1. Remove the cap from the mouthpiece.
2. Hold the inhaler upright (the arrow on the base of the container should be pointing upwards), breathe out for as long as is comfortable, and as slowly and deeply as possible and then close the lips over the mouthpiece.
3. Breathe in slowly and deeply, through the mouth and immediately after starting to breathe in press down firmly on the top of the inhaler to release one actuation (puff) and continue to breathe in steadily and deeply. Hold your breath for as long as is comfortable, for 10 seconds if possible, then remove the mouthpiece from the mouth and breathe out slowly.
4. If a second inhalation is required you should wait at least one minute and then repeat steps 2 and 3 above.
5. Replace the cap after use.

The plastic mouthpiece has been specially designed for use with Ipravent to ensure that each metered dose contains the correct amount of medicinal product. The mouthpiece must never be used with any other metered dose inhaler nor must Ipravent be used with any mouthpiece other than the one supplied with the product.

The mouthpiece should always be kept clean (see section 6.6).

The canister is not transparent. It is therefore not possible to see when it is empty. The inhaler will deliver 200 actuations. When these have all been used (usually after 3 - 4 weeks of regular use) the inhaler may still appear to contain a small amount of fluid. However the inhaler should be replaced in order to ensure that each metered dose contains the correct amount of medicinal product.

Please read the Patient Information Leaflet for appropriate instructions for use/inhalation.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Ipravent should not be used by patients with known hypersensitivity to atropine or its derivatives, hyoscyamine and scopolamine.

4.4 Special warnings and precautions for use

Immediate hypersensitivity reactions may occur following the use of ipratropium bromide have been seen and have presented as rare cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

If treatment with Ipravent does not produce significant improvement, if the patient's symptoms are getting worse or if a reduced response to treatment becomes apparent, medical advice must be sought. In the case of acute or rapidly deteriorating dyspnoea (difficulty in breathing) a doctor should be consulted immediately.

Ipravent can cause dry mouth, which in long term treatment can lead to dental and oral mucosal changes. Teeth should be thoroughly cleaned with fluoride toothpaste 2 times daily.

Caution is advocated in the use of anticholinergic agents in patients predisposed to or with narrow-angle glaucoma, or with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder-outflow obstruction).

As patients with cystic fibrosis may be prone to gastrointestinal motility disturbances, ipratropium bromide, as with other anticholinergics, should be used with caution in these patients.

There have been isolated reports of ocular complications (i.e. reversible accommodation disorder, mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide, either alone or in combination with an adrenergic β_2 adrenoceptor agonist, has come into contact with the eyes. Thus patients must be instructed in the correct administration of ipratropium and warned against the accidental release of the contents into the eyes. Since the inhaler is applied via mouth piece and manually controlled, the risk for the mist entering the eyes is limited. If Ipravent accidentally gets into the eyes, the eyes should be flushed with running water. Antiglaucoma therapy is effective in the prevention of acute narrow-angle glaucoma in susceptible individuals and patients who may be susceptible to glaucoma should be warned specifically on the need for ocular protection.

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 should be informed when starting treatment that the onset of action of ipratropium bromide is slower than that of inhaled sympathomimetic bronchodilators.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid acting bronchodilator and should be treated straight away. Ipratropium should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

This medicine contains 8.4 mg of alcohol (ethanol) in each spray. The amount in each dose of this medicine is equivalent to less than 4.3 ml beer or 1.72 ml wine.

The small amount of alcohol in this medicine will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

There is evidence that the administration of ipratropium bromide with beta-adrenergic medicinal products and xanthine preparations may produce an additive bronchodilatory effect.

A few cases have been reported where combination therapy with salbutamol and ipratropium in asthma (nebulizer) has triggered narrow-angle glaucoma. Terbutaline probably interacts in the same way as salbutamol with ipratropium when administered via nebulizer. The combination is discouraged in predisposed patients.

4.6 Fertility, pregnancy and lactation

Fertility

Preclinical studies of ipratropium bromide showed no adverse effect on fertility. There are no clinical data on fertility for ipratropium bromide.

Pregnancy

There are no data from the use of ipratropium in pregnant women. The benefits of using ipratropium bromide during a confirmed or suspected pregnancy must be weighed against the 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. As a precautionary measure, it is preferable to avoid the use of ipratropium during pregnancy.

Breast-feeding

It is unknown 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 ipratropium bromide is administered to nursing mothers.

Studies of HFA-134a administered to pregnant and lactating rats and rabbits have not revealed any special hazard.

4.7 Effects on ability to drive and use machines

Ipravent has moderate influence on the 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 Ipravent. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Many of the listed undesirable effects can be assigned to the anticholinergic properties of Ipravent. As with all inhalation therapy Ipravent 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 medicinal product.

The most frequent side effects known from clinical trials were headache, throat irritation, cough, dry mouth, gastro-intestinal motility disorders (including constipation, diarrhea and vomiting), nausea, and dizziness.

Frequencies

Very common $\geq 1/10$

Common $\geq 1/100$ to $< 1/10$

Uncommon $\geq 1/1,000$ to $< 1/100$

Rare $\geq 1/10,000$ to $< 1/1,000$

Very rare $< 1/10,000$

Not known: frequency cannot be estimated from the available data

Immune system disorder

Hypersensitivity ⁽¹⁾	Uncommon
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Anaphylactic reaction	Uncommon
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Angioedema of tongue, lips & face	Uncommon
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Nervous system disorders

Headache	Common
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Dizziness	Common
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Eye disorders

Blurred vision	Uncommon
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Mydriasis ⁽²⁾	Uncommon
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Intraocular pressure increased ⁽²⁾	Uncommon
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Glaucoma ⁽²⁾	Uncommon
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Eye pain ⁽²⁾	Uncommon
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Visual disturbances (Halo vision)	Uncommon
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Conjunctival hyperaemia	Uncommon
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Corneal oedema	Uncommon
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Accommodation disorder	Rare
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Cardiac disorders

Palpitations	Uncommon
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Supraventricular tachycardia	Uncommon
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Atrial fibrillation	Rare
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Heart rate increased	Rare
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Respiratory, thoracic and mediastinal disorders

Throat irritation	Common
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Cough	Common
Bronchospasm	Uncommon
Paradoxical bronchospasm ⁽³⁾	Uncommon
Laryngospasm	Uncommon
Pharyngeal oedema	Uncommon
Dry throat	Uncommon
Dyspnea	Not known
Nasal dryness and nasal congestion	Not known

Gastro-intestinal disorders

Dry mouth	Common
Nausea	Common
Gastro-intestinal motility disorder	Common
e.g. Diarrhoea	Uncommon
Constipation	Uncommon
Vomiting	Uncommon
Stomatitis	Uncommon
Mouth edema	Uncommon
Unpleasant taste	Not known

Skin and subcutaneous tissue disorders

Rash	Uncommon
Pruritus	Uncommon
Urticaria	Rare

Renal and urinary disorders

Urinary retention ⁽⁴⁾	Uncommon
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- (1) Hypersensitivity reactions following the use of ipratropium bromide have been seen and have presented as urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.
- (2) Ocular complications have been reported when aerolised ipratropium bromide, either alone or in combination with an adrenergic β_2 adrenoceptor agonist, has come into contact with the eyes - see section 4.4.

- (3) As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid – acting inhaled bronchodilator and should be treated straightaway. Ipratropium should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.
- (4) 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 the national reporting system listed in [To be completed nationally]

4.9 Overdose

Toxicity

Limited experience of overdose. Very low oral absorption.

Symptoms

It is conceivable mainly peripheral anticholinergic symptoms such as dry mouth, mydriasis, tachycardia, urinary retention, constipation, headache, dizziness. At massive doses may possibly exhibit central anticholinergic symptoms such as CNS excitation, and hallucinations may occur.

Treatment

Symptomatic treatment. For any central anticholinergic symptoms physostigmine is given for symptomatic relief.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anticholinergics, ATC Code: R03B B01

Ipratropium bromide is a quaternary ammonium compound with anti-cholinergic (parasympatholytic) properties. Bronchial muscle tone is affected in contracting direction by parasympathetic nervous system and the in relaxant direction by sympathetic nervous system. The contracting impulses communicated via the vagus nerve. This activity can be reversed with anticholinergics such as ipratropium. In preclinical 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 ipratropium bromide is induced by local drug concentrations sufficient for anticholinergic efficacy at the bronchial smooth muscle and not by systemic drug concentrations.

Ipratropium would give better effect in chronic bronchitis than in asthma, probably because vagal reflex plays major role in bronchospasm in chronic bronchitis.

In clinical trials using metered dose inhalers in patients with reversible bronchospasm associated with asthma or chronic obstructive pulmonary disease significant improvements in pulmonary function (FEV₁ increases of 15% or more) occurred within 15 minutes, reached a peak in 1-2 hours, and persisted for approximately 4 hours.

Preclinical and clinical evidence suggest no deleterious effect of ipratropium bromide on airway mucous secretion, mucociliary clearance or gas exchange. Effect occurs within 15 minutes. Maximum output is reached after 1-2 hours. The duration of action is about 4-6 hours.

Ipravent can be used with beta-adrenergic receptor agonist (see sections 4.4 and 4.5).

5.2 Pharmacokinetic properties

Absorption

The therapeutic effect of Ipravent is caused by a local action in the airways. Therefore, there is no progressive relationship between bronchodilation and systemic pharmacokinetics.

Depending on the formulation device and inhalation technique, after inhalation approximately 10 to 30% (13.3 % $\pm$ 6.9 % (mean $\pm$ SD)) of a dose reaches the lungs. The major part of the dose is swallowed and passes to the body via the gastro-intestinal tract.

The part of the dose that reaches to the lungs reaches the circulation within minutes.

Cumulative renal excretion (0-24 hrs) of parent drug is estimated at 46% of an intravenously administered dose, less than 1% of an oral dose and about 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 contribute significantly to systemic exposure.

Distribution

The kinetic parameters for ipratropium were calculated on the basis of plasma concentrations after intravenous administration. A rapid biphasic decline in plasma concentration can be observed. The apparent volume of distribution at steady state (V_{dss}) is approximately 176L (2.4L/kg).

The medicinal product is bound to plasma protein to a very small extent (on average 17 $\pm$ 4.2 % (mean $\pm$ SD)). Nonclinical data indicate that the quaternary amine ipratropium does not cross the blood-brain barrier..

Biotransformation

After intravenous administration approximately 59% (SD = $\pm$ 7.1%) of the dose is metabolised, most probably by oxidation in the liver.

Elimination

Ipratropium has a mean total clearance of 2.3 L / min (SD = $\pm$ 0.58%) and a renal clearance of 0.9 L / min. The average terminal half-life is approximately 1.6 hours. After inhalation of ipratropium bromide either with HFA 134a or CFC propellant, cumulative renal excretion over 24 hours was approximately 12% and 10%, respectively.

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 3.2 hours. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propellant: norflurane (HFA 134a),
Ethanol anhydrous,
Purified water,
Citric acid anhydrous.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Protect from direct sunlight, heat and frost.

If the Inhaler has been exposed to low temperatures, the patient should take the metal canister out of the plastic case and warm it in their hands for a minimum of two minutes.

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

The inner packaging is a 19 ml silver anodised aluminium container fitted with a suitable 50 microliter metering valve and the plastic actuator. The valve contains a thermoplastic 2-part core, cup (body), metering chamber, 2 elastomeric seats and gasket, a metallic ferrule and a spring. The plastic actuator body & cap are made up of polypropylene.

Each container is filled to deliver 200 metered doses.

Pack sizes

For DE, SE and PL.

Single pack

Each single pack contain a canister with 200 actuations.

For DE and PL

Multipack

400 actuations (2 x 200). Bundle pack of 2 single packs.

600 actuations (3 x 200). Bundle pack of 3 single packs.

For DE

Hospital pack

2000 actuations (10 x 200). Bundle pack of 10 single packs. Component of a hospital pack, can't be sold separately.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For detailed instructions on use of the medicinal product please refer to Patient Information Leaflet.

Cleaning

It is important to clean your inhaler regularly. Otherwise it may not work properly.

- Remove the canister and green cap.
- Wash and clean the white mouthpiece in warm soapy water.
- Rinse in warm water and allow to air dry without using any heating system.
- Make sure the small hole in the mouthpiece is washed through thoroughly.

Once the white mouthpiece is dry, replace the canister and the cap

DO NOT PUT THE METAL CANISTER INTO WATER

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<{To be completed nationally}>.

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

< {DD/MM/YYYY} > < {DD month YYYY} >

10. DATE OF REVISION OF THE TEXT

2021-02-18