Ipratropium Pressurised Inhalation

1. Name of the medicinal product

Ipratropium Pressurised Inhalation.

2. Qualitative and quantitative composition

Each canister provides 200 actuations. After priming, each actuation of the inhaler delivers 21 mcg of ipratropium bromide monohydrate from the valve and delivers 17 mcg of ipratropium bromide monohydrate from the actuator.

3. Pharmaceutical form

Pressurised inhalation, solution.

4. Clinical particulars

4.1 Therapeutic indications

Ipratropium Pressurised Inhalation is indicated for the regular treatment of reversible bronchospasm associated with chronic obstructive pulmonary disease (COPD) and chronic asthma.

4.2 Posology and method of administration

For inhalation use.

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.

Under 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, if the patient's condition gets worse or if a reduced response to treatment becomes apparent, medical advice must be sought. In the case of acute or rapidly worsening dyspnoea (difficulty in breathing) a doctor should be consulted immediately.

Administration

The correct administration of ipratropium bromide from the inhaler is essential for successful therapy.

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 protective cap.

2. Hold the inhaler as shown, breathe out gently and then close the lips over the mouthpiece

3. Breathe in slowly and deeply, pressing the base of the canister firmly at the same time; this releases one metered dose. Hold the breath for 10 seconds or as long as is comfortable, 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 Points 2 and 3 above.

5. Replace the protective cap after use.

4.3 Contraindications

Ipratropium Pressurised Inhalation should not be taken by patients with known hypersensitivity to atropine or its derivatives, or to ipratropium bromide or to any other component of the product.

4.4 Special warnings and precautions for use

When using Ipratropium Pressurised Inhalation for the first time, some patients may notice that the taste is slightly different from that of the CFC-containing formulation. Patients should be made aware of this when changing from one formulation to the other. They should also be told that the formulations have been shown to be interchangeable for all practical purposes and that the difference in taste has no consequences in terms of the safety or the efficacy of the new formulation.

Hypersensitivity reactions following the use of ipratropium bromide have been seen and have presented as urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

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. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide, either alone or in combination with an adrenergic beta2-agonist, has come into contact with the eyes. Thus patients must be instructed in the correct administration of Ipratropium Pressurised Inhalation 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. 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, inhalation induced bronchoconstriction may occur with an immediate increase in wheezing after dosing. This should be treated straight away with a fast acting inhaled bronchodilator. Ipratropium Pressurised Inhalation should be discontinued immediately, the patient assessed and, if necessary, alternative treatment instituted.

4.5 Interactions with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

There is no experience of the use of this product in pregnancy and lactation in humans. It should not be used in pregnancy or lactation unless the expected benefits to the mother are thought to outweigh any potential risks to the fetus or neonate.

The safety of ipratropium bromide during human pregnancy has not been established. 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.

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 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.

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

bromide

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 Ipratropium Pressurised Inhalation. 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 Ipratropium Pressurised Inhalation. As with all inhalation therapy Ipratropium Pressurised Inhalation 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, gastrointestinal 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 disorder

Hypersensitivity	Uncommon
Anaphylactic reaction	Uncommon
Angioedema of tongue, lips & face	Uncommon

Nervous system disorders

Headache	Common
Dizziness	Common

Eye disorders

Blurred vision	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
Paradoxical bronchospasm[(2)]	Uncommon
Laryngospasm	Uncommon
Pharyngeal oedema	Uncommon
Dry throat	Uncommon
Gastro-intestinal Disorders	
Dry mouth	Common
Nausea	Common
Gastro-intestinal motility disorder	Common
e.g. Diarrhoea	Uncommon
Constipation	Uncommon
Vomiting	Uncommon
Stomatitis	Uncommon
Skin and subcutaneous tissue disorders	

Rash	Uncommon
Pruritus	Uncommon
Urticaria	Rare

Renal and Urinary Disorders

Urinary retention	Uncommon

(1) ocular complications have been reported when aerolised ipratropium bromide, either alone or in combination with an adrenergic beta2-agonist, has come into contact with the eyes – see section 4.4.

(2) As with other inhalation therapy, inhalation induced bronchoconstriction may occur with an immediate increase in wheezing after dosing. This should be treated straight away with a fast acting inhaled bronchodilator. Ipratropium Pressurised Inhalation should be discontinued immediately, the patient assessed and, if necessary, alterative treatment instituted.

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

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anticholinergics

ATC Code: R03B B01

Ipratropium bromide 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 ipratropium bromide is induced by local drug concentrations sufficient for anticholinergic efficacy at the bronchial smooth muscle and not by systemic drug concentrations.

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.

5.2 Pharmacokinetic properties

Absorption

The therapeutic effect of Ipratropium Pressurised Inhalation 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.

Taking this into account, swallowed dose portions of ipratropium bromide do not contribute significantly to systemic exposure.

Distribution

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 the dose is metabolised, mainly by conjugation (40%), whereas after inhalation about 77% of the systemically available dose is metabolised by ester hydrolysis (41%) and conjugation (36%).

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

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 3.2 hours.

5.3 Preclinical safety data

The toxicity of ipratropium bromide has been investigated extensively in the following types of studies: acute, subchronic and chronic toxicity, carcinogenicity, reproductive toxicity and mutagenicity via oral, intravenous, subcutaneous, intranasal and/or inhalation routes. Based on these toxicity studies, the probability of systemic anticholinergic side effects decreases in the following order:

intravenous > subcutaneous > oral > inhalation > intranasal.

Pre-clinically, ipratropium bromide was found to be well-tolerated. Two-year carcinogenicity studies in rats and mice have revealed no carcinogenic activity at doses up to approximately 1,200 times the maximum recommended human daily dose for intranasal ipratropium. Results of various mutagenicity tests were negative.

Studies to investigate the possible influence of ipratropium bromide on fertility, embryo-fetotoxicity, and peri-/postnatal development have been performed on mice, rats and rabbits. High oral levels, i.e. 1000 mg/kg/day in the rat and 125 mg/kg/day in the rabbit were maternotoxic for both species and embryo-/fetotoxic in the rat, where the fetal weight was reduced. Treatment-related malformations were not observed. The highest, technically feasible doses for inhalation of the pressurised inhalation, solution, 1.5 mg/kg/day (human equivalent dose of 0.24 mg/kg/day) in rats and 1.8 mg/kg/day (human equivalent dose of 0.576 mg/kg/day) in rabbits, showed no adverse effects on reproduction.

These doses are 6- and 14-fold the maximum recommended human daily dose (MRHDD) of 2 mg or 0.04 mg/kg (based on a body weight of 50 kg).

6. Pharmaceutical properties

6.1 List of excipients

Citric Acid

Purified water

Levmenthol

Ethanol

Norflurane.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30 °C. Keep in airtight container.

6.5 Nature and contents of container

Stainless steel pressurised container with a metering valve and oral adaptor. Each canister contains 200 actuations.

6.6 Special precautions for disposal and other handling

None.