Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ipravent 500 micrograms/2 ml nebuliser solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains ipratropium bromide at 250 micrograms/1 ml i.e. 500 micrograms in 2 ml.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser Solution.
A clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ipratropium bromide is indicated for the treatment of reversible bronchospasm associated with chronic obstructive pulmonary disease (COPD).

Ipratropium bromide is indicated, when used concomitantly with inhaled $beta_2$-agonists, for treatment of reversible airways obstruction as in acute and chronic asthma.

4.2 Posology and method of administration

The dosage should be adapted to the individual needs of the patient. In children aged 12 years and under, only Ipravent Nebuliser Solution 1 ml should be used. The following doses are recommended:

Adults (including the elderly) and children over 12 years of age:

250 - 500 micrograms (i.e. one vial of 250 micrograms in 1 ml or one vial of 500 micrograms in 2ml) 3 to 4 times daily. The exact starting dose may vary depending on local guidelines.

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 children over 12 years of age should only be given under medical supervision.

Children 6 - 12 years of age:

250 micrograms (i.e. one vial of 250 micrograms in 1ml) up to a total daily dose of 1mg (4 vials).
The time interval between doses may be determined by the physician.

Children 0 – 5 years of age (for treatment of acute asthma only):

125 – 250 micrograms (i.e. half to one vial of 250 micrograms in 1ml) up to a total daily dose of 1 mg (4 vials).

Ipratropium bromide should be administered no more frequently than 6 hourly in children under 5 years of age.

For acute bronchospasm, repeated doses may be administered until the patient is stable.

If therapy does not produce a significant improvement or if the patient's condition gets worse, medical advice must be sought. In the case of acute or rapidly worsening dyspnoea (difficulty in breathing) a doctor should be consulted immediately.

Ipratropium bromide may be combined with a short-acting $beta_2$-agonist in the same nebuliser chamber, for simultaneous administration where co-administration is required, in line with local prescribing guidelines. The solution should be used as soon as possible after mixing and any unused solution should be discarded.

Ipratropium bromide can be administered using a range of commercially available nebulising devices. The dose of nebuliser solution may need to be diluted according to local prescribing guidelines and in order to obtain a final volume suitable for the particular nebuliser being used (usually 2 – 4 ml); if dilution is necessary use only sterile sodium chloride 0.9% solution.

4.3 Contraindications

Known hypersensitivity to atropine or ipratropium bromide.

4.4 Special warnings and precautions for use

Use of the nebuliser solution should be subject to close medical supervision during initial dosing.

Caution is advocated in the use of anticholinergic agents in patients with narrow-angle glaucoma, or with prostatic hyperplasia or bladder-outflow obstruction.

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

Immediate hypersensitivity reactions following the use of ipratropium bromide have been demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

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 during nebuliser therapy.

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 ipratropium bromide. 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.

4.5 Interaction 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.

The risk of acute glaucoma in patients with a history of narrow-angle glaucoma (see section 4.4; 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

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.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

The most common non-respiratory adverse reactions reported in clinical trials are headache, nausea (with or without vomiting) and dryness of the mouth.

<u>Common (>1/100, <1/10):</u>	
Nervous system disorders:	Headache
Respiratory, thoracic and mediastinal disorders:	Cough, local irritation
Gastrointestinal disorders:	Dryness of the mouth, nausea and disturbances in gastrointestinal motility (constipation, diarrhoea and vomiting).
<u>Uncommon (>1/1000,<1/100)</u>	
Immune system disorders:	Urticaria.
Eye disorders:	Accommodation disturbances, narrow-angle glaucoma
Cardiac disorders:	Tachycardia
Respiratory, thoracic and mediastinal disorders:	Spasms of larynx
Skin and subcutanous tissue disorders:	Exanthema
<u>Rare (>1/10,000, <1/1000):</u>	
Immune system disorders:	Anaphylactic reactions, angio-oedema on the tongue, lips and face
Eye disorders:	Increased intraocular pressure, pain in the eyes, mydriasis
Cardiac disorders:	Palpitations, supraventricular tachycardia, atrial fibrillation
Respiratory, thoracic and mediastinal disorders:	Bronchospasms induced by the inhalation
Renal and urinary disorders:	Urinary retention

4.9 Overdose

Palpitation and increases in heart rate have been produced with inhaled doses of 5 mg. Side effects have not been caused by single inhaled doses of 2 mg in adults and 1 mg in children. Single oral doses of 30 mg of ipratropium bromide caused anticholinergic side effects, but these did not require treatment.

Severe overdose is characterized by atropine-like symptoms like tachycardia, tachypnea, high fever and central effects like restlessness, confusion and hallucinations. These symptoms should be treated symptomatically. The use of fysostigmine is not recommended because of worsening of cardiotoxic symptoms and induction of convulsions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ipratropium bromide is a competitive antagonist of muscarinic acetylcholine receptors. It exhibits its greatest potency on bronchial receptors, whether given intravenously or inhaled, but causes no tachycardia. No anticholinergic effects have been observed on cardiac function, bladder function or in the eye.

Ipratropium bromide is able to inhibit reflex-induced bronchoconstriction following exercise, inhalation of cold air and the early response to inhaled antigens. It also reverses the bronchoconstriction induced by inhaled cholinergic agonists.

Inhalation of 0.04 mg of ipratropium from a metered dose aerosol causes bronchodilation, the maximal effect is seen after 30-60 minutes, with duration of four hours. This is a dose related effect and use of a nebuliser produces greater bronchodilation, a dose of 0.5 mg producing maximal bronchodilation.

5.2 Pharmacokinetic properties

Depending on the formulation and the inhalation technique, approximately 10-30 % of the inhaled dose reaches the lungs. The major part of the dose is swallowed.

Because of the negligible gastro-intestinal absorption, the bioavailability of the swallowed dose is only about 2 % of the total dose administered. The part of the dose that reaches the lungs has an almost complete systemic bioavailability and reaches the circulation within a few minutes.

From data on renal excretion (0-24 h) the total systemic bioavailability of inhaled ipratropium bromide is estimated to be 7-28 % (averages from three studies). It can be assumed that this interval is valid for the solution for nebuliser as well.

The kinetic parameters have been calculated from plasma concentrations after intravenous administration. The plasma concentration falls rapidly. The volume of distribution (V_z) is 338 L (approximately 4.6 L/kg). Ipratropium has a low degree of protein binding (<20 %). Because of its ammonium ion structure, ipratropium does not pass the blood-brain barrier. The elimination of ipratropium is biphasic. The half-life of elimination of the drug and metabolites is 3.6 hours. The half-life of the terminal elimination phase is about 1.6 hours.

The average total clearance has been estimated to be 2.3 L/min. About 60 % of the systemic available dose is metabolised, probably in the liver. The main metabolites that are found in the urine have a low affinity for muscarinic receptors and do not possess significant anticholinergic activity.

About 40 % of the systemic available dose is excreted via the kidneys, which corresponds to a renal clearance of 0.9 L/min.

From studies using radioactively labelled ipratropium, less than 10 % of the dose (ipratropium and metabolites) is excreted via bile and faeces. The major part of the radio labelled dose is excreted via the kidneys.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Water for Injections
Concentrated Hydrochloric Acid (for pH adjustment)

6.2 Incompatibilities

Ipravent Nebuliser Solution can be diluted only with sterile 0.9% sodium chloride solution.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original package.
The ampoule should be opened immediately before use and any solution remaining after use should be discarded.

6.5 Nature and contents of container

Sterile unit dose polyethylene ampoules, containing Ipravent Nebuliser Solution are available in one size: 2 ml. Ampoules, in strips of 10 overwrapped in aluminium foil, are packed into cartons available in packs of 20 or 60 ampoules. 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

Ipravent Nebuliser Solution is for inhalation from an intermittent positive pressure ventilator or from a suitable nebuliser which should be operated according to the manufacturer's instructions.

To open the plastic ampoule, take a strip of ampoules from the foil pack, remove one ampoule, replacing the rest back in the foil pack and replace the foil pack back in the carton. Hold the ampoule upright and open by twisting off the top. Squeeze the liquid into the solution holder of the machine.

7 MARKETING AUTHORISATION HOLDER

Breath Limited
Unit 2
Eastman Way
Stevenage
Herts SG1 4SZ
UK

8 MARKETING AUTHORISATION NUMBER

PA 1831/2/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 January 2006

Date of last renewal: 21 July 2008

10 DATE OF REVISION OF THE TEXT

September 2012