Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Combineb 0.5mg/2.5mg per 2.5ml Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5 ml single dose ampoule contains 0.5mg of ipratropium bromide (as monohydrate) and 2.5mg of salbutamol (as sulphate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser Solution
A 2.5ml ampoule containing 2.5ml of colourless nebuliser solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution is indicated for the management of bronchospasm in patients suffering from chronic obstructive pulmonary disease (COPD) who require regular treatment with both ipratropium bromide and salbutamol.

4.2 Posology and method of administration

For inhalation use.

The recommended dose is:
Adults (including elderly patients and children over 12 years): 1 ampoule three or four times daily.
Children under 12 years: There is no experience of the use of Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution in children under 12 years.

Administration:
Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution may be administered from a suitable nebuliser or an intermittent positive pressure ventilator after the single dose ampoule has been opened and its contents transferred to the nebuliser chamber. Administration should be in accordance with the manufacturer's instructions for the device. The solution in the single dose ampoules is intended for inhalation use only and should not be taken orally or administered parenterally.

1. Prepare the nebuliser by following the manufacturer's instructions and the advice of your doctor.
2. Carefully separate a new ampoule from the strip. Never use an ampoule that has been opened already.
3. Open the ampoule by simply twisting off the top, always taking care to hold it in an upright position.
4. Unless otherwise instructed by your doctor, squeeze all the contents of the plastic ampoule into the nebuliser chamber.
5. Assemble the nebuliser and use it as directed by your doctor.
6. After nebulisation, clean the nebuliser according to the manufacturer's instructions. It is important that the nebuliser is kept clean.

As the single dose units contain no preservatives it is important that the contents are used immediately after opening and a fresh ampoule is used for each administration to avoid microbial contamination. Partly used, opened or damaged single dose units should be discarded.

Any solution remaining in the nebuliser chamber should be discarded.

It is strongly recommended that Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution should not be mixed with other medicines in the same nebuliser.

4.3 Contraindications

Patients with hypertrophic obstructive cardiomyopathy or tachyarrhythmia.
Patients with known hypersensitivity to ipratropium bromide, salbutamol, atropine or its derivatives or to any of the excipients.

4.4 Special warnings and precautions for use

Patients should be instructed to consult a doctor immediately in the event of acute, rapidly worsening dyspnoea or if a reduced response to treatment becomes apparent.

Immediate hypersensitivity reactions may occur after administration as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

As with other inhalation therapy there is a risk of inhalation-induced bronchoconstriction or paradoxical bronchospasm. If this occurs the patient will experience an immediate increase in wheezing and shortness of breath after dosing which should be treated straightaway with an alternative presentation or different fast-acting inhaled bronchodilator. Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution should be discontinued immediately, the patient should be assessed and, if necessary, alternative therapy instituted.

There are also rare reports of a number of ocular complications when aerosolised ipratropium bromide, either alone or in combination with a $beta_2$-adrenergic agonist, has been inadvertently sprayed into the eye. Patients must therefore be instructed in the correct use of Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution with their nebuliser and must be warned not to allow the solution or mist to enter the eyes.

Such ocular complications may include acute angle glaucoma, mydriasis, blurring of vision, increased intraocular pressure, eye pain and narrow-angle glaucoma. Patients who may be susceptible to glaucoma should be warned specifically about the need for ocular protection. Antiglaucoma therapy is effective in the prevention of acute narrow-angle glaucoma in susceptible individuals.

Eye pain or discomfort, blurred vision, visual halos or coloured spots together with red eyes from conjunctival congestion or corneal oedema may be manifestations of acute narrow-angle glaucoma. If a combination of these symptoms develops, treatment with miotic eye drops should be initiated and the patient should seek specialist advice immediately.

In the following conditions Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution should only be used after careful risk/benefit assessment: inadequately-controlled diabetes mellitus, recent myocardial infarction and/or severe organic heart or vascular disorders, hyperthyroidism, pheochromocytoma, prostatic hypertrophy, bladder outflow obstruction and risk of narrow-angle glaucoma.

Potentially serious hypokalaemia may result from $beta_2$-agonist therapy. Particular caution is advised in severe airway obstruction, as this effect may be potentiated by concomitant treatment with xanthine derivatives, diuretics and steroids. Hypokalaemia can bring about increased sensitivity to arrhythmias in patients being treated with digoxin. Additionally hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm. It is recommended that serum levels of potassium are monitored in such situations.

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

If it is necessary to use higher doses than recommended to control the symptoms of bronchoconstriction (or bronchospasm) the patient's treatment plan should be reassessed.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with salbutamol. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving salbutamol should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use of additional $beta_2$-agonists, corticosteroids, anticholinergics and xanthine derivatives may enhance the effect of Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution on airway function and may increase the severity of side effects. Due to opposing pharmacodynamic interaction with the salbutamol element a potentially serious reduction in effect may occur during concurrent administration of beta-blockers such as propranolol.

Salbutamol should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants as these drugs can enhance the effect of beta adrenergic agonists.

Inhalation of anaesthetics containing halogenated hydrocarbons, e.g. halothane, trichloroethylene and enflurane, may increase the susceptibility to cardiovascular side effects of $beta_2$-agonists, which should therefore be monitored closely. Alternatively discontinuation of Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution prior to operation should be considered.

Potentially serious hypokalaemia may result from $beta_2$-agonist therapy. Particular caution is advised in severe airway obstruction, as this effect may be potentiated by concomitant treatment with xanthine derivatives, diuretics and steroids. Hypokalaemia can bring about increased sensitivity to arrhythmias in patients being treated with digoxin.

The effect of other anticholinergic compounds may be potentiated.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of ipratropium bromide and salbutamol together in pregnant women (in early stages of pregnancy). In animal studies there has been evidence of some harmful effects on the fetus at very high dose levels. The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women (especially in the first trimester).

Lactation
It is unknown whether ipratropium bromide and salbutamol are excreted in human breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution should be made taking into account the benefit of breast-feeding to the child and the benefit of Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution therapy to the woman.

4.7 Effects on ability to drive and use machines

This medicinal product has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Common (≥1/100 and <1/10)

Uncommon (≥1/1000 and ≤1/100)

Rare (≥1/10000 and <1/1000)

Not known (cannot be estimated from the available data)

System Organ Class	Common	Uncommon	Rare	Not known
Metabolism and nutrition disorders			Hypokalaemia	
Psychiatric disorders		Nervousness	Psychological influence, e.g. restlessness, memory disorders, anxiety, depression, hyperactivity in children	
Eye disorders	Accommodation disorders		Pain in the eyes, mydriasis, increased intraocular pressure, closed-angle glaucoma.	
Cardiac disorders	Palpitations, tachycardia	Increased systolic blood pressure, arrhythmias	Reduced diastolic blood pressure, peripheral vasodilatation	Myocardial ischaemia* (see section 4.4)
Respiratory, thoracic and mediastinal disorders	Coughing, dysphonia		Bronchospasm, laryngospasm, dyspnea, paradoxical bronchospasm (i.e. inhalation-induced bronchoconstriction)	
Gastrointestinal disorders	Dryness of mouth, nausea	Vomiting	Mouth and throat irritation, motility disorders	
Skin and subcutaneous tissue disorders			Rash, itching, urticaria, angioedema of the tongue, lips and face	

Musculoskeletal, connective tissue and bone disorders		Tremor	Myalgia, muscular cramp, muscular weakness	
Renal and urinary disorders		Urinary retention		
General disorders and administration site conditions	Headache	Dizziness	Anaphylactic reaction, sweating	

* reported spontaneously in post-marketing data therefore frequency regarded as unknown

4.9 Overdose

Acute effects of overdosage with ipratropium bromide are unlikely due to its poor systemic absorption after either inhalation or oral administration. Any effects of overdosage are therefore likely to be related to the salbutamol component.

Manifestations of overdosage with salbutamol may include anginal pain, hypertension, hypotension, hypokalaemia, tachycardia, arrhythmia, chest pain, tremor, flushing, restlessness and dizziness. Patients should therefore be monitored closely for the potential unwanted effects from overdosage of salbutamol.

Hypokalaemia may occur following overdose with salbutamol and therefore serum potassium levels should be monitored. The preferred antidote for overdosage with salbutamol is a cardioselective beta-blocking agent, but caution should be used in administering these drugs to patients with a history of bronchospasm.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
ATC Code: R03AK04 Adrenergics and other anti-asthmatics

Ipratropium bromide is an anticholinergic agent which inhibits vagally-mediated reflexes by antagonising the muscarinic action of acetylcholine.

The bronchodilation following inhalation of ipratropium bromide is primarily local and site specific to the lung and not systemic in nature.

Salbutamol sulphate is a $beta_2$-adrenergic agent which acts on airway smooth muscle resulting in relaxation.
Salbutamol relaxes all smooth muscles from the trachea to the terminal bronchioles and protects against bronchoconstrictor challenges.

Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution provides the simultaneous delivery of ipratropium bromide and salbutamol sulphate producing effects on both muscarinic and beta2-adrenergic receptors in the lung. This provides enhanced bronchodilation over that provided by each agent singly.

5.2 Pharmacokinetic properties

Ipratropium bromide is quickly absorbed after inhalation however systemic bioavailability is estimated to be less than 10% of the administered dose. Renal excretion is 46% of the dose and terminal elimination half-life is about 1.6 hours after intravenous administration and the half life is 3.6 hours for total drug and metabolites after radiolabelling. Ipratropium bromide does not cross the blood-brain barrier.

Salbutamol sulphate is rapidly and completely absorbed following inhalation. Peak plasma salbutamol concentrations are seen within three hours of administration and the drug is excreted unchanged in the urine after 24 hours. The elimination half-life is 3-7 hours. Salbutamol will cross the blood brain barrier reaching concentrations amounting to about 5% of the plasma concentrations.

Co-nebulisation of ipratropium bromide and salbutamol sulphate does not potentiate the systemic absorption of either component. The increased pharmacodynamic activity of Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution is due to the combined local effect of both drugs on the lung.

Impaired organ function
Ipratropium bromide and salbutamol are eliminated through renal excretion. Increased systemic exposures of ipratropium bromide and salbutamol are expected in patients with impaired renal function. Increased systemic exposure of salbutamol is expected in patients with impaired hepatic function.

5.3 Preclinical safety data

The individual active ingredients, ipratropium bromide and salbutamol sulphate, have been extensively investigated in animal models and there are no clinically relevant safety issues when Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution is used at the recommended doses by patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid
Water for injections

6.2 Incompatibilities

Combineb 0.5mg/2.5mg per 2.5ml nebuliser solution should not be mixed with other drugs in the same nebuliser.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Single dose polyethylene ampoules with a twist-off top containing 2.5 ml of solution.
The ampoules are packed in strips of ten in a foil sachet which is packed in cartons. The available pack sizes are 10, 20, 40, 60, 80, 100 or 120 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

See section 4.2.

7 MARKETING AUTHORISATION HOLDER

Breath Limited
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UK

8 MARKETING AUTHORISATION NUMBER

PA1831/3/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 13th March 2011

10 DATE OF REVISION OF THE TEXT

September 2012