Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Combivent UDVs 500 micrograms/2.5mg per 2.5ml Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5 ml single dose unit contains:
500 micrograms ipratropium bromide (as the monohydrate) and 2.5 mg salbutamol (as the sulphate)

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

Combivent UDVs are indicated for the management of bronchospasm in patients suffering from chronic obstructive pulmonary disease who require regular treatment with both ipratropium and salbutamol

4.2 Posology and method of administration

The recommended dose is:

Adults (including elderly patients and children over 12 years):

1 vial three or four times daily.

Children:
There is no experience of the use of COMBIVENT UDVs in children under 12 years.

COMBIVENT UDVs are intended for inhalation only and may be administered from a suitable nebuliser or an intermittent positive pressure ventilator. The single dose units should not be taken orally or administered parenterally.

The dose of nebuliser solution may need to be diluted in order to obtain a final volume suitable for the particular nebuliser being used; if dilution is necessary use only sterile sodium chloride 0.9% solution.

Instructions for Use:

1. Prepare the nebuliser by following the manufacturer's instructions and the advice of your doctor.
2. Carefully separate a new vial from the strip. NEVER use one that has been opened already.
3. Open the vial 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 vial 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.

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

It is strongly recommended not to mix COMBIVENT with other drugs in the same nebuliser.

4.3 Contraindications

COMBIVENT UDVs are contraindicated in patients with hypertrophic obstructive cardiomyopathy or tachyarrhythmia.

COMBIVENT UDVs are also contraindicated in patients with a history of hypersensitivity to ipratropium bromide, salbutamol sulphate or to atropine or its derivatives.

4.4 Special warnings and precautions for use

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

There have been rare reports of ocular complications (i.e. mydriasis, blurring of vision, narrow-angle glaucoma and eye pain) when the contents of metered aerosols containing ipratropium bromide have been sprayed inadvertently into the eye.

Patients must be instructed in the correct use of COMBIVENT UDVs and warned not to allow the solution or mist to enter the eyes. This is particularly important in patients who may be pre-disposed to glaucoma. Such patients should be warned specifically to protect their eyes. 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.

In the following conditions COMBIVENT UDVs 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, phaeochromocytoma, prostatic hypertrophy, risk of narrow-angle glaucoma or bladder-neck obstruction.

The patient should be instructed to consult a doctor immediately in the event of acute, rapidly worsening dyspnoea. In addition, the patient should be warned to seek medical advice should a reduced response become apparent.

Potentially serious hypokalaemia may result from beta2-agonist therapy. Particular caution is advised in severe airway obstruction as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm (especially in patients receiving digoxin). It is recommended that serum potassium levels are monitored in such situations.

Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances.

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, tachyarrhythmia or severe heart failure) who are receiving salbutamol for respiratory disease, 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

The use of additional beta-agonists, xanthine derivatives and corticosteroids may enhance the effect of COMBIVENT UDVs. The concurrent administration of other beta-mimetics, systemically absorbed anticholinergics and xanthine derivatives may increase the severity of side effects.

A potentially serious reduction in effect may occur during concurrent administration of beta-blockers.

Beta-adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of beta-adrenergic agonists may be enhanced.

Inhalation of halogenated hydrocarbon anaesthetics such as halothane, trichloroethylene and enflurane may increase the susceptibility to the cardiovascular effects of beta-agonists.

4.6 Fertility, pregnancy and lactation

Ipratropium bromide has been in general use for several years and there is no definite evidence of ill-consequence during pregnancy; animal studies have shown no hazard.

Salbutamol has been in widespread use for many years without apparent ill-consequence during pregnancy. There is inadequate published evidence of safety in the early stages of human pregnancy but in animal studies there has been evidence of some harmful effects on the foetus at very high dose levels.

As with all medicines, COMBIVENT should not be used in pregnancy, especially the first trimester, unless the expected benefit is thought to outweigh any possible risk to the foetus. Similarly, COMBIVENT should not be administered to breast-feeding mothers unless the expected benefit is thought to outweigh any possible risk to the neonate.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

The following side effects have been reported based on clinical trials involving 821 patients.

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
Not known cannot be estimated from the available data

Immune system disorders:
Not known: Anaphylactic reaction
Not known: Hypersensitivity

Metabolism and nutrition disorders:
Not known: Hypokalaemia

Psychiatric disorders:
Not known: Mental disorder
Uncommon: Nervousness

Nervous system disorders:
Uncommon: Dizziness
Uncommon: Headache
Uncommon: Tremor

Eye disorders:
Not known: Angle closure glaucoma

Not known: Eye pain
Not known: Intraocular pressure increased
Not known: Mydriasis
Not known: Vision blurred

There have been isolated reports of ocular complications with symptoms mentioned above when aerosolised ipratropium bromide either alone or in combination with an adrenergic beta$_2$-agonist, has escaped into the eyes

Cardiac disorders:
Very rare: Arrhythmia
Very rare: Atrial fibrillation
Very rare: Myocardial ischaemia
Uncommon: Palpitations
Uncommon: Tachycardia
Not known: Blood pressure diastolic decreased
Not known: Blood pressure systolic increased

Respiratory, thoracic and mediastinal disorders:
Not known: Bronchospasm
Not known: Laryngospasm
Not known: Pharyngeal oedema
Uncommon: Cough
Uncommon: Dysphonia
Not known: Throat irritation

Gastrointestinal disorders:
Not known: Oedema mouth
Common: Dry mouth
Not known: Gastrointestinal motility disorder
Uncommon: Nausea
Not known: Vomiting

Skin and subcutaneous tissue disorders:
Not known: Angioedema
Not known: Hyperhidrosis
Not known: Rash
Not known: Skin reaction
Not known: Urticaria

Musculoskeletal and connective tissue disorders
*Not known :*Muscle spasms
Not known: Muscular weakness
Not known: Myalgia

Renal and urinary disorders:
Uncommon: Urinary retention

General disorders and administration site conditions:
Uncommon: Asthenia

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, hypokalaemia and tachycardia. The preferred antidote for overdosage with salbutamol is a cardioselective beta-blocking agent but caution should be used in administering these drugs in patients with a history of bronchospasm.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ipratropium bromide is an anticholinergic agent which inhibits vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. The bronchodilation following inhalation of ipratropium bromide is primarily local and site specific to the lung and not systemic in nature.

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

COMBIVENT UDVs provide the simultaneous delivery of ipratropium bromide and salbutamol sulphate allowing effects on both muscarinic and beta2-adrenergic receptors in the lung leading to increased bronchodilation over that provided by each agent singly.

5.2 Pharmacokinetic properties

Ipratropium bromide is quickly absorbed after oral inhalation. The systemic bioavailability after inhalation is estimated to be less than 10% of the dose. Renal excretion of ipratropium bromide is given as 46% of the dose after intravenous administration. The half life of the terminal elimination phase is about 1.6 hours as determined after intravenous administration. The half life for elimination of drug and metabolites is 3.6 hours, as determined after radio labelling. Ipratropium bromide does not cross the blood-brain barrier.

Salbutamol is rapidly and completely absorbed following oral administration either by the inhaled or gastric route. 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 4 hours. Salbutamol will cross the blood brain barrier reaching concentrations amounting to about five percent of the plasma concentrations.

It has been shown that co-nebulisation of ipratropium bromide and salbutamol sulphate does not potentiate the systemic absorption of either component and that therefore the additive activity of COMBIVENT UDVs is due to the combined local effect on the lung following inhalation.

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 COMBIVENT UDVs are used at the recommended doses by patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.
As the product contains no preservative, a fresh vial should be used for each administration and the vial should be opened immediately before use. Any solution left in the vial should be discarded.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.
Do not freeze.

6.5 Nature and contents of container

Low density polyethylene vials containing 2.5 ml solution, formed into strips of 10 and packed into cartons containing 20 or 60 vials.

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

For instructions for use, please refer to section 4.2

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 465/105/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th March 2004
Date of last renewal: 5th March 2010

10 DATE OF REVISION OF THE TEXT

April 2011