

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1328/123/001

Case No: 2072302

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

B & S Healthcare

Unit 4, Bradfield Road, Ruislip, Middlesex, HA4 0NU, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Combivent UDV's 500 micrograms/2.5mg per 2.5ml Nebuliser Solution

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **08/01/2010**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Combivent UDV's 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

Product imported from UK

Nebuliser solution.

Clear, colourless or almost colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Combivent UDV's 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 UDV's in children under 12 years.

COMBIVENT UDV's 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.

Administration

- i) Prepare the nebuliser by following the manufacturer's instructions and the advice of your doctor.
- ii) Carefully separate a new vial from the strip. NEVER use one that has been opened already.
- iii) Open the vial by simply twisting off the top, always taking care to hold it in an upright position.
- iv) Unless otherwise instructed by your doctor squeeze all the contents of the plastic vial into the nebuliser chamber.
- v) Assemble the nebuliser and use it as directed by your doctor.
- vi) 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 UDV's with other drugs in the same nebuliser.

4.3 Contraindications

Combivent UDV's are contraindicated in patients with hypertrophic obstructive cardiomyopathy or tachyarrhythmia.

Combivent UDV's 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 UDV's, 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 UDV's 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 UDV's 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, risk of narrow-angle glaucoma, prostatic hypertrophy 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 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

The use of additional beta-agonists, xanthine derivatives and corticosteroids may enhance the effect of Combivent UDV's. 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 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 UDV's 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 UDV's 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

<i>Very common</i>	$\geq 1/10$
<i>Common</i>	$\geq 1/100 < 1/10$
<i>Uncommon</i>	$\geq 1/1,000 < 1/100$
<i>Rare</i>	$\geq 1/10,000 < 1,000$
<i>Very rare</i>	$< 1/10,000$
<i>Not known</i>	<i>cannot be estimated from the available data</i>

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 beta₂-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 beta₂-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 bronchoconstrictor challenges.

Combivent UDV's 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 the 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 UDV's 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 UDV's 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

In the absence of compatibility studies, it is strongly recommended not to mix COMBIVENT UDV's with other drugs in the same nebuliser.

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Store below 25°C. Do not freeze. Keep vials in the outer carton in order to protect from light.

6.5 Nature and contents of container

Low density polyethylene (LDPE) vials containing 2.5 ml of solution, formed into strips of 10 and packed into cartons containing 60 vials.

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

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. Do not use if solution is discoloured.

7 Parallel Product Authorisation Holder

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Ruislip
Middlesex HA4 0NU
United Kingdom

8 Parallel Product Authorisation Number

PPA1328/123/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th January 2010

10 DATE OF REVISION OF THE TEXT

