IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA1151/032/001
Case No: 2069197

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

Imbat Limited

Unit L2, **North Ring Business Park**, **Santry**, **Dublin 9**

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

Combivent Metered Aersol, 20/100 Mcg/Acutuation

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 **26/08/2009** until **21/06/2012**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Combivent Metered Aerosol 20 micrograms/100 micrograms per metered dose Pressurised Inhalation, Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose delivers 20 micrograms of ipratropium bromide (as monohydrate) and 100 micrograms of salbutamol (as sulphate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation, suspension.
Product imported from Greece.
Pressurised metered dose inhaler with a metal canister covered with a transparent plastic cover and a grey mouthpiece and cap containing a creamy-white suspension.
Boehringer logo is embossed on the base of the grey mouthpiece.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

COMBIVENT is indicated for the treatment of bronchospasm associated with chronic obstructive pulmonary disease in patients who require regular treatment with both ipratropium and salbutamol.

4.2 Posology and method of administration

Adults: Two inhalations four times a day.
(including elderly patients)
Children: There is no experience of the use of COMBIVENT in children below the age of 12 years.

Administration
The correct operation of the metered aerosol apparatus is essential for successful therapy.
The aerosol should be shaken and the valve depressed once or twice before the apparatus is initially used.
Before each use the following rules should be observed:
1) Remove protective cap.
2) Shake the metered aerosol well before each use
3) Breathe out deeply.
4) Hold the metered aerosol and close lips over the mouthpiece. The arrow and the base of the container should be pointing upwards.
5) Breathe in as deeply as possible, pressing the base of the container firmly at the same time, this releases one metered dose. Hold the breath for a few seconds, then remove the mouthpiece from the mouth and breathe out.
6) Replace the protective cap after use.

As the container is not transparent it is not possible to see when the contents are used up, but shaking the container will show if there is any remaining fluid.

The mouthpiece should always be kept clean and can be washed with warm water. If soap or detergent is used, the mouthpiece should be thoroughly rinsed in clear water.

4.3 Contraindications

COMBIVENT Metered Aerosol is contraindicated in patients with hypertrophic obstructive cardiomyopathy or tachyarrhythmia, and in patients with a history of hypersensitivity to any of its components, or to atropine or its derivatives.
COMBIVENT Metered Aerosol is also contraindicated in patients with a history of hypersensitivity to soya lecithin or related food products such as soya bean and peanut. For such patients COMBIVENT Unit Dose Vials without soya lecithin can be used.

4.4 Special warnings and precautions for use

Immediate hypersensitivity reactions may occur after administration of COMBIVENT Metered Aerosol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and oropharyngeal oedema.
Ocular complications: There have been rare reports of ocular complications (i.e. mydriasis, blurring of vision, narrow-angle glaucoma, eye pain) when the contents of metered aerosols containing ipratropium bromide have been sprayed inadvertently into the eye. Care must be taken to prevent COMBIVENT from entering the eye, particularly in patients who may be pre-disposed to glaucoma. Such patients should be specifically warned 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.
Patients must be instructed in the correct administration of COMBIVENT Metered Aerosol.
In the following conditions COMBIVENT should only be used after careful risk/benefit assessment:
Insufficiently controlled diabetes mellitus, recent myocardial infarction and/or severe organic heart or vascular disorders, hyperthyroidism, pheochromocytoma, prostatic hypertrophy and risk of narrow-angle glaucoma.
In the case of acute, rapidly worsening dyspnoea (difficulty in breathing) a doctor should be consulted immediately.
If bronchial obstruction deteriorates it is inappropriate and possibly hazardous to simply increase the use of COMBIVENT beyond the recommended dose over extended periods of time. If higher than recommended doses of COMBIVENT are required to control symptoms, the patient's therapy plan should be reviewed.
Potentially serious hypokalemia 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 hypokalemia 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.

4.5 Interaction with other medicinal products and other forms of interaction

Beta-adrenergics, xanthine derivatives and corticosteroids may enhance the effect of COMBIVENT. The concurrent administration of other beta-mimetics, systemically absorbed anticholinergics and xanthine derivatives may increase the side effects. A potentially serious reduction in effect may occur during concurrent administration of beta-blockers.
Beta-adrenergic agonists should be administered with caution in 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.
Anticholinergic effects of other drugs can be enhanced.

4.6 Pregnancy and lactation

COMBIVENT should only be used in pregnancy and during the lactation period if the potential benefit justifies the potential risks.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

In common with other beta-agonists more frequent undesirable effects of COMBIVENT are fine tremor of skeletal muscles and nervousness, less frequent are tachycardia, dizziness, palpitations or headache, especially in hypersensitive patients.
Potentially serious hypokalemia may result from beta2-agonist therapy.
In isolated cases there may be local reactions such as dryness of the mouth, throat irritation, dysphonia or allergic reactions.
As with other bronchodilators, in some cases cough, in very rare instances paradoxical bronchoconstrictions have been observed.
As with other beta-mimetics, nausea, vomiting, sweating, weakness and myalgia/muscle cramps may occur. In rare cases decrease in diastolic blood pressure, increase in systolic blood pressure, arrhythmias, particularly after higher doses may occur.
In individual cases psychological alterations have been reported under inhalational therapy with beta-mimetics.
Isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, angle-closure glaucoma, eye pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic beta2-agonist has escaped into the eyes.
Ocular side effects, gastro-intestinal motility disturbances and urinary retention may occur in rare cases and are reversible (see Special Precautions).
Allergic-type reactions such as skin rash, angioedema of the tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported. Many of the patients have had a history of allergy to other drugs and/or foods, including soya bean (see Contraindications). The possibility of anaphylactic reactions to active or inactive constituents of COMBIVENT is acknowledged.

4.9 Overdose

The effects of overdosage are expected to be primarily related to salbutamol because acute overdosage with ipratropium bromide is unlikely as it is not well absorbed systemically after inhalation or oral administration.
Manifestations of overdosage with salbutamol may include anginal pain, hypertension, hypokalemia and tachycardia.
The preferred antidote for overdosage with salbutamol is a cardioselective beta-blocking agent but due care and attention 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 sulphate 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 all bronchoconstrictor challenges.

5.2 Pharmacokinetic properties

Ipratropium bromide is not readily absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract as compared by blood level and renal excretion studies. The half-life elimination is about 3 - 4 hours after inhalation or intravenous administration. Ipratropium bromide does not penetrate the blood brain barrier.
Salbutamol sulphate 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.

Intravenous salbutamol will cross the blood brain barrier reaching concentrations amounting to about five percent of the plasma concentrations.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dichlorodifluoromethane
Cryofluorane
Trichloromonofluoromethane
Soya lecithin

6.2 Incompatibilities

Not applicable.

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

Do not store above 25°C.
Do not freeze.
The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.

6.5 Nature and contents of container

A 17 ml pressurised aluminium container containing 10 ml of suspension closed with a 50 microlitre metering valve containing 200 metered doses, supplied with a plastic actuator.

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

No special requirements.

7 Parallel Product Authorisation Holder

Imbat Limited
Unit L2
North Ring Business Park
Santry
Dublin 9

8 Parallel Product Authorisation Number

PPA 1151/32/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 22nd June 2007

10 DATE OF REVISION OF THE TEXT

August 2009