IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0007/052/001
Case No: 2062024

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

Boehringer Ingelheim Limited

Ellesfield Avenue, **Bracknell**, **Berkshire RG12 8YS**, **United Kingdom**

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

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

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 **27/02/2009** until **12/11/2010**.

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 excipients, see 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation, suspension.

Pressurised aluminium container closed with a metering valve containing a creamy-white suspension inserted into a grey plastic actuator (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 (including elderly patients)
Two inhalations four times a day.

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.

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, risk of narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.
- 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 beta$_2$-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.

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

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

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 know: 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 know: 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

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 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.

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
Dichlorotetrafluoroethane
Trichloromonofluoromethane
Soya Lecithin

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Store below 25°C.

Protect from direct sunlight. Do not freeze.

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50ºC. Do not pierce the canister.

6.5 Nature and contents of container

A 17ml pressurised aluminium container containing 10ml 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 MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Limited
Ellesfield Avenue
Bracknell
Berkshire
RG12 8YS
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0007/052/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th April 1994

Date of last renewal: 13th November 2005

10 DATE OF REVISION OF THE TEXT

February 2009