SCHEDULING STATUS: S3

PROPRIETARY NAME (and dosage form):

Combivent® U.D.V.

Boehringer Ingelheim

solution for inhalation

COMPOSITION:

Each 2,5 mL unit dose vial contains 3,01 mg salbutamol sulphate (equivalent to 2,5 mg salbutamol base) and 0,52 mg ipratropium bromide (equivalent to 0,5 mg ipratropium bromide anhydrous).

PHARMACOLOGICAL CLASSIFICATION:

A 10.2.1 Bronchodilators - inhalants

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties 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.

The simultaneous delivery of ipratropium bromide and salbutamol sulphate allows stimulation of both muscarinic and $beta_2$-adrenergic receptors in the lung leading to increased bronchodilation over that provided by each agent singly.

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 determined by blood level and renal excretion studies. The elimination half-life is about 3 - 4 hours after inhalation or intravenous administration. Ipratropium bromide does not cross 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. The elimination half-life is 4 hours. Intravenous 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 the combination is due to the local effect on the lung following inhalation.

INDICATIONS:
COMBIVENT U.D.V.s are indicated for the management of reversible bronchospasm associated with obstructive pulmonary disease.

CONTRA-INDICATIONS:
COMBIVENT U.D.V.s are contra-indicated in patients with hypertrophic obstructive cardiomyopathy or tachyarrhythmia. They are also contra-indicated in patients with a history of hypersensitivity to salbutamol sulphate, ipratropium bromide or to atropine or its derivatives.

There is no experience of the use of COMBIVENT U.D.V.s in children under 12 years.

INTERACTIONS:
The concurrent administration of xanthine derivatives (e.g. theophylline) as well as other beta-adrenergics and anticholinergics may increase the side-effects.

Beta-agonist induced hypokalaemia may be increased by concomitant treatment with xanthine derivatives, glucocorticosteroids and diuretics. This should be taken into account particularly in patients with severe airway obstruction. (See ***Special Precautions.***)

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

Salbutamol 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.

Anticholinergic effects of other medicines may be enhanced.

PREGNANCY AND LACTATION:
Safety during pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:
COMBIVENT U.D.V. solution for inhalation may be administered from a suitable nebuliser or an intermittent positive pressure ventilator.

The recommended dose is:

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

Treatment of acute attacks:
1 Unit dose vial is sufficient for prompt symptom relief in many cases.

In severe cases if an attack has not been relieved by one unit dose vial, two unit dose vials may be required. In these cases, patients should consult their doctor or the nearest hospital immediately.

Maintenance treatment:
1 Unit dose vial three or four times daily.

There is no experience in the use of COMBIVENT U.D.V.s in children under 12 years of age.

Do not exceed the recommended dose.

Instructions for use:
The unit dose vials are intended for inhalation with suitable nebulising devices and should not be taken orally or administered parenterally.

1. Prepare the nebuliser for filling, according to the instructions provided by the manufacturer or your doctor.
2. Tear one unit dose vial from the strip.
3. Open the unit dose vial by firmly twisting the top.
4. Squeeze the contents of the unit dose vial into the nebuliser reservoir.
5. Assemble the nebuliser and use as directed.
6. After use throw away any solution left in the reservoir and clean the nebuliser, following the manufacturer's instructions.

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

It is strongly recommended not to mix COMBIVENT U.D.V. solution for inhalation with other medicines in the same nebuliser reservoir.

If dilution is necessary this should be carried out using ONLY sterile sodium chloride 0,9 % solution and as instructed by your doctor.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:
Frequency classes: 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).

Immune system disorders:
Unknown frequency: Anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders:
Unknown frequency: Hypokalaemia

Psychiatric disorders:
Unknown frequency: Mental disorder
Uncommon: Nervousness

Nervous system disorders:
Uncommon: Dizziness, headache, tremor

Eye disorders:
Unknown frequency: Vision blurred, mydriasis, angle closure glaucoma, eye pain, intraocular pressure increased
Ocular complications with symptoms mentioned above may occur when aerosolised ipratropium bromide either alone or in combination with an adrenergic $beta_2$-agonist, has escaped into the eyes.

Cardiac disorders:
Unknown frequency: Blood pressure diastolic decreased
Uncommon: Palpitations, tachycardia, blood pressure systolic increased
Very rare: Atrial fibrillation, dysrhythmia, myocardial ischaemia

Respiratory, thoracic and mediastinal disorders:
Unknown frequency: Bronchospasm, laryngospasm, throat irritation, pharyngeal oedema
Uncommon: Cough, dysphonia

Gastro-intestinal disorders:
Unknown frequency: Gastro-intestinal motility disorder, oedema mouth, vomiting
Common: Dry mouth
Uncommon: Nausea

Skin and sub-cutaneous tissue disorders:
Unknown frequency: Angio-oedema, hyperhidrosis, rash, skin reaction, urticaria

Musculoskeletal and connective tissue disorders:
Unknown frequency: Muscle spasms, muscular weakness, myalgia

Renal and urinary disorders:
Uncommon: Urinary retention

General disorders and administration site conditions:
Uncommon: Asthenia

Special precautions:
Immediate hypersensitivity reactions may occur after administration of COMBIVENT U.D.V. solution for inhalation, as demonstrated by less frequent cases of urticaria, angio-oedema, rash, bronchospasm and oropharyngeal oedema.

Ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) may occur when aerosolised ipratropium bromide either alone or in conjunction with a beta$_2$-agonist, has escaped into the 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 use of COMBIVENT U.D.V.s. Care must be taken not to expose the eyes to the solution or mist of COMBIVENT. It is recommended that the nebulised solution be administered via a mouth piece. If this is not available and a nebuliser mask is used, it must fit properly. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.

In the following conditions COMBIVENT U.D.V. should only be used after careful risk/benefit assessment, especially when doses higher than recommended are used: insufficiently controlled diabetes mellitus, recent myocardial infarction and/or severe organic heart or vascular disorders, hyperthyroidism, phaeochromocytoma, risk of narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.

There is some evidence from post-marketing data and published literature of occurrences of myocardial ischaemia associated with salbutamol. Patients with underlying heart disease (ischaemic heart disease, tachydysrhythmia 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.

In the case of acute, rapidly worsening dyspnoea (difficulty in breathing) a doctor should be consulted immediately.

If higher than recommended doses of COMBIVENT are required to control symptoms, the patient's therapy plan should be reviewed by a doctor.

The maximum dose should not be exceeded.

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, steroids and diuretics.
Additionally, hypoxia and acidosis may aggravate the effects of hypokalaemia on cardiac rhythm.

Hypokalaemia may result in an increased susceptibility to dysrhythmias 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms:

The effects of overdosage are expected to be primarily related to salbutamol.
The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation, the most prominent being tachycardia, palpitation, tremor, hypertension, hypotension, widening of the pulse pressure, anginal pain, dysrhythmias and flushing.

Expected symptoms of overdosage with ipratropium bromide (such as dry mouth and visual accommodation disturbances) are mild and transient in nature in view of the wide therapeutic range and topical administration.

Treatment:

Administration of sedatives, tranquillisers and, in severe cases, intensive therapy.
Beta-receptor blockers, preferably $beta_1$-selective, are suitable as specific antidotes; however, a possible increase in bronchial obstruction must be taken into account and the dose should be adjusted carefully in patients suffering from bronchial asthma.
Further treatment is symptomatic and supportive.

IDENTIFICATION:

COMBIVENT U.D.V.s are polyethylene unit dose vials containing a clear, colourless, or almost colourless solution, free from suspended particles.

PRESENTATION:

Strips of 10 unit dose vials enclosed in a laminated aluminium pouch, in cartons of 60 unit dose vials.

STORAGE INSTRUCTIONS:

Store below 30 °C. Protect from light. Store in original carton. Do not freeze. Do not use if the solution is discoloured.
Keep out of reach of children.

REGISTRATION NUMBER:

30/10.2.1/0476

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Ingelheim Pharmaceuticals (Pty) Ltd
Suite 1, Building 4, 2nd Floor
Waterfall Corporate Campus

74 Waterfall Drive
Midrand
South Africa

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