Combivent®
Unit Dose Vials

Composition
1 unit dose vial (2.5 ml) solution for inhalation contains:
(8r)-3α-hydroxy-8-isopropyl-1αH,5αH-tropanium bromide
(±)-tropate monohydrate 0.52 mg (= ipratropium bromide)
corresponding to 0.5 mg ipratropium bromide anhydrous
di[(RS)-2-tert-butylamino-1-(4-hydroxy-3-hydroxymethyl-phenyl)ethanol] sulphate
3.01 mg (= salbutamol sulphate) corresponding to 2.5 mg salbutamol base

Properties
Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In preclinical studies, it appears to inhibit vagally mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase in intracellular concentration of cyclic guanosine monophosphate (cyclic GMP) caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle.
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.
COMBIVENT unit dose vials provide the simultaneous release of ipratropium bromide and salbutamol sulphate allowing the additive effect on both muscarinic and beta$_2$-adrenergic receptors in the lung resulting in a bronchodilation which is superior to that provided by each single agent.
Controlled studies in patients with moderate to severe chronic obstructive pulmonary disease (COPD) have demonstrated that COMBIVENT unit dose vials have a greater bronchodilator effect than either of its components and there was no potentiation of adverse events.

Indications
COMBIVENT unit dose vial is indicated as a bronchodilator for the treatment of bronchospasm associated with moderate to severe chronic obstructive airway disease in patients who require more than a single bronchodilator.

Contraindications
Hypertrophic obstructive cardiomyopathy, tachyarrhythmia. Hypersensitivity to any of the components of the drug, to atropine or its derivatives.

Side Effects
In common with other beta-agonist containing products more frequent undesirable effects of COMBIVENT are headache, dizziness, nervousness, tachycardia, fine tremor of skeletal muscles and palpitations, especially in susceptible patients.
Potentially serious hypokalaemia may result from beta$_2$-agonist therapy.
As with use of other inhalation therapy, cough, local irritation and less common inhalation induced bronchocospasm can occur.
As with other beta-mimetics, nausea, vomiting, sweating, muscle 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 rare cases skin reactions or allergic reactions have been reported, especially in hypersensitive patients.
In individual cases psychological alterations have been reported under inhalational therapy with beta-mimetics.
There have been 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 beta$_2$-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).

Special Precautions
Ocular complications
There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic beta$_2$-agonist, has escaped into the eyes.
Eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal congestion 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 unit dose vials. Care must be taken *not to expose the eyes to the solution or aerosol 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 should only be used after careful risk/benefit assessment, especially when doses higher than recommended are used:
insufficiently controlled diabetes mellitus, recent myocardial infarction, severe organic heart or vascular disorders, hyperthyroidism, phaeochromocytoma, risk of narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.
Potentially serious hypokalaemia may result from beta$_2$-agonist therapy. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm.
Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances.
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 patients's therapy plan should be reviewed by a doctor.

Drug Interactions

The concurrent administration of xanthine derivatives 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.

Hypokalaemia may result in an increased susceptibility to arrhythmias in patients receiving digoxin.

It is recommended that serum potassium levels are monitored in such situations.

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

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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.

Pregnancy and Lactation
The safety of COMBIVENT during human pregnancy is not established. The usual precautions regarding the use of drugs in pregnancy, especially during the first trimester, should be observed.
The inhibitory effect of COMBIVENT on uterine contraction should be taken into account.
Salbutamol sulphate and ipratropium bromide are probably excreted in breast milk and their effects on the neonate are not known. Although lipid-insoluble quaternary bases pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to an important extent, especially when taken by inhalation. However, because many drugs are excreted in breast milk, caution should be exercised when COMBIVENT is administered to a nursing woman.

Dosage and Administration
COMBIVENT inhalation solution in unit dose vials may be administered from a suitable nebuliser or an intermittent positive pressure ventilator.

The recommended dose is:
Adults (including elderly patients) and adolescents over 12 years of age:
1 unit dose vial three or four times daily.

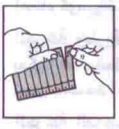
Fig. 1


Fig. 2

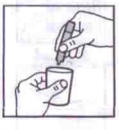
Fig. 3

Instructions for Use
The unit dose vials are intended only for inhalation with suitable nebulising devices and should not be taken orally.

1. Prepare the nebuliser for filling, according to the instructions provided by the manufacturer or doctor
2. Tear one unit dose vial from the strip (see fig. 1)
3. Open the unit dose vial by firmly twisting the top (see fig. 2)
4. Squeeze the content of the unit dose vial into the nebuliser reservoir (see fig. 3)
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 solution for inhalation with other drugs in the same nebuliser.

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

Therapy
Administration of sedatives, tranquillizers, 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.

Availability
Solution for inhalation in unit dose vials

Manufacturer:
Boehringer Ingelheim Ltd.
Bracknell, Berkshire, England
for
Boehringer Ingelheim International GmbH

This is a medicament
- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctors and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children!

Council of Arab Health Ministers – Union of Arab Pharmacists