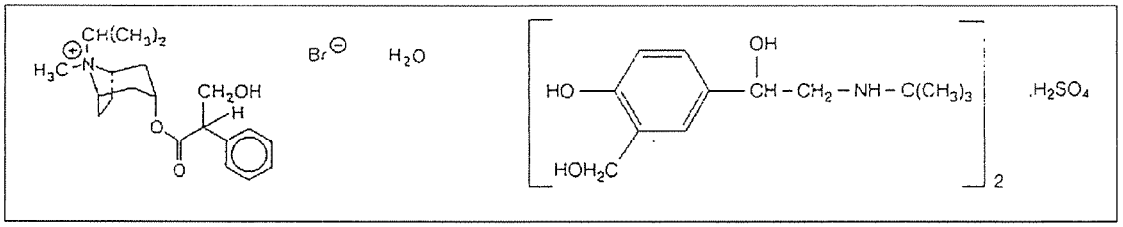
COMBIVENT® UNIT DOSE VIALS

(Ipratropium bromide / salbutamol sulfate)

DESCRIPTION

COMBIVENT® Unit Dose Vials (UDVs) contain the active ingredients ipratropium bromide and salbutamol sulfate.

The structural formulae for ipratropium bromide and salbutamol sulfate are as follows:



ipratropium bromide salbutamol sulfate

Ipratropium bromide is a synthetic quaternary ammonium compound, chemically related to atropine. It is a white or off-white crystalline odourless substance, and is freely soluble in water and lower alcohols but insoluble in lipophilic solvents. The molecular weight for ipratropium bromide is 430.3. The chemical name of ipratropium bromide is (8r)-3-α-hydroxy-8-isopropyl-1α,5α-tropanium bromide (±)-tropate. The CAS number is 0022254-24-6.

Salbutamol sulfate is a white or almost white nearly odourless crystalline powder, soluble in water and slightly soluble in ethanol. Salbutamol sulfate has a molecular weight of 576.7. The chemical name of salbutamol sulfate is di[(RS)-2-tert-butylamino-1-(4-hydroxy-3-hydroxymethyl-phenyl)ethanol] sulfate. The CAS number is 51022-70-9.

Each COMBIVENT® UDV (2.5 mL) contains 0.52 milligrams ipratropium bromide [equivalent to 0.5 milligrams ipratropium bromide (anhydrous)] and 3.01 milligrams salbutamol sulfate (equivalent to 2.5 milligrams salbutamol). In addition to ipratropium bromide and salbutamol sulfate, COMBIVENT® UDVs also contain sodium chloride, hydrochloric acid and purified water.

PHARMACOLOGY

Ipratropium bromide is an anticholinergic bronchodilator. In preclinical studies, it appears to inhibit vagally mediated reflexes by antagonising 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 sulfate is a relatively selective $beta_2$-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® UDVs provide the simultaneous release of ipratropium bromide and salbutamol sulfate, 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 have demonstrated that COMBIVENT® has a greater bronchodilator effect than either of its components and there was no potentiation of adverse events. Chronic obstructive pulmonary disease (COPD) is characterised by the presence of airways obstruction involving a range of airway pathology, including chronic bronchitis and emphysema. COPD is a widely used term that is interchangeable with other terminology, including chronic obstructive airways disease (COAD), chronic airways obstruction (CAO), chronic obstructive lung disease (COLD) and chronic airflow limitation (CAL).

Clinical Trials

In the pivotal study, a total of 652 patients with moderate-severe COPD (mean baseline FEV_1 = 0.9 L) were randomised to receive either COMBIVENT®, ipratropium bromide or salbutamol delivered by a compressor-driven nebuliser.

The primary efficacy measure was FEV_1 response to treatment on days 1, 29, 57 and 85. COMBIVENT® produced a greater and more long lasting bronchodilation on each of the test days than either of its components alone. The mean peak FEV_1 response to COMBIVENT® was 0.34-0.37 L compared with 0.27-0.29 L for ipratropium bromide ($p<0.001$) and 0.29-0.31 L for salbutamol ($p = 0.013$-0.001). Peak bronchodilator advantage for COMBIVENT® translates into a persisting advantage compared with ipratropium bromide and salbutamol over the 4 hours following administration. FEV $AUC_{0\text{-}4h}$ above baseline for COMBIVENT® was significantly superior on all test days over salbutamol ($p<0.0001$) and over ipratropium bromide ($p<0.0001$-0.0006). However, the spirometric benefits benefits did not translate into significant differences in clinical symptoms or quality of life. Overall, the statistical superiority for COMBIVENT® represents a clinically valuable increment in bronchodilator effect for patients as severely compromised as the study population.

Pharmacokinetics

The bronchodilation following inhalation of ipratropium bromide is primarily a local, site-specific effect. It is not readily absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract as confirmed by blood level and renal excretion studies. The systemic bioavailability after inhalation is approximately 7% of the dose. Renal excretion of ipratropium bromide is approximately 3% of the dose after oral inhalation. 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 3.5 hours, as determined after radio labelling. Studies in rats have shown that ipratropium bromide does not penetrate the blood brain barrier.

Salbutamol sulfate is rapidly and completely absorbed following oral administration. Peak plasma salbutamol concentrations are seen within 3 hours of administration and 27% of the dose is excreted unchanged in the urine after 24 hours. The elimination half-life is 4 hours. Studies in rats have shown that salbutamol will cross the blood brain barrier reaching concentrations amounting to about 5% of the plasma concentrations.

It has been shown that co-adminstration of ipratropium bromide and salbutamol sulfate does not potentiate the systemic absorption of either component; therefore the additive activity of COMBIVENT® is due to the combined local effect on the lung following inhalation.

INDICATIONS

For the treatment of bronchospasm associated with chronic obstructive pulmonary disease in patients on treatment with both ipratropium bromide and salbutamol.

CONTRAINDICATIONS

Known hypersensitivity to any of the components of COMBIVENT®, to atropine or its derivatives.

COMBIVENT® is contraindicated in patients with hypertrophic obstructive cardiomyopathy or tachyarrhythmia.

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.

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 mouthpiece. If this is not available and a nebuliser mask is used, it must be fitted properly. Patients who may be predisposed to glaucoma 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 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.

General

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, ischaemic heart disease, cardiac arrhythmia, 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, a doctor should be consulted immediately.

COMBIVENT® is not recommended within treatment guidelines for the management of asthma in children.

The results of animal experiments indicate that high dosages of some sympathomimetic agents may cause cardionecrosis. In view of this evidence, the possibility of cardiac lesions occurring in humans cannot be excluded. The administration of COMBIVENT® by inhalation results in only low plasma concentrations of salbutamol so the risk of this effect is lower than for some other routes of administration.

Immediate hypersensitivity reactions may occur after administration of COMBIVENT® UDV, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and oropharyngeal oedema.

Patients must be instructed in the correct administration of COMBIVENT® UDVs.

Prolonged use

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.

Use in Pregnancy

Category B1. The benefits of using COMBIVENT® when pregnancy is present or suspected must be weighed against possible hazards to the foetus. If COMBIVENT® is used during pregnancy, care is recommended, particularly in the first trimester. The inhibitory effect of COMBIVENT® on uterine contraction should be taken into account.

Use in Lactation

Ipratropium bromide and salbutamol 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 a significant extent, especially when taken by inhalation. However, caution should be exercised when COMBIVENT® is administered to a nursing woman.

Use in Children

COMBIVENT® UDV is not recommended for children.

Interactions with Other Drugs

The concurrent administration of xanthine derivatives as well as other beta-adrenergics and anticholinergics may increase the side effects of COMBIVENT®.

Beta-agonist induced hypokalaemia may be increased by concomitant treatment with xanthine derivatives, steroids 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.

Beta-adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or within two weeks of the discontinuation of such agents, 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 and the risk of cardiac arrhythmia.

ADVERSE REACTIONS

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. The most frequent non-respiratory anticholinergic related adverse events were dryness of the mouth and dysphonia.

As with use of other inhalation therapy, cough, local irritation, taste disturbance and less common inhalation induced bronchospasm can occur. As with other beta-mimetics, nausea, vomiting, sweating, muscle weakness and myalgia/muscle cramps may occur.

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. In individual cases psychological alterations have been reported under inhalational therapy with beta-mimetics.

Ocular side effects, gastro-intestinal motility disturbances and urinary retention may occur in rare cases and are reversible (see Precautions). In rare cases decrease in diastolic blood pressure, increase in systolic blood pressure and arrhythmias, particularly after higher doses, may occur. Potentially serious hypokalaemia may result from $beta_2$-agonist therapy. In rare cases skin reactions or allergic reactions have been reported, especially in hypersensitive patients. There have been rare reports of application site reactions such as swollen tongue and lips, mouth ulcers and rash on the skin of the face.

Clinical Trial Data

The table below lists treatment-related adverse events in the pivotal clinical trial which occurred in two or more patients receiving either COMBIVENT®, ipratropium bromide or salbutamol.

	Number (%) of patients		
	COMBIVENT® n=222	Ipratropium bromide n=214	Salbutamol n=216
Total	24 (10.8)	17 (7.9)	24 (11.1)
Body as a whole			
headache	2 (0.9)	0 (0.0)	4 (1.9)
Central and peripheral nervous system			
dysphonia	3 (1.4)	1 (0.5)	1 (0.5)
nervousness	1 (0.5)	0 (0.0)	7 (3.2)
Gastrointestinal			
dry mouth	4 (1.8)	5 (2.3)	5 (2.3)
nausea	0 (0.0)	1 (0.5)	4 (1.9)
Cardiovascular			
palpitation	2 (0.9)	0 (0.0)	0 (0.0)
Respiratory (lower)			
cough	2 (0.9)	2 (0.9)	0 (0.0)
bronchitis	0 (0.0)	0 (0.0)	2 (0.9)
dyspnoea	2 (0.9)	2 (0.9)	2 (0.9)
Respiratory (upper)			
pharyngitis	2 (0.9)	4 (1.9)	2 (0.9)

DOSAGE AND ADMINISTRATION

Adults (including elderly patients): The contents of 1 unit dose vial, administered by nebulisation and inhalation, three or four times daily.

Counselling on smoking cessation should be the first step in treating patients with COPD who smoke. Smoking cessation produces symptomatic benefits and has been shown to confer a survival advantage by slowing or stopping the progression of COPD.

Patients should be advised to consult a doctor immediately in the case of acute or rapidly worsening dyspnoea.

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 accommodation disturbances) are mild and transient in nature in view of the wide therapeutic range and topical administration.

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. Patients should be monitored for the development of hypokalaemia and cardiovascular complications such as tachycardia, hyper- or hypotension, arrhythmia and ischaemia.

PRESENTATION

COMBIVENT® Unit Dose Vials (UDVs). Preservative-free, clear, colourless or almost colourless solution. Each 2.5 mL contains 0.52 milligrams ipratropium bromide [equivalent to 0.5 milligrams ipratropium bromide (anhydrous)] and 3.01 milligrams salbutamol sulfate (equivalent to 2.5 milligrams salbutamol). Packs of 10 and 30.

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