

# New Zealand Datasheet

## Name of Medicine

COMBIVENT<sup>®</sup>

Salbutamol / Ipratropium bromide

## Presentation

Inhaler: 100 mcg / 20 mcg per inhalation.

COMBIVENT metered dose inhaler has an opaque shaft with a grey mouthpiece and cap. The canister contains a creamy-white homogenous suspension of micronised substances in a chlorofluorohydrocarbon propellant mixture filled in an aluminium canister with a metering valve. Each metered dose contains salbutamol 100 mcg (equivalent to 120 mcg salbutamol sulphate), and ipratropium bromide mcg (equivalent to 21 mcg of ipratropium bromide monohydrate).

## Uses

### Actions

COMBIVENT contains two active bronchodilating substances, salbutamol sulphate and ipratropium bromide.

Salbutamol sulphate is a beta<sub>2</sub>-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.

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. 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 of intracellular concentration of Ca<sup>++</sup> which is caused by interaction of acetylcholine with muscarinic receptors on bronchial smooth muscle. Ca<sup>++</sup> release is mediated by the second messenger system consisting of IP<sub>3</sub> (inositol triphosphate) and DAG (diacylglycerol). The bronchodilation following inhalation of ipratropium bromide is primarily local and site specific to the lung and not systemic in nature.

COMBIVENT provides the simultaneous release of ipratropium bromide and salbutamol allowing the synergistic efficacy on the muscarinic and beta<sub>2</sub>-adrenergic receptors in the lung resulting in a bronchodilation which is superior to that provided by each single agent.

Controlled studies in patients with reversible bronchospasm have demonstrated that COMBIVENT has a greater bronchodilator effect than either of its components and there was no potentiation of adverse events

### Pharmacokinetics

From a pharmacokinetic perspective, the efficacy observed in the COMBIVENT Inhalation Aerosol pulmonary clinical trials is due to a local effect on the lung following inhalation.

Following inhalation 10 to 39% of a dose is generally deposited in lungs, depending on the formulation, inhalation technique and device, while the remainder of the delivered dose is deposited in the mouthpiece, mouth and the upper part of the respiratory tract (oropharynx). The portion of the dose deposited in the lungs reaches the circulation rapidly (within minutes). The amount of the active substance deposited in the oropharynx is slowly swallowed and passes the gastrointestinal tract. Therefore the systemic exposure is a function of both oral and lung bioavailability.

## Ipratropium

Cumulative renal excretion (0-24 hrs) of ipratropium (parent compound) is approximated to 46% of an intravenously administered dose, below 1% of an oral dose and approximately 3-4% of an inhaled dose. Based on these data, the total systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7 to 9% respectively. Taking this into account, swallowed dose portions of ipratropium bromide do not relevantly contribute to systemic exposure.

Kinetic parameters describing the disposition of ipratropium were calculated from plasma concentrations after i.v. administration. A rapid biphasic decline in plasma concentrations is observed. The apparent volume of distribution at steady-state ( $V_{dss}$ ) is approximately 176 L ( $\approx 2.4$  L/kg). The drug is minimally (less than 20%) bound to plasma proteins. Preclinical studies with rats and dogs revealed that the quaternary amine ipratropium does not cross the blood-brain barrier.

The half-life of the terminal elimination phase is approximately 1.6 hours. Ipratropium has a total clearance of 2.3 L/min and a renal clearance of 0.9 L/min. After intravenous administration approximately 60% of a dose is metabolised probably mainly in the liver by oxidation.

In an excretion balance study cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 72.1% after intravenous administration, 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was 6.3% following intravenous application, 88.5% following oral dosing and 69.4% after inhalation. Regarding the excretion of drug-related radioactivity after intravenous administration, the main excretion occurs via the kidneys. The half-life for elimination of drug-related radioactivity (parent compound and metabolites) is 3.6 hours. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

Salbutamol is rapidly and completely absorbed following administration either by the inhaled or gastric route and has an oral bioavailability of approximately 50%. Mean peak plasma salbutamol concentrations of 492 pg/ml occur within three hours after inhalation of COMBIVENT. Following this single inhaled administration, approximately 27% of the estimated mouthpiece dose is excreted unchanged in the 24 hour urine. Kinetic parameters were calculated from plasma concentrations after i.v. administration. The apparent volume of distribution ( $V_z$ ) is approximately 156 L ( $\approx 2.5$  L/kg). Only 8% of the drug is bound to plasma proteins. Salbutamol will cross the blood brain barrier reaching concentrations amounting to about 5% of the plasma concentrations [90]. The mean terminal half-life is approximately 4 hours with a mean total clearance of 480 mL/min and a mean renal clearance of 291 mL/min.

Salbutamol is conjugatively metabolised to salbutamol 4'-O-sulphate. The R(-)-enantiomer of salbutamol (levosalbutamol) is preferentially metabolised and is therefore cleared from the body more rapidly than the S(+)-enantiomer. Following intravenous administration, urinary excretion was complete after approximately 24 hours. The majority of the dose was excreted as parent compound (64.2%) and 12.0% were excreted as sulphate conjugate. After oral administration urinary excretion of unchanged drug and sulphate conjugate were 31.8% and 48.2% of the dose, respectively.

Co-administration of ipratropium bromide and salbutamol sulphate does not potentiate the systemic absorption of either component and therefore the additive activity of COMBIVENT is due to the combined local effect on the lung following inhalation.

## **Indications**

COMBIVENT is indicated for the treatment of reversible bronchospasm associated with obstructive airway diseases in patients who require more than a single bronchodilator.

## **Dosage and Administration**

Because of insufficient information in children COMBIVENT is not indicated for pediatric patients.

COMBIVENT has not been studied in patients with hepatic or renal insufficiency. It should be used with caution in those patient populations.

Patients should be advised to consult a doctor or the nearest hospital immediately in the case of acute or rapidly worsening dyspnoea (difficulty in breathing) if additional inhalations of COMBIVENT do not produce an adequate improvement.

In asthma, concomitant anti-inflammatory therapy should be considered.

The following doses of COMBIVENT are recommended for adults (including elderly patients):

Adults (including elderly): Two inhalations four times daily. The dose may be increased as required up to a maximum of 12 inhalations in 24 hours.

Children: There has been no experience with the use of COMBIVENT in children below the age of 12 years.

Patients should be advised to consult a doctor or the nearest hospital immediately in the case of acute or rapidly worsening dyspnoea if additional inhalations do not produce an adequate improvement.

## **Contraindications**

COMBIVENT is contraindicated in patients with hypertrophic obstructive cardiomyopathy and tachyarrhythmia and in patients with a history of hypersensitivity to atropine or its derivatives, or to any other component of the product.

COMBIVENT metered dose aerosol is also contraindicated in patients with a sensitivity to soya lecithin or related food products such as soyabean and peanut.

## **Warnings and Precautions**

In the case of acute, rapidly worsening dyspnoea a doctor should be consulted immediately.

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

There have been isolated reports of ocular complications (e.g. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic beta<sub>2</sub>-agonist containing ipratropium bromide have 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 should be instructed in the correct administration of COMBIVENT and care must be taken to prevent COMBIVENT from entering the eye. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.

In the following situations 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.

Cardiovascular effects may be seen with sympathomimetic drugs, including COMBIVENT. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with salbutamol. Patients with underlying severe heart disease (e.g. ischaemic heart disease, tachyarrhythmia 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. Attention should be paid to assessment of symptoms as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Potentially serious hypokalaemia may result from prolonged and / or high dose beta<sub>2</sub>-agonist therapy. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm.

Patients with cystic fibrosis may be more prone to gastrointestinal motility disturbances.

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

The use of COMBIVENT may lead to positive results with regards to salbutamol in tests for nonclinical substance abuse, e.g. in the context of athletic performance enhancement (doping).

### **Use in Pregnancy**

The safety of COMBIVENT during human pregnancy has not been 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. The benefits of using COMBIVENT during a confirmed or suspected pregnancy must be weighed against possible hazards to the unborn child.

For ipratropium bromide, preclinical studies have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man. For salbutamol sulphate, non-inhalation preclinical studies did not indicate direct or indirect harmful effects unless the inhalation Maximum Recommended Human Daily Dose (MRHDD) was exceeded (please refer to section Toxicology).

No studies on the effect on human fertility have been conducted for COMBIVENT. Preclinical studies performed with ipratropium bromide and salbutamol showed no adverse effect on fertility (please refer to section Toxicology).

### **Use in Lactation**

It is not known whether ipratropium bromide and salbutamol sulphate are excreted in breast milk.

Although lipid-insoluble quaternary cations pass into breast milk, it is considered unlikely that ipratropium bromide would reach the infant to an important extent when administered by inhalation. However, because many drugs are excreted in breast milk, caution should be exercised when COMBIVENT is administered to nursing mothers.

### **Effects on Ability to Drive and Use Machines**

No studies on the effects on the ability to drive and use machines have been performed.

However, patients should be advised that they may experience undesirable effects such as dizziness, accommodation disorder, mydriasis and blurred vision during treatment with COMBIVENT. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

### **Adverse Effects**

Many of the listed undesirable effects can be assigned to the anticholinergic and beta<sub>2</sub>-sympathomimetic properties of COMBIVENT. As with all inhalation therapy COMBIVENT may show symptoms of local irritation. Adverse drug reactions were identified from data obtained in clinical trials and pharmacovigilance during post approval use of the drug.

The most frequent side effects reported in clinical trials were headache, throat irritation, cough, dry mouth, gastro-intestinal motility disorders (including constipation, diarrhoea and vomiting), nausea, and dizziness.

Immune system disorders:

Anaphylactic reaction  
Hypersensitivity

Metabolism and nutrition disorders:

Hypokalaemia

Psychiatric disorders:

Mental disorder  
Nervousness

Nervous system disorders:

Dizziness  
Headache  
Tremor

Eye disorders:

Accommodation disorder  
Corneal oedema  
Glaucoma  
Eye pain  
Intraocular pressure increased  
Mydriasis  
Vision blurred  
Conjunctival hyperaemia  
Halo vision

Cardiac disorders:

Arrhythmia  
Atrial fibrillation  
Myocardial ischaemia  
Palpitations  
Tachycardia  
Supraventricular tachycardia

Respiratory, thoracic and mediastinal disorders:

Bronchospasm  
Bronchospasm paradoxical  
Laryngospasm  
Pharyngeal oedema  
Cough  
Dysphonia  
Dry throat

Gastrointestinal disorders:

Oedema mouth  
Dry mouth  
Throat irritation  
Diarrhoea  
Gastrointestinal motility disorder  
Constipation

Nausea  
Vomiting  
Stomatitis

Skin and subcutaneous tissue disorders:

Skin reactions such as:

Rash  
Pruritus  
Urticaria

Angioedema  
Hyperhidrosis

Musculoskeletal and connective tissue disorders

Muscle spasms  
Muscular weakness  
Myalgia

Renal and urinary disorders:

Urinary retention

General disorders and administration site conditions:

Asthenia

Investigations:

Blood pressure diastolic decreased  
Blood pressure systolic increased

## **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 be 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, 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.

## **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 disorders) are mild and transient in nature in view of the wide therapeutic range and topical administration.

## Treatment

Administration of sedatives, tranquillisers, in severe case intensive therapy.

Beta-receptor blockers, preferably beta<sub>1</sub>-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.

## Pharmaceutical Precautions

Store below 30°C.

Shake well before use.

Do not expose the aerosol canister to high temperatures.

Do not force open even when apparently empty.

## Medicine Classification

Prescription Medicine

## Package Quantities

Inhaler: 10ml, 200 actuations.

## Further Information

COMBIVENT® is a registered trademark.

## Excipients

Aerosol: CFC (Freon 11, 12, 114) soya lecithin

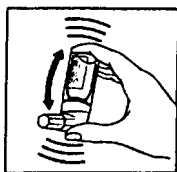
Source Document BPI No.: 0178-02 dated 9.9.08

## Instructions for Use of Inhaler

**When using the aerosol for the first time it should be shaken and the valve depressed once or twice to prime the metering valve before initial use.**

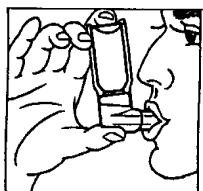
The correct operation of the metered aerosol apparatus is essential for successful therapy.

- 1) Remove the protective cap.
- 2) Shake the metered dose aerosol well before each use. (See Fig 1)



(fig. 1)

- 3) Breathe out deeply.
- 4) Hold the metered dose aerosol (as shown in Fig 2), and close lips over the mouthpiece.



(fig. 2)

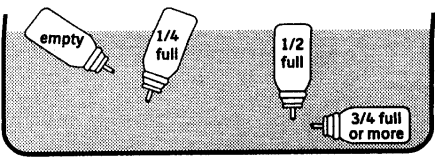
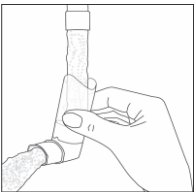
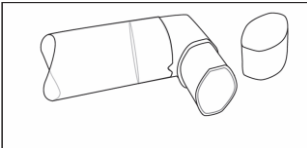
- 5) Breathe in as deeply as possible, pressing the base of the container firmly at the same time, this releases one metered dose. Hold the breath for a few seconds, then remove the mouthpiece from the mouth and breathe out.
- 6) Replace the protective cap after use.

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

The plastic mouthpiece has been specially designed for use with COMBIVENT metered dose aerosol to ensure that you always get the right amount of the medicine. The mouthpiece must never be used with any other metered dose aerosol nor must the COMBIVENT metered dose aerosol be used with any mouthpiece other than the one supplied with the product.

The container is under pressure and should on no account be opened by force or exposed to temperatures exceeding 50°C.

#### Test for remaining solution and cleaning instructions

|   |  |
|---|--|
| <p>The container is not transparent. It is not therefore possible to see when it is empty. The inhaler will deliver <b>200</b> doses. When these have all been used the canister may still appear to contain a small amount of fluid. The inhaler should, however, be replaced because you may not get the right amount of treatment.</p> <p>The amount of treatment in your inhaler can be checked as follows:</p> |  |
| <ul style="list-style-type: none"> <li>- Shaking the canister will show if there is any remaining fluid.</li> <li>- Alternatively remove the canister from the plastic mouthpiece and put it into a container of water. The contents of the canister can be estimated by observing its position in the water.</li> </ul>  |  |
| (fig. 3)  |  |
| <p>Clean your inhaler at least once a week.</p> <p>It is important to keep the mouthpiece of your inhaler clean to ensure that medicine does not build up and block the spray.</p> <p>For cleaning, first take off the dust cap and remove the canister from the inhaler. Rinse warm water through the inhaler until no medication build-up and/or dirt is visible.</p>   |   |
| (fig. 4)  |  |
| <p>After cleaning shake out the inhaler and let it air-dry <b>without</b> using any heating system. Once the mouthpiece is dry, replace the canister and the dust cap.</p>  |  |
| (fig. 5)  |  |

## **Toxicology**

The acute toxicity of COMBIVENT after single inhalation administration was tested in rats and dogs. Up to the highest technically feasible dose (rat: 887/5397 µg/kg ipratropium bromide/salbutamol, dog: 164/861 µg/kg ipratropium bromide/salbutamol) there were no

indications of systemic toxic effects, the combination was locally well tolerated. The approximate LD<sub>50</sub> after intravenous administration was calculated for the individual substances to be between 12 and 20 mg/kg for ipratropium bromide and between 60 and 73 mg/kg for salbutamol sulphate depending on the species tested (mouse, rat, dog).

Two 13-week inhalation toxicity studies in rats and dogs have been performed with the combination of ipratropium bromide and salbutamol sulphate. In these studies, the heart proved to be the target organ. In the rat at dosages of 34/197 to 354.5/2604 µg/kg/day ipratropium bromide/salbutamol sulphate, a non dose dependent increase in heart weights was present, however without any histopathological correlate. In the dog at doses of 32/198 to 129/790 µg/kg/day ipratropium bromide/salbutamol sulphate, slightly increased heart rates and, at higher dosages, histopathologically detectable scars and/or fibrosis in the papillary muscle of the left ventricle, sometimes accompanied with mineralisation, were observed.

The cardiovascular findings obtained in the above mentioned studies must be regarded as well known effects of β-adrenergics such as salbutamol. The toxicological profile of ipratropium bromide is also well known for many years and characterised by typical anticholinergic effects as dryness of the mucosal membranes of the head, mydriasis, keratoconjunctivitis sicca (dry eye) in dogs only, reduction in tone and inhibition of motility in the gastrointestinal tract (rat).

Reproduction toxicity studies are available for the two individual components of COMBIVENT.

Salbutamol sulphate caused cleft palates at high subcutaneous dosages in mice, starting at dosages in the range of the inhalation MRHDD (based on mg/m<sup>2</sup>). However this phenomenon is well known and occurs also after the administration of other beta-adrenergic compounds. Today it is assumed that this effect is caused by an increase in the maternal corticosterone level and might be regarded as a result of general stress not relevant for other species. Apart from these findings, the studies performed with salbutamol sulphate and with ipratropium bromide revealed only marginal effects, if any, on embryos, foetuses and pups and these only in the range of maternal toxicity.

Both individual substances were tested in numerous *in-vivo* and *in-vitro* genotoxicity tests. Neither salbutamol sulphate nor ipratropium bromide showed any evidence of mutagenic properties. In addition COMBIVENT did not show genotoxic activity in *in vitro* assays.

Salbutamol sulphate and ipratropium bromide were tested individually for neoplastic properties in several carcinogenicity studies. After oral administration of salbutamol sulphate in rats, but not in mice, hamsters and dogs, an increased incidence of leiomyomas of the mesovarium was observed at dosages about ≥ 20-fold higher than inhalation MRHDD. The development of the leiomyomas was found to be preventable by simultaneous administration of beta-blockers. These findings were assessed to be species specific and therefore without clinical relevance, consequently not leading to any restriction of the clinical use of salbutamol sulphate.

Ipratropium bromide revealed no carcinogenic potential when tested orally in mice and rats.

No evidence was found of any immunotoxicological effect caused by COMBIVENT or its individual active ingredients.

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