

Combivent



1. NAME OF THE MEDICINAL PRODUCT

COMBIVENT® nebuliser solution in unit dose vials

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 unit-dose vial (2.5 mL) nebuliser solution contains:

(8r) -3 α -hydroxy-8-isopropyl-1 α H,5 α H-tropanium bromide (+)-tropate monohydrate (= ipratropium bromide) corresponding to 500 mcg ipratropium bromide anhydrous	522mcg
Di[(RS)-2-tert-butylamino-1-(4-hydroxy-3-hydroxymethyl-phenyl) ethanol] sulphate (= salbutamol sulphate) corresponding to 2500 mcg salbutamol base	3013mcg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nebuliser solution.

Clear, colourless or almost colourless liquid, free from suspended particles, filled into polyethylene unit dose vials.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COMBIVENT® nebuliser solution in unit dose vials are indicated for the management of reversible bronchospasm associated with obstructive airway diseases in patients who require more than a single bronchodilator.

4.2 Posology and method of administration

SPECIAL POPULATIONS

Patients with hepatic or renal impairment

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

Paediatric population

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

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

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

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

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

COMBIVENT® nebuliser solution in unit dose vials (UDVs)

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

Treatment should be initiated and administered under medical supervision, e.g. in the hospital setting. Home based treatment can be recommended in exceptional cases (severe symptoms or experienced patients requiring higher doses) when a low dose rapid acting beta-agonist bronchodilator has been insufficient in providing relief after consultation with an experienced physician.

The treatment with the nebuliser solution in UDVs should always be started with the lowest recommended dose (1 UDV). In very severe cases two unit dose vials may be required for symptom relief. Administration should be stopped when sufficient symptom relief is achieved.

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, the administration of a second unit dose vial may be required. Patients should be advised to consult the physician or the nearest hospital immediately in these cases.

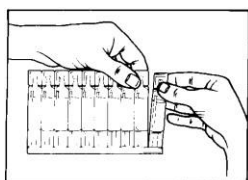
Maintenance treatment:

1 unit dose vial three or four times daily.

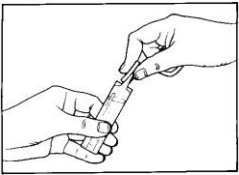
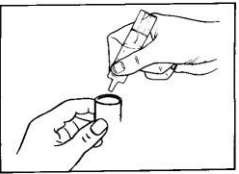
Instructions for use

The unit dose vials are intended only for inhalation with suitable nebulising devices and must not be taken orally or administered parenterally.

The content of the unit dose vials does not need to be diluted for nebulization.



1. Prepare the nebulizer for filling, according to the instructions provided by the manufacturer or physician.
2. Open the pouch foil and tear one unit dose vial from the strip.

	3. Open the unit dose vial by firmly twisting the top. 4. Squeeze the content of the unit dose vial into the nebulizer 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® nebuliser solution with other drugs in the same nebuliser.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypersensitivity

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

Paradoxical bronchospasm

As with other inhaled medicines COMBIVENT® may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, COMBIVENT® should be discontinued immediately and substituted with an alternative therapy.

Ocular complications

There have been isolated cases 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 beta2- agonist, has come in contact with the eyes.

Eye pain or discomfort, blurred vision, visual halos or colored 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®. Care must be taken not to allow the solution or mist to enter into the eyes. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.

It is recommended that COMBIVENT® nebuliser solution in unit dose vials (UDV) be administered via a mouth piece. If this is not available and a nebuliser mask is used, it must fit properly.

Systemic effects

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.

Cardiovascular effects

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, arrhythmia 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.

Hypokalaemia

Potentially serious hypokalaemia may result from beta2-agonist therapy. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm. In such situations, monitoring of serum potassium levels is recommended.

Gastro-intestinal motility disturbances

Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances.

Dyspnoea

In the case of acute, rapidly worsening dyspnoea patients should be advised to consult a physician immediately.

Interference with laboratory tests or other diagnostic measures

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).

4.5 Interaction with other medicinal products and other forms of interaction

The chronic co-administration of COMBIVENT® with other anticholinergic drugs has not been studied.

Therefore, the chronic co-administration of COMBIVENT® with other anticholinergic drugs is not recommended.

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

Beta₂-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.

Beta₂-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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of COMBIVENT® during human pregnancy has not been established. 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. The usual precautions regarding the use of drugs in pregnancy, especially during the first trimester, should be observed.

For ipratropium bromide, nonclinical 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 nonclinical studies did not indicate direct or indirect harmful effects unless the inhalation Maximum Recommended Human Daily Dose (MRHDD) was exceeded.

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, especially when administered by inhalation. However, because many drugs are excreted in breast milk, caution should be exercised when COMBIVENT® is administered to nursing mothers.

Fertility

No studies on the effect on human fertility have been conducted for COMBIVENT®. Clinical data on fertility are neither available for the combination of ipratropium bromide and salbutamol sulphate nor for each of the two components of the combination. Nonclinical studies performed with ipratropium bromide and salbutamol showed no adverse effect on fertility.

4.7 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.

4.8 Undesirable effects

Summary of the safety profile

Many of the listed undesirable effects can be assigned to the anticholinergic and beta2-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.

The following adverse reactions have been reported during use of COMBIVENT® in clinical trials and during the post-marketing experience.

Immune system disorders:

Anaphylactic reaction

Hypersensitivity

Metabolism and nutrition disorders:

Hypokalaemia

Psychiatric disorders:

Nervousness

Mental disorder

Nervous system disorders:

Headache

Tremor Dizziness

Eye disorders:

Accommodation disorder

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

Cardiac disorders:

Palpitations
Tachycardia
Arrhythmia
Atrial fibrillation
Supraventricular tachycardia
Myocardial ischaemia

Respiratory, thoracic and mediastinal disorders:

Cough
Dysphonia
Dry throat
Bronchospasm
Bronchospasm paradoxical
Laryngospasm
Pharyngeal oedema

Gastrointestinal disorders:

Dry mouth
Nausea
Throat irritation
Diarrhoea
Vomiting
Constipation
Gastrointestinal motility disorder
Mouth oedema
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

4.9 Overdose

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, hypokalaemia, widening of the pulse pressure, anginal pain, arrhythmias and flushing. Metabolic acidosis has also been observed with overdosage of salbutamol.

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

Therapy

Treatment with COMBIVENT® should be discontinued. Acid base and electrolyte monitoring should be considered.

Administration of sedatives, and in severe cases intensive therapy may be needed.

Beta-receptor blockers, preferably beta₁-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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergics in combination with anticholinergics for obstructive airway diseases.

ATC Code: R03AL02

Mode of action and pharmacodynamics

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In nonclinical 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 Ca^{++} which is caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. Ca^{++} release is mediated by the second messenger system consisting of IP₃ (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.

Salbutamol sulphate is a beta₂-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® provides the simultaneous release of ipratropium bromide and salbutamol sulphate allowing the additive effect on both muscarinic and beta₂-adrenergic receptors in the lung resulting in a bronchodilation which is superior to that provided by each single agent.

Paediatric population

COMBIVENT® has not been studied in the paediatric population.

Clinical Trials

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.

5.2 Pharmacokinetic properties

From a pharmacokinetic perspective, the efficacy observed in the COMBIVENT® pressurized inhalation, suspension 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 the 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.

Coadministration 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

Ipratropium

Absorption

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 3-13% 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 28% respectively. Taking this into account, swallowed dose portions of ipratropium bromide do not relevantly contribute to systemic exposure.

Distribution

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. Nonclinical data indicate that the quaternary amine ipratropium does not cross the placental or the blood-brain barrier. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective

Biotransformation

After intravenous administration approximately 60% of a dose is metabolised, the major portion probably in the liver by oxidation.

Elimination

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. In an excretion balance study cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for, 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. The half-life for elimination of drug-related radioactivity (parent compound and metabolites) is 3.6 hours.

Salbutamol

Absorption and Distribution

Salbutamol is rapidly and completely absorbed following oral 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®. 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. In nonclinical trials, levels of approximately 5% of the plasma level of salbutamol are found in the brain. However, this amount probably represents the distribution of the substance in the extracellular water of the brain.

Biotransformation and Elimination

Following this single inhaled administration, approximately 27% of the estimated mouthpiece dose is excreted unchanged in the 24-hour urine. 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. After oral administration urinary excretion of unchanged drug and sulphate conjugate were 31.8% and 48.2% of the dose, respectively.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Please refer to the packaging for information on shelf-life.

6.4 Special precautions for storage

For single use only. Discard any remaining solution. Store below 30°C.

6.5 Nature and contents of container

Polyethylene unit dose vials containing 2.5 ml of solution
Box of 20's

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER/MANUFACTURER

Manufactured by
Laboratoire Unither Amiens Cedex 2, France
for
Boehringer Ingelheim International GmbH Binger Strasse 173 D55126
Ingelheim Am Rhein Germany

8. MARKETING AUTHORISATION NUMBER

MAL10100034ACZ
SIN09558P
BRU10020406P

9. DATE OF REVISION OF THE TEXT

14 June 2023