Composition
1 unit-dose vial (2.5 ml) solution for inhalation contains:
Ipratropium bromide corresponding to 0.5 mg ipratropium bromide anhydrous 0.52 mg
Salbutamol sulphate corresponding to 2.5 mg salbutamol base 3.01 mg
Excipients : sodium chloride, hydrochloric acid, purified water

Indications
COMBIVENT UDV is indicated for the management of reversible bronchospasm associated with obstructive pulmonary diseases and acute asthma attack in patients who require more than a single bronchodilator.

Dosage and Administration
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.

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

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

Dosage:
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 the doctor or the nearest hospital immediately.

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 should 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 nebuliser for filling, according to the instructions provided by the manufacturer or doctor.

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 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 solution for inhalation with other drugs in the same nebuliser.

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

**Special Warnings and Precautions**
Immediate hypersensitivity reactions may occur after administration of COMBIVENT solution for inhalation, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and oropharyngeal oedema.

**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 beta2-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 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 UDV. 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.

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 beta2-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 patient's therapy plan should be reviewed by a doctor.

The result of animal experiments indicates 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 UDV 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.

Patients must be instructed in the correct administration of COMBIVENT UDV.

**Prolonged use**

If bronchial obstruction deteriorates it is inappropriate and possibly hazardous to simply increase the use of COMBIVENT UDV beyond the recommended dose over extended periods of time.

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).
**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.

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 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, preclinical studies have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man.

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.

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).

**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.

**Side Effects**

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.

**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:**
Arrhythmia
Atrial fibrillation
Myocardial ischaemia
Palpitations
Supraventricular tachycardia
Tachycardia
Blood pressure diastolic decreased
Blood pressure systolic increased

**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
Oedema mouth
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

**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, 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 accomodation disorders) 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 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.

**Pharmacological 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 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).

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 unit dose vials provide 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.

Controlled studies in patients with reversible bronchospasm 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.
Pharmacokinetics

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 (Vdss) is approximately 176 L (≈ 2.4 L/kg). The drug is minimally (less than 20%) bound to plasma proteins. Preclinical studies with rats and dogs revealed that the quarternary 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.

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
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. 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 (Vz) is approximately 156 L (= 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. 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.

**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\(_{50}\) 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\(^2\)). 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* tests. Neither salbutamol sulphate nor ipratropium bromide showed any evidence of mutagenic properties.

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 $\geq 20$-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.

**Availability**
Solution for inhalation in unit dose vials
Box contains 10 vials of 2.5 ml
Box contains 10 vials of 2.5 ml (ASKES)
Box contains 20 vials of 2.5 ml
Box contains 20 vials of 2.5 ml (ASKES)

**Store below 30°C, protect from light.**
**Store in a safe place out of the reach of children**
**Only on doctor's prescription.**

Manufactured by:
Laboratoire UNITHER
Amiens, France

Shelflife:
24 months

For:
Boehringer Ingelheim International Gmbh
Germany

Imported by:
PT. Boehringer Ingelheim Indonesia
Bogor, Indonesia.