

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Combiprasal 0.5 mg / 2.5 mg per 2.5 ml nebuliser solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose container (2.5 ml) contains 0.5 mg ipratropium bromide (as monohydrate) and 2.5 mg salbutamol (as salbutamol sulfate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.

A clear, colourless solution (pH approx. 3.5, osmolality approx. 300 mOsm/kg).

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Combiprasal is indicated for the management of bronchospasm in patients suffering from chronic obstructive pulmonary disease (COPD) who require regular treatment with both ipratropium bromide and salbutamol.

4.2 Posology and method of administration

Posology

The recommended dose is:

Adults (including elderly patients and children over 12 years)

The content of one single-dose container three or four times daily.

Paediatric population (under 12 years)

The safety and efficacy of Combiprasal in children aged under 12 years have not been established. Combiprasal is not recommended in children below 12 years of age.

Method of administration

Inhalation use.

Drug delivery characteristics were studied *in vitro* using an eFlow rapid electronic nebuliser and a PARI LC Sprint nebuliser:

Nebuliser	Droplet size distribution [micrometer]			Drug delivery rate [microgram/minute]	Total drug delivered [microgram]
	D10	D50*	D90		
eFlow rapid electronic nebuliser	2.5	4.7	10.4	Salbutamol: 361.2 Ipratropium: 73.6	Salbutamol: 1185.7 Ipratropium: 240.6
PARI LC Sprint nebuliser (used with PARI Boy SX compressor)	1.4	4.2	13.2	Salbutamol: 137.9 Ipratropium: 28.1	Salbutamol: 1031.7 Ipratropium: 206.7

* Median Mass Diameter

No information is available in respect of pulmonary inhalation and deposition patterns across nebuliser systems that have not been studied.

The use of an alternative untested nebuliser system may alter the pulmonary deposition of the active substances, this in turn may alter the efficacy and safety of the product and dose adjustment may then become necessary.

Instructions for use with the eFlow rapid electronic nebuliser:

1. The nebuliser should be prepared by following the manufacturer's instructions.
2. A new single-dose container should be carefully separated from the strip.
3. The remaining single-dose containers should be put back in the sachet and the sachet should be closed by crimping over the lap. The sachet should be stored in the carton.
4. The single-dose container should be held upright and opened by simply twisting off the top.
5. Unless otherwise indicated the content of one single-dose container should be squeezed into the nebuliser chamber.
6. The nebuliser chamber should be closed by placing the cap on the nebuliser chamber so that the slots in the side of the cap are positioned above the notches in the chamber. Pressing gently the cap should be turned clockwise as far as it will go. The closing mechanism is functioning correctly if the cap seal rises with the turning motion to form a seal. It should be checked that all parts are connected tightly and that the nebuliser chamber is sealed.
7. The patient should hold the nebuliser handset in his/her hand and sit in an upright position and relax. The mouthpiece should be taken between the teeth and

the lips should be closed around it. The lips should not touch the blue expiratory valve. The ON/OFF button on the control unit should be pressed. A green LED beside the ON/OFF button lights up and an audible signal (1 beep) is emitted to indicate proper functioning. The patient should be instructed to inhale and exhale through the mouthpiece as slowly and deeply as possible.

8. The nebuliser device switches off automatically when the nebuliser solution is used up. When inhalation has been completed successfully a tick will appear on the display. Any remaining solution (about 1 ml cannot be nebulised and remains in the nebuliser chamber) should be discarded.

9. When the inhalation session has ended the power adapter plug should be disconnected from the socket.

Instructions for use with the PARI LC Sprint nebuliser:

1. The nebuliser is operated with the PARI Boy SX compressor and should be prepared by following the manufacturer's instructions.

2. A new single-dose container should be carefully separated from the strip.

3. The remaining single-dose containers should be put back in the sachet and the sachet should be closed by crimping over the lap. The sachet should be stored in the carton.

4. The single-dose container should be held upright and opened by simply twisting off the top.

5. The closure on the nebuliser upper section should be released by pressing the thumb against the underside of the cap.

6. Unless otherwise indicated the content of one single-dose container should be squeezed into the nebuliser chamber.

7. The cap of the nebuliser should be closed. The cap should snap into place. All parts of the nebuliser should be firmly connected to each other.

8. The patient should sit in an upright position and relax. The compressor should be switched on. The mouthpiece should be taken between the teeth and the lips should be closed around it. The patient should be instructed to breathe in through the mouthpiece as slowly and deeply as possible and to breathe out in their own time.

9. The inhalation should be continued until the solution in the nebuliser chamber is used up (signalled by a change in the sound of the nebuliser).

10. The compressor should be switched off as soon as inhalation is finished. Any remaining solution in the nebuliser chamber (some solution will remain after inhalation) should be discarded.

For eFlow rapid electronic nebuliser and PARI LC Sprint nebuliser:

The manufacturer's instructions should be followed for cleaning the nebuliser. It is important that the nebuliser is kept clean.

The full instructions for use of the nebuliser in the leaflet provided with the nebuliser system should be read before starting the inhalation.

As the single-dose containers contain no preservatives it is important that the contents are used immediately after opening and a fresh single-dose container is used for each administration to avoid microbial contamination. Partly used, opened or damaged single-dose containers should be discarded.

4.3 Contraindications

Patients with hypertrophic obstructive cardiomyopathy or tachyarrhythmia.

Patients with known hypersensitivity to the active substances or to atropine or its derivatives or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

If it is necessary to use higher doses than recommended to control the symptoms of bronchoconstriction (or bronchospasm) the patient's treatment plan should be reassessed.

Dyspnoea

Patients should be instructed to consult a doctor immediately in the event of acute, rapidly worsening dyspnoea or if a reduced response to treatment becomes apparent.

Hypersensitivity

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

Paradoxical bronchospasm

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. COMBIPRASAL should be discontinued immediately, the patient should be assessed and alternative therapy instituted if necessary.

Ocular complications

There have been rare reports of ocular complications when aerosolised ipratropium bromide, either alone or in combination with a beta₂-adrenergic agonist, has been inadvertently sprayed into the eye. Patients must therefore be instructed in the correct use of COMBIPRASAL with their nebuliser and warned not to allow the solution or mist to enter the eyes. To avoid inadvertent entry of drug into the eye, it is preferable to administer the nebulised solution using a mouthpiece rather than a face mask.

Such ocular complications may include, mydriasis, blurring of vision, increased intraocular pressure, eye pain and narrow-angle glaucoma (including acute narrow-angle glaucoma). Patients who may be susceptible to glaucoma should be warned specifically about the need for ocular protection. Antiglaucoma therapy is effective in the prevention of acute narrow-angle glaucoma in susceptible individuals.

Eye pain or discomfort, blurred vision, visual halos or coloured images, in association with red eyes from conjunctival congestion or corneal oedema may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develops, treatment with miotic eye drops should be initiated and the patient should seek specialist advice immediately.

Systemic effects

In the following conditions COMBIPRASAL should only be used after careful risk/benefit assessment: inadequately controlled diabetes mellitus, recent myocardial infarction and/or severe organic heart or vascular disorders, hyperthyroidism, pheochromocytoma, prostatic hypertrophy, bladder-neck obstruction and risk of narrow-angle glaucoma.

Cardiovascular effects

Cardiovascular effects may be seen with sympathomimetic drugs, including medicinal products containing salbutamol. 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, arrhythmias 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 such as dyspnoea and chest pain, as they may be either respiratory or cardiac in origin.

Hypokalaemia

Potentially serious hypokalaemia may result from beta₂-agonist therapy. Particular caution is advised in severe airway obstruction, as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics.

Hypokalaemia can bring about increased sensitivity to arrhythmias in patients being treated with digoxin. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm. It is recommended that serum levels of potassium are monitored in such situations.

Gastro-intestinal motility disturbances

Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances and therefore ipratropium bromide, as with other anticholinergics, should be used with caution in these patients.

Lactic acidosis

Lactic acidosis has been reported in association with high therapeutic doses of intravenous and nebulised short-acting beta-agonist therapy, mainly in patients being treated for an acute exacerbation of bronchospasm in severe asthma or chronic obstructive pulmonary disease (see section 4.8 and 4.9). Increase in lactate levels may lead to dyspnoea and compensatory hyperventilation, which could be misinterpreted as a sign of asthma treatment failure and lead to inappropriate intensification of short-acting beta-agonist treatment. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting.

Interference with laboratory tests or other diagnostic measures

The use of COMBIPRASAL may lead to positive results in doping tests.

Paediatric population

COMBIPRASAL should not be used in children under 12 years of age (see section 4.2).

Dental caries

Dental caries has been reported with salbutamol use. It is recommended, particularly in children, to pay attention to proper oral hygiene and perform regular dental checkups.

4.5 Interaction with other medicinal products and other forms of interactions

The chronic co-administration of COMBIPRASAL with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of COMBIPRASAL with other anticholinergic drugs is not recommended.

The effect of other anticholinergic products may be potentiated.

Concurrent use of additional beta-agonists, corticosteroids, anticholinergics and xanthine derivatives may enhance the effect of COMBIPRASAL on airway function and may increase the severity of side effects. Due to opposing pharmacodynamic interaction with the salbutamol element, a potentially serious reduction in effect may occur during concurrent administration of beta-blockers.

Beta-adrenergic agents 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 cardiovascular side effects of beta₂-agonists. These patients should therefore be monitored closely. Alternatively, discontinuation of COMBIPRASAL prior to surgical operation should be considered.

Potentially serious hypokalaemia may result from beta₂-agonist therapy. Particular caution is advised in severe airway obstruction, as this effect may be potentiated by concomitant treatment with xanthine derivatives, diuretics and steroids.

Potentially serious arrhythmias may occur during concomitant administration of digoxin and COMBIPRASAL. The interaction risk is aggravated by hypokalaemia and should be monitored regularly. Hypokalaemia can bring about increased sensitivity to arrhythmias in patients being treated with digoxin (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the concomitant use of ipratropium bromide and salbutamol in pregnant women (in early stages of pregnancy). In animal studies there has been evidence of some harmful effects on the foetus at very high dose levels. The potential risk for humans is unknown. Combiprasal should not be used during pregnancy unless clearly necessary and caution should be exercised when prescribing to pregnant women (especially in the first trimester). At the end of pregnancy the inhibitory effect of Combiprasal on uterine contraction should be taken into account.

Breast-feeding

It is unknown whether ipratropium bromide is excreted into human breast milk. Salbutamol is excreted in human breast milk. There is insufficient/limited information on the excretion of Combiprasal in human or animal breast milk. A risk to the suckling child cannot be excluded. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Combiprasal should be made taking into account the benefit of breast-feeding to the child and the benefit of Combiprasal to the mother.

Fertility

No studies on the effect on human fertility have been conducted for Combiprasal. Animal studies reveal no special hazard for humans based on conventional studies of toxicity to reproduction (see section 5.3).

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 the treatment with Combiprasal. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machines.

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 the medicinal product. As with all inhalation therapy COMBIPRASAL may show symptoms of local irritation.

Adverse reactions were identified from data obtained in clinical trials and post-approval data of nebuliser solutions containing the combination ipratropium bromide and salbutamol.

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

Tabulated list of adverse reactions

Based on the MedDRA system organ class and frequencies, adverse events are listed in the table below.

Frequencies are defined as:

very common ($\geq 1/10$)

common ($\geq 1/100$ to $< 1/10$)

uncommon ($\geq 1/1,000$ to $< 1/100$)

rare ($\geq 1/10,000$ to $< 1/1,000$)

very rare ($< 1/10,000$)

not known (cannot be estimated from the available data)

The following side effects have been reported based on clinical trials involving 3488 patients.

System organ class	Frequency	Symptom
Immune system disorders	Rare	Anaphylactic reaction, Hypersensitivity, Angioedema of the face, lips and tongue
Metabolism and nutritional disorders	Rare	Hypokalaemia
	Not known	Lactic acidosis

System organ class	Frequency	Symptom
		(see section 4.4)
Psychiatric disorders	Uncommon	Nervousness
	Rare	Mental disorders
Nervous system disorders	Uncommon	Headache, Dizziness, Tremor
Eye disorders	Rare	Accommodation disorders, Corneal oedema, Glaucoma ⁽¹⁾ , Eye pain ⁽¹⁾ , Mydriasis ⁽¹⁾ , Blurred vision, Conjunctival hyperaemia, Increased intraocular pressure ⁽¹⁾ , Halo vision
Cardiac disorders	Uncommon	Palpitations, Tachycardia
	Rare	Arrhythmia, Atrial fibrillation, Supraventricular tachycardia, Myocardial ischaemia
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough, Dysphonia, Throat irritation
	Rare	Bronchospasm, Laryngospasm, Paradoxical bronchospasm ⁽²⁾ , Dry throat, Pharyngeal oedema
Gastrointestinal disorders	Uncommon	Dry mouth, Nausea

System organ class	Frequency	Symptom
	Rare	Gastrointestinal motility disorder, e.g.: Diarrhoea, Constipation, Vomiting; Mouth oedema, Stomatitis
	Not known	Dental caries
Skin and subcutaneous tissue disorders	Uncommon	Skin reactions
	Rare	Hyperhidrosis, Rash, Pruritus, Urticaria
Musculoskeletal, connective tissue and bone disorders	Rare	Myalgia, Muscle spasms, Muscular weakness
Renal and urinary disorders	Rare	Urinary retention ⁽³⁾
General disorders and administration site conditions	Rare	Asthenia
Investigations	Uncommon	Systolic blood pressure increased
	Rare	Diastolic blood pressure decreased

⁽¹⁾ ocular complications have been reported when aerolised ipratropium bromide, either alone or in combination with an adrenergic beta₂-agonist, has come into contact with the eyes - see section 4.4.

⁽²⁾ as with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. COMBIPRASAL should be discontinued immediately, the patient should be assessed and alternative therapy instituted if necessary - see section 4.4.

⁽³⁾ the risk of urinary retention may be increased in patients with pre-existing urinary outflow tract obstruction.

The following other side effects have also been reported rarely for nebuliser solutions containing ipratropium bromide and salbutamol: restlessness, hyperactivity in children, anxiety, depression, extrasystoles, dyspnoea.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRC Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms

Acute effects of overdosage with ipratropium bromide are mild and transient (such as dry mouth, visual accommodation disorders) due to its poor systemic absorption after either inhalation or oral administration. Any effects of overdosage are therefore likely to be related to the salbutamol component.

Manifestations of overdosage with salbutamol may include tachycardia, anginal pain, hypertension, palpitations, tremor, hypokalaemia, hypotension, widening of the pulse pressure, arrhythmias, flushing, chest pain, restlessness and dizziness.

Metabolic acidosis has also been observed with overdosage of salbutamol, including lactic acidosis which has been reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy, therefore monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of tachypnea despite resolution of other signs of bronchospasm such as wheezing) may be indicated in the setting of overdose.

Patients should therefore be monitored closely for potential unwanted effects from overdosage of salbutamol.

Treatment

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

The preferred antidote for overdose with salbutamol is a cardioselective beta-blocking agent, but caution should be used in administering these drugs to patients with a history of bronchospasm.

Hypokalaemia may occur following overdose with salbutamol and therefore serum potassium levels should be monitored.

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 an anticholinergic agent, which inhibits vagally-mediated reflexes by antagonising the muscarinic action of acetylcholine. The bronchodilation following inhalation of ipratropium bromide is primarily local and specific to the lung and not systemic in nature.

Salbutamol is a beta₂-adrenergic agonist, which acts on airway smooth muscle resulting in relaxation. Salbutamol relaxes all smooth muscle from the trachea to the terminal bronchioles and protects against bronchoconstrictor challenges.

COMBIPRASAL provides the simultaneous delivery of ipratropium bromide and salbutamol sulfate producing effects on both muscarinic and beta₂-adrenergic receptors in the lung. This provides increased bronchodilation over that provided by each agent singly.

5.2 Pharmacokinetic properties

Absorption characteristics of the combination ipratropium bromide - salbutamol sulfate

Co-nebulisation of ipratropium bromide and salbutamol sulfate does not potentiate the systemic absorption of either component. The increased pharmacodynamic activity of TRADENAME is due to the combined local effect of both substances on the lung.

Ipratropium

Absorption

Based on a cumulative excretion value of about 3-4%, the range of total systemic bioavailability of inhaled doses of ipratropium bromide is estimated at 7 to 9%.

Distribution

Kinetic parameters describing the disposition of ipratropium bromide 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 (≈ 2.4 l/kg). The drug is minimally (less than 20%) bound to plasma proteins. Ipratropium bromide, like any other quaternary ammonium compound, is not expected to readily cross the blood brain barrier.

Biotransformation

Ipratropium has a total clearance of 2.3 l/min and a renal clearance of 0.9 l/min. After administration via inhalation approximately 87-89% of a dose is metabolised probably mainly in the liver by oxidation.

Elimination

After administration via inhalation about 3.2% of drug related radioactivity, i.e. parent compound and metabolites, is eliminated in urine. Total radioactivity excreted via the faeces was 69.4% for this route of administration. The half-life for elimination of drug-related radioactivity following inhalation is 3.6 hours. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

Salbutamol

Absorption

Salbutamol is rapidly and completely absorbed following oral administration either by the inhaled or the 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 COMBIPRASAL.

Distribution

Kinetic parameters were calculated from plasma concentrations after i.v. administration. The apparent volume of distribution (V_z) is approximately 156 l (≈ 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

Salbutamol is conjugatively metabolised to salbutamol 4'-O-sulfate. The R(-)-enantiomer of salbutamol (levosalbutamol) is preferentially metabolised and is therefore cleared from the body more rapidly than the S(+)-enantiomer.

Elimination

Following a 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.

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 sulfate conjugate. After oral administration urinary excretion of unchanged drug and sulfate conjugate were 31.8% and 48.2% of the dose, respectively.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, carcinogenic potential or toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sulfuric acid 10% (for pH-adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products in the same nebuliser.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze. Store in the original package in order to protect from light and evaporation.
Do not use if solution is discoloured.

6.5 Nature and contents of container

COMBIPRASAL is bottled in low-density polyethylene (LDPE) single-dose containers containing 2.5 ml of solution. The single-dose containers are formed into strips of 5 containers which are packed in an aluminium laminated sachet.

COMBIPRASAL is available in pack sizes containing 10, 20, 50, 60, 100 or 150 single-dose containers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Use immediately after first opening the single-dose container. Discard immediately after first use.

Partly used, opened or damaged single-dose containers should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pharma Stulln GmbH
Werksstrasse 3
92551 Stulln
Germany

8 MARKETING AUTHORISATION NUMBER

PA1815/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th January 2014

Date of last renewal: 23rd September 2018

10 DATE OF REVISION OF THE TEXT

September 2018