1. NAME OF THE MEDICINAL PRODUCT

Ipratropiumbromide/Salbutamol Sandoz 0,5/2,5 mg per 2,5 ml, verneveloplossing

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5ml ampoule contains 0.5 mg of ipratropium bromide (as 525 micrograms ipratropium bromide monohydrate) and 2.5 mg of salbutamol (as sulphate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nebuliser Solution.

A polyethylene ampoule containing clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

[Nationally completed name] 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 and children over 12 years): The content of one ampoule three or four times daily.

Paediatric population: [nationally completed name] is not recommended in children below 12 years of age due to lack of data on safety and efficacy

Method of administration

Inhalation use.

[nationally completed name] may be administered from a suitable nebuliser, e.g. PARI LC PLUS Nebuliser, jet nebulizer, or an intermittent positive pressure ventilator after the single dose ampoule has been opened and its contents transferred to the nebuliser chamber. The use of the solution for nebulization is not only limited to the given examples, but can also be based on the experience of the clinical professional. For full instructions on the use of the nebuliser the patient should be instructed to read the leaflet of the respective device carefully before starting the inhalation.

Drug delivery characteristics were studied in vitro using the PARI LC PLUS nebuliser device:

Droplet size distribution (micrometer)			**Drug delivery rate** (micrograms/min)	**Total drug delivered** (micrograms/2,5 ml)
D10	D50	D90		
1	4	10	Salbutamol: 78.30 Ipratropium: 15.31	Salbutamol: 532.96 Ipratropium: 106.23

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.

The nebuliser solution in the single dose ampoules is intended for inhalation use only and should not be taken orally or administered parenterally.

i. Prepare the nebuliser by following the manufacturer's instructions and the advice of your doctor.

ii. Carefully separate a new ampoule from the strip. Never use an ampoule that has been opened already.

iii. Open the ampoule by simply twisting off the top always taking care to hold it in an upright position.

iv. Unless otherwise instructed by your doctor, squeeze all the contents of the plastic ampoule into the nebuliser chamber.

v. Assemble the nebuliser and use it as directed by your doctor. The duration of treatment for the inhalation of a complete dose is usually between five and 15 minutes.

vi. After nebulisation clean the nebuliser according to the manufacturer's instructions. It is important that the nebuliser is kept clean.

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

Any nebuliser solution remaining in the nebuliser chamber should be discarded.

It is strongly recommended that [nationally completed name] should not be mixed with other medicines in the same nebuliser

4.3 Contraindications

Hypersensitivity to the active substances (salbutamol and/or ipratropium bromide), to atropine or its derivatives, or to any of the excipients listed in section 6.1.

Patients with hypertrophic obstructive cardiomyopathy or tachyarrhythmia.

4.4 Special warnings and precautions for use

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 all inhaled medicinal products, ipratropium/salbutamol may result in paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, ipratropium/salbutamol must be discontinued immediately and a replacement therapy initiated.

Dyspnoea
In case of an acute, rapidly deteriorating dyspnoea (tightness of the chest), patients should be advised to consult a physician immediately.

Systemic effects
In the following conditions [nationally completed name] should only be used after careful assessment of risk/benefit, particularly if higher doses than recommended are used:

- inadequately controlled diabetes mellitus,
- recent myocardial infarction and/or severe heart and/or vascular disorders,
- hyperthyroidism,
- phaeochromocytoma,
- increased risk of narrow-angle glaucoma,
- prostatic hypertrophy,
- bladder outflow obstruction.

Cardiovascular effects
Cardiovascular effects may be seen with sympathomimetics, including 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 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.

Ocular complications
Rare cases of ocular complications have been reported (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma and eye pain) when ipratropium bromide, alone or in combination with a $beta_2$-agonist, comes into contact with the eyes.

Eye pain, eye discomfort, blurred vision, visual halos and coloured images, together 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 miotics should be initiated and specialist advice should be sought.

Therefore, patients should be instructed properly about the correct use of ipratropium/salbutamol. Care must be taken to ensure that no solution or mist comes into contact with the eyes. Particularly patients who may be pre-disposed to glaucoma should protect their eyes well. It is recommended to administer the nebuliser solution with a mouthpiece. If this is not available and a face mask is used, this should be connected properly.

Gastrointestinal motility complaints
Patients with cystic fibrosis may have an increased risk of gastrointestinal motility complaints.

Hypokalaemia
Potentially serious hypokalaemia may result from beta$_2$-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. 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.

Lactate 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.

Paediatric population
[nationally completed name] should not be used in children (see section 4.2).

[Athletes must be aware that this medicine may cause a positive reaction to 'anti-doping' tests. - Information on doping warning – to be completed according to national requirements]

4.5 Interactions with other medicinal products and other forms of interaction

Chronic use of ipratropium/salbutamol concomitantly with other anticholinergics has not been investigated. Therefore, chronic use of ipratropium/salbutamol concomitantly with other anticholinergics is not recommended.

Beta$_2$-mimetics, anticholinergics, xanthine derivatives and corticosteroids can enhance the effect of ipratropium/salbutamol. Combined administration with other beta-mimetics, anticholinergics and xanthine derivatives may increase the severity of side effects.

Concomitant use of beta-blockers may adversely affect the bronchodilator effect of salbutamol. Concomitant use of ipratropium/salbutamol with non-cardioselective beta-blocker should be avoided.
Hypokalaemia induced by beta-mimetics may be aggravated by the concomitant use of xanthine derivatives (e.g. theophylline), glucocorticosteroids and diuretics. This should be taken into account especially in patients with severe airway obstruction.
Hypokalaemia may result in an increased risk of arrhythmias in patients treated with digoxin. It is recommended to monitor serum potassium levels.

The risk of hyperglycemia is increased when ipratropium/salbutamol is used in combination with corticosteroids.

The effect of other anticholinergic products may be potentiated.

Caution should be exercised in patients treated with monoamine oxidase inhibitors or tricyclic antidepressants, as the effect of beta$_2$-agonists may be potentiated.

Inhalation of halogenated carbohydrateanaesthetics, such as halothane, trichlorethylene and enflurane may increase the susceptibility to cardiovascular effects of beta$_2$-agonists.

4.6 Fertility, pregnancy and lactation

Pregnancy
Salbutamol
Experience with the use of beta$_2$-agonists during early pregnancy suggests that there is no harmful effect at the doses normally used in inhalation therapy. High systemic doses at the end of pregnancy can cause inhibition of uterine contractions and may give rise to the occurrence of beta$_2$-specific foetal/neonatal reactions such as tachycardia and hypoglycaemia. With inhalation therapy at recommended doses, the occurrence of these adverse side effects at the end of pregnancy is not expected.

Ipratropium
There are no human data on its use during pregnancy. Experimental animal studies show no direct or indirect harmful effects during pregnancy. The potential risk for humans is unknown. Ipratropium/salbutamol may therefore be used during pregnancy only if clearly indicated.

Breast-feeding
Salbutamol may be used during breast-feeding. It is not known to what extent ipratropium is excreted in human milk. Due to its pharmacokinetic properties, it is not likely that an extended amount is excreted in breast milk. Ipatropium/salbutamol may therefore be used during breastfeeding.

Fertility
Data on effects of ipratropium bromide and salbutamol on fertility do not suggest particularities.

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 [nationally completed name]. If patients experience the above mentioned side effects, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile
The most common side effects reported during clinical trials were headache, throat irritation, cough, dry mouth, gastrointestinal motility disorders (including constipation, diarrhoea and vomiting), nausea and dizziness.

Table of side effects
Adverse side effects were identified from data obtained in clinical trials and pharmacovigilance during post-marketing use.

The side effects are ranked according to the following classification:
very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to < 1/100), rare (≥1/10 000 to <1/1 000), very rare (≤1/10 000) and not known (cannot be estimated from the available data).

System organ class	Symptom	Frequency

Immune system disorders	Anaphylactic reaction*, hypersensitivity*	Rare
Metabolism and nutritional disorders	Hypokalaemia*	Rare
	Lactic acidosis (see section 4.4)	Not known
Psychiatric disorders	Nervousness	Uncommon
	Mental disorders*	Rare
Nervous system disorders	Headache, tremor, dizziness	Uncommon
Eye disorders	Accommodation disorders, corneal oedema, glaucoma*, increased intraocular pressure*, mydriasis*, blurred vision*, eye pain*, conjunctival hyperaemia*, halo vision*	Rare
Cardiac disorders	Palpitations, tachycardia, increased systolic blood pressure	Uncommon
	Arrhythmias, atrial fibrillation, supraventricular tachycardia*, myocardial infarction*, reduced diastolic blood pressure	Rare
Respiratory, thoracic and mediastinal disorders	Cough, dysphonia	Uncommon
	Dry throat, bronchospasm*, laryngospasm*, paradoxical bronchospasm*, pharyngeal oedema*	Rare
Gastrointestinal disorders	Dry mouth, nausea, throat irritation, dysgeusia	Uncommon
	Diarrhoea, vomiting, constipation, gastrointestinal motility disorders, oral oedema*, stomatitis*, dental caries	Rare
Skin and subcutaneous tissue disorders	Skin reactions	Uncommon
	Rash, pruritus, urticaria*, angioedema*, hyperhidrosis*	Rare
Musculoskeletal and connective tissue disorders	Myalgia*, muscle spasms, muscle weakness*	Rare
Renal and urinary disorders	Urinary retention	Rare
General disorders and site of administration disorders	Asthenia	Rare

* The adverse reaction has not been reported in the clinical trials of ipratropium/salbutamol. The frequency “rare” is calculated based on the total number of patients treated, in accordance with the EU SmPC guideline (3/3488 = 0.00086, which corresponds to 'rare').

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 the national reporting system listed in Appendix V*.

4.9 Overdose

Symptoms
Any effects of overdose are likely to be related to the salbutamol component.

Manifestations of overdose with salbutamol may include tachycardia, palpitations, arrhythmia, restlessness, sleep disturbances, and tremor particularly of the hands but also of whole body. Nausea, increased systolic blood pressure and decreased diastolic blood pressure can also be observed.

Occasionally, psychotic reactions have been observed after massive overdose of salbutamol.

In case of a salbutamol overdose, there may be an increasing displacement of potassium to the intracellular space, resulting in hypokalaemia and hyperglycaemia.

Metabolic acidosis has also been observed with overdose 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.

Due to the wide therapeutic window and the topical administration, the symptoms of ipratropium overdose (such as dry mouth and accommodation disorders) are expected to be mild and transient.

Treatment
Treatment with ipratropium/salbutamol should be discontinued. Control of the pH value and electrolytes should be considered.

Treatment after an overdose with a beta-sympathomimetic is mainly symptomatic. Depending on the individual circumstances, the following measures can be considered:

- Cardiac symptoms of salbutamol overdose may be treated with a cardioselective beta-blocker, but an elevated risk of bronchospasticity in patients with bronchial asthma has to be considered. In these patients, ECG control is recommended.
- In case of more pronounced hypotension, volume substitution (e.g. plasma substitutes) is recommended.
- In case of hypokalaemia, the electrolyte balance should be monitored and, if necessary, substitutions are to be recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergics in combination with anticholinergicsfor obstructive airway diseases ATC code: R03AL02.

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 beta$_2$-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.

[nationally completed name] provides the simultaneous delivery of ipratropium bromide and salbutamol sulphate producing effects on both muscarinic and beta$_2$-adrenergic receptors in the lung. This provides enhanced bronchodilation over that provided by each agent singly.

5.2 Pharmacokinetic properties

Ipratropium bromide is poorly absorbed after inhalation and systemic bioavailability is estimated to be less than 10% of the administered dose. Renal excretion is 46% of the dose and terminal elimination half-life is about 1.6 hours after intravenous administration. The half-life is 3.6 hours for total drug and metabolites after radiolabelling. Ipratropium bromide does not cross the blood-brain barrier.

Salbutamol is rapidly and completely absorbed following inhalation. Peak plasma salbutamol concentrations are seen within three hours of administration and the drug is excreted unchanged in the urine after 24 hours. The elimination half-life is 3-7 hours. Salbutamol will cross the blood-brain barrier reaching concentrations about 5% of plasma concentrations.

Co-nebulisation of ipratropium bromide and salbutamol sulphate does not potentiate the systemic absorption of either component. The increased pharmacodynamic activity of [nationally completed name] is due to the combined local effect of both drugs on the lung.

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 (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

After first opening the pouch, the closed ampoule can be stored for 3 months.

After first opening the ampoules:
Use immediately, discard any unused contents

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze.
Keep ampoules in the outer pouch or carton in order to protect from light.

6.5 Nature and contents of container

The pack is a Plastic Form fill Seal (FFS) ampoule (made of low-density polyethylene) containing 2.5 ml of nebuliser solution, 5 of which are over wrapped in a triple laminated pouch (polyester film/aluminium foil/ polyethylene film) and then packed into cardboard cartons.
Mutlipacks may contain 10 ampoules (2 pouches of 5 ampoules), 20 ampoules (4 pouches of 5 ampoules), 30 ampoules (6 pouches of 5 ampoules), 40 ampoules (8 pouches of 5 ampoules), 50 ampoules (10 pouches of 5 ampoules), 60 ampoules (12 pouches of 5 ampoules), 80 ampoules (16 pouches of 5 ampoules), 100 ampoules (20 pouches of 5 ampoules), 120 ampoules (24 pouches of 5 ampoules) and 150 ampoules (30 pouches of 5 ampoules).
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 ampoule.
Discard immediately after first use.
Partly used, opened or damaged ampoules should be disposed in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sandoz B.V.
Hospitaaldreef 29
1315 RC Almere
Nederland

8. MARKETING AUTHORISATION NUMBER

RVG 109136

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Datum van eerste verlening van de vergunning: 17 oktober 2012
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10 DATE OF REVISION OF THE TEXT

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