Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ipramol Steri-Neb 0.5mg / 2.5mg per 2.5ml Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5 ml ampoule contains 0.5 mg ipratropium bromide (as the monohydrate) and 2.5 mg salbutamol (as the sulfate).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.

A low density polyethylene ampoule containing a colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ipramol Steri-Neb is indicated in adults, adolescents and children aged 12 years and above.
Ipramol Steri-Neb 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

Inhalation use.

Posology

Adults (including elderly patients and children over 12 years):

The content of one ampoule three or four times daily.

Paediatric population

The safety and efficacy of Ipramol Steri-Neb in children aged below 12 years have not been established.

Method of administration
Ipramol Steri-Neb may be administered from a suitable nebuliser or an intermittent positive pressure ventilator after the single dose ampoule has been opened and its contents transferred to the nebuliser chamber. Administration should be in accordance with the manufacturer's instructions for the devices. The 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 solution remaining in the nebuliser chamber should be discarded.

It is strongly recommended that Ipramol Steri-Neb should not be mixed with other drugs in the same nebuliser.

4.3 Contraindications

Patients with hypertrophic obstructive cardiomyopathy or tachyarrhythmia.
Hypersensitivity to the active substances or to atropine and its derivatives or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Ipramol Steri-Neb should not be used in children (see section 4.2).

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.

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

There are also rare reports of a number of ocular complications when aerosolised ipratropium bromide, either alone or in combination with a $beta_2$-adrenergic agonist, has been inadvertently sprayed into the eye. Patients must therefore be instructed in the correct use of Ipramol Steri-Neb with their nebuliser and must be 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 suspension using a mouthpiece rather than a face mask.

Such ocular complications may include acute angle glaucoma, mydriasis, blurring of vision, increased intraocular pressure, eye pain and 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 spots together with red eyes from conjunctival congestion or corneal oedema may be manifestations of acute narrow-angle glaucoma. If a combination of these symptoms develops, treatment with miotic eye drops should be initiated and the patient should seek specialist advice immediately.

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

Caution should be exercised when Ipramol Steri-Neb is used by patients with cardiac disease (severe heart disease, ischaemic disease, arrhythmias). Patients should be advised if they experience chest pain and or dyspnoea that they should contact their emergency services.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with beta-agonists. 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.

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.

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

As with other inhalation therapy there is a risk of inhalation-induced bronchoconstriction or paradoxical bronchospasm. If this occurs the patient will experience an immediate increase in wheezing and shortness of breath after dosing, which should be treated straight away with an alternative presentation or different fast-acting inhaled bronchodilator. Ipramol Steri-Neb should be discontinued immediately, the patient should be assessed and, if necessary, alternative therapy instituted.

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.

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.

The use of Ipramol Steri-Neb may lead to positive results with regards to salbutamol in tests for non clinical substance abuse, e.g. in the context of athletic performance enhancement (doping).

Paediatric population
Ipramol Steri-Neb should not be used in children below 12 years (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interactions

Concurrent use of corticosteroids, beta$_2$-adrenoceptor agonists, anticholinergics and xanthine derivatives may enhance the effect of Ipramol Steri-Neb 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 such as propranolol.

Salbutamol should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of the beta$_2$ adrenoceptor agonist may be enhanced.

Inhalation of anaesthetics containing halogenated hydrocarbons, e.g. halothane, trichloroethylene and enflurane, may increase the susceptibility to cardiovascular side effects of beta$_2$-agonists, which should therefore be monitored closely. Alternatively discontinuation of Ipramol Steri-Neb prior to surgical operation should be considered.

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. Potentially serious arrhythmias may occur during concomitant administration of digoxin and Ipramol Steri-Neb. 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.

The effect of other anticholinergic products may be potentiated.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of ipratropium bromide and salbutamol together in pregnant women (in early stages of pregnancy). The potential risk for humans is unknown. Ipramol Steri-Neb should not be used during pregnancy unless clearly necessary and caution should be exercised when prescribing to pregnant women (especially in the first trimester).

In animal studies there has been evidence of some harmful effects on the foetus at very high dose levels.

Breastfeeding
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 Ipramol Steri-Neb 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 Ipramol Steri-Neb should be made taking into account the benefit of breast-feeding to the child and the benefit of Ipramol Steri-Neb to the mother.

Fertility
Unknown.

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 disorders, mydriasis and blurred vision during treatment with Ipramol Steri-Neb. If patients experience the above mentioned side effects, they should avoid potentially hazardous tasks such as driving or operating machines.

4.8 Undesirable effects

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

Frequencies are defined as: 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	**Frequency**	**Symptom**
Immune system disorders	Rare	Hypersensitivity including angioedema of the tongue, lips and face
Metabolism and nutritional disorders	Rare Not known	Hypokalaemia Lactic acidosis (see section 4.4)
Psychiatric disorders	Uncommon Rare	Restlessness Memory disorders, anxiety, hyperactivity in children
Nervous system disorders	Uncommon	Headache, Dizziness, tremor
Eye disorders	Rare	Accommodation disorders Pain in the eye, mydriasis, increased intraocular pressure, closed-angle glaucoma
Cardiac disorders	Uncommon Rare Not known	Palpitations, tachycardia Arrhythmias Decrease in diastolic blood pressure, peripheral vasodilatation, cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) and coronary ischaemic disease. Myocardial ischaemia (see Section 4.4)
Respiratory, thoracic and mediastinal disorders	Uncommon Rare	Cough, dysphonia Bronchospasm, laryngospasm, dyspnoea, paradoxical bronchospasm (i.e., inhalation-induced bronchospasm)
Gastrointestinal disorders	Uncommon Rare	Dry mouth, nausea, Mouth and throat irritations Vomiting, motility disturbances
Skin and subcutaneous tissue disorders	Rare	Rash, urticaria, pruritus, hyperhidrosis

Musculoskeletal, connective tissue and bone disorders	Rare	Myalgia, muscle cramp and weakness
Renal and urinary disorders	Uncommon	Urinary retention
Investigations	Uncommon	Systolic blood pressure increased
	Rare	Diastolic blood pressure decreased

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 HPRA 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

Acute effects of overdosage with ipratropium bromide are unlikely 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.

The most significant symptom of a large overdose of salbutamol is reflex tachycardia. Manifestations of overdosage with salbutamol may include anginal pain, hypertension, hypotension, hypokalaemia, tachycardia, arrhythmia, chest pain, tremor, flushing, restlessness and dizziness. Patients should therefore be monitored closely for the potential unwanted effects from overdosage of salbutamol. Hypokalaemia may occur following overdose with salbutamol and therefore serum potassium levels should be monitored. The recommended antidote for overdosage with salbutamol is a cardio selective beta-blocking agent, but caution should be used in administering these drugs to patients with a history of bronchospasm.

Metabolic acidosis has also been observed with over dosage 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.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Salbutamol and ipratropium bromide for obstructive airway disease
ATC code : R03A L02

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, selective to the lung and is not systemic in nature.

Salbutamol is a beta$_2$-adrenoceptor 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.

Ipramol Steri-Neb provides the simultaneous delivery of ipratropium bromide and salbutamol sulfate producing effects on both muscarinic and beta$_2$-adrenoceptor receptors in the lung. This provides enhanced bronchodilatation over that provided by each drug alone.

5.2 Pharmacokinetic properties

Ipratropium bromide is quickly absorbed after inhalation however 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 sulfate does not potentiate the systemic absorption of either component. The increased pharmacodynamic activity of Ipramol Steri-Neb is due to the combined local effect of both drugs on the lung.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Dilute Hydrochloric Acid for pH adjustment
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not freeze. Store below 25ºC. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Low Density Polyethylene Ampoule called a Steri-Neb containing 2.5 ml of solution, formed into strips of 5 and packed into a foil overwrap pouch that is then packed into cardboard cartons containing 5, 10, 15, 20, 25, 30, 40, 50 or 60 Steri-Nebs and 2 x 30 ampoule-pack, then packed into a cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Since the single dose units contain no preservatives, it is important that the contents are used soon 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 disposed of in accordance with local requirements.

After nebulisation, clean the nebuliser according to the manufacturer's instructions as follows: the oral mouthpiece should be cleaned with hot water. If soap is used, the mouthpiece should be rinsed thoroughly with water. When dry, the cap should be replaced on the mouthpiece.

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/082/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 14th April 2010

10 DATE OF REVISION OF THE TEXT

February 2019