Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ipratropium bromide/Salbutamol Neutec 0.5 mg/2.5 mg per 2.5 ml nebuliser solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5 mL single-dose container contains 0.5 mg ipratropium bromide (as ipratropium bromide monohydrate) and 2.5 mg salbutamol (as salbutamol sulphate), which is equivalent to 0.2 mg ipratropium bromide and 1 mg of salbutamol per 1 mL.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.
A clear, colourless or almost colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ipratropium bromide/salbutamol Neutec is indicated for the symptomatic treatment of bronchospasm in adults and adolescents over 12 years of age with chronic obstructive pulmonary disease who require treatment with both ipratropium bromide and salbutamol.

4.2 Posology and method of administration

Posology

The recommended dose for adults (including elderly patients) and adolescents over 12 years:
1 single-dose container inhaled via nebuliser three or four times daily.

Special patient groups
Patients with hepatic or renal impairment
Ipratropium bromide/salbutamol has not been studied in patients with hepatic or renal insufficiency and must therefore be administered with caution in these patient groups.

Paediatric population
The safety and efficacy of ipratropium bromide/salbutamol in children under 12 years of age has not been established, therefore Ipratropium bromide/salbutamol Neutec is not intended for use in this group of patients.

If higher doses than those recommended are required to achieve a good effect, the patient's overall treatment must be reviewed by a doctor.

Method of administration

Inhalation use.

The use of Ipratropium bromide/salbutamol Neutec follows five simple steps, which are outlined below:

1. The nebuliser is prepared for use according to the manufacturer's instructions.
2. The pouch is opened and a single-dose container is separated from the strip.
3. The top is removed from the ampoule.
4. The contents of the ampoule is squeezed into the nebuliser chamber.
5. The patient inhales the nebulised solution through the mouthpiece/nebuliser mask with calm and even breaths.

Ipratropium bromide/salbutamol Neutec may be administered from a suitable nebuliser, e.g. jet nebuliser 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 must be instructed to read the leaflet of the respective device carefully before starting the inhalation.

Active substance delivery characteristics were studied *in vitro* using a jet nebuliser:

Nebuliser	**Active substance**	**Mass median aerodynamic diameter** (micrometer)	**Active substance delivery rate** (mg/min)	**Total active substance delivered** (mg/2.5 mL)
Jet nebuliser*	Salbutamol	4.5	0.14	0.41
	Ipratropium	4.3	0.03	0.08

* PARI LC PLUS Nebuliser was used in *in vitro* studies

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.

Since Ipratropium bromide/salbutamol Neutec is deposited in the lungs through inhalation, it is important that the patient is instructed to inhale the product through the nebuliser's mouthpiece with calm and even breaths (see section 4.4).

Treatment must be initiated and administered under medical supervision, e.g. in the hospital setting. Home based treatment can be recommended in exceptional cases for experienced patients after consultation with a doctor provided that adequate treatment with a powder or spray inhaler is not possible.

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

4.3 Contraindications

Ipratropium bromide/salbutamol Neutec is contraindicated in:

- Patients with hypertrophic obstructive cardiomyopathy.
- Patients with tachyarrhythmia.
- Patients with a history of hypersensitivity to ipratropium bromide, salbutamol sulphate, atropine or its derivatives, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Dyspnoea
Patients must be advised to contact a doctor or the nearest hospital immediately in the event of acute or rapidly worsening dyspnoea (breathing difficulties), or if a reduced response to treatment becomes apparent. This could be a sign of a worsening of the patient's chronic obstructive pulmonary disease, and other therapy may be required.

Hypersensitivity
Immediate hypersensitivity reactions may occur after administration of ipratropium bromide/salbutamol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and oropharyngeal oedema.

Paradoxical bronchospasm
As with other inhaled medicines, ipratropium bromide/salbutamol can cause paradoxical bronchospasm, which may be life-threating. If paradoxical bronchospasm occurs, ipratropium bromide/salbutamol must be discontinued immediately, the patient has to be assessed and provided with an alternative therapy.

Eye problems
Eye problems (i.e. mydriasis, blurring of vision, increased intraocular pressure, narrow-angle glaucoma and eye pain) have been reported when an ipratropium bromide aerosol alone or in combination with a beta-2 agonist has come into contact with the eyes.

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 any combination of these symptoms develops, treatment with miotic eye drops should be initiated and the patient must seek specialist advice immediately.

Patients must be instructed in the correct use of ipratropium bromide/salbutamol and warned not to allow the solution or mist to enter into the eyes. This is particularly important in patients who may be pre-disposed to glaucoma. Such patients must be warned specifically to protect their eyes.

To avoid inadvertent entry of this medicine into the eye, the nebulised ipratropium bromide/salbutamol solution for inhalation must be inhaled with the help of a mouthpiece. If this is not available and a nebuliser mask should be used instead, this must fit the patient.

Systemic effects
In the following conditions ipratropium bromide/salbutamol must only be used after careful analysis of risk/benefit: recent myocardial infarction and/or severe organic heart or vascular disorders, pheochromocytoma, prostatic hypertrophy, bladder-neck obstruction, hyperthyroidism, risk of narrow-angle glaucoma, intestinal obstruction, or inadequately controlled diabetes mellitus.

Blood glucose monitoring is recommended initially when treating diabetics due to the increased risk of hyperglycaemia.

Lactic acidosis
Lactic acidosis has been reported in association with high therapeutic doses of intravenous and nebulised short-acting beta-2 agonist therapy, mainly in patients being treated for an acute exacerbation of bronchospasm in severe asthma or chronic obstructive pulmonary disease (see sections 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-2 agonist treatment. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting.

Cardiovascular effects
Cardiovascular effects may be seen with sympathomimetic medicinal products including ipratropium bromide/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, arrhythmia or severe heart failure), who are receiving salbutamol for respiratory disease, must be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention must be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Hypokalaemia
Potentially serious hypokalaemia may result from beta-2 agonist therapy, which may be serious, especially with concomitant hypoxia (see section 4.5). Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm (especially in patients receiving digoxin). It is recommended that serum potassium levels 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, must be used with caution in these patients.

Dental Caries
In the event of dry mouth, it is important to observe good oral hygiene due to the increased risk of caries.

Interference with laboratory tests or other diagnostic measures
The use of ipratropium bromide/salbutamol may lead to positive results with regards to salbutamol in tests for non-therapeutic substance abuse.

4.5 Interaction with other medicinal products and other forms of interaction

The long-term co-administration of ipratropium bromide/salbutamol with other anticholinergic medicinal products has not been studied. Therefore, the long-term co-administration of ipratropium bromide/salbutamol with other anticholinergic medicinal products is not recommended.

Concurrent use of corticosteroids (e.g. prednisolone), beta-2 agonists (e.g. fenoterol), anticholinergics (e.g. tiotropium) and xanthine derivatives (e.g. theophylline or aminophylline) may enhance the effect of ipratropium bromide/salbutamol on airway function and may increase the severity of side effects.

Treatment with ipratropium bromide/salbutamol can lead to hypokalaemia (see section 4.4). This effect may be enhanced by the concomitant treatment with xanthines, steroids and diuretics. Special consideration must be given to this when treating patients with severe airway obstruction.

A potentially serious reduction in bronchodilatory effect may occur during concurrent administration of beta-blockers, such as propranolol.

Beta-2 adrenergic agonists must be administered with caution to patients being treated with monoamine oxidase inhibitors (e.g. Phenelzine) or tricyclic antidepressants (e.g. Amitriptyline), since the action of beta-2 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-2 agonists.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of ipratropium bromide and salbutamol in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Ipratropium bromide/salbutamol should not be used during pregnancy unless the benefit outweighs the potential risks to the foetus. At the end of pregnancy, the inhibitory effect of ipratropium bromide/salbutamol on uterine contraction has to be taken into account.

Breastfeeding

There is insufficient information on the excretion of ipratropium bromide and salbutamol in human milk.A risk to the newborns/infants cannot be excluded. Caution should be exercised when prescribing to breast-feeding mothers. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ipratropium bromide/salbutamol therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There is no information on the effect of salbutamol and ipratropium bromide on human fertility, neither for combination of both active substances neither nor for each substance separately
Pre-clinical studies with ipratropium bromide and salbutamol did not show any adverse effect on fertility (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 must be advised that they may experience undesirable effects such as dizziness, accommodation disorder, mydriasis and blurred vision during treatment with ipratropium bromide/salbutamol. If patients experience the above-mentioned side effects, they must 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 beta-2 sympathomimetic properties of the medicinal product. As with all inhalation therapy ipratropium bromide/salbutamol may show symptoms of local irritation. Adverse drug reactions were identified from data obtained in clinical trials and pharmacovigilance during the post approval phase of this medicine.

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.

Based on the MedDRA system organ class and frequencies, adverse reactions 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).

MedDRA system organ class	**Adverse reaction**	**Frequency**
Immune system disorders	Anaphylactic reaction	Rare
	Hypersensitivity	Rare
	Angioedema of the tongue, lips and face	Rare
Metabolism and nutrition disorders	Hypokalaemia	Rare
	Lactic acidosis (see section 4.4)	Not known
Psychiatric disorders	Nervousness	Uncommon
	Mental disorder	Rare
Nervous system disorders	Dizziness	Uncommon
	Headache	Uncommon
	Tremor	Uncommon
Eye disorders	Accommodation disorder	Rare
	Corneal oedema	Rare
	Glaucoma	Rare
	Eye pain	Rare
	Intraocular pressure increased	Rare
	Mydriasis	Rare
	Vision blurred	Rare
	Conjunctival hyperaemia	Rare
	Halo vision	Rare
Cardiac disorders	Palpitations	Uncommon
	Tachycardia	Uncommon
	Arrhythmia	Rare
	Atrial fibrillation	Rare
	Myocardial ischaemia	Rare
	Supraventricular tachycardia	Rare
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon
	Dysphonia	Uncommon
	Throat irritation	Uncommon
	Bronchospasm	Rare
	Bronchospasm paradoxical	Rare
	Dry Throat	Rare
	Laryngospasm	Rare
	Pharyngeal oedema	Rare
Gastrointestinal disorders	Dry mouth	Uncommon
	Nausea	Uncommon
	Gastrointestinal motility disorder	Rare
	Diarrhoea	Rare
	Constipation	Rare
	Vomiting	Rare
	Oedema mouth	Rare
	Stomatitis	Rare
Skin and subcutaneous tissue disorders	Skin reaction	Uncommon
	Hyperhidrosis	Rare
	Rash	Rare
	Urticaria	Rare
	Pruritus	Rare
Musculoskeletal and connective tissue disorders	Muscle spasms	Rare
	Muscular weakness	Rare
	Myalgia	Rare
Renal and urinary disorders	Urinary retention	Rare
General disorders and administration site conditions	Asthenia	Rare
Investigations	Blood pressure systolic increased	Uncommon
	Blood pressure diastolic decreased	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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Acute effects of overdosage with ipratropium bromide (such as dry mouth, visual accommodation disorders) are mild and transient.

Any effects of overdosage are therefore likely to be related to the salbutamol component.
Manifestations of overdosage with salbutamol are the result of beta-2 adrenergic overstimulation, which may include tachycardia, anginal pain, hypertension, palpitations, tremor, hypokalaemia, hypotension, widening of the pulse pressure, arrhythmias and flushing.

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-2 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.

Treatment
Treatment with ipratropium bromide/salbutamol must be discontinued. Acid base and electrolyte monitoring should be considered. Hypokalaemia may occur following overdose with salbutamol and therefore serum potassium levels must be monitored.

The preferred antidote for overdosage with salbutamol is a cardioselective beta-blocking agent, but caution must be used in administering these medicinal products to patients with a history of bronchospasm.
In these patients ECG monitoring must take place.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids, ATC code: R03AL02

Mechanism of action and pharmacodynamic effects

Ipratropium bromide has anticholinergic (parasympatholytic) properties. In non-clinical studies, it appears to inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics inhibit the increase in intracellular Ca^{2+} that is caused by the action of acetylcholine on the muscarinic receptors in bronchial smooth muscle. Ca2+ release is mediated through a "second messenger" system which consists of IP3 (inositol triphosphate) and DAG (diacylglycerol).

Salbutamol is a beta-2 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 bronchoconstrictor challenges.

IIpratropium bromide/salbutamol Neutec provides the simultaneous delivery of ipratropium bromide and salbutamol sulphate allowing effects on both muscarinic and beta-2 adrenergic receptors in the lung leading to increased bronchodilation over that provided by each agent singly.

Paediatric population

Ipratropium bromide/salbutamol Neutec has not been studied in the paediatric population (see section 4.2).

5.2 Pharmacokinetic properties

The part of the dose that is deposited in the lungs reaches the circulation quickly (within minutes). The part of the dose that is deposited in the oropharynx is swallowed slowly and passes the gastrointestinal tract. The systemic exposure is therefore a function of both oral bioavailability and bioavailability via the lungs.

Ipratropium

Absorption
Cumulative renal excretion (0 to 24 hours) of ipratropium (the parent substance) is estimated at 46 % after an intravenously administered dose, less than 1 % of an oral dose and around 3 to 13 % of an inhaled dose. Based on these data, the total systemic bioavailability of oral and inhaled doses of ipratropium bromide are estimated at 2 % and 7 to 28 % respectively. Given this, the oral part of the ipratropium dose is not of great importance for systemic exposure.

Distribution
Kinetic parameters describing the disposition of ipratropium bromide were calculated from plasma concentrations after IV 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 active substance is minimally (less than 20 %) bound to plasma proteins. Non-clinical data indicate that the quaternary amine ipratropium does not cross the blood-brain barrier.

Biotransformation
After intravenous administration, around 60 % of the dose is metabolised, the largest part through probable oxidation in the liver. The main urinary metabolites bind poorly to the muscarinic receptor and have been regarded as ineffective.

Elimination
The half-life in the terminal elimination phase is around 1.6 hours. Ipratropium has a total clearance of 2.3 L/min and a renal clearance of 0.9 L/min. In an equilibrium study of excretion (6 days), medicinal product-related radioactivity (including the parent substance and all metabolites) was 72.1 % after intravenous administration, 9.3 % after oral administration and 3.2 % after inhalation.
Total radioactivity excreted via the faeces was 6.3 % after intravenous administration, 88.5 % after oral administration and 69.4 % after inhalation. The principal excretion of medicinal product-related radioactivity after intravenous administration was via the kidneys. The half-life for elimination of medicinal product-related radioactivity (parent substance and metabolites) following inhalation is 3.6 hours.

Salbutamol
Absorption and distribution
Salbutamol is rapidly and completely absorbed following inhalation or oral administration and has an oral bioavailability of approximately 50 %. Mean peak plasma salbutamol concentrations of 492 pg/mL occur within three hours after inhalation of ipratropium bromide/salbutamol nebuliser solution. Pharmacokinetic parameters were calculated from plasma concentrations after IV administration. The apparent volume of distribution (Vz) is approximately 156 L (≈ 2.5 L/kg). Only 8 % of the active substance is bound to plasma proteins. In non-clinical 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 a single inhalation, approximately 27 % of the estimated mouthpiece dose is excreted unchanged in the urine within 24-hours. 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 metabolised via conjugation 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 intravenous administration, urinary excretion was completed after around 24 hours. The majority of the dose was excreted as parent substance (64.2 %), and 12 % was excreted as sulphate conjugate. After oral administration urinary excretion of unchanged active substance and sulphate conjugate were 31.8 % and 48.2 % of the dose, respectively.

5.3 Preclinical safety data

Both ipratropium bromide and salbutamol sulphate have been tested extensively in animal models with no clinically relevant safety issues observed at the doses relevant in Ipratropium bromide/salbutamol Neutec.

Animal studies have shown no embryotoxic or teratogenic effects of ipratropium bromide after inhalation or intranasal administration at doses much higher than those recommended.

Animal studies of non-inhaled salbutamol sulphate indicated no direct or indirect harmful effects on embryofoetal development, provided that the maximum recommended inhaled dose for humans was not exceeded.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid 1 N (for pH-adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Keep single-dose containers in the outer pouch and carton in order to protect from light and moisture.

Do not use if solution is discoloured.

6.5 Nature and contents of container

Polyethylene single-dose containers containing 2.5 mL of solution.

Five polyethylene single-dose containers are overwrapped in a triple laminated pouch (polyester film/aluminium foil/polyethylene film) and packed in a carton box.
Pack sizes of 10, 20, 40, 60, 80 or 100 single-dose containers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

7 MARKETING AUTHORISATION HOLDER

Neutec Inhaler Ireland Limited
22 Northumberland Road
Ballsbridge
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23030/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th September 2023

10 DATE OF REVISION OF THE TEXT