Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ipratropium bromide/salbutamol Azure 0.5 mg/2.5 mg per 2.5 ml Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5 ml single dose unit contains 500 micrograms ipratropium bromide (as monohydrate) and 2.5 mg salbutamol (as sulfate).

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.

Clear, colourless or almost colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ipratropium bromide/salbutamol Azure is indicated in adults 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):
The contents of one ampoule three or four times daily.

Paediatric population:
The safety and efficacy of Ipratropium bromide/salbutamol Azure in children has not been established.

Renal and hepatic impairment:
Ipratropium bromide/salbutamol Azure has not been studied in patients with liver or kidney impairment and should be used with caution in these patient populations.

The patient should be instructed to consult a doctor immediately in the event of acute, rapidly worsening dyspnoea. In addition, the patient should be warned to seek medical advice should a reduced response become apparent.

Treatment should be initiated and administered under medical supervision, e.g. in the hospital setting. Home based treatment can be recommended in exceptional cases (patients with severe symptoms, and very experienced patients) when a low dose rapid acting beta-agonist bronchodilator has been insufficient in providing relief after consultation with an experienced physician.

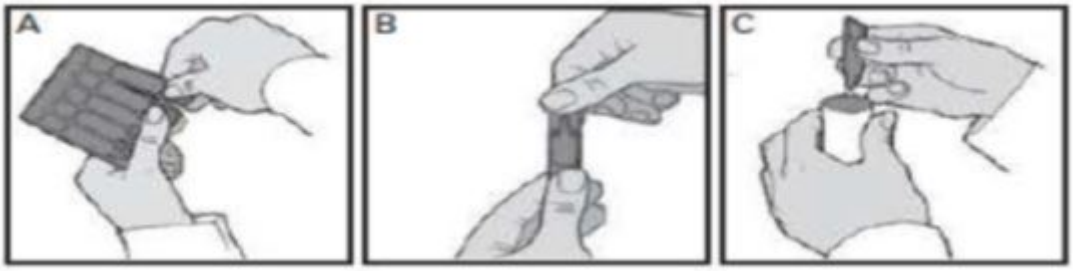
The treatment with the nebuliser solution should always be started with the lowest recommended dose. In very severe cases two single-dose ampoules may be required for symptom relief. Administration should be stopped when sufficient symptom relief is achieved.

Method of administration
For inhalation use only.

Ipratropium bromide/salbutamol Azure should be used with a suitable nebuliser, e.g. PARI Turboboy Nebuliser, jet nebuliser. Please read the full instructions for use of the nebuliser in the leaflet provided with PARI Turboboy before starting the inhalation.

The nebuliser solution in single dose ampoules is intended for inhalation use only and should not be taken orally or administered parenterally. The single-dose units do not need to be diluted for nebulisation.

- Prepare your nebuliser for use according to the manufacturer's instructions and advice from your doctor.
- Carefully remove an ampoule from the labelled strip by twisting and pulling. Never use an ampoule that has been opened already or if the solution is discoloured (diagram A).
- Hold the ampoule upright and twist off the cap (diagram B).
- Squeeze the contents into the reservoir of your nebuliser (diagram C).
- Follow the manufacturer's instructions and the advice from your doctor on how to assemble and how to use your nebuliser.
- After you have used your nebuliser, throw away any solution that is left in the reservoir. Any solution left in the ampoule should also be thrown away.
- Clean your nebuliser thoroughly 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.

Drug delivery characteristics have been studied in vitro using the Pari Turboboy nebulizer (as representative among jet nebulizers) because of its common characteristics with the other jet nebulizers on the market (air flow 6-8 l/min and fill volume 2-6 ml):

Drop size distribution [micrometer]			Drug release rate [microgram/minute]	Overall delivery [microgram/2.5 ml]
D10	D50	D90	Salbutamol (Child): 105.3 Salbutamol (Adult): 147.9	Salbutamol (Child): 740.2 Salbutamol (Adult): 909.7
1.549	3.646	8.016	Ipratropium (Child): 17.6 Ipratropium (Adult): 24.8	Ipratropium (child): 125.9 Ipratropium (Adult): 153.3

4.3 Contraindications

- Hypersensitivity to the active substances, to atropine or its derivatives or to any of the excipients listed in section 6.1
- Hypertrophic obstructive cardiomyopathy
- 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 and oropharyngeal oedema.

Paradoxical bronchospasm

As with other inhalation therapy paradoxical bronchospasm may occur which may be life-threatening. Ipratropium bromide/salbutamol Azure should be discontinued immediately andsubstituted with an alternative therapy.

Ocular complications
There have been rare reports of a number of ocular complications (i.e., mydriasis, blurring of vision, narrow-angle glaucoma and eye pain) when aerosolised ipratropium bromide, either alone or in combination with a beta$_2$-adrenergic agonist, has been inadvertently sprayed into the eye.
Patients must be instructed in the correct use of Ipratropium bromide/salbutamol Azure and must be warned not to allow the solution or mist to enter the eyes. This is particularly important in patients who may be pre-disposed to glaucoma. Such patients should be warned specifically to protect their eyes. It is recommended that Ipratropium bromide/salbutamol Azure be administered via a mouthpiece. If this is not possible, an appropriately-fitted nebuliser mask should be used.

Eye pain or discomfort, blurred vision, visual halos or coloured images together with red eyes from conjunctival congestion and 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.

Systemic effects
In the following conditions Ipratropium bromide/salbutamol Azure should only be used after careful risk/benefit assessment particularly when higher than recommended doses are used: insufficiently controlled diabetes mellitus, recent myocardial infarction and/or severe organic heart or vascular disorders, hyperthyroidism, phaeochromocytoma, risk of narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.

Cardiovascular effects
Cardiovascular effects may be seen with sympathomimetic drugs, including Ipratropium bromide/salbutamol Azure. 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 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. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm (especially in patients receiving digoxin). It is recommended that serum levels of potassium are monitored in such situations.

Gastrointestinal motility disturbances
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.

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.

Lactic acidosis
Lactic acidosis has been reported in association with high therapeutic doses of intravenous and treatment with 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 Ipratropium bromide/salbutamol Azure may lead to positive results with regards to salbutamol in tests for nonclinical substance abuse, e.g., in the context of athletic performance enhancement (doping).

4.5 Interaction with other medicinal products and other forms of interaction

The chronic co-administration of Ipratropium bromide/salbutamol Azure with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of Ipratropium bromide/salbutamol Azure with other anticholinergic drugs is not recommended.

The use of additional beta-agonists, xanthine derivatives and corticosteroids may enhance the effect of Ipratropium bromide/salbutamol Azure. The concurrent administration of other beta-mimetics, systemically absorbed anticholinergics and xanthine derivatives may increase the severity of side effects. A potentially serious reduction in effect may occur during concurrent administration of beta-blockers.

Beta$_2$-agonist-induced hypokalaemia may be increased by concomitant treatment with xanthine derivatives, glucocorticosteroids and diuretics. This should be taken into account particularly in patients with severe airway obstruction.

Hypokalaemia may result in an increased susceptibility to arrhythmias in patients taking digoxin. In such situations, it is recommended that serum potassium levels be monitored.

Beta$_2$-adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, 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-agonists.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of Ipratropium bromide/salbutamol Azure during pregnancy has not been established. The inhibitory effect of Ipratropium bromide/salbutamol Azure on uterine contraction should be taken into account. The benefits of using Ipratropium bromide/salbutamol Azure during a confirmed or suspected pregnancy must be weighed against possible hazards to the unborn child. The usual precautions regarding the use of drugs in pregnancy, especially during the first trimester, should be observed.

For ipratropium bromide, nonclinical studies have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man. For salbutamol sulfate, non-inhalation nonclinical studies did not indicate direct or indirect harmful effects unless the inhalation Maximum Recommended Human Daily Dose (MRHDD) was exceeded (see section 5.3).

Lactation
It is not known whether ipratropium bromide and salbutamol sulfate are excreted in breast milk. It is considered unlikely that ipratropium bromide would reach the infant to a significant extent, especially when administered by inhalation. However, caution should be exercised when Ipratropium bromide/salbutamol Azure is administered to nursing mothers.

Fertility
Clinical data on fertility are not available for ipratropium bromide. Nonclinical studies performed with ipratropium bromide showed no adverse effect on fertility (see section 5.3).

Clinical data on fertility are not available for salbutamol. Nonclinical studies performed with salbutamol showed no 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 should be advised that they may experience undesirable effects such as dizziness, accommodation disorders, mydriasis and blurred vision during treatment with Ipratropium bromide/salbutamol Azure. 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 beta$_2$-sympathomimetic properties of Ipratropium bromide/salbutamol Azure. As with all inhalation therapy Ipratropium bromide/salbutamol Azuremay show symptoms of local irritation.
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 summary of adverse reactions
The following adverse reactions have been reported during use of in clinical trials and during the post-marketing experience.

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	Anaphylactic reaction, hypersensitivity
Metabolism and nutritional disorders	Rare	Hypokalaemia
	Not known	Lactic acidosis (see section 4.4)
Psychiatric disorders	Uncommon	Nervousness
	Rare	Mental disorder
Nervous system disorders	Uncommon	Headache, dizziness, tremor
Eye disorders	Rare	Accommodation disorders, pain in the eye[(1)], mydriasis[(1)], increased intraocular pressure[(1)], corneal oedema, glaucoma[(1)], blurred vision, conjunctival hyperaemia, halo vision
Cardiac disorders	Uncommon	Palpitations, tachycardia
	Rare	Arrhythmias, atrial fibrillation, myocardial ischaemia, supraventricular tachycardia
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough, dysphonia
	Rare	Bronchospasm, paradoxical bronchospasm[(2)], dry throat, laryngospasm, pharyngeal oedema
Gastrointestinal disorders	Uncommon	Dry mouth, nausea, throat irritation
	Rare	Gastrointestinal motility disorder, diarrhoea, constipation, vomiting, mouth oedema, stomatitis
Skin and subcutaneous tissue disorders	Rare	Skin reactions such as: Hyperhidrosis, rash, urticaria, pruritus, angioedema
Musculoskeletal and connective tissue disorders	Rare	Muscle spasms, muscular weakness, myalgia
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 beta$_2$-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. Ipratropium bromide/salbutamol Azure 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.

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 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 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-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 with Ipratropium bromide/salbutamol Azure should be discontinued. Acid base and electrolyte monitoring should be considered. The preferred 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: Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids. ATC code: R03AL02.

Mode of action and pharmacodynamics
Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In nonclinical studies, it appears to inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase in intracellular concentration of Ca++ which is caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. Ca++ release is mediated by the second messenger system consisting of IP3 (inositol triphosphate) and DAG (diacylglycerol).

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.

Ipratropium bromide/salbutamol Azure provides the simultaneous delivery of ipratropium bromide and salbutamol sulfate producing effects on both muscarinic and beta$_2$-adrenergic receptors in the lung. This provides enhanced bronchodilation over that provided by each agent singly.

Paediatric population
Ipratropium/salbutamol nebuliser solution has not been studied in the paediatric population.
(See section 4.2).

5.2 Pharmacokinetic properties

Absorption characteristics of the combination ipratropium bromide – salbutamol sulfate
Co-administration of ipratropium bromide and salbutamol sulfate does not potentiate the systemic absorption of either component. The increased pharmacodynamic activity of Ipratropium bromide/salbutamol Azure is due to the combined local effect of both drugs on the lung.

Ipratropium

Absorption
Cumulative renal excretion (0-24 hrs) of ipratropium (parent compound) is approximated to 46% of an intravenously administered dose, below 1% of an oral dose and approximately 3 to 4% of an inhaled dose. Based on these data, the total systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7 to 9% respectively. Taking this into account, swallowed dose portions of ipratropium bromide do not relevantly contribute to systemic exposure.

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 (Vdss) is approximately 176 L (≈ 2.4 L/kg). The drug is minimally (less than 20%) bound to plasma proteins. Nonclinical data indicate that the quaternary amine ipratropium does not cross the placental or the blood-brain barrier.

Biotransformation
The half-life of the terminal elimination phase is approximately 1.6 hours.
Ipratropium has a total clearance of 2.3 L/min and a renal clearance of 0.9 L/min. After intravenous administration approximately 60% of a dose is metabolised, the major portion probably in the liver by oxidation.

Elimination
In an excretion balance study cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 72.1% after intravenous administration, 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was 6.3% following intravenous application, 88.5% following oral dosing and 69.4% after inhalation. Regarding the excretion of drug-related radioactivity after intravenous administration, the main excretion occurs via the kidneys. The half-life for elimination of drug-related radioactivity (parent compound and metabolites) is 3.6 hours. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

Salbutamol

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 combination ipratropium bromide – salbutamol sulfate.

Distribution
Kinetic parameters were calculated from plasma concentrations after i.v. administration. The apparent volume of distribution (Vz) is approximately 156 L (≈ 2.5 L/kg). Only 8% of the drug is bound to plasma proteins. 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 and Elimination
Following this 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 291mL/min.
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. 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 with ipratropium bromide reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential or toxicity to reproduction and development.

Non-clinical data with salbutamol sulfate reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, or genotoxicity. 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. The results in carcinogenesis studies with salbutamol sulfate were considered to be species specific and therefore without clinical relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.
After the opening of the pouch: 7 days.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep single-dose containers in the outer pouch and carton in order to protect from light.

Do not freeze.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Strips of 5 LDPE single-dose containers containing 2.5 ml of solution.
Each strip of 5 ampoules is overwrapped in a laminated pouch (PET/Al/PE) and packed in a carton box.
Pack sizes of 20, 30 or 60 single-dose containers.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not use the solution if it is discoloured. Single-dose containers are intended for inhalation only with suitable nebuliser devices and must not be administered orally or parenterally. Since the single dose units do not contain 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 disposed of in accordance with local requirements. It is strongly recommended not to mix Ipratropium bromide/salbutamol Azure with other medicinal products in the same nebuliser.

After nebulisation, clean the nebuliser according to the manufacturer's instructions.

Any unused product or waste should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA22871/033/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th March 2026

10 DATE OF REVISION OF THE TEXT