Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zerseos 0.5 mg/2.5 mg per 2.5 ml nebuliser solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effects
Each 2.5 ml single dose ampoule contains 8.8 mg sodium

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.

Apolyethylene ampoule containing clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zerseos is indicated in the treatment of bronchospasm in patients older than 12 years of age with chronic obstructive pulmonary disease who require symptomatic treatment with both ipratropium bromide and salbutamol.

4.2 Posology and method of administration

Posology

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

The treatment with Zerseos nebuliser solution should always be started with the recommended dose. (1 Unit Dose Ampoules). In very severe cases, two unit dose ampules may be required for symptom relief. 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. Administration should be stopped when sufficient symptom relief is achieved.

The recommended dose is

Adults (including elderly patients and children over 12 years)

The contents of one ampoule three or four times daily.

Repeated administration should be done at the earliest after 6 hours.

The daily dosage should not exceed 4 ampoules.

Paediatric population

Zerseos is not recommended in children below 12 years of age due to lack of data on safety and efficacy.

Renal or hepatic impairment

No data are available. Zerseos has not been studied in patients with renal or hepatic impairment and should therefore be administered with caution in these patients.

Method of administration

For inhalation use only.

For single use only. Use immediately after first opening the ampoule.

Discard immediately after first use.

Zerseos 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.

Active substance delivery characteristics were studied *in vitro* using the PARI LC PLUS nebuliser device:

Droplet size distribution (micrometer)			**Active substances delivery rate** (micrograms/min)	**Total active substances delivered** (micrograms/2.5 ml)
D10	D50	D90		
1	4	11	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 not to mix Zerseos with other medicinal products in the same nebuliser.

Each ampoule is ready to use and requires no dilution. However, some types of appliances require over 2.5 ml volume: in these cases, add saline to ipratropium bromide/ salbutamol to reach the minimum volume required.

4.3 Contraindications

Zerseos is contraindicated in patients with hypertrophic obstructive cardiomyopathy or tachyarrhythmia.

Hypersensitivity to salbutamol or ipratropium bromide or to atropine or its derivatives or to any of the excipients listed in section 6.1 and/or other anticholinergics/beta-sympathomimetics.

4.4 Special warnings and precautions for use

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.

Patients who are prescribed regular anti-inflammatory therapy (e.g., inhaled corticosteroids) should be advised to continue taking their anti-inflammatory medication even when symptoms decrease, and they do not require Zerseos.

Increasing use of short-acting bronchodilators, in particular beta-2 agonists to relieve symptoms indicates deterioration of asthma control, and patients should be warned to seek medical advice as soon as possible. Under these conditions, the patient's therapy plan should be reassessed.

Overuse of short-acting beta-agonists may mask the progression of the underlying disease and contribute to deteriorating asthma control, leading to an increased risk of severe asthma exacerbations and mortality.

Patients who take more than twice a week "as needed" salbutamol, not counting prophylactic use prior to exercise, should be re-evaluated (i.e., daytime symptoms, nighttime awakening, and activity limitation due to asthma) for proper treatment adjustment as these patients are at risk for overuse of salbutamol.

Hypersensitivity

Immediate hypersensitivity reactions may occur after administration of ipratropium bromide/salbutamol nebuliser solution as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, or pharyngeal oedema and anaphylaxis.

Paradoxical bronchospasm

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 straightaway with an alternative presentation or different fast-acting inhaled bronchodilator. Ipratropium bromide/salbutamol should be discontinued immediately, the patient should be assessed and, if necessary, alternative therapy instituted.

Ocular complications

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 ipratropium bromide/salbutamol with their nebuliser and must be warned not to allow the nebuliser solution or mist to enter the eyes. To avoid inadvertent entry of medicinal product into the eye, it is preferable to administer the nebulised suspension using a mouthpiece rather than a face mask.

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

Eye pain or discomfort, blurred vision, visual halos or coloured 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 should seek specialist advice immediately.

Systemic effects

In the following conditions ipratropium bromide/salbutamol 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, prostatic hypertrophy, bladder outflow obstruction and risk of narrow-angle glaucoma.

Cardiovascular effects

Caution should be exercised when ipratropium bromide/salbutamol is used by patients with cardiac disease (severe heart disease, ischaemic disease, arrhythmias). Cardiovascular effects may be seen with sympathomimetic medicinal products, including salbutamol. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with short acting beta-agonists.

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. 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.

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.

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.

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

Lactic acidosis

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

Paediatric population

Zerseos should not be used in children (see section 4.2).

Excipient

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The use of additional beta-agonists, xanthine derivatives and corticosteroids may enhance the effect of Zerseos. Concurrent use of additional $beta_2$-agonists, corticosteroids, anticholinergics and xanthine derivatives (e.g theophylline) 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 $beta_2$ adrenergic agonists 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 Zerseos 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 Zerseos. The interaction risk is aggravated by hypokalaemia and potassium levels 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.

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

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). In animal studies there has been evidence of some harmful effects on the foetus at very high dose levels. The potential risk for humans is unknown. Zerseos should not be used during pregnancy unless clearly necessary and caution should be exercised when prescribing to pregnant women (especially in the first trimester).

Salbutamol

Experience with the use of beta-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 fetal/neonatal reactions such as tachycardia and hypoglycemia. With inhalation therapy at recommended doses, the occurrence of these adverse side effects at the end of pregnancy is not expected.

Ipratropium bromide

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.

Breast-feeding

Salbutamol can be used during breast-feeding. It is not known to what extent ipratropium bromide is excreted in human milk. Because of its pharmacokinetic properties, it is not likely that there is a lot excreted in breast milk.

Ipratropium bromide/ salbutamol can therefore be used during breast-feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as dizziness, accommodation disorder, mydriasis and blurred vision during treatment with Zerseos. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Many of the listed undesirable effects can be assigned to the anticholinergic and beta$_2$-sympathomimetic properties of ipratropium bromide/salbutamol. 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 post approval of the drug.

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 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	Symptom	Frequency
Immune system disorders	Anaphylactic reaction	Rare
	hypersensitivity	Rare
	angioedema of the face, lips and tongue	Rare
Metabolism and nutritional disorders	Hypokalaemia	Rare
	Lactic acidosis	Not known
Psychiatric disorders	Nervousness	Uncommon
	Mental disorders	Rare
Nervous system disorders	Headache	Uncommon
	Dizziness, feeling nervous, tremor, vertigo	Uncommon
	Sweating	Rare
Eye disorders	Accommodation disorders	Rare
	Closed-angle glaucoma*, increased intraocular pressure*, pain in the eye*, mydriasis*, corneal oedema, blurred vision, conjunctival hyperaemia, halo vision	Rare
Cardiac disorders	Palpitations, tachycardia	Uncommon
	Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia)	Rare
	Myocardial ischaemia	Rare
	Arrhythmias	Very rare
Respiratory, thoracic and mediastinal disorders	Cough, dysphonia, throat irritation	Uncommon
	Bronchospasm, laryngospasm, paradoxical bronchospasm* (i.e., inhalation-induced bronchospasm), dry throat, pharyngeal oedema	Rare
Gastrointestinal disorders	Nausea, dry mouth, throat irritation	Common
	Motility disturbances (e.g diarrhoea, constipation, vomiting), dental caries, mouth oedema, stomatitis, taste changes	Rare
Skin and subcutaneous tissue disorders	Skin reactions	Uncommon
	Rash, itching, Urticaria,	Rare
	Hyperhidrosis, angioedema	Rare
Musculoskeletal and connective tissue disorders	Myalgia, muscle cramp and weakness, muscle spasm	Rare
Renal and urinary disorders	Urinary retention*	Uncommon
General disorders and administrative site conditions	Asthenia	Rare
Investigations	Systolic blood pressure increase	Uncommon
	Diastolic blood pressure decreased	Rare

*See 4.4 for Special warnings and precautions for use

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. By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms

Acute effects of overdosage with ipratropium bromide are mild and transient 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. Patients should therefore be monitored closely for the potential unwanted effects from overdose of salbutamol.

Manifestations of overdosage with salbutamol may include anginal pain, hypertension, hypotension, widening of the pulse pressure, palpitations, hypokalaemia, tachycardia, arrhythmia, chest pain, tremor, flushing, restlessness, nausea, hyperglycemia, metabolic acidosis, psychotic reactions and dizziness. Metabolic acidosis has also been observed with overdosage of salbutamol, including lactic acidosis.

Management

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

The preferred antidote for overdosage with salbutamol is a cardio selective beta-blocking agent, but caution should be used in administering these medicinal products to patients with a history of bronchospasm.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway disease, Adrenergics inhalants, adrenergics in combination with anticholinergics, ATC code: R03AL02

Mechanism of action and pharmacodynamic effects

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.

Zerseos 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.

Paediatric population

Ipratropium bromide/salbutamol has not been studied in the paediatric population.

5.2 Pharmacokinetic properties

Ipratropium

Absorption

Based on a cumulative excretion value (CRE0-24h) of about 3-4%, the range of total systemic bioavailability of inhaled doses of ipratropium bromide is estimated at 7 to 9%.

Distribution

Kinetic parameters describing the disposition of ipratropium bromide were calculated from plasma concentrations after i.v. administration. A rapid biphasic decline in plasma concentrations is observed.

The apparent volume of distribution at steady-state (Vdss) is approximately 176 L (≈ 2.4 L/kg). The active substance is minimally (less than 20%) bound to plasma proteins. Ipratropium bromide like any other quaternary ammonium compound, is not expected to readily cross the blood brain barrier.

Biotransformation

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

Elimination

After administration via inhalation about 3.2% of active substance related radioactivity, i.e. parent compound and metabolites, is eliminated in urine. Total radioactivity excreted via the faeces was for this route of administration. The half-life for elimination of active substance-related radioactivity following inhalation is 3.2 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 ipratropium/salbutamol.

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 active substance 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-sulphate. 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 sulphate conjugate. After oral administration urinary excretion of unchanged active substance and sulphate conjugate we 31.8% and 48.2 of the dose, respectively.

Absorption characteristics of the combination ipratropium bromide – salbutamol sulphate
Co-administration of ipratropium bromide and salbutamol sulphate does not potentiate the systemic absorption of either component and that therefore the additive activity of Zerseos is due to the combined local effect on the lung following inhalation.

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

Unopened: 2 years

After removal from foil overwrap: 3 months

After opening the ampoule: 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 sachet or carton in order to protect from light.

6.5 Nature and contents of container

Each low density polyethylene ampoule contains 2.5 ml of colourless nebuliser solution.

Five plastic ampoules are overwrapped in a triple laminated sachet (polyester film/aluminium foil/polyethylene film) and packed into cardboard cartons containing 10, 20, 40, 60, 80 or 100 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Partly used, opened or damaged ampoules should be disposed in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Azure Pharmaceuticals Ltd
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Ireland

8 MARKETING AUTHORISATION NUMBER

PA22871/011/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 13th December 2021

10 DATE OF REVISION OF THE TEXT

February 2024