1. Name of the medicinal product

ZENSALBU NEBULES 2.5

2. Qualitative and quantitative composition

Each ml contains Salbutamol (as Salbutamol Sulfate) 1 mg

3. Pharmaceutical form

Solution for inhalation via a nebuliser.

4. Clinical particulars

4.1 Therapeutic indications

ZENSALBU NEBULES 2.5 is indicated in adults, adolescents and children aged 4 to 11 years. For babies and children under 4 years of age.

Salbutamol is a selective β2-agonist providing short-acting (4-6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction.

ZENSALBU NEBULES 2.5 is indicated for use in the routine management of chronic bronchospasm unresponsive to conventional therapy, and in the treatment of acute severe asthma.

4.2 Posology and method of administration

ZENSALBU NEBULES 2.5 is for inhalation use only, to be breathed in through the mouth, under the direction of a physician, using a suitable nebuliser.

The solution should not be injected or swallowed.

Adults (including the elderly): 2.5 mg to 5 mg salbutamol up to four times a day. Up to 40 mg per day can be given under strict medical supervision in hospital.

Paediatric Population

Children aged 12 years and over: Dose as per adult population.

Children aged 4-11 years: 2.5 mg to 5 mg up to four times a day.

Other pharmaceutical forms may be more appropriate for administration in children under 4 years old.

Infants under 18 months old: Clinical efficacy of nebulised salbutamol in infants under 18 months is uncertain. As transient hypoxia may occur supplemental oxygen therapy should be considered.

ZENSALBU NEBULES 2.5 is intended to be used undiluted. However, if prolonged delivery time (more than 10 minutes) is required, the solution may be diluted with sterile normal saline.

The nebulised solution may be inhaled through a face mask, T-piece or via an endotracheal tube. Intermittent positive pressure ventilation (IPPV) may be used but is rarely necessary. When there is a risk of anoxia through hypoventilation, oxygen should be added to the inspired air.

As many nebulisers operate on a continuous flow basis, it is likely that some nebulised drug will be released into the local environment. ZENSALBU NEBULES 2.5 should therefore be administered in a well-ventilated room, particularly in hospitals when several patients may be using nebulisers at the same time.

Dilution: ZENSALBU NEBULES 2.5 may be diluted with sterile normal saline. Solutions in nebulisers should be replaced daily.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients.

Non-IV formulations of salbutamol must not be used to arrest uncomplicated premature labour or threatened abortion

4.4 Special warnings and precautions for use

Zensalbu nebules 2.5 must only be used by inhalation, to be breathed in through the mouth, and must not be injected or swallowed.

Bronchodilators should not be the only or main treatment in patients with severe or unstable asthma. Severe asthma requires regular medical assessment, including lung-function testing, as patients are at risk of severe attacks and even death. Physicians should consider using the maximum recommended dose of inhaled corticosteroid and/or oral corticosteroid therapy in these patients.

Patients receiving treatment at home should seek medical advice if treatment with Zensalbu nebules 2.5 becomes less effective. The dosage or frequency of administration should only be increased on medical advice.

Patients being treated with Zensalbu nebules 2.5 may also be receiving other dosage forms of short-acting inhaled bronchodilators to relieve symptoms. Increasing use of bronchodilators, in particular short-acting inhaled β2-agonists to relieve symptoms, indicates deterioration of asthma control. The patient should be instructed to seek medical advice if short-acting relief bronchodilator treatment becomes less effective or more inhalations than usual are required. In this situation patients should be assessed and consideration given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroid or a course of oral corticosteroid).

Severe exacerbations of asthma must be treated in the normal way.

Salbutamol should be administered cautiously to patients suffering from thyrotoxicosis.

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 salbutamol. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia 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 of either respiratory or cardiac origin.

Zensalbu nebules 2.5 should be used with care in patients known to have received large doses of other sympathomimetic drugs.

Potentially serious hypokalaemia may result from β2-agonist therapy, mainly from parenteral and nebulised administration. Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and by concomitant treatment with xanthine derivatives, steroids and diuretics. Serum potassium levels should be monitored in such situations.

In common with other β-adrenoceptor agonists, salbutamol can induce reversible metabolic changes such as increased blood glucose levels. Diabetic patients may be unable

to compensate for the increase in blood glucose and the development of ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

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 asthma exacerbation (see Section 4.8). 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.

A small number of cases of acute angle-closure glaucoma have been reported in patients treated with a combination of nebulised salbutamol and ipratropium bromide. A combination of nebulised salbutamol with nebulised anticholinergics should therefore be used cautiously. Patients should receive adequate instruction in correct administration and be warned not to let the solution or mist enter the eye.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator. Zensalbu nebules 2.5 should be discontinued, and if necessary a different fast-acting bronchodilator instituted for on-going use.

4.5 Interaction with other medicinal products and other forms of interaction

Salbutamol and non-selective β-blocking drugs such as propranolol, should not usually be prescribed together.

4.6 Fertility, pregnancy and lactation

Pregnancy

Administration of drugs during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus. As with the majority of drugs, there is little published evidence of the safety of salbutamol in the early stages of human pregnancy, but in animal studies there was evidence of some harmful effects on the fetus at very high dose levels.

Breast-feeding

As salbutamol is probably secreted in breast milk, its use in nursing mothers requires careful consideration. It is not known whether salbutamol has a harmful effect on the neonate, and so its use should be restricted to situations where it is felt that the expected benefit to the mother is likely to outweigh any potential risk to the neonate.

Fertility

There is no information on the effects of salbutamol on human fertility. There were no adverse effects on fertility in animals

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000). Very common and

common events were generally determined from clinical trial data. Rare, very rare and unknown events were generally determined from spontaneous data.

Immune system disorders

Very rare:	Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse

Metabolism and nutrition disorders

Rare:	Hypokalaemia. Potentially serious hypokalaemia may result from beta$_2$ agonist therapy.
Unknown:	**Lactic acidosis**

Nervous system disorders

Common:	Tremor, headache.
Very rare:	Hyperactivity.

Cardiac disorders

Common:	Tachycardia.
Uncommon:	Palpitations
Very rare:	Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles
Unknown:	Myocardial ischaemia*

Vascular disorders

Rare:	Peripheral vasodilatation.

Respiratory, thoracic and mediastinal disorders

Very rare:	Paradoxical bronchospasm.

Gastrointestinal disorders

Uncommon:	Mouth and throat irritation.

Musculoskeletal and connective tissue disorders

Uncommon:	Muscle cramps.

* reported spontaneously in post-marketing data therefore frequency regarded as unknown

4.9 Overdose

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events, including tachycardia, tremor, hyperactivity and metabolic effects including hypokalaemia and lactic acidosis.

Hypokalaemia may occur following overdose with salbutamol. Serum potassium levels should be monitored. Lactic acidosis 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Andrenergics, inhalants. Selective beta-2-andrenoreceptor agonists

ATC code: R03AC02

Salbutamol is a selective β2-agonist providing short-acting (4-6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction. At therapeutic doses it acts on the β2-adrenoceptors of bronchial muscle. With its fast onset of action, it is particularly suitable for the management and prevention of attack in asthma.

5.2 Pharmacokinetic properties

Salbutamol administered intravenously has a half-life of 4 to 6 hours and is cleared partly renally, and partly by metabolism to the inactive 4'-O-sulfate (phenolic sulfate) which is also excreted primarily in the urine. The faeces are a minor route of excretion. Most of a dose of salbutamol given intravenously, orally or by inhalation is excreted within 72 hours. Salbutamol is bound to plasma proteins to the extent of 10%.

After administration by the inhaled route between 10 and 20% of the dose reaches the lower airways. The remainder is retained in the delivery system or is deposited in the oropharynx from where it is swallowed. The fraction deposited in the airways is absorbed into the pulmonary tissues and circulation, but is not metabolised by the lung. On reaching the systemic circulation it becomes accessible to hepatic metabolism and is excreted, primarily in the urine, as unchanged drug and as the phenolic sulfate.

The swallowed portion of an inhaled dose is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism to the phenolic sulfate. Both unchanged drug and conjugate are excreted primarily in the urine.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride

Sulfuric acid if required to adjust pH

water for injection

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months from manufacture’s date.

6.4 Special precautions for storage

Store in tight container, in cool dry place, protect from light, at temperature below 30^{o}C

6.5 Nature and contents of container

2.5 mL per plastic ampoule packed, 5 plastic ampoule in aluminum bag. Box of 10, 20, 50 plastic ampoules

6.6 Special precautions for disposal and other handling

The nebulised solution may be inhaled through a face mask, T-piece or via an endotracheal tube. Intermittent positive pressure ventilation (IPPV) may be used but is rarely necessary. When there is a risk of anoxia through hypoventilation, oxygen should be added to the inspired air.

As many nebulisers operate on a continuous flow basis, it is likely that some nebulised drug will be released into the local environment. Zensalbu Nebules 2.5 should therefore be administered in a well-ventilated room, particularly in hospitals when several patients may be using nebulisers at the same time.

Dilution: Zensalbu Nebules 2.5 may be diluted with sterile normal saline. Solutions in nebulisers should be replaced daily.

Manufacturer

HA NOI CPC1 PHARMACEUTICAL JOINT STOCK COMPANY

Plant Address: Ha Binh Phuong Industrial Zone, Thuong Tin District, Hanoi City, Vietnam