SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SALRES 5 mg/2.5 ml Inhalation Solution for Nebulisation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each 2.5 ml vial contains
Active substance: 6 mg Salbutamol sulfate equivalent to 5 mg Salbutamol.
Excipient(s):
Sodium chloride 22.50 mg
For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for inhalation via a nebuliser.
Clear, colorless, particle-free solution for nebulisation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

These are reliever medications used to reduce bronchoconstriction in asthma and alleviate symptoms. They should not be used as controller medications.

They are used to reduce the symptoms in COPD and as rescue medication. They are not preferred in regular treatment.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
SALRES has a duration of action of 4 to 6 hours in most patients.

A suitable starting dose of salbutamol by wet inhalation is 2.5 mg.

This dose may be increased to 5 mg. Treatment can be repeated 4 times daily. In very severe airway obstruction, higher doses of up to 40 mg per day may be administered to adults in hospital under very close medical supervision.

Increasing use of beta$_2$-agonists may be a sign of worsening asthma. Under these conditions a reassessment of the patient's therapy plan may be required and concomitant glucocorticosteroid therapy should be considered.

Delivery of the aerosol may be by facemask, 'T' piece or via an endotracheal tube. Intermittent positive pressure ventilation 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 there may be adverse effects associated with excessive dosing, the dosage or frequency of

administration should only be increased on doctor advice.

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

Method of administration
SALRES is to be used with a nebuliser, under the monitor of a physician.

SALRES is intended to be used undiluted. However, if prolonged delivery time is desirable (more than 10 minutes) dilution with physiological serum for injection may be necessary.

The solution must not be injected or swallowed.

Additional information on special populations:
Renal/Hepatic impairment
No data available.

Pediatric population
Children aged 12 years and over: Dose as per adult population.
Children aged 4 to 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 of age.
Infants under 18 months:
Clinical efficacy of nebulised salbutamol in infants under 18 months is uncertain. As transient hypoxia may occur, supplemental oxygen therapy should be considered.

SALRES is intended to be used undiluted. However, if a prolonged delivery time is indicated (more than 10 minutes) then solution may be diluted with sterile normal saline.

Geriatric population
No data available.

4.3 Contraindications
It is contraindicated in patients with history of hypersensitivity to any of SALRES components.

Non-intravenous formulations of SALRES must not be used to arrest uncomplicated premature labor risk. Salbutamol preparations should not be used for threatened abortion.

4.4 Special warnings and precautions for use
In the treatment of asthma, a stepwise treatment program should be followed and the patient's response should be monitored clinically and with lung function tests.

Increasing use of short-acting inhaled beta$_2$-agonists to control symptoms indicates deterioration of asthma control. Under these conditions, the patient's therapy plan should be reassessed. Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to starting corticosteroid therapy or increasing the dose. In patients considered at risk, daily peak flow monitoring may be instituted.

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

Patients receiving treatment at home with SALRES must be warned that if either the usual relief is diminished or the usual duration of action reduced, they should not increase the dose or its frequency of administration but should seek medical advice.

It should be used with caution in patients known to have received large doses of other sympathomimetic drugs.

Salbutamol should be administered cautiously to patients with thyrotoxicosis.

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 be informed about correct administration and be warned not to let the solution or mist enter the eye.

Potentially serious hypokalemia may result from beta$_2$-agonist therapy mainly from parenteral and nebulised administration. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids, diuretics and by hypoxia. It is recommended that serum potassium levels are monitored in such situations.

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

In common with other beta-adrenoceptor agonists, SALRES can cause reversible metabolic changes, for example increased blood sugar levels. The diabetic patient may be unable to compensate for this and the development of ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

Lactic acidosis has been reported very rarely 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 Undesirable effects). Increase in lactate levels may lead to dyspnea 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.

Cardiovascular effects may be seen with the use of sympathomimetic drugs, including salbutamol. There are post-marketing data and published literature regarding the rare occurrence of myocardial ischemia associated with salbutamol.

Patients with severe heart disease (e.g. ischemic 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 dyspnea and chest pain, as they may be of either respiratory or cardiac origin.

It contains less than 1 mmol (23 mg) sodium in each dose; no sodium related side effect is expected at this dose.

4.5 Interactions with other medicinal products and other forms of interaction

SALRES and non-selective beta-blocking agents, such as propranolol, should not usually be given together.

SALRES is not contraindicated in patients under treatment with monoamine oxidase inhibitors (MAOIs).

4.6 Pregnancy and Lactation

General recommendation

Pregnancy category: C.

Women of child-bearing potential/ Birth control (Contraception)

There are no data from the use of salbutamol in women of child-bearing potential and in women using birth control (contraception).

Pregnancy

Animal studies are insufficient with respect to effects on pregnancy /and-or/ embryonal/fetal development/ and-or/ parturition/ and-or/ postnatal development (see section 5.3). The potential risk for humans is unknown.

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. It should not be used during pregnancy unless it is absolutely necessary.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects have been reported in the offspring of patients being treated with salbutamol. Some of the mothers were taking multiple medications during their pregnancies.

Because no consistent pattern of defects can be discerned, and baseline rate for congenital anomalies is 2-3%, a relationship with salbutamol use cannot be established.

Breast-feeding

As salbutamol is probably secreted in breast milk its use in nursing mothers is not recommended unless the expected benefits outweigh any potential risk. It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

Reproductive ability/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

No data available.

4.8 Undesirable effects

Following adverse effects are given according to system organ classification and frequency.

Classification of frequency:
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,
Not known cannot be estimated from the available data

Very common and common events were generally determined from clinical trial data. Rare and very rare 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: Hypokalemia.

$Beta_2$ agonist therapy can potentially cause serious hypokalemia.

Very rare: Lactic acidosis

Lactic acidosis has been reported very rarely in patients receiving intravenous and nebulised salbutamol therapy for the treatment of acute asthma or asthma exacerbations.

Nervous system disorders:
Common: Tremor, headache
Very rare: Hyperactivity

Cardiac disorders:
Common: Tachycardia
Uncommon: Palpitations
Very rare: Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardias and extrasystoles
Not known: Myocardial ischemia* (see Special warnings and precautions for use)

* Reported spontaneously in post-marketing data therefore frequency is unknown.

Vascular disorders:
Rare: Peripheral vasodilatation

Respiratory, thoracic and mediastinal disorders:
Very rare: Paradoxical bronchospasm

Gastrointestinal disorders:
Uncommon: Irritation in mouth and throat

Musculoskeletal, connective tissue and bone disorders:
Common: Muscle cramps

Rare*:* Feeling of tension in muscles

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 in accordance with local requirements.

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 lactic acidosis (see sections Special warnings and precautions for use; Undesirable effects).

Hypokalemia may occur following overdose with SALRES. 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 recommended in the setting of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Selective $Beta_2$ adrenoreceptor agonists
ATC code: R03AC02

Mechanism of action
Salbutamol is selective $beta_2$ adrenoceptor agonist. At therapeutic doses it acts on the $beta_2$ adrenoceptors of bronchial smooth muscle.

Pharmacodynamic effects
Salbutamol is a selective $beta_2$ adrenoceptor agonist. At therapeutic doses it acts on the $beta_2$ adrenoceptors of bronchial muscle providing short acting (4-6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction.

5.2 Pharmacokinetic properties

General Properties

Absorption:
After administration by the inhaled route between 10 to 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 metabolized by the lung.

Distribution:
Salbutamol is bound to plasma proteins to the extent of 10%.

Biotransformation:
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 sulphate.

The swallowed portion is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism to the phenolic sulphate.

Elimination:
Both unchanged drug and conjugate are excreted primarily in the urine. Salbutamol administered intravenously has a half-life of 4-6 hours and is cleared partly renally and partly by metabolism to the inactive 4'-O-sulphate (phenolic sulphate) which is also excreted primarily in the urine. The feces are a minor route of excretion. The majority of a dose of salbutamol given intravenously, orally or by inhalation is excreted within 72 hours.

Characteristics in patients
No data is available.

5.3 Preclinical safety data
In common with other potent selective $beta_2$ receptor agonists, salbutamol has been shown to be teratogenic in mice when given subcutaneously. In a reproductive study, 9.3% of fetuses were found to have cleft palate, at 2.5 mg/kg, 4 times the maximum human oral dose. In rats, treatment at the levels of 0.5, 2.32, 10.75 and 50 mg/kg/day orally throughout pregnancy resulted in no significant fetal abnormalities. The only toxic effect was an increase in neonatal mortality at the highest dose level as the result of lack of maternal care. A reproductive study in rabbits revealed cranial malformations in 37% of fetuses at 50 mg/kg/day, 78 times the maximum human oral dose.

In an oral fertility and general reproductive performance study in rats at doses of 2 and 50 mg/kg/day, with the exception of a reduction in number of weanlings surviving to day 21 post partum at 50 mg/kg/day, there were no adverse effects on fertility, embryofetal development, litter size, birth weight or growth rate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride
Sulfuric acid
Water for injection

6.2 Incompatibilities
There are no known incompatibilities.

6.3 Shelf life
24 months.
After opening of the sachets, the vials must be used within 3 months.

6.4 Special precautions for storage
Store at room temperature below 25°C. Protect from light.
After opening of the sachets, the vials must be protected from light.

6.5 Nature and contents of container

There are 4 sachets in a box and 5 single-dose 2.5 ml transparent low-density polyethylene vials in each sachet.

6.6. Special precautions for disposal and other handling

Dilution:
SALRES can be diluted with normal saline.
The unused solution in the nebuliser should be disposed.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

2017/332

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 23.05.2017
Date of last renewal :

10. DATE OF REVISION OF THE TEXT