SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SALRES 2.5 mg / 2.5 ml Inhalation Solution for Nebulization
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5 mL solution contains:
Active substance: 3 mg salbutamol sulfate equivalent to 2.5 mg salbutamol
Excipient(s):
For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation solution administered by nebulizer.
Clear, colorless solution for nebulization, free of particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is a reliever medication to reduce the symptoms in asthma by reducing bronchoconstriction. It should not be used as a controller medication.
It is used as a rescue medication and to reduce the symptoms in chronic obstructive pulmonary disease (COPD). It is not preferred to be used 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.
The initial dose of salbutamol is 2.5 mg by moist inhalation.

This dose may be increased up to 5 mg. The treatment may be repeated 4 times a day. In cases of very severe airway obstruction, adults may be administered high doses up to 40 mg per day in the hospital under strict medical supervision.

Increased use of $beta_2$ agonist may be a sign that asthma has been aggravated. In this situation, it may be required to reassess the patient's treatment plan, and corticosteroid therapy in combination should be considered.

Aerosol may be administered via a face mask, "T" piece or an endotracheal tube. Intermittent positive pressure ventilation technique may be used, but this is rarely necessary. When there is a risk of anoxia due to hypoventilation, oxygen should be added to the inspired air.

Since adverse effects may be observed in the case of overdose, dose or frequency of administration cannot be increased unless recommended otherwise by the physician.

Since many nebulizers are operated on a continuous flow basis, it is likely that the nebulized drug will be released into the local environment. Therefore, SALRES should be administered in well-ventilated rooms, especially in hospitals where many patients use nebulizers in the same area simultaneously.

Method of administration
SALRES is intended to be used with a nebulizer under the supervision of a physician.

SALRES is to be used without dilution. However, if it is needed to be administered for a long time (longer than 10 minutes), it may be necessary to dilute it with a physiological saline for injection.

The solution should not be injected or swallowed.

Additional information on special populations

Renal/Hepatic impairment:

No data is available.

Pediatric population:

Children aged 12 years and older: According to adult dose.

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

Other pharmaceutical forms may be more appropriate for children under 4 years of age.

Infants under 18 months: The clinical efficacy of nebulized salbutamol in infants under 18 months is uncertain. Supportive oxygen therapy should be considered since transient hypoxemia may occur.

SALRES nebule is administered undiluted. However, if a longer administration time (longer than 10 minutes) is required, the solution may be diluted with a sterile normal saline.

Geriatric population:

No data is available.

4.3 Contraindications

- It is contraindicated in patients with a history of hypersensitivity to the active substance of SALRES or to any of the excipients listed in section 6.1.
- Non-intravenous SALRES formulations should not be used in the management of threatened uncomplicated premature labor or miscarriage.

4.4 Special warnings and precautions for use

A gradual treatment regimen should be followed in the treatment of asthma and the patient's response should be observed clinically and using pulmonary function tests.

Sudden and progressive deterioration of asthma control is potentially life-threatening and the using corticosteroid therapy or the increasing its dose should be considered. Daily peak flow controls can be initiated in patients at risk.

SALRES nebules should only be used via inhalation, administered through oral-to-inhalation and should not be injected or swallowed.

Bronchodilators should not be the sole or main treatment in patients with severe or unstable

asthma. Severe asthma requires regular medical evaluation, including pulmonary function test, because patients are at risk for severe attacks and even death. Physicians should consider administering the highest recommended dose of inhaled corticosteroid and/or oral corticosteroid therapy in these patients.

Patients receiving SALRES treatment at home should be warned that if either the relief they get from medication is diminished or the effectiveness of SALRES is reduced, they should not increase the dose or its frequency of use, but consult the doctor.

Patients treated with SALRES may also be using other dosage forms of short-acting inhaled bronchodilators to control symptoms. Increased use of bronchodilators, especially short-acting inhaled $beta_2$ agonists to control symptoms, indicates worsening of asthma control. If the effect of short-acting reliever bronchodilator therapy decreases or more inhalations than usual are required, patients should be instructed to consult a physician. In this case, patients should be evaluated and the need for increased anti-inflammatory therapy considered (e.g., higher doses of inhaled corticosteroid or an oral corticosteroid therapy).

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

SALRES should be administered with caution in patients with thyrotoxicosis.

Cardiovascular effects may be observed with the administration of sympathomimetic drugs, including salbutamol. There are post-marketing data and published literature on the rare development 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 should be used with caution in patients who are known to take high doses of other sympathomimetic drugs.

Potentially serious hypokalemia may result from beta-2 agonist therapy, mainly from parenteral and nebulized administration. Particular caution is required in acute severe asthma because this effect may be exacerbated by hypoxia and concomitant treatment with xanthine derivatives, steroids and diuretics. Serum potassium levels should be monitored in such situations.

As with other beta adrenoceptor agonists, SALRES may cause reversible metabolic changes such as increased blood sugar levels. Diabetic patients may be unable to compensate for the increase in blood glucose and the development of ketoacidosis has been reported. Concomitant administration of corticosteroids may exacerbate this effect.

Lactic acidosis has been reported very rarely in patients receiving intravenous or nebulized short-acting beta agonist therapy at high therapeutic doses to treat major acute asthma exacerbations (see section 4.8). Increased lactate levels may cause dyspnea and balancing hyperventilation; this may be misinterpreted as a sign of the failure of asthma treatment and lead to the unnecessary intensification of short-acting beta agonist therapy. Therefore, these patients should be monitored for elevated serum lactate levels and consequent development of metabolic acidosis.

A small number of cases of acute angle-closure glaucoma have been reported in patients receiving concomitant nebulized salbutamol and ipratropium bromide. Therefore, caution should be exercised in the concomitant use of nebulized salbutamol and nebulized anticholinergics. Patients should be informed about the correct administration of the medicines and warned not to let the solution or nebulized droplets get into the eyes.

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

4.5 Interactions with other medicinal products and other forms of interaction
SALRES and non-selective beta-blocking drugs such as propranolol should not usually be administered concurrently.

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

Additional information on special populations
No interaction studies have been conducted in elderly patients or patients with renal or hepatic impairment.

Pediatric population
No interaction studies have been conducted in pediatric patients.

4.6 Pregnancy and lactation
General recommendation
Pregnancy category is “C”.

Women of childbearing potential/Birth control (Contraception)
There is no data on its use in women of childbearing potential and in those using birth control methods (contraception).

Pregnancy
There are no sufficient data from the use of SALRES in pregnant women. Studies on animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

SALRES should not be used during pregnancy unless necessary.

Drug administration should be restricted to situations where the expected benefit to the mother outweighs any potential risk to the fetus. As with most medications, there is little published evidence regarding the safety of salbutamol in the early stages of pregnancy in humans. However, animal studies have found evidence of some harmful effects on the fetus at very high dose levels.

During the worldwide marketing experiences, various congenital anomalies, including cleft palate and arm/leg deformities have been reported rarely in infants of patients treated with salbutamol. Some mothers have used multiple medications during their pregnancies.

Since no consistent pattern has been observed in these deformities and the basal rate of congenital anomalies is 2-3%, the deformities could not be correlated with salbutamol use.

Lactation
As salbutamol is probably secreted in breast milk, its use in breastfeeding mothers requires careful evaluation. It is not known whether salbutamol has a harmful effect on the newborn. Therefore, the use of salbutamol should be limited to situations where the expected benefit to the mother is considered to outweigh any possible risk to the newborn.

Fertility
There is no available information on the effects of salbutamol on human fertility. It has no adverse effect on animal fertility (see section 5.3).

4.7 Effects on the ability to drive and use machines
SALRES is not expected to have any effect on your ability to drive or use machines. A nebulizer should not be used while driving or using machines as it will create a vapor for you to inhale.

4.8 Undesirable effects
Adverse effects are listed below based on system organ classification and frequency. The frequency classification is as follows:
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); unknown (cannot be estimated from available data).

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: Hypokalemia
Potentially serious hypokalemia may result from $beta_2$ agonist therapy.
Very rare: Lactic acidosis (see section 4.4)

Lactic acidosis has been reported very rarely in patients receiving intravenous or nebulized salbutamol therapy to treat exacerbations of acute asthma.

Nervous system disorders
Common: Headache, tremors
Very rare: Hyperactivity

Cardiac disorders
Common: Tachycardia
Uncommon: Palpitations
Very rare: Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles
Unknown: Myocardial ischemia* (see section 4.4)

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

Vascular disorders
Rare: Peripheral vasodilation

Respiratory, thoracic and mediastinal disorders
Very rare: Paradoxical bronchospasm

Gastrointestinal disorders
Uncommon: Mouth and throat irritation

Musculoskeletal, connective tissue and bone disorders
Uncommon: Muscle cramps

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 via the national reporting system.

4.9 Overdose and treatment
The most common signs and symptoms of overdose with SALRES are transient beta agonist pharmacologically mediated events, including tachycardia, tremor, hyperactivity and hypocalemia and lactic acidosis (see sections 4.4 and 4.8).

SALRES overdose may lead to hypokalemia. Serum potassium levels should therefore 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 **:** Selective beta$_2$ adrenoreceptor agonists
ATC code **:** R03AC02

Mechanism of action
Salbutamol is a selective beta$_2$ adrenoceptor agonist. It acts on beta$_2$ adrenoceptors in the bronchial smooth muscles at therapeutic doses.

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 hours) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction. With its rapid effect, it is especially suitable for managing and preventing attacks of asthma.

5.2 Pharmacokinetic properties

General properties

Absorption:
After administration by inhalation, 10 to 20% of the dose reaches the lower airways. The remainder is retained in the delivery system or 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 by 10%.

Biotransformation:
Once in the systemic circulation, salbutamol is metabolized in the liver and excreted primarily in the urine as unchanged drug and phenolic sulfate.

The swallowed portion of the 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.

Elimination:
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. Feces is a minor excretion route. Majority of the salbutamol administered intravenously, orally or by inhalation is excreted within 72 hours.

Patient characteristics
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 administered subcutaneously. In a reproductive study, 9.3% of fetuses were found to have cleft palate at 2.5 mg/kg dose, 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 a result of the lack of maternal care. A reproductive study in rabbits at doses of 50 mg/kg/day (i.e. 78 times the maximum oral human dose) has shown cranial malformation in 37% of the fetuses.

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 postpartum 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
No known incompatibilities.

6.3 Shelf life
24 months.
After the sachets are opened, the vials should be used within 3 months.

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

6.5 Nature and contents of the container
Each carton contains 4 sachets, and each sachet contains 5 single-dose 2.5 mL transparent low density polyethylene vials.

6.6 Special precautions for disposal and other handling
Dilution: SALRES can be diluted with normal saline. The unused solution in the nebulizer should be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. 34303 No:1
Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORISATION NUMBER(S)
2017/331

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION
Date of First Authorization : 18.05.2017
Date of renewal of MA :

10. DATE OF REVISION OF THE TEXT