SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE HUMAN MEDICINAL PRODUCT

SALRES 2 mg/5 mL Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL syrup (1 spoonful of dose) contains:
Active substance(s):
Salbutamol sulfate (equivalent to 2 mg salbutamol……2.4 mg
Excipient(s):
Trisodium citrate dihydrate……7.5 mg
Sodium benzoate……..10 mg
Sodium saccharine……2.5 mg
Sodium chloride……5 mg
For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Syrup.
Homogenous, colorless and orange-scented solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is used as a reliever medication for relief of symptoms by reducing bronchoconstriction in asthma. It should not be used as a controller medication.

In COPD, it is used to reduce symptoms and as reliever medication. It is not preferred for regular treatment.

4.2 Posology and method of administration

Posology/frequency and duration of administration
Duration of action of SALRES is 4 to 6 hours in most patients.

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.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice.

The usual therapeutic dose for adults is 10 ml salbutamol (4 mg salbutamol) administered 3 or 4 times per day. If adequate bronchodilation is not achieved, each single dose may be increased gradually to a maximum of 20 ml of syrup (8 mg salbutamol).

Some patients may achieve adequate relief with 5 ml of syrup (2 mg salbutamol) administered 3 or 4 times per day.

SALRES syrup is suitable for oral therapy in children or adults who prefer liquid medications.

Method of administration
SALRES is administered via the oral route.

Additional information on special populations

Renal/Hepatic impairment
No data available.

Pediatric population
Children aged 2 - 6 years: 2.5 – 5 ml of syrup (1-2 mg salbutamol) taken 3 or 4 times daily.
Children aged 6 - 12 years: 5 ml of syrup (2 mg salbutamol) taken 3 or 4 times daily.
Children over 12 years: 5 – 10 ml of syrup (2-4 mg salbutamol) taken 3 or 4 times daily.

Geriatric population
In elderly patients and patients known to be sensitive to beta-adrenergic stimulant drugs, a treatment initiated with 5 ml of syrup (2 mg salbutamol) 3 or 4 times per day is advisable.

4.3 Contraindications

SALRES is contraindicated in patients with history of hypersensitivity to any of its components.
Non-intravenous formulations of salbutamol must not be used to arrest uncomplicated premature labor or threatened abortion.

4.4 Special warning and precautions for use

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 oral corticosteroid therapy and/or the maximum recommended dose of inhaled corticosteroid in those patients.

Patients should seek medical advice if treatment with SALRES becomes less effective.

The dosage or frequency of administration should only be increased on medical advice.

Patients taking SALRES may also receive short-acting inhaled bronchodilators for symptom relief.

The management of asthma should normally follow a stepwise program, and patient response should be monitored clinically and by 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.

In this situation, patients should be reassessed and consideration given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroids or a course of oral corticosteroid). Severe exacerbations of asthma must be treated in the normal way.

Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to starting or increasing corticosteroid therapy. In patients considered at risk, daily peak flow monitoring may be instituted.

Patients should not increase the dose or its frequency of administration, but should seek medical advice if either the usual relief is diminished or the usual duration of action is reduced.

SALRES should be administered cautiously to patients with thyrotoxicosis.

Potentially serious hypokalemia may result from beta$_2$ agonist therapy mainly from parenteral and nebulized 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.

In common with other beta-adrenoceptor agonists, salbutamol can induce 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.

Tocolysis
Oral short-acting beta$_2$ agonists have been associated with fatal cardiovascular events such as maternal myocardial infarction, pulmonary edema, and infant cardiomegaly, which increase during treatment with these drugs, although they do not provide sustained efficacy in acute tocolysis of preterm delivery and uterine muscle relaxation. Therefore, oral short-acting beta$_2$ agonists should not be used for any obstetric indication because the benefits of oral formulations for this indication do not outweigh the risks.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of myocardial ischemia associated with salbutamol in rare cases. Patients with underlying severe heart disease (e.g. ischemic heart disease, arrhythmia or severe heart attack) 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.

SALRES contains 5.59 mg sodium per 5 ml. This should be taken into account for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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

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 the elderly or in patients with renal or hepatic failure.

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

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category is "C".

Women of child-bearing potential/Contraception
There are no data regarding the use of salbutamol in women of child-bearing potential and in women using 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.

SALRES should not be used during pregnancy unless clearly necessary.

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.

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
Treatment with salbutamol in nursing mothers requires caution as this substance is probably secreted in breast milk.

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.

Reproduction ability / Fertility
There is no information on the effects of salbutamol on human fertility. No adverse effects on fertility were observed in animals (see section 5.3).

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, 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.

Nervous system disorders
Very common: Tremor
Common: Headache
Very rare: Hyperactivity

Cardiac disorders
Common: Tachycardia, palpitations
Very rare: Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardias and extrasystoles
Not known: Myocardial ischemia* (see section 4.4)

*: Reported spontaneously in post-marketing data therefore frequency regarded as “not known”.

Vascular disorders
Rare: Peripheral vasodilatation

Musculoskeletal, connective tissue and bone disorders
Common: Muscle cramps
Rare: Feeling of muscle tension

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 product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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 hypokalemia (see sections 4.4 and 4.8).

SALRES overdose may cause 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.
Nausea, vomiting and hyperglycemia have been reported, predominantly in children and when salbutamol overdose has been taken via the oral route.

Treatment
Management for an overdose treatment should be as clinically indicated or as recommended by the national poisons center, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Respiratory system, drugs for obstructive airway diseases, adrenergics for systemic use, selective beta$_2$-adrenergic-receptor agonists.
ATC code: R03CC02

Mechanism of action
Salbutamol is a selective beta$_2$-adrenoceptor agonist. At therapeutic doses, it has an action on beta$_2$-adrenoceptors of bronchial smooth muscle.

Pharmacodynamic effects
Salbutamol is a selective beta$_2$-adrenoceptor agonist. At therapeutic doses, it has an action on beta$_2$-adrenoceptors of bronchial smooth muscle providing short acting (4-6 hour) bronchodilation in reversible airway obstruction.

5.2 Pharmacokinetic properties

General properties
Absorption
After oral administration, salbutamol is absorbed from the gastrointestinal tract.

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

Biotransformation
After oral administration, salbutamol is absorbed from the gastrointestinal tract and undergoes considerable first pass metabolism to the phenolic sulfate. The bioavailability of orally administered salbutamol is about 50%.

Elimination
Urinary excretion is the major elimination route for both unchanged drug and its conjugate. Fecal excretion, on the other hand, is the minor route of elimination. Salbutamol administered intravenously has a half-life of 4 to 6 hours and is cleared partly by the kidneys and partly by metabolism to the inactive 4'-O-sulphate (phenolic sulfate), which is excreted primarily in the urine. The majority of a dose of salbutamol given intravenously, orally or by inhalation is excreted within 72 hours.

Characteristics in patients
No data 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.

Reproductive studies in the rabbit at doses of 50 mg/kg/day orally (i.e. much higher than the normal human dose) have shown fetuses with treatment related changes; these included open eyelids (ablepharia), secondary palate clefts (palatoschisis), changes in ossification of the frontal bones of the cranium (cranioschisis) and limb flexure.

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.
Reproductive studies in rats showed no evidence of impaired fertility at oral doses of salbutamol up to 50 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trisodium citrate dihydrate
Citric acid anhydrous
Hydroxypropyl methyl cellulose 4000 SR
Sodium benzoate
Saccharine sodium
Sodium chloride
Orange flavor 506304 CE
Deionized water

6.2 Incompatibilities

Sugar-free formulation:
Dilution of SALRES with syrup or sorbitol solution is not recommended as the thickening substance cellulose may precipitate the agent.

6.3 Shelf life

24 months.
After dilution, it should be used within 28 days, protected from light.

6.4 Special precautions for storage

It should be stored at room temperature below 25°C, protected from light.

6.5 Nature and contents of container

SALRES 2 mg/5 mL Syrup is packaged using 25 PP 150 mL amber glass bottles and 25/16 plastic caps. The bottles are packed in cardboard boxes.
It is presented in a box in a glass bottle, a 5 ml plastic spoon with 1.25 ml, 2.5 ml and 5 ml lines, and a package leaflet.

6.6 Special precautions for disposal and other handling

Dilution:
Sugar-free formulation:
SALRES may be diluted with purified water (50%v/v). The resulting mixture should be protected from light and used within 28 days.

A 50% v/v dilution of SALRES has been shown to be adequately preserved against microbial contamination. However, to avoid the possibility of introducing excessive microbial contamination, the purified water used for dilution should be recently prepared or alternatively it should be boiled and cooled immediately before use.

Admixture of SALRES with other liquid preparation is not recommended.

Any unused product or waste material should be disposed of in accordance with local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. 34303 No: 1
Küçükçekmece / İSTANBUL / TURKEY

8. MARKETING AUTHORIZATION NUMBER

2022/114

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 19.03.2022
Date of last renewal :

10. DATE OF REVISION OF THE TEXT