Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Salamol Steri-Neb 5 mg/2.5 ml Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Steri-Neb nebuliser solution (2.5ml) contains Salbutamol Sulphate equivalent to 5 mg Salbutamol (2mg/ml).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.
Clear, colourless to pale yellow, aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Salamol Steri-Nebs are indicated in adults, adolescents and children 4 to 11 years. For babies and children under 4 years of age, see section 4.2.

Salamol Steri-Nebs are indicated for the treatment or routine management of bronchospasm. They provide short-acting (four hours) bronchodilation in reversible airways obstruction due to asthma and chronic obstructive pulmonary disease (COPD) such as chronic bronchitis and emphysema. For patients with asthma salbutamol may be used to relieve symptoms when they occur and to manage them prior to a known trigger.

4.2 Posology and method of administration

Posology

Adults and adolescents aged 12 years and over:

A suitable starting dose of salbutamol by wet inhalationis 2.5 milligrams.

This may be increased to 5 milligrams. Treatment may berepeated up to four times daily.

The maximum daily dose in adults is normally 20 mg/day. Inadult dosing, up to 40 milligrams per day, can be given under strict medicalsupervision in hospital for the treatment of severe airways obstruction.

Paediatric population:

For children aged 4 to 11 years: A suitable starting doseof salbutamol by wet inhalation is 2.5 milligrams.

This may be increased to 5 milligrams. Treatment may berepeated up to four times daily.

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

Clinical efficacy of nebulised salbutamol in infantsunder 18 months is uncertain.
As transient hypoxaemia may occur, supplemental oxygentherapy should be considered.

Method of administration

Salbutamol inhaled formulations are administered by theinhaled route only, to be breathed in through the mouth.

Salbutamol has a duration of action of 4 to 6 hours inmost patients.

Salamol Steri-Nebs are intended to be used undiluted.However, if prolonged delivery time is desirable (more than 10 minutes)dilution using sterile normal saline as a diluent may be required.

Salamol Steri-Nebs are to be used with a nebuliser, underthe direction of a physician.

The solution must not be injected, or swallowed.

Increasing use of beta-2 agonists may be a sign ofworsening asthma. Under these conditions a reassessment of the patient'stherapy plan may be required and concomitant glucocorticosteroid therapy shouldbe considered.

Delivery of the aerosol may be by facemask, 'T' piece orvia an endotracheal tube. Intermittent positive pressure ventilation may beused but is rarely necessary. When there is a risk of anoxia throughhypoventilation, oxygen should be added to the inspired air.

As there may be adverse effects associated with excessivedosing, the dosage or frequency of administration should only be increased onmedical advice.

As many nebulisers operate on a continuous flow basis, itis likely that nebulised drug will be released in the local environment.Salamol Steri-Nebs should therefore be administered in a well-ventilated room,particularly in hospitals when several patients may be using nebulisers at thesame time.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Although intravenous salbutamol is used in the management of premature labour uncomplicated by conditions such as placenta praevia, ante-partum haemorrhage or toxaemia of pregnancy, inhaled salbutamol preparations are not appropriate for managing premature labour. Salbutamol presentations should not be used for threatened abortion.

4.4 Special warnings and precautions for use

The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.

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 Salamol Steri-Nebs.

Increasing use of short-acting bronchodilators, in particular beta-2 agonists to relieve symptoms indicate 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, night-time awakening, and activity limitation due to asthma) for proper treatment adjustment as these patients are at risk for overuse of salbutamol.

Bronchodilators should not be the only or main treatment in patients with persistent asthma. In patients with persistent asthma unresponsive to salbutamol, treatment with inhaled corticosteroids is recommended to achieve and maintain control. Failing to respond to treatment with salbutamol may signal a need for urgent medical advice or treatment.

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.

Severe asthma requires regular medical assessment 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.

During treatment of severe asthma crisis concomitant oxygen therapy should be used to avoid hypoxaemia, especially in young children.

For patients with asthma, use of salbutamol should not delay the introduction and regular use of inhaled corticosteroid therapy. Daily self-assessment of asthma control following instructions regarding the use of salbutamol and any other drugs required for the management of asthma is important in order that the course of the disease can be followed and the success of both bronchodilator and anti-inflammatory therapy monitored. If disease control does not improve satisfactorily or deteriorates, or if the short-acting relief bronchodilator treatment becomes less effective, or more inhalations than usual are required, medical advice must be sought in order that the clinical condition can be re-assessed and therapeutic management revised appropriately. In this situation, the dose of anti-inflammatory therapy may need to be increased or a short course of oral glucocorticoids may be needed.

If acute asthma symptoms are not relieved or gets even worse following a second inhalation, medical assistance should be sought immediately.

Patients requiring long-term management with bronchodilators should be kept under regular surveillance.

Steri-Nebs solution 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 Salamol Steri-Nebs 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.

A responsible adult should supervise the treatment with Salamol Steri-Nebs in children.

Salamol Steri-Nebs should be used with caution in patients known to have received large doses of other sympathomimetic drugs.

Salbutamol should be administered with caution to patients with severe cardiovascular disease, hypertrophic obstructive cardiomyopathy, tachyarrhythmia, severe and untreated hypertension, aneurysm, thyrotoxicosis or untreated hypokalaemia, hyperthyroidism, diabetes which is difficult to control and pheochromocytoma.

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 receive adequate instruction in correct administration and be warned not to let the solution or mist enter the eye.

Potentially serious hypokalaemia 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.

In common with other beta-adrenoceptor agonists, Salamol Steri-Nebs 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 ketacidosis 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 section 4.8, Undesirable effects)*. 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.

Salbutamol should not cause difficulty in micturition because unlike sympathomimetic drugs such as ephedrine, it does not stimulate α-adrenoceptors. However there have been reports of difficulty in micturition in patients with prostatic enlargement.

Use with caution in diabetic patients as salbutamol may cause an increase in blood sugar level.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature 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.

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, if immediately available. The specific salbutamol presentation should be discontinued, and if necessary, a different fast-acting bronchodilator instituted for ongoing use.

Patients should be instructed in the proper use of salbutamol and the nebuliser. Children and their caregivers should be encouraged and trained to use a mouth-piece instead of a face mask as soon as possible.

The use of salbutamol may cause a positive outcome in anti-doping control tests.

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.

Salbutamol is not contra-indicated in patients under treatment with monoamine oxidase inhibitors (MAOIs), however the effects of salbutamol may be altered by guanethidine, reserpine, methyldopa and tricyclic antidepressants.

Caution should be exercised in its use with anaesthetic agents such as chloroform, cyclopropane, halothane and other halogenated agents. If anaesthesia with halogenated anaesthetics is planned, care should be taken to ensure that salbutamol is not used for at least 6 hours before initiation of the anaesthesia.

Treatment with salbutamol can lead to hypokalaemia (see section "*Special warnings and precautions for use*" and section "*Undesirable effects*"). This effect may be potentiated by the concomitant administration of other drugs, in particular xanthine derivatives, glucocorticoids and diuretics. Cardiac glycosides should be used with caution.

Isolated cases of acute angle glaucoma have been reported in patients treated with a combination of nebulised salbutamol and ipratropium; this combination should therefore be used with caution and, in particular, should avoid any contact with the eye.

4.6 Fertility, pregnancy and lactation

Pregnancy

Administration of drugs during pregnancy should only beconsidered if the expected benefit to the mother is greater than any possiblerisk to the foetus.

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

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

Breastfeeding
As salbutamol is probably secreted in breast milk its usein nursing mothers is not recommended unless the expected benefits outweigh anypotential risk. It is not known whether salbutamol in breast milk has a harmfuleffect on the neonate.

Fertility
There is no information on the effects of salbutamol onhuman fertility. There were no adverse effects on fertility in animals (seesection 5.3, Preclinical Safety Data).

4.7 Effects on ability to drive and use machines

Salamol Steri-Nebs have no or negligible influence on the ability to drive and use machines.

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 and < 1/10), uncommon (≥ 1/1000 and < 1/100), rare (≥ 1/10,000 and < 1/1000) and very rare (< 1/10,000) including isolated reports. 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: Hypokalaemia.
Potentially serious hypokalaemia may result from beta-2 agonist therapy.

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 exacerbation.

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* (see section 4.4, special warnings and precautions for use).

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

Vascular disorders
Rare: Peripheral vasodilatation.

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

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. Salamol Steri-Nebs should be discontinued immediately, the patient assessed, and, if necessary, alternative therapy instituted.

Gastrointestinal disorders
Uncommon: Mouth and throat irritation.

Musculoskeletal and connective tissue disorders
Uncommon: Muscle cramps.

Paediatric population
There are reports about stimulating effects on the central nervous system after inhalation of salbutamol which manifest themselves in hyperexcitability, hyperactive behaviour, sleeping disturbances and hallucinations. These observations were predominantly made in children up to 12 years of age.

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, Website: www.hpra.ie.

4.9 Overdose

The most common signs and symptoms of overdose with salbutamol are transient beta-agonist pharmacologically-mediated events (see section 4.4 *Special warnings and precautions for use* and section 4.8, *Undesirable effects*).

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.

Treatment after an overdose of a β-sympathomimetic is mainly symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective $ß_2$-adrenoreceptor agonists, ATC Code: R03AC02

Salbutamol is a selective $ß_2$-adrenoceptor agonist. At therapeutic doses it acts on the $ß_2$-adrenoceptors of bronchial muscle providing short acting (4 to 6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction.

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-sulphate (phenolic sulphate) which is also excreted primarily in the urine. The faeces are a minor route of excretion. The majority 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 sulphate. Both unchanged drug and conjugate are excreted primarily in the urine.

5.3 Preclinical safety data

In common with other potent selective $ß_2$ receptor agonists, salbutamol has been shown to be teratogenic in mice when given subcutaneously. In a reproductive study, 9.3% of foetuses were found to have cleft palate, at 2.5mg/kg, 4 times the maximum human oral dose. In rats, treatment at the levels of 0.5, 2.32, 10.75 and 50mg/kg/day orally throughout pregnancy resulted in no significant foetal 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 foetuses at 50mg/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
Dilute Sulphuric Acid (for pH adjustment)
Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 2 years.
Once opened: Use immediately. Discard any unused portion.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze.
Keep container in the outer carton to protect from light.

6.5 Nature and contents of container

A unit dose blow moulded hermetically sealed, low density polyethylene Steri-Neb containing 2.5ml of solution.
Available in cartons of 20 and 100 Steri-Nebs (Steri-Nebs are packed into foil laminate pouches, containing strips of 5x Steri-Nebs per pouch).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Salamol Steri-Neb 5mg/2.5ml should be administered from a power operated nebuliser via a face mask or mouthpiece.

Single use only. Discard any unused portion.
Do not use this medicine if the solution is cloudy.

Salamol Steri-Neb 5mg/2.5ml is intended to be used undiluted. However, if prolonged delivery time is desirable (more than10minutes) dilution with normal saline for injection may be required.

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
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8 MARKETING AUTHORISATION NUMBER

PA1986/086/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 January 1993

Date of last renewal: 04 January 2008

10 DATE OF REVISION OF THE TEXT

April 2024