SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Terbutaline Sulfate 2.5mg/ml Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 5mg terbutaline sulfate in 2ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.

A clear, colourless to yellow solution contained within clear plastic single dose ampoules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Terbutaline is a selective beta$_2$-adrenergic agonist recommended for the relief of severe bronchospasm in bronchial asthma and in chronic bronchitis and other bronchopulmonary disorders in which bronchospasm is a complicating factor.

4.2 Posology and method of administration

Posology

When used as maintenance therapy the patient should also receive optimal anti-inflammatory therapy, e.g. inhaled corticosteroids, leukotriene receptor antagonists.
In most patients, the use of terbutaline sulfate, based on the doses below, given 2-4 times daily will be sufficient to relieve bronchospasm. In acute severe asthma, additional doses may be necessary.

Dosage:
Adults (including the elderly): One or two ampoules (5 or 10mg).
Children (>25kg): One ampoule (5mg).
Children (<25kg): Not recommended.

Method of administration

Instructions for use and cleaning are provided in the Patient Information Leaflet which can be found in each pack.

Private purchase of nebuliser devices for use at home to deliver rescue therapy for the acute treatment of asthma in children and adolescents is not recommended.

Only specialists in respiratory medicine should initiate and clinically manage use of nebulisers and associated nebulised medicines at home for acute treatment of asthma in children and adolescents.

Children should be trained in the correct use of their device to deliver rescue therapy and use should be supervised by a responsible adult.

Urgent medical assistance should be sought if worsening asthma symptoms are not relieved by rescue medicines, even if there is short-term recovery following use of prescribed medication.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Patients should be instructed in proper use and their inhalation technique checked regularly.

Patients with persistent asthma who require maintenance therapy with $beta_2$-agonists should also receive optimal anti-inflammatory therapy e.g. inhaled corticosteroids, leukotriene receptor antagonists. Patients who are prescribed regular anti-inflammatory therapy should be advised to continue taking their anti-inflammatory medication after the introduction of Terbutaline Sulfate Nebuliser Solution, even when symptoms decrease and they do not require Terbutaline Sulfate Nebuliser Solution.

Should symptoms persist, or if a previously effective dosage regimen no longer gives the same symptomatic relief, the patient should seek medical advice as soon as possible, as this could be a sign of worsening of the underlying condition and warrants a reassessment of the therapy. Consideration should be given to the requirements for additional therapy (including increased dosages of anti-inflammatory medication). Severe

exacerbations of asthma should be treated as an emergency in the usual manner.

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 additional "as needed" Terbutaline Sulfate Nebuliser Solution should be re-evaluated for proper treatment adjustment, as these patients are at risk for overuse of Terbutaline Sulfate Nebuliser Solution.

As for all $beta_2$-agonists caution should be observed in patients with thyrotoxicosis.

Due to the positive inotropic effect of the $beta_2$-agonists, these drugs should not be used in patients with hypertrophic cardiomyopathy.

Cardiovascular effects may be seen with sympathomimetic drugs, including Terbutaline Sulfate Nebuliser Solution. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with beta agonists. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving Terbutaline Sulfate Nebuliser Solution 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.

Due to the hyperglycaemic effects of $beta_2$-agonists, additional blood glucose controls are recommended initially in diabetic patients.

Potentially serious hypokalaemia may result from $beta_2$-agonist therapy. Particular caution is recommended in acute severe asthma as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatments (see section 4.5). It is recommended that serum potassium levels are monitored in such situations.

Lactic acidosis has been reported in association with high therapeutic doses of parenteral and nebulised short-acting beta-agonist therapy, mainly in patients being treated for an acute asthma exacerbation (see sections 4.8 & 4.9). In patients not adequately responding to acute Terbutaline Sulfate Nebuliser Solution therapy, consideration should be given to the presence of lactic acidosis as a possible contributing factor to ongoing respiratory symptoms.

Information on sodium content
This medicine contains less than 1 mmol sodium (23 mg) per 2ml ampoule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Beta-blocking agents (including eye drops), especially the non-selective ones such as propranolol, may partially or totally inhibit the effect of beta-stimulants. Therefore, Terbutaline Sulfate Nebuliser Solution and non-selective beta-blockers should not normally be administered concurrently. Terbutaline Sulfate Nebuliser Solution should be used with caution in patients receiving other sympathomimetics.

Halogenated anaesthetics
Halothane anaesthesia should be avoided during $Beta_2$-agonists treatment, since it increases the risk of cardiac arrhythmias. Other halogenated anaesthetics should be used cautiously together with $Beta_2$-agonists.

Potassium depleting agents and hypokalemia
Owing to the hypokalaemic effect of beta-agonists, concurrent administration with Terbutaline Sulfate Nebuliser Solution of serum potassium depleting agents known to exacerbate the risk of hypokalaemia, such as diuretics, methyl xanthines and corticosteroids, should be administered cautiously after careful evaluation of the benefits and risks with special regard to the increased risk of cardiac arrhythmias arising as a result of hypokalaemia (see section 4.4). Hypokalaemia also predisposes to digoxin toxicity.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
Although no teratogenic effects have been observed in animals or in patients, terbutaline should only be administered with caution during the first trimester of pregnancy.

If used in maintenance therapy for asthma and other pulmonary diseases, Terbutaline Sulfate Nebuliser Solution should be used with caution at the end of pregnancy because of the potential tocolytic effect.

Breast-feeding
Terbutaline is secreted via breast milk, but effect on the infant is unlikely at therapeutic doses.

4.7 Effects on ability to drive and use machines

Terbutaline Sulfate Nebuliser Solution has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

The frequency of adverse reactions is low at the recommended dose. Terbutaline given by inhalation is unlikely to produce significant systemic effects when given in recommended doses. Most of the adverse reactions are characteristic of sympathomimetic amines. The majority of these effects have reversed spontaneously within the first 1-2 weeks of treatment.
The frequency of side-effects is low at the recommended doses.

Tabulated list of adverse reaction
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 (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

System Organ Class (SOC)	**Frequency Classification**	**Adverse Drug Reaction Preferred term (PT)**
Immune system disorders	Not known^	Hypersensitivity reactions includi angioedema, bronchospasm, hypotension and collapse
Metabolism and nutritional disorders	Common	Hypokalaemia (see section 4.4)
	Not known^	Lactic acidosis
Psychiatric disorders	Not known^	Sleep disorder and behavioural disturbances, such as agitation and restlessness
Nervous system disorders	Very Common	Tremor Headache
Cardiac disorders	Common	Tachycardia Palpitations
	Not known^	Arrhythmias, e.g. atrial fibrillation supraventricular tachycardia and extrasystoles Myocardial ischaemia (see section
Vascular disorders	Not known^	Peripheral vasodilation
Respiratory, thoracic and mediastinal Disorders	Not known^	Paradoxical bronchospasm*
Gastrointestinal disorders	Not known^	Nausea Mouth and throat irritation
Skin and subcutaneous tissue disorders	Not known^	Urticaria Rash
Musculoskeletal and connective tissue disorders#	Common	Muscle spasms

#A few patients feel tense; this is also due to the effects on skeletal muscle and not to direct CNS stimulation.

^ Reported spontaneously in post-marketing data and therefore frequency regarded as unknown.
* In rare cases, through unspecified mechanisms, paradoxical bronchospasm may occur, with wheezing immediately after inhalation. This should be immediately treated with a rapid-onset bronchodilator. Terbutaline Sulfate Nebuliser Solution therapy should be discontinued and, after assessment, an alternative therapy initiated.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and symptoms of overdose
Headache, anxiety, tremor, nausea, tonic cramp, palpitations, tachycardia and arrhythmia. A fall in blood pressure sometimes occurs. Laboratory findings; hypokalaemia, hyperglycaemia and metabolic acidosis sometimes occur (see section 4.4).

Treatment
Mild and moderate cases: Reduce the dose.
Severe cases: Gastric lavage, administration of activated charcoal (where suspected that significant amounts have been swallowed). Determination of acid-base balance, blood sugar and electrolytes, particularly serum potassium levels. Monitoring of heart rate and rhythm and blood pressure. Metabolic changes should be corrected. A cardioselective beta-blocker (e.g. metoprolol) is recommended for the treatment of arrhythmias causing haemodynamic deterioration. The beta-blocker should be used with care because of the possibility of inducing bronchoconstriction: use with caution in patients with a history of bronchospasm. If the beta-mediated reduction in peripheral vascular resistance significantly contributes to the fall in blood pressure, a volume expander should be given.

Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective beta$_2$-adrenoreceptor agonists, terbutaline, ATC code: R03A C03.

Terbutaline is a selective beta$_2$-adrenergic stimulant, having the following pharmacological effects:
i) In the lung: bronchodilation; increase in mucociliary clearance; suppression of oedema and anti-allergic effects.

ii) In skeletal muscle: stimulates Na+/K+ transport and also causes depression of subtetanic contractions in slow-contracting muscle.
iii) In uterine muscle: Inhibition of uterine contractions.
iv) In the C.N.S: Low penetration into the blood-brain barrier at therapeutic doses, due to the highly hydrophilic nature of the molecule.
v) In the C.V.S.: Administration of terbutaline results in cardiovascular effects mediated through beta2-receptors in the peripheral arteries and in the heart e.g. in healthy subjects, 0.25 - 0.5 mg injected s.c., is associated with an increase in cardiac output (up to 85% over controls) due to an increase in heart rate and a larger stroke volume. The increase in heart rate is probably due to a combination of a reflex tachycardia, via a fall in peripheral resistance, and a direct positive chronotropic effect of the drug.

5.2 Pharmacokinetic properties

Basic parameters have been evaluated in man after i.v. and oral administration of therapeutic doses, e.g.

I.V. single dose
Volume distribution (VSS) - 114L.
Total body clearance (CL) - 213 ml/min.
Mean residence time (MRT) - 9.0 h.
Renal clearance (CLR) - 149 ml/min (males).

Oral dose
Renal clearance (CLR) - 1.925 ml/min (males).
Renal clearance (CLR) - 2.32 ml/min (females).
The plasma concentration/time curve after i.v. administration is characterised by a fast distribution phase, an intermediate elimination phase and a late elimination phase.
Terminal half-life $t_{½}$ has been determined after single and multiple dosing (mean values varied between 16-20 h.).

Bioavailability
Food reduces bioavailability following oral dosing (10% on average) fasting values of 14-15% have been obtained.

Metabolism
The main metabolite after oral dosing is the sulfate conjugate and also some glucoronide conjugate can be found in the urine.

5.3 Preclinical safety data

The major toxic effect of terbutaline, observed in toxicological studies in rats and dogs at exposures in excess of maximum human exposure, is focal myocardial necrosis. This type of cardiotoxicity is a well known pharmacological manifestation seen after the administration of high doses of $beta_2$-agonists.

In rats, an increase in the incidence of benign uterine leiomyomas has been observed. This effect is looked upon as a class-effect observed in rodents after long term exposure to high doses of $beta_2$-agonists.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Disodium edetate
Water for injections in bulk
Sulfuric acid

6.2 Incompatibilities

None known.

6.3 Shelf life

Three years.
Ampoules must be used within six months of opening the foil wrap.

6.4 Special precautions for storage

No special precautions for storage.

Ampoule should be opened immediately before use and any solution remaining after use should be discarded.

6.5 Nature and contents of container

Unit dose polyethylene ampoules packed into cartons. Each carton contains 20 ampoules in foil wrapped strips of 5 or 10

6.6 Special precautions for disposal

Terbutaline Sulfate Nebuliser Solution is for inhalation from a suitable nebuliser which should be operated according to the manufacturer's instructions. The method of opening the ampoules is to hold upright, twist and pull off the plastic seal.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited

Sage House

319 Pinner Road

North Harrow

Middlesex

HA1 4HF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0713

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/05/2006

10 DATE OF REVISION OF THE TEXT

14/04/2023