The format of this leaflet as determined by the Ministry of Health and its content was checked and approved in September 2007

VENTOLIN PARENTERAL PREPARATIONS

TITLE

Salbutamol sulphate

SCOPE

Trade Names

Ventolin™ Injection
Ventolin™ Intravenous Infusion

Formulation and Strength

Salbutamol Injection 500mcg (0.5mg) in 1ml (500mcg/ml) is presented as ampoules of 1ml each containing 500mcg salbutamol sulphate BP, in a sterile isotonic solution adjusted to pH 3.5 with sulphuric acid.

Salbutamol Solution for intravenous infusion 5mg in 5ml (1mg/ml) is presented as ampoules of 5ml each containing 5mg salbutamol sulphate BP, in a sterile isotonic solution adjusted to pH 3.5 with sulphuric acid.

The ampoules are of clear, neutral glass and the solution is colourless or faintly straw coloured.

Excipients

Ventolin™ Injection
Sodium Chloride
Dilute Sulphuric Acid
Sodium hydroxide
Nitrogen
Water for Injection

Ventolin™ Intravenous Infusion
Sodium Chloride
Sulphuric Acid Dilute
Sodium hydroxide Pellets
Water for Injection

CLINICAL INFORMATION

Indications

Salbutamol BP is a beta-adrenergic stimulant that has a selective action on the $beta_2$-adrenoceptors in the bronchi and uterus and much less action on the $beta_1$-adrenoceptors in the heart.

Salbutamol parenteral preparations are indicated for two distinct clinical situations under the direction of a physician:

1. For the relief of severe bronchospasm associated with asthma or bronchitis and for the management of status asthmaticus.

2. For the management of premature labour uncomplicated by conditions such as placenta praevia, ante-partum haemorrhage or toxaemia of pregnancy, in the last trimester of pregnancy.

Dosage and Administration

Salbutamol has a duration of action of four to six hours in most patients.

Salbutamol parenteral preparations are to be used under the direction of a physician.

Note: The contents of the ampoules of Salbutamol Solution for intravenous infusion must not be injected undiluted. The concentration should be reduced by 50% before administration.

Salbutamol parenteral preparations should not be administered in the same syringe or infusion as any other medication

Populations

RESPIRATORY

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.

- **Adults**

<u>In severe Bronchospasm and Status Asthmaticus:</u>

Subcutaneous route: 500mcg (8mcg/kg body weight) and repeated every four hours as required.

Intramuscular route: 500mcg (8mcg/kg body weight) and repeated every four hours as required.

Intravenous route: 250mcg (4mcg/kg body weight) injected slowly. If necessary the dose may be repeated.

If Salbutamol Injection 500mcg in 1ml (0.5mg/ml) is used, the injection may be facilitated by dilution with water for injections BP.

Infusion: In status asthmaticus, infusion rates of 3 to 20mcg/minute are generally adequate, but in patients with respiratory failure, higher dosage has been used with success. A starting dose of 5mcg/minute is recommended with appropriate adjustments in dosage according to patient response.

A suitable solution for infusion may be prepared by diluting 5ml of Salbutamol Solution for intravenous infusion in 500ml of an infusion solution such as Sodium chloride and Dextrose Injection BP to provide a salbutamol dose of 10mcg/ml of solution.

- **Children:**

At present there is insufficient evidence to recommend a dosage regimen for routine use in children.

OBSTETRIC

In the Management of Premature Labour

For this indication Salbutamol Solution for intravenous infusion is recommended using a solution prepared as above. It should be administered as early as possible after the diagnosis of premature labour, and after evaluation of the patient to eliminate any contra-indications to the use of salbutamol (see *Contraindications*). It is essential that the volume of infusion fluid is kept to a minimum to control the level of hydration and so avoid the risk of maternal pulmonary oedema (see *Adverse Reactions*). A controlled infusion device, preferably a syringe pump, should be used. Infusion rates of 10-45mcg/minute are generally adequate to control uterine contractions, but greater or less infusion rates may be required according to the strength and frequency of contractions. A starting rate of 10mcg/minute is recommended, increasing the rate at 10-minute intervals until there is evidence of patient response shown by diminution in strength, frequency or duration of contractions .Thereafter the infusion rate may be increased slowly until contractions cease. Careful attention should be given to cardio- respiratory function and fluid balance monitoring. The maternal pulse rate should be monitored and the infusion rate adjusted to avoid excessive maternal heart rates (above 140 beats/minute). Treatment discontinuation should be considered should signs of pulmonary oedema or myocardial ischaemia develop (see *Warnings and Precautions* and *Adverse Reactions*).

Once uterine contractions have ceased the infusion rate should be maintained at the same level for one hour and then reduced by 50% decrements at 6-hourly intervals. If labour progresses despite treatment the infusion should be stopped. If contractions have been successfully inhibited by the infusion, treatment may be continued orally with Salbutamol Tablets 4mg given three or four times daily.

Dilution: The recommended diluent is 5% Dextrose (see *precautions for use in diabetic patients*).
For use in a syringe pump: Prepare a solution providing 200 micrograms salbutamol/ml by diluting 10ml Ventolin solution for intravenous infusion with 40ml diluent. An infusion rate of 10 to 45 micrograms/minute is equivalent to 0.05 to 0.225 ml/minute of this solution.

As an alternative procedure or to counteract inadvertent overdosage with oxytocic drugs, Salbutamol Injection may be administered as a single injection by the intravenous or intramuscular routes. The usual recommended dose is 100 to 250mcg of Salbutamol. The dose may be repeated according to the response of the patient. Data suggest that the main effect of tocolytic therapy is a delay in delivery of up to 48 hours. This delay may be used to administer glucocorticoids or to implement other measures known to improve perinatal health.

Contraindication

- Salbutamol parenteral preparations are contra-indicated in patients with a history of hypersensitivity to any of their components.

- 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, salbutamol presentations should not be used for threatened abortion.

- Salbutamol should not be used as a tocolytic agent in patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease.

Warnings and Precautions

The management of asthma should normally follow a stepwise programme, 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.

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.

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.

Salbutamol should be administered cautiously to patients with thyrotoxicosis.

The use of Salbutamol parenteral preparations in the treatment of severe bronchospasm or status asthmaticus does not obviate the requirement for glucocorticoid steroids therapy as appropriate.

When practicable, administration of oxygen concurrently with parenteral Salbutamol is recommended, particularly when it is given by intravenous infusion to hypoxic patients.

In common with other beta-adrenoceptor agonists, Salbutamol can induce reversible metabolic changes such as reversible hypokalaemia and increased blood glucose levels. The diabetic patient may be unable to compensate for the increase in blood glucose and the development of ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

Diabetic patients and those concurrently receiving corticosteroids should be monitored frequently during intravenous infusion of Salbutamol so that remedial steps (e.g. an increase in insulin dosage) can be taken to counter any metabolic change occurring. For these patients it may be preferable to dilute Salbutamol Solution for intravenous infusion in Sodium Chloride Injection BP rather than Sodium Chloride and Dextrose Injection BP.

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 *Adverse Reaction* section). 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.

In the treatment of premature labour by intravenous infusion of salbutamol, increases in maternal heart rate of the order 20 to 50 beats/minute usually accompany the infusion. The maternal pulse rate should be monitored and not normally allowed to exceed a steady rate of 140 beats/minute.

Maternal blood pressure may fall slightly during the infusion. The effect being greater on diastolic than on systolic pressure. Falls in diastolic pressure are usually within the range of 10 to 20mmHg. The effect of infusion on foetal rate is less marked, but increases of up to 20 beats/minute may occur.

In the treatment of premature labour, before Salbutamol parenteral preparations are given to any patient with known heart disease, an adequate assessment of the patient's cardiovascular status should be made by a physician experienced in cardiology.

As maternal pulmonary oedema and myocardial ischaemia have been reported during or following treatment of premature labour with beta-2 agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG, should be monitored. If signs of pulmonary oedema or myocardial ischaemia develop, discontinuation of treatment should be considered. (see *Dosage and Administration* and *Adverse Reactions*)

In order to minimise the risk of hypotension associated with tocolytic therapy, special care should be taken to avoid caval compression by keeping the patient in the left or right lateral positions throughout the infusion.
Patients being treated with Salbutamol Solution for Intravenous Infusion may also be receiving short-acting inhaled bronchodilators to relieve symptoms.

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.

Tocolysis

Salbutamol should be used with caution in tocolysis and supervision of cardiorespiratory function, including ECG monitoring, should be considered. Treatment should be discontinued if signs of myocardial ischaemia (such as chest pain or ECG changes) develop. Salbutamol should not be used as a tocolytic agent in patients with significant risk factors for or pre-existing heart disease (see section *Contraindication*).

Respiratory indications

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.

Interactions

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

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

Pregnancy and Lactation

Pregnancy

Administration of drugs during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

During worldwide marketing experience, rare cases of 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 to 3%, a relationship with salbutamol use cannot be established.

Lactation

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.

Adverse Reactions

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

Very common:	Tremor.
Common:	Headache.
Very rare:	Hyperactivity.

Cardiac disorder

Very common:	Tachycardia, palpitations.
Rare:	Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles.

Respiratory indication

Uncommon:	Myocardial ischaemia*.

* In the management of pre-term labour with salbutamol infusion.

Obstetric indication

Unknown:	Myocardial ischaemia** (see section Warning and Precautions)

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

Vascular disorders:

Rare:	Peripheral vasodilatation.

Respiratory, thoracic and mediastinal disorders:

Uncommon:	Pulmonary oedema.

In the management of pre-term labour, salbutamol injection/solution for infusion have uncommonly been associated with pulmonary oedema. Patients with predisposing factors including multiple pregnancies, fluid overload, maternal infection and pre-eclampsia may have an increased risk of developing pulmonary oedema.

Gastrointestinal disorders

Very rare:	Nausea, vomiting.

In the management of premature labour, intravenous infusion of salbutamol has very rarely been associated with nausea and vomiting.

Musculoskeletal and connective tissue disorders

Common:	Muscle cramps.

Injury, poisoning and procedural complications

Very rare:	Slight pain or stinging on i.m. use of undiluted injection.

Overdosage

Symptoms and Signs

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events (see *Warnings and Precautions* and *Adverse Reactions*).

Hypokalaemia may occur following overdose with salbutamol. Serum potassium levels should be monitored.

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

Treatment

Consideration should be given to discontinuation of treatment and appropriate symptomatic therapy such as cardio-selective beta-blocking agents in patients presenting with cardiac symptoms (e.g. tachycardia,

palpitations). Beta-blocking drugs should be used with caution in patients with a history of bronchospasm.

Clinical Pharmacology

Pharmacodynamics

Mechanism of Action

Salbutamol is a selective beta-2 adrenoceptor agonist. At therapeutic doses it acts on the beta-2 adrenoceptors of bronchial muscle, with little or no action on the beta-1 adrenoceptors of cardiac muscle.

Pharmacokinetics

Salbutamol administered intravenously has a half-life of 4 to 6 h 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 h. Salbutamol is bound to plasma proteins to the extent of 10%.

NON-CLINICAL INFORMATION

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 foetuses 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 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 50 mg/kg/day, 78 times the maximum human oral dose.

PHARMACEUTICAL PRECAUTIONS

Shelf-Life

3 years.

Storage

Salbutamol parenteral preparations should be protected from light and stored at a temperature below 30^0C.

All unused admixtures of Salbutamol parenteral preparations with infusion fluids should be discarded twenty-four hours after preparation.

Use and Handling

Salbutamol parenteral preparations may be diluted in Water for injections BP, Sodium chloride Injection BP, Sodium chloride and Dextrose Injection BP, or Dextrose Injection BP. These are the only recommended diluents.

Salbutamol parenteral preparations should not be administered in the same syringe or infusion as any other medication.

The contents of the ampoule of Salbutamol Solution for intravenous infusion must not be injected in the undiluted form. The concentration should be reduced by at least 50% before administration.

FURTHER INFORMATION

Salbutamol does not cause difficulty in micturition because, unlike sympathomimetic drugs such as ephedrine, it does not stimulate alpha-adrenoceptors. Salbutamol is not contra-indicated in patients under treatment with monoamine oxidase inhibitors (MAOIs).

Manufacturer: GlaxoSmithKline Manufacturing SPA, Italy

License holder: GlaxoSmithKline (Israel) Ltd 25 Basel St., Petach-Tikva 49002

Registration numbers: Ventolin Injection : 27-64-21556-05
Ventolin Intravenous Infusion : 21-81-21555-05