VENTOLIN INJECTION

Salbutamol sulphate

QUALITATIVE AND QUANTITATIVE COMPOSITION

VENTOLIN ampoules contain 500 micrograms (0.5 mg), salbutamol, as sulphate, in 1 ml (500 micrograms/ml).

PHARMACEUTICAL FORM

Injection

The solution is colourless to very pale straw coloured and adourless. Its specific gravity and viscosity are similar to water.

CLINICAL PARTICULARS

Indications

RESPIRATORY

VENTOLIN is a selective beta-$_2$ adrenoceptor agonist indicated for the treatment or prevention of bronchospasm. It provides short acting bronchodilation in reversible airways obstruction due to asthma, chronic bronchitis and emphysema.

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

VENTOLIN is indicated for the relief of severe bronchospasm associated with asthma or bronchitis and for the treatment of status asthmaticus. It is suitable for the management of an asthma attack under the direction of a physician.

OBSTETRIC

VENTOLIN is a selective beta-$_2$ adrenoceptor agonist. At therapeutic doses it acts on the beta-$_2$ adrenoceptors in the uterus, with little or no action on the beta-$_1$ adrenoceptors of the heart. It is indicated to arrest uncomplicated labour between 22 and 37 weeks of

gestation in patients with no medical or obstetric contraindication to tocolytic therapy, under the direction of a physician.

Dosage and Administration

VENTOLIN has a duration of action of 4 to 6 hours in most patients.

VENTOLIN are to be used under the direction of a physician.

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.

VENTOLIN should not be administered in the same syringe or infusion as any other medication.

In severe bronchospasm and status asthmaticus

- **Adults**

Subcutaneous Route:

500 micrograms (8 micrograms /kg bodyweight) and repeated every 4 hours as required.

Intramuscular Route:

500 micrograms (8 micrograms /kg bodyweight) and repeated every 4 hours as required.

Intravenous Route:

250 micrograms (4 micrograms /kg bodyweight) injected slowly. If necessary the dose may be repeated.

VENTOLIN Injection 250 micrograms in 5 ml (50 micrograms /ml) is a suitably dilute preparation for slow intravenous injection but if *VENTOLIN* Injection 500 micrograms in 1 ml (500 micrograms /ml) is used the injection may be facilitated by dilution with water for injections.

- **Children**

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

In the management of premature labour

Treatment with *VENTOLIN* should only be initiated by obstetricians/physicians experienced in the use of tocolytic agents. Ideally, it should be carried out in facilities adequately equipped to perform continuous monitoring of maternal and foetal health status.

Duration of treatment should not exceed 48 hours as data show that the main effect of tocolytic therapy is a delay in delivery of up to 48 hours. No statistically significant effect on perinatal mortality or morbidity has been observed in randomised, controlled trials. This delay may be used to administer glucocorticoids or to implement other measures known to improve perinatal health.

VENTOLIN should be administered as early as possible after the diagnosis of premature labour, and after evaluation of the patient to eliminate any contraindications to the use of *VENTOLIN* (see *Contraindications*). This should include an adequate assessment of the patient's cardiovascular status with continuous ECG monitoring throughout treatment (see *Warnings and Precautions*).

As an alternative procedure or to counteract inadvertent overdosage with oxytocic drugs, *VENTOLIN* may be administered as a single injection by the intravenous route. The usual recommended dose is 100 to 250 micrograms of salbutamol. The dose may be repeated according to the response of the patient.

Contraindications

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

Non-i.v. formulations of *VENTOLIN* must not be used to arrest uncomplicated premature labour or threatened abortion.

OBSTETRIC

VENTOLIN, when used in the management of premature labour, is contra-indicated in the following conditions:

- at a gestational age < 22 weeks.
- intrauterine foetal death, known lethal congenital or lethal chromosomal malformation.
- any condition of the mother or foetus in which prolongation of the pregnancy is hazardous.
- in patients with pulmonary hypertension, 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.

The use of *VENTOLIN* in the treatment of severe bronchospasm or status asthmaticus does not obviate the requirement for glucocorticoid steroid therapy as appropriate.

When practicable, administration of oxygen concurrently with parenteral *VENTOLIN* is recommended.

In common with other beta-adrenoceptor agonists, *VENTOLIN* can induce reversible metabolic changes such as reversible hypokalaemia and increased blood glucose 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.

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.

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.

VENTOLIN should be administered cautiously to patients with thyrotoxicosis.

Obstetric use only:

In the treatment of premature labour, before *VENTOLIN* is given to any patient with known or suspected heart disease, an adequate assessment of the patient's cardiovascular status should be made by a physician experienced in cardiology.

Tocolysis with *VENTOLIN* is not recommended when membranes have ruptured or the cervix has dilated beyond 4 cm. 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 the treatment of premature labour by intravenous infusion of *VENTOLIN* increases in maternal heart rate of the order 20 to 50 beats per minute usually accompany the infusion. The maternal pulse rate should be monitored and not normally allowed to exceed a sustained rate of 120 beats per minute. The effect of infusion on foetal rate is less marked but increases of up to 20 beats per minute may occur.

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.

Interactions

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

VENTOLIN is not contra-indicated in patients under treatment with monoamine oxidase inhibitors (MAOIs).

Pregnancy and Lactation

Fertility

There is no information on the effects of salbutamol on human fertility. There were no adverse effects on fertility in animals (see *Pre-clinical Safety Data*).

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. As 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.

Effects on Ability to Drive and Use Machines

Not applicable.

Adverse Reactions

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000) including isolated

reports. Very common and common reactions were generally determined from clinical trial data. Rare and very rare reactions 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 disorders

Very common: Tachycardia, palpitations.

Uncommon: Myocardial ischaemia*

*In the management of pre-term labour with *VENTOLIN*.

Rare: Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles.

Vascular disorders

Rare: Peripheral vasodilatation.

Respiratory, thoracic and mediastinal disorders

Uncommon: Pulmonary oedema.

In the management of pre-term labour, *VENTOLIN* has 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.

Musculoskeletal and connective tissue disorders

Common: Muscle cramps.

Injury, poisoning and procedural complications

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

Overdose

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

Hypokalaemia may occur following overdose with *VENTOLIN*. 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.

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

Treatment

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

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 to 6 hour) bronchodilation in reversible airways obstruction.

Pharmacokinetics

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%.

Pre-clinical 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 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.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of *VENTOLIN* up to 50 mg/kg.

PHARMACEUTICAL PARTICULARS

List of Excipients

Sodium chloride

Dilute sulphuric acid or sodium hydroxide for pH adjustment

Water for Injections

Incompatibilities

None reported

Shelf Life

3 years

Special Precautions for Storage

Keep out of reach of children.

VENTOLIN should be protected from light and stored at a temperature below 30°C.

All unused admixtures of *VENTOLIN* with infusion fluids should be discarded twenty-four hours after preparation.

Nature and Contents of Container

1 ml ampoules in boxes of 5.

Instructions for Use/Handling

Dilution:

VENTOLIN may be diluted with Water for Injections BP, Sodium Chloride Injection BP, Sodium Chloride and Dextrose Injection BP or Dextrose Injection BP. These are the only recommended diluents.

Name and address of the holder of the certificate of registration

GlaxoSmithKline South Africa (Pty) Ltd

57 Sloane Street

Bryanston, 2021

South Africa

Manufacturer

GLAXOSMITHKLINE MANUFACTURING S.p.A.

Strada Provinciale Asolana, 90

43056 San Polo di Torrile, Parma

Italy

Registration details

Botswana: Reg No B9303915 S2

Namibia: Reg No 90/10.2.2/00588 NS2

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