VENTOLIN® INJECTION

Salbutamol sulphate

QUALITATIVE AND QUANTITATIVE COMPOSITION

VENTOLIN Solution for Intravenous Infusion 5mg salbutamol, as sulphate, in 5ml (1mg/ml).

PHARMACEUTICAL FORM

Solution for Infusion

CLINICAL PARTICULARS

Indications

VENTOLIN is a selective β_2 adrenoceptor agonist. At therapeutic doses it acts on the β_2 adrenoceptors in the bronchi and uterus, with little or no action on the β-1 adrenoceptors of the heart. It is suitable for the management of an asthmatic attack, and for uncomplicated premature labour, under the direction of a physician.

Bronchodilators should not be the only or main treatment in patients with severe or unstable asthma. Severe asthma requires regular medical assessment as death may occur. Patients with severe asthma have constant symptoms and frequent exacerbations, with limited physical capacity, and PEF values below 60% predicted at baseline with greater than 30% variability, usually not returning entirely to normal after a bronchodilator. These patients will require high dose inhaled (e.g >1mg/day beclomethasone dipropionate) or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

Relief of severe bronchospasm associated with asthma or bronchitis and for the treatment of status asthmaticus.

Management of uncomplicated premature labour in the last trimester of pregnancy.

Dosage and Administration

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

VENTOLIN parenteral preparations 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.

Note : The contents of the ampoules of *VENTOLIN* Solution For Intravenous Infusion must not be injected undiluted. The concentration should be reduced by 50% before administration.

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

In severe bronchospasm and status asthmaticus

- **Adults**

Infusion:

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

A suitable solution for infusion may be prepared by diluting 5ml of *VENTOLIN* Solution for Intravenous Infusion in 500ml of an infusion solution such as sodium chloride and dextrose injection BP to provide a salbutamol dose of 10 micrograms /ml of solution.

- **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* Solution for Infusion 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 Solution for infusion 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*).

For this indication *VENTOLIN* Solution for Intravenous Infusion is recommended using a solution prepared as above. Infusion rates of 10 to45 micrograms per minute are generally adequate to control uterine contractions but greater or lesser infusion rates may be required according to the strength and frequency of contractions. A starting rate of 10 micrograms per 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, including increases in pulse rate and changes in blood pressure, electrolytes, glucose and lactate levels and fluid balance monitoring. A maximum sustained maternal heart rate of 120 beats/min should not be exceeded. Treatment should be discontinued 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 1 hour and then reduced by 50% decrements at 6-hourly intervals.

Contraindications

VENTOLIN parenteral preparations are contraindicated 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 solution for infusion, 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.
- threatened abortion during the 1st and 2nd trimester

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* parenteral preparations 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, particularly when it is given by intravenous infusion to hypoxic patients.

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.

Diabetic patients and those concurrently receiving corticosteroids should be monitored frequently during intravenous infusion of *VENTOLIN* so that remedial steps (e.g. an increase in insulin dosage) can be taken to counter any metabolic change occurring. For these patients *VENTOLIN* Solution for Intravenous Infusion should be diluted with 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.

VENTOLIN should be administered cautiously to patients with thyrotoxicosis.

Obstetric use only:

In the treatment of premature labour, before *VENTOLIN* parenteral preparations are 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* parenteral preparations is not recommended when membranes have ruptured or the cervix has dilated beyond 4 cm.

Tocolysis: Serious adverse reactions including death have been reported after administration of terbutaline/ salbutamol to women in labor. In the mother, these include increased heart rate, transient hyperglycaemia, hypokalaemia, cardiac arrhythmias,

pulmonary oedema and myocardial ischarmia. Increased fetal heart rate and neonatal hypoglycaemia may occur as a result of maternal administration.

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.

Cautious use of salbutamol injections is required in pregnant patients when it is given for relief of bronchospasm so as to avoid interference with uterine contractibility.

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.

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

None

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 injection/solution for infusion.

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 injection and solution for intravenous infusion 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.

In the management of premature labour, intravenous infusion of VENTOLIN 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 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 2.5mg/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.

PHARMACEUTICAL PARTICULARS

List of Excipients

Dilute sulphuric acid or sodium hydroxide for pH adjustment

Nitrogen

Sodium Chloride

Water for Injections

Incompatibilities

None

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

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

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

Nature and Contents of Container

VENTOLIN Solution for Intravenous Infusion 5 miligrams in 5ml (1mg/ml) is presented as ampoules of 5ml each containing 5mg Salbutamol BP as Salbutamol Sulphate BP, in a clear, colourless to pale-straw coloured solution.

Instructions for Use/Handling

Dilution:

VENTOLIN parenteral preparations 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.

Manufactured by:

GlaxoSmithKline S.p.A
Parma, Italy

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