Ventolin™ parenteral preparations
Salbutamol

QUALITATIVE AND QUANTITATIVE COMPOSITION

Ventolin Injection 500 micrograms (0.5mg), salbutamol, as sulphate, in 1ml (500 micrograms/ml).

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

CLINICAL PARTICULARS

INDICATIONS

Respiratory

Salbutamol is a selective beta-$_2$ 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 Injection/Solution for Infusion 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 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

Subcutaneous Route:-
500mcg (8mcg/kg bodyweight) and repeated every 4 hours as required.

Intramuscular Route:-
500mcg (8mcg/kg bodyweight) and repeated every 4 hours as required.

Intravenous Route:-
250mcg (4mcg/kg bodyweight) injected slowly. If necessary the dose may be repeated.

If *VENTOLIN* Injection 500mcg in 1ml (500mcg/ml) is used the injection may be facilitated by dilution with water for injections.

Infusion:-
In status asthmaticus, infusion rates of 3 to 20mcg per minute are generally adequate but in patients with respiratory failure, higher dosage has been used with success. A starting dose of 5mcg 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 10mcg/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* Injection/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 randomized, controlled trials. This delay may be used to administer glucocorticoids or to implement other measures known to improve perinatal health.

VENTOLIN Injection/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 to 45mcg 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 10mcg 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.

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

CONTRA-INDICATIONS

VENTOLIN parenteral preparations 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 injection/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.
- Threatened abortion during 1st and 2nd trimester.
- Any condition of the mother or foetus in which prolongation of the pregnancy is hazardous e.g. severe toxaemia, intrauterine infection, vagina bleeding resulting from placenta previa, eclampsia or severe preeclampsia, placenta abruption, or cord compression.
- 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* 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.

Any decision to initiate with *VENTOLIN* Solution for Intravenous Infusion should be undertaken after careful consideration of the risks and benefits of treatment.

Treatment should be carried out in facilities adequately equipped to perform continuous monitoring of maternal and foetal health status.

Tocolysis with *VENTOLIN* parenteral preparations is not recommended when membranes have ruptured or the cervix has dilated beyond 4 cm.

VENTOLIN Solution for Intravenous Infusion should be used with caution in tocolysis and supervision of cardiorespiratory function and ECG monitoring, should be performed throughout treatment. The following monitoring measures must be constantly applied to the mother and, when feasible/appropriate, to the foetus:

- blood pressure and heart rate
- ECG
- electrolyte and fluid balance – to monitor for pulmonary oedema
- glucose and lactate levels – with particular regard to diabetic patients
- potassium levels – beta-agonists are associated with a decrease in serum potassium which increases the risk of arrhythmias.

Treatment should be discontinued if signs of myocardial ischaemia (such as chest pain or ECG changes) develop.

VENTOLIN Solution for Intravenous Infusion should not be used as a tocolytic agent in patients with significant risk factors, or a suspicion of any kind of pre-existing heart disease (e.g. tachyarrhythmias, heart failure, or valvular heart disease).

In premature labour in a patient with known or suspected cardiac disease, a physician experienced in cardiology should assess the suitability of treatment before intravenous infusion with *VENTOLIN* Solution for Intravenous Infusion.

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 salbutamol 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 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.

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
Common: *Hypokalaemia.
Rare: *Hyperglycaemia
Unknown: Lactic acidosis (see section *Warnings and Precautions*)

*These reactions have been reported in association with the use of short acting beta-agonists in obstetric indications and are considered class effects (see section *Warnings and Precautions*).

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 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.

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 fetuses were found to have clef palate, at 2.5 mg/kg 4 times the maximum human oral dose. In rats, treatment-related effects observed were an increase in neonatal mortality at the high dose (50 mg/kg/day) in

an oral study, as a result of lack of maternal care, and a dose-related inhibition of fetal development in oral and subcutaneous studies. A reproductive study in rabbits revealed cranial malformations in 37% of fetuses at 50 mg/kg/day, 78 times the maximum human oral dose.

Reproduction studies in rats demonstrated no evidence of impaired infertility 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

SHELF LIFE

3 years

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 Infusion is supplied in 5 ml clear neutral Type I glass ampoules, packed into printed cartons.

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.

Not all presentations are available in every country.

Version number: GDS21/IPI06 (SI)
Date of issue: 05 February 2014

Manufactured by:
GlaxoSmithKline Manufacturing S.p.A
Parma, Italy

Packed by:
GlaxoSmithKline Australia Pty Ltd
Boronia, Victoria 3155, Australia

[GlaxoSmithKline logo]