NEW ZEALAND DATA SHEET

1. PRODUCT NAME

VENTOLIN INJECTION 500 micrograms/mL

VENTOLIN SOLUTION FOR INTRAVENOUS INFUSION 5 mg/5 mL.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VENTOLIN INJECTION 500 micrograms (0.5mg) in 1 mL (500 micrograms/mL) is presented in ampoules of 1 mL each containing 0.5 mg Salbutamol as Salbutamol Sulphate, in a sterile isotonic solution adjusted to pH 3.5 with sulphuric acid.

VENTOLIN SOLUTION FOR INTRAVENOUS INFUSION 5 mg in 5 mL (1 mg/mL) is presented as ampoules of 5 mL each containing 5 mg Salbutamol as Salbutamol Sulphate, 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.

For full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Respiratory

Salbutamol 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 salbutamol, treatment with inhaled corticosteroids is recommended to achieve and maintain control. Failing to respond to treatment with salbutamol may signal a need for urgent medical advice or treatment.

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

Management of premature labour

Salbutamol 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.

For the management of uncomplicated premature labour between 22 and 37 weeks of gestation in patients with no medical or obstetric contraindication to tocolytic therapy. Treatment should not be continued for more than 48 hours.

4.2 Dose and method of administration

Salbutamol 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.

Dose

Adults:

In severe bronchospasm and status asthmaticus:

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.

250 micrograms in 5 mL (50 micrograms/mL) is a suitably dilute preparation for slow intravenous injection. VENTOLIN INJECTION 500 micrograms in 1 mL (500 micrograms/mL) may be facilitated by dilution with water for injections.

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 500 mL of an infusion solution such as

sodium chloride and dextrose injection to provide a salbutamol dose of 10 micrograms/mL of solution.

In the management of premature labour:

Treatment with VENTOLIN INJECTION/SOLUTION FOR INTRAVENOUS 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 INJECTION/SOLUTION FOR INTRAVENOUS 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 salbutamol (see Section 4.3 Contraindications). This should include an adequate assessment of the patient's cardiovascular status with continuous ECG monitoring throughout treatment (see Section 4.4 Special warnings and precautions for use).

For this indication VENTOLIN SOLUTION FOR INTRAVENOUS INFUSION is recommended using a solution prepared as above. Infusion rates of 10-45 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 Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects).

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

Paediatric population:

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

4.3 Contraindications

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

Treatment of premature labour

VENTOLIN INJECTION/SOLUTION FOR INTRAVENOUS 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.

Non-intravenous formulations of salbutamol must not be used to arrest uncomplicated premature labour or threatened abortion.

4.4 Special warnings and precautions for use

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, rather than Sodium Chloride and Dextrose Injection.

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 Section 4.8 Undesirable effects). 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. The population at risk primarily includes patients with an acute exacerbation of the underlying respiratory disease undergoing high dose treatment regimens, particularly with intravenous and nebulised salbutamol. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting.

Salbutamol should be administered cautiously to patients with thyrotoxicosis.

Treatment of premature labour

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.

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 steady 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 20 mmHg. 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 Section 4.2 Dose and method of administration and Section 4.8 Undesirable effects).

4.5 Interaction with other medicines and other forms of interaction

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

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

4.6 Fertility, 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.

As no consistent pattern of defects can be discerned, and baseline rate for congenital anomalies is 2-3%, 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.

Fertility

There is no information on the effects of salbutamol on human fertility. There were no adverse effects on fertility in animals (see Section 5.3 Pre-clinical safety data).

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

Summary of 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 anaphylactic shock, 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.

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/SOLUTION FOR INTRAVENOUS INFUSION have uncommonly been associated with pulmonary oedema; in some cases this has proved fatal. Patients with predisposing factors including multiple pregnancies, fluid overload, pre-existing cardiac disease, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events (see Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable Effects).

Hypokalaemia may occur following overdose with salbutamol. 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.

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective beta-2-adrenoreceptor agonists**.**

ATC Code: R03CC02

Mechanism of action

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.

5.2 Pharmacokinetic properties

Distribution

Salbutamol is bound to plasma proteins to the extent of 10%.

Biotransformation/Elimination

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.

5.3 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 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 salbutamol up to 50 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Sodium hydroxide

Dilute sulphuric acid

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf Life

48 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

VENTOLIN INJECTION 0.5 mg in 1 mL (500 micrograms/mL) is available in boxes of 5 ampoules.

VENTOLIN SOLUTION FOR INTRAVENOUS INFUSION 5 mg in 5 mL (1 mg/mL) is available in boxes of 10 ampoules.

6.6 Special precautions for disposal and other handling

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

Dilution

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

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

15 March 1976

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Version: 5.0

Section changed	Summary of new information
6.3	Update to shelf-life from 36 to 48 months