AUSTRALIAN PRODUCT INFORMATION

VENTOLIN OBSTETRIC INJECTION (salbutamol sulfate) concentrated injection

1 NAME OF THE MEDICINE

Salbutamol sulfate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ampoules of 5 mL containing salbutamol sulfate equivalent to 5 mg (1 mg/mL) salbutamol BP in a sterile isotonic solution.

List of excipients with known effect

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Concentrated injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the management of uncomplicated premature labour. To arrest labour between 24 and 33 weeks of gestation in patients with no medical or obstetric contraindication to tocolytic therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

FOR INTRAVENOUS INFUSION ONLY. FOR OBSTETRIC USE ONLY – DILUTE BEFORE USE.

Treatment with VENTOLIN OBSTETRIC INJECTION 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.

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

Infusion: Use of an infusion pump will facilitate accurate adjustment and control of salbutamol infusion.

The infusion should be administered as early as possible after the diagnosis of premature labour, and after evaluation of the patient to rule out 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).

In premature labour infusion rates of 10-50 micrograms per minute are usually adequate to control uterine contractions. The infusion rate required varies according to the strength and frequency of contractions. A starting dose of 10 micrograms per minute is recommended, increasing the rate at 10-minute intervals until there is evidence of patient response shown by a 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. The maternal pulse rate should be monitored and the infusion rate adjusted to avoid maternal heart rates in excess of 120 beats per minute. Treatment should be discontinued should signs of pulmonary oedema or myocardial ischaemia develop (See Section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE and See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

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. The infusion should be stopped if labour progresses despite treatment.

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. This delay may be used to implement measures known to improve perinatal health.

Careful control of the level of hydration is essential to avoid the risk of maternal pulmonary oedema (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). The volume of fluid in which the drug is administered should thus be kept to a minimum.

A suitable solution for infusion may be prepared by diluting the contents of ampoules of VENTOLIN OBSTETRIC INJECTION (5 mg in 5 mL) in 500 mL of Sodium Chloride Injection BP, Dextrose Injection BP, or Sodium Chloride and Dextrose Injection BP.

A guide to aid in preparation of the infusion (and drip rates for guidance where an infusion pump is not available) follows:

Desired Dose	Ampoules of VENTOLIN OBSTETRIC INJECTION per 500 mL of diluent	Concentration	Infusion Rate in drops per minute (assuming 20 drops = 1 mL)
10 mcg/minute	1	10 mcg/mL	20
20 "	2	20 "	20
30 "	3	30 "	20
40 "	4	40 "	20
50 "	5	50 "	20

Note: The contents of the ampoules of VENTOLIN OBSTETRIC INJECTION 5 mg in 5 mL should not be injected undiluted by any route.

Pharmaceutical precautions: Sodium Chloride Injection BP, Dextrose Injection BP or Sodium Chloride and Dextrose Injection BP are the only recommended diluents and it is inadvisable to administer VENTOLIN OBSTETRIC INJECTION in an infusion containing any other medication.

AFTER DILUTION THE SOLUTION SHOULD BE USED WITHIN 24 HOURS.

Salbutamol is stable for 24 hours at 30°C when 1 mg/mL injection is diluted to 12 mcg/mL in the following solutions:

5% dextrose
5% dextrose in normal saline
saline/dextrose 0.18%/4.3%

4.3 CONTRAINDICATIONS

Hypersensitivity to any component of the preparation or related sympathomimetic amines.

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

- at a gestational age < 24 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 (e.g. maternal cardiac disease, uncontrolled hypertension, severe pre-eclampsia, active uterine bleeding, premature rupture of the membranes with associated chorioamnionitis, compression of the umbilical cord, foetal acidosis (pH 7.2) or hypoxia (PaO_2 18 mm Hg), foetal distress; See Section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- in patients with pulmonary hypertension, pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease.
- Bronchial asthma
- Diabetes
- Uncompensated potassium depletion, hypercalcaemia
- Maternal hyperthyroidism
- Ileus
- Unconsciousness
- Renal insufficiency
- Glaucoma
- Paroxysmal tachycardia

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

Since salbutamol is a sympathomimetic drug, great care should be used in patients with hypertension or with heart disease, especially in patients with tachyarrhythmias, coronary artery disease, or congestive cardiac failure.

Animal studies suggest that cardionecrotic effects may occur with extremely high doses of some sympathomimetics. No instance of such damage has been reported when salbutamol has been used in humans.

Salbutamol should be administered cautiously to patients suffering from thyrotoxicosis.

In common with other beta-adrenoceptor agonists, Ventolin can induce metabolic changes such as 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.

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

Central nervous system stimulation is an unwanted side effect of sympathomimetic drugs.

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 hypoxia. It is recommended that serum potassium levels are monitored in such situations.

Cardiovascular effects: When VENTOLIN OBSTETRIC INJECTION is used cardiovascular effects should be monitored carefully. As experience with prolonged use and with high dosage is limited, caution should be exercised and the patient carefully observed by regular monitoring of clinical signs and ECG status if VENTOLIN OBSTETRIC INJECTION administration is deemed necessary.

Hypotension, tachycardia and therefore increased cardiac oxygen demands may occur when VENTOLIN OBSTETRIC INJECTION is given to patients with established or latent ischaemic heart disease. VENTOLIN OBSTETRIC INJECTION may be dangerous in patients with angina as it may precipitate coronary insufficiency (See Section 4.3 CONTRAINDICATIONS).

Disturbances of cardiac rhythm and rate are sometimes seen. VENTOLIN OBSTETRIC INJECTION may cause tachycardia but the incidence and severity is less than with some other beta-receptor agonists, eg, isoxsuprine.

In patients with tachyarrhythmias the benefit/risk should be weighed prior to therapy and reconsidered at intervals during therapy.

During intravenous infusion of VENTOLIN OBSTETRIC INJECTION for premature labour careful monitoring of maternal pulse rate and blood pressure is recommended in addition to careful observation of foetal heart rate and status of the infant. Monitoring checks should be continuous during general or epidural anaesthesia. It is recommended such checks should be made at intervals of every 15 minutes. These intervals may then be reduced to every 1-6 hours according to the condition of the foetus (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Foetal acidosis should be monitored continuously if VENTOLIN OBSTETRIC INJECTION is administered in acute foetal distress. If acid-base balance levels continue to decrease then therapy should be discontinued and labour allowed to proceed. As well, if foetal hypoxia does not improve during acute foetal distress prior to assisted delivery, then therapy should be discontinued and delivery allowed to proceed. If blood pH rises significantly during infusion, continued infusion for a further 15-30 minutes may be useful (See Section 4.3 CONTRAINDICATIONS).

The occurrence of excessive maternal sinus tachycardia from VENTOLIN OBSTETRIC INJECTION in healthy subjects require that a careful evaluation be carried out of the clinical status of the patient balanced against the therapeutic effects. Increases in maternal heart rate of the order of 20 to 40 beats per minute usually accompany the infusion. The maternal heart rate should be monitored and not normally allowed to exceed a sustained rate of 120 beats per minute. When sustained maternal heart rate in excess of 120 occurs from administration of Ventolin infusion the dose rate should be reduced or the drug should be discontinued.

The effect of VENTOLIN OBSTETRIC INJECTION on maternal blood pressure is greater on diastolic than on systolic pressure. Falls in diastolic pressure are usually within the range of 15 to 25 mmHg. The effect of infusion on foetal heart rate is less marked, but increases of the order of 15 beats per minute may occur.

To prevent hypotension due to aortocaval compression, the patient should lie on her side during an infusion with VENTOLIN OBSTETRIC INJECTION.

Since VENTOLIN OBSTETRIC INJECTION may cause a fall in blood pressure, extreme caution should be used to avoid hypotensive response in patients whose condition is complicated by blood loss with severe anaemia.

Before VENTOLIN OBSTETRIC INJECTION 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 salbutamol parenteral preparations 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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Membrane rupture and cervical dilation: A reduction in the effectiveness of salbutamol should be anticipated if the membrane ruptures or if cervical dilation exceeds 4 cm.

Use in hepatic impairment

Reduction in the dosage may be necessary in the presence of impaired hepatic or renal function, as salbutamol is metabolised in the liver and excreted predominantly in the urine. Toxic effects manifest themselves as tremor and tachycardia. It is not known whether or not salbutamol is dialysed. Continuing strong contractions with evidence of progression of labour despite the highest tolerated dose of VENTOLIN OBSTETRIC INJECTION is an indication to discontinue therapy.

Use in renal impairment

See Section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in hepatic impairment.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

VENTOLIN should be given only with extreme caution to patients who have already received large doses of sympathomimetics.

In experimental animals salbutamol potentiates the action of imipramine in preventing noradrenaline-induced hypothermia. Salbutamol has also been found to antagonise the anti-convulsant effect of chlordiazepoxide and to potentiate the tranquilizing effect of chlorpromazine; however the latter effect was not statistically significant. The clinical significance of these drug interactions is not known.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There is no information on the effects of salbutamol on human fertility.

Use in pregnancy

(Pregnancy category A)

The safety of high dosage salbutamol before the twentieth week of pregnancy is not established (See Section 4.3 CONTRAINDICATIONS). No teratogenic effects have been observed in rabbits or rats dosed orally throughout pregnancy. Neonatal mortality was increased in rats administered 50 mg/ kg/day throughout pregnancy.

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.

Use in lactation

No data available.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Maternal effects

Majority of patients. Cardiovascular. Maternal sinus tachycardia, palpitations, increased maternal pulse pressure and increased cardiac output.

More common reactions. Cardiovascular. High doses of beta-adrenergic stimulants can cause peripheral vasodilation with associated hypotension, flushing and headache. Conduction disturbances, such as supraventricular tachycardia and extrasystoles, have been reported with high doses.

Endocrine. Disturbance of carbohydrate metabolism and ketosis (particularly in diabetic patients).

Nervous system. Hand tremors, nervousness, restlessness, headache, emotional upset or anxiety have been reported.

Less common reactions. Nausea, vomiting and dizziness have been reported. Hypersensitivity reactions including anaphylactic shock, angioedema, urticaria, bronchospasm, hypotension and collapse have been reported rarely. There have been very rare reports of muscle cramps and hyperactivity.

Other infrequently reported maternal effects include skin rash, heart murmur, angina, epigastric distress, ileus, bloating, constipation, diarrhoea, dyspnoea, hyperventilation, haemolytic icterus, glycosuria, lactic acidosis, sweating, chills, insomnia, drowsiness and weakness.

Maternal pulmonary oedema has been reported in association with use of beta-agonists including salbutamol for the management of premature labour; in some cases this has proved fatal. Predisposing factors include fluid overload, multiple pregnancy, pre-existing cardiac disease, maternal infection and pre-eclampsia. Close monitoring of the patient's state of hydration is essential. If signs of pulmonary oedema develop (eg. cough, shortness of breath), treatment should be discontinued immediately and diuretic therapy instituted.

Myocardial ischaemia has been uncommonly reported in the management of pre-term labour with salbutamol injection/solution for infusion.

Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) have been reported. Peripheral vasodilation and a compensatory small increase in heart rate may occur in some patients. Tachycardia may occur in some patients.

Since elevations of blood glucose and depression of serum potassium levels have been reported, close monitoring of these levels is desirable. Attempts to rectify glucose or potassium levels could be dangerous. Such changes are reversible on discontinuing VENTOLIN OBSTETRIC INJECTION. In doses above those recommended patients have complained of chest pain. Potentially serious hypokalaemia may result from beta-2-agonist therapy.

Neonatal effects

Foetal tachycardia has been reported after maternal administration by the intravenous route. Infrequently reported symptoms include hypo-glycaemia and ileus.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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 See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). Salbutamol overdosage is manifest by significant tachycardia and/or skeletal muscle tremor. Consideration should be given to discontinuation of treatment and appropriate symptomatic treatment such as a selective beta-adrenergic receptor blocking agent given by intravenous injection, in patients presenting with cardiac symptoms (e.g. tachycardia, palpitations). Beta-blockers should be used cautiously in patients with a history of bronchospasm.

Hypokalaemia may occur following overdosage 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.

Combined use of glucocorticoids and salbutamol may exacerbate the metabolic effects described, resulting in marked elevation of blood glucose and very low serum potassium levels.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

ATP is known to be intimately associated with adrenergic receptors. Beta-2-receptor stimulants have been shown to catalyse the cyclization of ATP to cyclic AMP by activation of the enzyme adenyl cyclase. High levels of cyclic AMP have been found to inhibit the entry of calcium ions into smooth muscle cells, thus inhibiting contraction of the smooth muscle of the uterus as well as of the bronchial tree. It is believed that similar mechanisms promote insulin release and glycogenolysis. The rise in free fatty acids and the potassium shift are thought to be consequential. Elevated levels of cyclic AMP also prevent allergen-induced release of histamine, SRS-A and other mediators of the allergic response from sensitised mast cells.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Salbutamol is a beta-adrenergic stimulant which is more specific for beta-2-adrenoreceptors than isoprenaline. When given by the parenteral route relative specificity decreases with increased dosage.

Stimulation of beta-2-adrenoreceptors causes relaxation of the smooth muscle of the bronchi, uterus and skeletal muscle blood vessels. Salbutamol, when given by the intravenous route, produces uterine relaxation in most instances, but the onset is variable and depends on dosage.

Salbutamol has a variety of metabolic effects mediated by beta-2-receptor stimulation. Intravenous administration of salbutamol causes a marked rise in non-esterified fatty acid levels and also an increase in insulin levels. There is a significant rise in lactate levels and a slight rise in plasma glucose values. The release of insulin is thought to be due to beta-2-receptor stimulation and not due to rises in plasma glucose levels, which are only slight and occur after the insulin rise. Intravenous salbutamol also causes significant falls in plasma potassium levels due to an intracellular shift of potassium associated with increased glucose and insulin levels. With high dosage intravenous administration beta-1-receptor stimulation produces positive inotropic and chronotropic effects on the heart.

Salbutamol is not bound to plasma protein and does not cross the blood brain barrier to any significant extent. Salbutamol administered intravenously has a half-life of 4 to 6 hours. Following a single intravenous injection of salbutamol, 75% of a given dose is excreted in the urine after 24 hours, 27% is recovered as metabolite and the remainder as unchanged salbutamol. The major urinary metabolite of salbutamol has been identified as the 4'-o-sulfate ester of salbutamol. Salbutamol is known to cross the placental barrier, as evidenced by increases in foetal heart rate.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

VENTOLIN OBSTETRIC INJECTION contains the following excipients: sodium chloride, sulfuric acid and water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

VENTOLIN OBSTETRIC INJECTION ampoules should be stored below 30°C and protected from light.

6.5 NATURE AND CONTENTS OF CONTAINER

The ampoules are of clear, neutral glass.

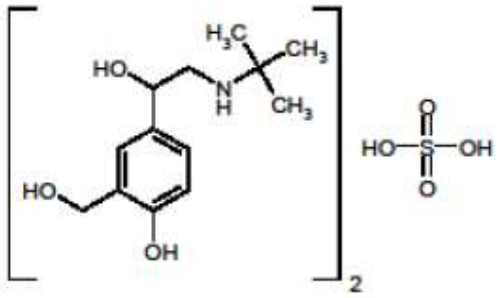
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Name: 1-(4-hydroxy-3-hydroxymethylphenyl)-2-(t-butylamino) ethanol Sulfate

Chemical structure



Salbutamol sulfate is a white or almost white odourless powder. It is soluble in 4 parts of water; slightly soluble in 95% alcohol, chloroform and solvent ether.

The solution is colourless, or faintly straw coloured

CAS number

51022-70-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd

Level 4, 436 Johnston Street,

Abbotsford, Victoria, 3067

9 DATE OF FIRST APPROVAL

31 January 1995

10 DATE OF REVISION

10 February 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI Reformat
Title	Addition of dosage form
3.0	Addition of pharmaceutical form as per ARTG entry
6.7	Addition of chemical structure Addition of physiochemical data from Section 2 Addition of CAS number
End of document	Update to trademark statement and addition of copyright statement

Version 4.0