PRODUCT MONOGRAPH

^{Pr}VENTOLIN® I.V. infusion solution

salbutamol sulfate for injection

1000 mcg/mL

BP

Bronchodilator

(beta$_2$-adrenergic agonist)

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intravenous (I.V.)	salbutamol I.V. Infusion / 1000 mcg/mL	sodium chloride, sulphuric acid, and/or sodium hydroxide, water for injection

For a complete listing see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

VENTOLIN® (salbutamol sulfate) I.V. infusion solution is indicated in adults (≥ 18 years of age) for:

- the relief of severe bronchospasm associated with acute exacerbations of chronic bronchitis and bronchial asthma,
- the treatment of status asthmaticus.

In many patients, VENTOLIN® infusion solution will be no more effective, and likely less well tolerated, than VENTOLIN® HFA inhalation aerosol or VENTOLIN® respirator solution. However, patients who are severely ill with airway inflammation and mucus plugging may respond well to parenteral salbutamol after failing to benefit from the inhaled drug.

This product should be administered under the supervision of a qualified health professional who is experienced in the use of parenteral preparations and in the management of asthma. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

CONTRAINDICATIONS

VENTOLIN® (salbutamol sulfate) I.V. infusion solution is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- Patients with cardiac tachyarrhythmias.
- As a tocolytic in patients at risk of premature labour or threatened abortion.

WARNINGS AND PRECAUTIONS

General

The dosage or frequency of administration should only be increased on medical advice. Patients being treated with VENTOLIN® I.V. infusion solution may also be receiving short-acting inhaled bronchodilators to relieve symptoms. Increasing use of bronchodilators, in particular short-acting inhaled beta$_2$-agonists to relieve symptoms, indicates deterioration of asthma control. Sudden or progressive deterioration in asthma control is potentially life threatening; the treatment plan must be re-evaluated, and consideration be given to corticosteroid therapy.

The use of VENTOLIN® infusion solution in the treatment of severe bronchospasm does not obviate the requirement for corticosteroid therapy as appropriate. When practicable, administration of oxygen, concurrently with VENTOLIN® infusion solution is recommended, particularly when salbutamol is given by intravenous infusion to hypoxic patients.

Cardiovascular

VENTOLIN® I.V. infusion solution should be used with caution in patients, particularly pregnant women, with pre-existing ischaemic heart disease or with significant risk factors for ischaemic heart disease (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

In individual patients, any beta$_2$-adrenergic agonist, including salbutamol, may have a clinically significant cardiac effect. Care should be taken with patients suffering from cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension. Special care and supervision are required in patients with idiopathic hypertrophic subvalvular aortic stenosis, in whom an increase in the pressure gradient between the left ventricle and the aorta may occur, causing increased strain on the left ventricle.

Fatalities have been reported following excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest

following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with salbutamol. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving salbutamol should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnea and chest pain, as they may be of either respiratory or cardiac origin.

Endocrine and Metabolism

Metabolic Effects

In common with other beta-adrenergic agents, salbutamol can induce reversible metabolic changes, such as potentially serious hypokalemia, particularly following infused administration. Particular caution is advised in acute severe asthma since hypokalemia may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics, and by hypoxia. Hypokalemia will increase the susceptibility of digitalis-treated patients to cardiac arrhythmias. It is recommended that serum potassium levels be monitored in such situations.

Large doses of intravenous salbutamol have been reported to aggravate pre-existing diabetes mellitus. The diabetic patient may be unable to compensate for the increased blood glucose levels 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® I.V. infusion solution so that remedial steps (e.g. an increase in insulin dosage) can be taken to counter any metabolic change that is occurring. For these patients, VENTOLIN® I.V. infusion solution 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 Adverse Reaction section). Increase in lactate levels may lead to dyspnea 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.

Care should be taken with patients with hyperthyroidism.

Hypersensitivity
Immediate hypersensitivity reactions may occur after administration of salbutamol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, hypotension, anaphylaxis and oropharyngeal edema.

Care should be taken in patients who are unusually responsive to sympathomimetic amines.

Neurologic
Care should be taken with patients with convulsive disorders.

Special Populations

Pregnant Women: Salbutamol, in common with other beta-mimetics, is not approved to stop or prevent premature labour.

Due to the risk of pulmonary edema and myocardial ischaemia that has been observed during the use of betamimetics in the treatment of premature labour, before VENTOLIN® infusion solution 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.

There are no adequate and well-controlled studies in pregnant women and there is little published evidence of its safety in the early stages of human pregnancy. Administration of any drug to pregnant women should only be considered if the anticipated benefits to the expectant woman are greater than any possible risks 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.

Labour and Delivery: High doses of salbutamol, administered intravenously, inhibit uterine contractions. Therefore, cautious use of VENTOLIN® infusion solution is required in pregnant patients when it is given for relief of bronchospasm so as to avoid interference with uterine contractibility.

During I.V. infusion of salbutamol, 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 fetal heart rate is less marked but increases of up to 20 beats per minute may occur.

As maternal pulmonary edema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta$_2$-agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG, should be monitored. If signs of pulmonary edema or myocardial ischaemia develop, discontinuation of treatment should be considered. Patients with predisposing factors including multiple pregnancies, fluid overload, maternal infection and pre-eclampsia may have an increased risk of developing pulmonary edema.

Nursing Women: As salbutamol is probably secreted in breast milk and because of the potential for tumorigenicity of salbutamol shown in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is not known whether salbutamol has a harmful effect on the neonate.

Children and Adolescents (< 18 years of age): The dosage of VENTOLIN® infusion solution in the pediatric age group has not been established. At present there are insufficient data to recommend a dosage regimen for use in children.

Geriatrics: As with other beta$_2$-agonists, special caution should be observed when using VENTOLIN® I.V. infusion solution in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug.

Monitoring and Laboratory Tests

In accordance with the present practice for asthma treatment, patient response should be monitored clinically and by lung function tests.

Electrocardiogram, and serum potassium and glucose should be monitored during continuous infusions of salbutamol.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse events are listed below; frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common and common events were generally determined from clinical trial data. Rare, very rare and unknown events were generally determined from spontaneous data.

Fine muscle tremor is a very common side effect of VENTOLIN® infusion solution. This is due to direct beta$_2$-stimulation by salbutamol of skeletal muscle. Transient muscle cramps and headache have been commonly reported.

A dose-dependent increase in heart rate, secondary to a reduction in peripheral resistance, due to vasodilation, occurs very commonly with parenteral salbutamol, and may cause

palpitations. This is most likely to occur in patients with normal heart rates. In patients with pre-existing sinus tachycardia, especially those in status asthmaticus, the heart rate tends to fall as the condition of the patient improves. Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) and peripheral vasodilation have been reported rarely.

Occurrences of potentially serious hypokalemia have been reported rarely.

Other side effects which may occur with salbutamol are sweating, dizziness, flushing, nausea, vomiting, muscle cramps, insomnia, drowsiness, restlessness, irritability, chest discomfort, difficulty in micturition, hypertension, angina, vertigo, central nervous system stimulation, unusual taste and drying or irritation of the oropharynx.

Immediate hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension, rash, oropharyngeal edema, anaphylaxis and collapse have been reported very rarely.

Lactic acidosis has also been reported very rarely in patients receiving intravenous salbutamol therapy for the treatment of acute asthma exacerbation.

DRUG INTERACTIONS

Drug-Drug Interactions

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

Table 1: Established or Potential Drug-Drug Interactions

Drug Type	Ref	Effect	Clinical comment
Monoamine oxidase inhibitors or tricyclic antidepressants.	CS	May potentiate action of salbutamol on cardiovascular system.	Salbutamol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants.
Other sympathomimetic bronchodilators or epinephrine.	CS	May lead to deleterious cardiovascular effects.	Other sympathomimetic bronchodilators or epinephrine should not be used concomitantly with salbutamol. If additional adrenergic drugs are to be administered by any route to the patient using salbutamol, the adrenergic drugs should be used with caution to avoid deleterious cardiovascular effects. Such concomitant use must be individualised and not given on a routine basis. If regular co-administration is required then alternative therapy must be considered.
Beta-blockers	CS	May effectively antagonize the action of salbutamol.	Beta-adrenergic blocking drugs, especially the non-cardioselective ones, such as propranolol, should not usually be prescribed together with salbutamol.
Diuretics	CS	May lead to ECG changes and/or hypokalemia, although the clinical significance of these effects is not known.	The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Caution is advised in the co-administration of beta-agonists with non-potassium sparing diuretics.
Digoxin	CS	May lead to mean decrease in serum digoxin levels. The clinical significance of these findings for patients with obstructive airways disease who are receiving salbutamol and digoxin on a chronic basis is unclear.	Mean decreases of 16-22% in serum digoxin levels were demonstrated after single doses intravenous and oral administration of salbutamol, respectively, to normal volunteers who had received digoxin for 10 days. It would be prudent to carefully evaluate serum digoxin levels in patients who are currently receiving digoxin and salbutamol.

Legend CS = Class Statement

DOSAGE AND ADMINISTRATION

VENTOLIN® I.V. INFUSION SOLUTION MUST NEVER BE INJECTED UNDILUTED.

VENTOLIN® I.V. INFUSION SOLUTION MUST NEVER BE USED IN THE SAME INFUSION WITH OTHER MEDICATIONS.

Recommended Dose, Dosage Adjustment, and Administration

Adults:
VENTOLIN® I.V. infusion solution is used to prepare a solution for continuous intravenous infusion. It should not be injected undiluted. A suitable solution for infusion may be prepared by diluting 5 mL of VENTOLIN® I.V. infusion solution (1000 mcg/mL) in 500 mL of a chosen i.v. solution to provide a salbutamol concentration of 10 mcg/mL.

The only recommended diluents are Sodium Chloride Injection, or Sodium Chloride and Dextrose Injection.

Infusion rates providing 3 to 20 micrograms salbutamol/minute (0.3 to 2ml/minute of the above infusion solution) are usually adequate. Infusion rates can be started at 5 mcg of salbutamol/min., and can be increased to 10 mcg/min., and 20 mcg/min. at 15 - 30 minute intervals, if necessary.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration.

All unused admixtures of VENTOLIN® infusion solution with infusion fluids should be discarded 24 hours after preparation.

Children and Adolescents (< 18 years of age)
The dosage of VENTOLIN® infusion solution in the pediatric age group has not been established. At present, there are insufficient data to recommend a dosage regimen for children.

Instructions to open the ampoule

Ampoules are equipped with the OPC (One Point Cut) opening system and must be opened using the following instructions:

- Hold with one hand the bottom part of the ampoule as indicated in Picture 1.
- Put the other hand on the top of the ampoule positioning the thumb above the coloured point and press as indicated in Picture 2.

Picture 1

Picture 2

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms and signs

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events (see Warning and Precautions and Adverse Reactions). Overdosage may cause tachycardia, cardiac arrhythmia, hypokalemia, hypertension, nausea, vomiting, hyperglycaemia and, in extreme cases, sudden death. 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.

Treatment

Consideration should be given to discontinuation of treatment and appropriate symptomatic therapy. To antagonise the effect of salbutamol, the judicious use of a cardioselective beta-adrenergic blocking agent (e.g. metoprolol, atenolol) may be considered, bearing in mind the danger of inducing an asthmatic attack.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Salbutamol produces bronchodilation through stimulation of $beta_2$-adrenergic receptors in bronchial smooth muscle, thereby causing relaxation of bronchial muscle fibers. This action is manifested by an improvement in pulmonary function as demonstrated by spirometric measurements.

STORAGE AND STABILITY

VENTOLIN® infusion solution should be protected from light and stored at controlled room temperature (15 - 30°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

VENTOLIN® I.V. infusion solution 5 mg in 5 mL (1000 micrograms/mL) is presented as ampoules of 5 mL each containing 5 mg salbutamol as salbutamol sulfate, in a sterile isotonic solution adjusted to pH 3.5 with sulphuric acid and/or sodium hydroxide.

The ampoules are of clear, neutral glass. The solution is clear, colourless to pale straw coloured.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

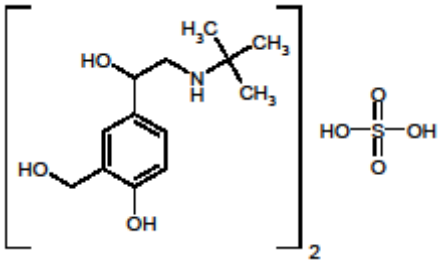
Drug Substance

Proper name: salbutamol sulfate

Chemical name: α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α, α'-diol sulfate (2:1) (salt)

Molecular formula and molecular mass: $[C_{13}H_{21}NO_3]_2 \cdot H_2SO_4$ 576.71

Structural formula:



Physicochemical properties:

Description: White or almost white powder. It is odourless or almost odourless.

Solubility: Salbutamol sulfate is soluble in 4 parts of water; slightly soluble in ethanol (96%), in chloroform and in ether.

pH value: A 5% solution of salbutamol sulfate in distilled water has a pH value of 4.3

pKa values: Salbutamol has pKa values of 9.3 and 10.3.

Melting Point: Salbutamol melts at approximately 155°C, with decomposition.

VENTOLIN® I.V. infusion solution: Salbutamol (1000 mcg/mL as salbutamol sulfate); Sodium chloride (8.8 mg/mL); Sulphuric acid (5% v/v) and/or sodium hydroxide, for pH adjustment; Water for Injection.

DETAILED PHARMACOLOGY

Animal

Salbutamol exerts a relatively selective action on the beta$_2$-adrenergic receptors of the bronchial and vascular smooth muscles. In anesthetized guinea pigs, salbutamol completely prevents acetylcholine-induced bronchospasm at the dose of 100 mcg/kg intravenously.

In anesthetized dogs, salbutamol is one-fifth as potent as isoprenaline in skeletal muscle vasodilation.

In the isolated atrium preparation of guinea pigs, salbutamol was 500 and 2500 times less potent than isoprenaline in increasing the rate and force of contraction, respectively.

Administration of salbutamol aerosol at the dose of 250 mcg/mL for one minute to guinea pigs, prevented acetylocholine-induced bronchospasm without any effect on the heart rate.

In anesthetized cats and dogs, salbutamol prevented the bronchospasm elicited by vagal stimulation, without any significant effect on heart rate and blood pressure. Comparative tests of salbutamol and isoprenaline in isolated dog papillary muscle, guinea pig atrial muscle and human heart muscle, have shown that the effect of salbutamol on beta-adrenergic receptors in the heart is minimal.

In 6 dogs with right-sided cardiac bypass, salbutamol, given at the dose of 25 mcg/mL, improved left ventricular efficiency and increased coronary blood flow.

Recent studies in laboratory animals (minipigs, rodents and dogs) recorded the occurrence of cardiac arrhythmias and sudden deaths (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

Human

Intravenous salbutamol had approximately one-tenth the positive chronotropic potency of intravenous isoprenaline.

Salbutamol and isoprenaline were equipotent bronchodilators when given intravenously. However, 7 times the infusion rate of salbutamol was necessary to increase the heart rate by the same amount as with isoprenaline.

Intravenous salbutamol increased ventilatory response to inhaled CO_2 in both hypoxia and hyperoxia. There was an increase in heart rate which was most pronounced when hypoxia was combined with hypercapnia. Plasma potassium was decreased in association with an increase in plasma glucose and serum insulin.

Intravenous salbutamol raised the blood levels of insulin, non-esterified fatty acids, glucose, lactate and ketone bodies. Serum potassium, bicarbonate, phosphate, calcium, magnesium and corticosteroids were lowered.

Aminophylline potentiated the metabolic effects of salbutamol when the two drugs were infused in combination.

It was found in asthmatic patients that salbutamol, administered orally, by aerosol, or intravenously, was metabolized to its 4' -O-sulfate ester. Both free salbutamol and the metabolite were excreted in the urine, the ratio of the two varying with the route of administration and suggesting that metabolism occurred in the gut and/or the liver. Pharmacological testing showed that the metabolite had negligible beta-adrenoceptor stimulant and no blocking activity.

TOXICOLOGY

Acute Toxicity

Intravenous LD_{50}	
Mouse (10)	72 mg/kg
Mouse (10)	60 mg/kg

Oral LD_{50}	
Mouse (10)	> 2000 mg/kg
Rat (10)	> 2000 mg/kg

Intraperitoneal LD_{50} in Rat	
Newborn (155)	216 mg/kg
Weanling (100)	524 mg/kg
Six-Weeks Old (90)	437 mg/kg

(Number of animals in brackets)

The rate of respiration in test animals initially increased, but subsequently became abnormally slow and deep. Death, preceded by convulsions and cyanosis, usually occurred within four hours after administration.

Rabbits, cats and dogs survived a single oral dose of 50 mg/kg salbutamol.

Intermediate (Four Months) Toxicity

Rat

Salbutamol was given orally from 0.5 mg/kg up to 25 mg/kg daily on an increasing scale. There were no significant hematological changes except a small increase in hemoglobin and packed cell volumes. BUN and SGOT values were elevated while blood glucose and plasma protein levels remained unchanged. Pituitaries had an increased amount of PAS-positive material in the cleft at higher dose levels.

Dog

Salbutamol was given orally from 0.05 mg/kg up to 12.5 mg/kg daily on an increasing scale. Hemoglobin and packed cell volumes were slightly decreased, particularly at higher doses. Leukocyte count decreased after 16 weeks of treatment at each dose level. Platelet count was increased after eight weeks at the highest dose. No significant effects were seen on biochemical values. The only significant histological change was the appearance of corpora amylacea in the stomach, attributed to altered mucus secretion. Inhalation of 1000 mcg of salbutamol aerosol for 3 months did not produce any morphological changes in lungs, trachea, lymph nodes, liver or heart. Inhalation of salbutamol dry powder for 30 days in average daily doses of up to 144 mg/day resulted in the expected pharmacological effects but no apparent compromise of good health. All animals survived the study and examination of organs and tissues revealed no significant changes.

Long-Term Toxicity

Chronic toxicity studies were carried out in 2 separate centres. Fifty female, Charles River CD Albino rats received salbutamol orally at 2, 10 and 50 mg/kg/day for 104 weeks; fifty female Charles River CD Sprague-Dawley derived rats received orally 20 mg/kg/day for 50 weeks, and 50 female Charles River Long-Evans rats received

orally, 20 mg/kg/day for 96 weeks. These studies demonstrated a dose-related incidence of mesovarian leiomyomas. No similar tumors were seen in mice.

Mutagenicity
In vitro tests involving four micro-organisms revealed no mutagenic activity.

Carcinogenicity
In a two-year study in the rat, salbutamol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at doses corresponding to 111, 555, and 2,800 times the maximum human inhalation dose. In another study, the effect was blocked by the co-administraton of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity.

Teratogenicity Studies

Mouse
Salbutamol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human aerosol dose; when given subcutaneusly in doses corresponding to 0.2 times the maximum human (child weighing 21 kg) oral dose; and when given subcutaneously in doses corresponding to 0.4 times the maximum human oral dose.

A reproduction study in CD-1 mice given salbutamol at doses of 0.025, 0.25, and 2.5 mg/kg subcutaneously, corresponding to 1.4, 14 and 140 times the maximum human aerosol dose respectively, showed cleft palate formation in 5 of 111 (4.5%) foetuses at 0.25 mg/kg and in 10 of 108 (9.3%) foetuses at 2.5 mg/kg. No cleft palates were observed at a dose of 0.025 mg/kg salbutamol. Cleft palates occurred in 22 of 72 (30.5%) foetuses treated with 2.5 mg/kg isoprenaline (positive control).

Rat
No adverse effect was seen when salbutamol was given orally at 0.5, 2.32, 10.75 and 50 mg/kg/day throughout pregnancy. When given to 2 consecutive generations at doses up to 50 mg/kg/day, no adverse effect was observed on the reproductive function of either male or female rats. The only toxic effect was an increase in neonatal mortality in the highest dose level group.

Rabbit
Given orally at 0.5, 2.32, and 10.75 mg/kg/day doses, throughout pregnancy, salbutamol had no adverse effect. A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at 50 mg/kg, corresponding to 78 times the maximum human oral dose of salbutamol. At the dose of 50 mg/kg/day, it inhibited the weight gain of the does.

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PART III: CONSUMER INFORMATION

[Pr]VENTOLIN® I.V. infusion solution
salbutamol sulfate for injection

This leaflet is part III of a three-part "Product Monograph" for VENTOLIN® I.V. infusion solution and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VENTOLIN® I.V. infusion solution. Contact your doctor or pharmacist if you have any questions about the drug. Only a doctor can prescribe it for you.

ABOUT THIS MEDICATION

What the medication is used for:
VENTOLIN® I.V. infusion solution is used in adults to:
- relieve severe bronchospasm in patients with sudden worsening of chronic bronchitis or bronchial asthma
- treat asthma flare ups, including acute severe asthma attacks.

Bronchospasm is a sudden worsening of shortness of breath and wheezing.

The safety and effectiveness of VENTOLIN® I.V. infusion solution in children under the age of 18 are not known.

What it does:
Salbutamol is one of a group of medicines called bronchodilators. Salbutamol relaxes the muscles in the walls of the small air passages in the lungs. This helps to open up the airways and so helps to relieve chest tightness, wheezing and cough so that you can breathe more easily.

When it should not be used:
Do not use VENTOLIN® I.V. infusion solution:
- if you are allergic to salbutamol sulfate or any of the components of its formulation
- if your heart beats faster than normal
- for the treatment of preterm labour or miscarriage.

What the medicinal ingredient is:
Salbutamol sulfate.

What the nonmedicinal ingredients are:
Sodium chloride, sulphuric acid and/or sodium hydroxide, water for injection.

What dosage forms it comes in:
Solution for injection; 5 mg/5 mL.

WARNINGS AND PRECAUTIONS

Before you are given VENTOLIN® I.V. infusion solution, talk to your doctor or pharmacist if you:
- Have ever had to stop taking other medications for this illness because you were allergic to them or they caused problems.
- Are having treatment for a thyroid condition.
- Are having treatment for chest pain, high blood pressure or another heart problem.
- Have diabetes. Diabetic patients may need some additional blood sugar tests.
- Have a past history of seizures.
- Have low levels of potassium in your blood (hypokalemia), especially if you are taking:
    - Drugs known as xanthine derivatives (such as theophylline)
    - steroids to treat asthma
    - Water pills (diuretics)
- Are pregnant or intend to become pregnant. Taking VENTOLIN® I.V. infusion solution during pregnancy may cause harm to your baby. Your doctor will consider the benefit to you and the risk to your baby of taking VENTOLIN® I.V. infusion solution while you're pregnant
- Are breastfeeding. It is not known if VENTOLIN® I.V. infusion solution passes into breast milk

If you notice that your shortness of breath or wheeze is becoming worse, tell your doctor as soon as possible. If the relief of wheezing or chest tightness is not as good as usual, tell your doctor as soon as possible. It may be that your chest condition is worsening and you may need to add another type of medicine to your treatment.

Labour and delivery

High doses of VENTOLIN® I.V. infusion solution can slow down labour (delay the delivery of the baby). **In Canada, VENTOLIN® I.V. infusion solution is not approved for the treatment of women who have unexpectedly gone into early labour (premature labour)**. Due to the risk of heart and circulation side effects and to avoid interference with uterine contractions, VENTOLIN® I.V. infusion solution should be used with caution if given to pregnant patients with breathing problems during labour.

INTERACTIONS WITH THIS MEDICATION

VENTOLIN® I.V. infusion solution should not be mixed with any other medicine.

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other

doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with VENTOLIN® I.V. infusion solution:

- Anti-depressants
- Allergy medication
- Blood pressure-lowering drugs, including propanolol
- Diuretics ("water pills")
- Bronchodilators used to open the airway (such as other asthma medication)
- Epinephrine
- Digoxin, a heart medication

PROPER USE OF THIS MEDICATION

VENTOLIN® I.V. infusion solution must only be administered by a health professional. It is given into your vein by continuous intravenous infusion. **Do not try to use VENTOLIN® I.V. infusion solution on your own.**

VENTOLIN® I.V. infusion solution will be diluted before it is given to you.

You will never be expected to give yourself this medicine. It will always be given to you by a person who is qualified to do so.

When using VENTOLIN® I.V. infusion solution, other medicines (including asthma medicines) should only be used when prescribed by your doctor.

Usual Adult Dose:
Continuous intravenous infusion.

Your doctor or nurse will find information about how to dilute the medicine in Part I of this Product Monograph.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you are accidentally given a **larger dose than recommended**, you are more likely to get side effects like a faster heart beat, headaches, nausea, vomiting and feeling shaky or restless. These effects usually wear off within a few hours, but talk to your doctor as soon as possible as you may have to stop treatment with VENTOLIN® I.V. infusion solution.

Rare cases of lactic acidosis (too much lactic acid in the blood) have been reported in patients receiving high doses of VENTOLIN® I.V. infusion solution. If you suffer symptoms (see **Serious Side Effects Table**), contact your doctor immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- feeling a little shaky
- headache
- faster heart beat than usual, hypertension, palpitation
- muscle cramps, tremor
- sweating
- dizziness, vertigo
- flushing
- nausea and vomiting
- feeling tired or weak
- insomnia
- drowsiness
- restlessness
- irritability
- trouble urinating
- hyperactivity in children
- unusual taste
- drying/irritation in your throat
- chest pain or discomfort
- rash, hives

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Rare	**Allergic Reactions**: sudden wheeziness and chest pain or tightness; or swelling of the eyelids, face, lips, tongue or throat.			✓
	Lactic Acidosis: Deep and rapid breathing, vomiting, abdominal pain, weight loss, fatigue, malaise (sign of lactic acidosis-too much lactic acid in the blood)			✓
Rare	**Low Blood Potassium (hypokalemia):** muscle weakness and muscle spasms		✓	
	Cardiac Arrhythmias: heart beat is uneven or it gives an extra beat.		✓	
Very Common	**Tachycardia:** fast heart beat		✓	

This is not a complete list of side effects. If you have any unexpected effects after receiving VENTOLIN® I.V. infusion solution, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of sight and reach of children.

Keep VENTOLIN® I.V. infusion solution away from light and store between 15°C and 30°C.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- **Fax toll-free to 1-866-678-6789, or**
- **Mail to: Canada Vigilance Program**
  Health Canada
  Postal Locator 0701E
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

You may need to read this leaflet again. **PLEASE DO NOT THROW IT AWAY** until you have finished your medicine.

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
1-800-387-7374

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