PRODUCT MONOGRAPH

PrVENTOLIN DISKUS

salbutamol sulfate dry powder for inhalation

200 mcg salbutamol/blister

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
Oral Inhalation	Powder for inhalation/200 mcg / salbutamol	Lactose (which contains milk protein).

INDICATIONS AND CLINICAL USE

Adults and Children (4 years and older):
VENTOLIN (salbutamol sulfate) DISKUS inhalation powder is indicated for:

- the symptomatic relief and prevention of bronchospasm due to bronchial asthma, chronic bronchitis and other chronic bronchopulmonary disorders in which bronchospasm is a complicating factor.
- the prevention of exercise-induced bronchospasm.

Pediatrics (< 4 years of age):
The safety and efficacy in children below the age of 4 years has not been established.

CONTRAINDICATIONS

- 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 IgE mediated allergic reactions to lactose (which contains milk protein) or milk.
- As a tocolytic in patients at risk of premature labour or threatened abortion.

WARNINGS AND PRECAUTIONS

General
Patients should always carry their VENTOLIN DISKUS inhalation powder to use immediately if an episode of asthma is experienced. If therapy does not produce a significant improvement or if the patient's condition worsens, medical advice must be sought to determine a new plan of treatment. In the case of acute or rapidly worsening dyspnea, a doctor should be consulted immediately.

Deterioration of Asthma
Asthma may deteriorate over time. If the patient needs to use VENTOLIN DISKUS more often than usual, this may be a sign of worsening asthma. This requires re-evaluation of the patient and treatment plan and consideration of adjusting the asthma maintenance therapy. If inhaled salbutamol treatment alone is not adequate to control asthma, concomitant anti-inflammatory therapy should be part of the treatment regimen. It is essential that the physician instruct the patient in the need for further evaluation if the patient's asthma becomes worse (see **DOSAGE AND ADMINISTRATION**).

Cardiovascular
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 in association with 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.

Endocrine And Metabolism

Metabolic Effects
In common with other beta-adrenergic agents, salbutamol sulfate can induce reversible metabolic changes such as potentially serious hypokalemia, particularly following nebulised or especially 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.

Care should be taken with patients with diabetes mellitus. Salbutamol can induce reversible hyperglycemia during nebulised administration or especially during infusions of the drug. 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.

Care should be taken with patients with hyperthyroidism.

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

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

Neurologic
Care should be taken with patients with convulsive disorders.

Respiratory
As with other inhaled medications, paradoxical bronchospasm may occur characterized by an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator to relieve acute asthmatic symptoms. VENTOLIN DISKUS inhalation powder should be discontinued immediately, the patient assessed and if necessary, alternative therapy instituted (see ADVERSE REACTIONS).

Special Populations

Pregnant Women: Salbutamol has been in widespread use for many years in humans without apparent ill consequence. However, 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 fetus (See TOXICOLOGY; Teratogenicity Studies).

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. Because 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: Because of the potential for beta-agonist interference with uterine contractility, use of VENTOLIN DISKUS inhalation powder for relief of bronchospasm during labour should be restricted to those patients in whom the benefits clearly outweigh the risk.

Nursing Women: It is not known whether salbutamol sulfate is excreted in breast milk after inhalation at recommended doses. Because of the potential for tumorigenicity shown in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother. It is not known whether salbutamol sulfate in breast milk has a harmful effect on the neonate.

Pediatrics (4 years and older): The application of this inhalation system in children depends on the ability of the individual child to learn the proper use of the inhaler. During inhalation, children should be assisted or supervised by an adult who knows the proper use of the inhaler.

Rarely, in children, hyperactivity occurs and occasionally, sleep disturbances, hallucination or atypical psychosis have been reported.

Pediatrics (< 4 years of age): Safety and efficacy in children below 4 years of age have not been established.

Geriatrics: As with other beta$_2$-agonists, special caution should be observed when using VENTOLIN DISKUS 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.

Monitoring Control of Asthma

Failure to respond for at least three hours to a previously effective dose of VENTOLIN DISKUS inhalation powder indicates a deterioration of the condition and the physician should be contacted promptly. Patients should be warned not to exceed the recommended dose as there may be adverse effects associated with excessive dosing.

The increasing use of fast acting, short duration inhaled beta$_2$-adrenergic agonists to control symptoms indicates deterioration of asthma control, and the patient's therapy plan should be reassessed. In worsening asthma it is inadequate to increase beta$_2$-agonist use only, especially over an extended period of time. In the case of acute or rapidly worsening dyspnea, a doctor should be consulted immediately. 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 (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

As with other bronchodilator inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Potentially serious hypokalemia may result from β_2-agonist therapy, primarily from parenteral and nebulised routes of administration (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

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

The adverse reactions to salbutamol are similar in nature to reactions to other sympathomimetic agents, although the incidence of certain cardiovascular effects is lower with salbutamol.

Other adverse reactions associated with salbutamol are nervousness and tremor. In some patients inhaled salbutamol may cause a fine tremor of skeletal muscle, particularly in the hands. This effect is common to all beta$_2$-adrenergic agonists. Adaptation occurs during the first few days of dosing and the tremor usually disappears as treatment continues.

In addition, salbutamol, like other sympathomimetic agents, can cause adverse effects such as drowsiness, flushing, restlessness, irritability, chest discomfort, difficulty in micturition, hypertension, angina, vertigo, central nervous system stimulation, hyperactivity in children, unusual taste, drying or irritation of the oropharynx, palpitations, transient muscle cramps, insomnia, weakness and dizziness.

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

Rarely, in children, hyperactivity occurs and occasionally, sleep disturbances, hallucination or atypical psychosis have been reported.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Clinical trials with VENTOLIN (salbutamol sulfate) DISKUS inhalation powder 200 mcg in 268 adolescents and adults and 142 children aged 4 to 11 years demonstrated generally similar adverse event profiles in both patient populations. The most common

adverse events were headache and throat irritation. Combined results are shown in the following table:

Table 1 Adverse Experiences With ≥3% Incidence in Two 4-Week Chronic Dosing Studies With Patients 4 Years of Age and Older

Adverse Experience	Placebo*	VENTOLIN DISKUS* Inhalation Powder 200 mcg four times daily	VENTOLIN Inhalation Aerosol* 200 mcg four times daily
Number of patients	136	139	135
Central nervous system			
Headache	10%	13%	9%
Gastrointestinal			
Nausea and vomiting	2%	4%	1%
General			
Fever	1%	3%	1%
Muscle pain	<1%	3%	1%
Musculoskeletal pain	1%	3%	0
Oropharyngeal			
Throat irritation	3%	6%	3%
Respiratory system			
Upper respiratory tract infections	6%	6%	7%
Ear, nose, and throat infections	1%	0%	3%

* Patients in all groups could use VENTOLIN Inhalation Aerosol 100 mcg prn as rescue medication.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 2 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 inhaled sympathomimetic bronchodilators or epinephrine.	CS	May lead to deleterious cardiovascular effects.	Other inhaled sympathomimetic bronchodilators or epinephrine should not be used concomitantly with salbutamol sulfate. If additional adrenergic drugs are to be administered by any route to the patient using inhaled salbutamol sulfate, the adrenergic drugs should be used with caution. Such concomitant use must be individualized and not given on a routine basis. If regular coadministration 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.
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 coadministration of beta-agonists with non-potassium sparing diuretics.
Digoxin	CS	May lead to decrease in serum digoxin levels. The clinical significance of these findings for patients with obstructive airways disease who are receiving salbutamol sulfate and digoxin on a chronic basis is unclear.	Mean decreases of 16-22% in serum digoxin levels were demonstrated after single dose 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 sulfate.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosage should be individualised, and the patient's response should be monitored by the prescribing physician on an ongoing basis.

Increasing demand for VENTOLIN DISKUS in bronchial asthma is usually a sign of poorly controlled or worsening asthma and indicates that the patient should be re-evaluated, the treatment plan should be reviewed and the regular asthma controller treatment should be optimized. If inhaled salbutamol treatment alone is not adequate to control asthma, concomitant anti-inflammatory therapy should be part of the treatment regimen.

If a previously effective dose fails to provide the usual relief, or the effects of a dose last for less than three hours, patients should seek prompt medical advice since this is usually a sign of worsening asthma.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice. However, if a more severe attack has not been relieved by the usual dose, additional doses may be required. In these cases, patients should immediately consult their doctors or the nearest hospital.

Recommended Dose And Dosage Adjustment

	Relief of acute Episodes of Bronchospasm*	**Prevention of Bronchospasm****	**Prevention of Exercise – induced Bronchospasm**	**Maximum Daily Dose (Total daily dose should not exceed)**
Adults and Children (4 years and older)	One Inhalation (200 mcg) as needed	One Inhalation (200 mcg) every 4 – 6 hours to a maximum of three to four times per day	One Inhalation (200 mcg) 15 minutes before exercise.	Four Inhalations (800 mcg)

* If a more severe attack has not been relieved by the usual dose, further inhalations may be needed every 4 to 6 hours. More frequent or a larger number of inhalations is not recommended. In these cases, patients should immediately consult their doctors or the nearest hospital.

** If despite appropriate maintenance therapy, regular use of the VENTOLIN DISKUS inhalation powder remains necessary for the control of bronchospasm due to bronchial asthma.

Missed Dose

If a single dose is missed, instruct the patient to take the next dose when it is due or if they become wheezy.

Administration
VENTOLIN DISKUS inhalation powder is administered by the inhaled route only. To ensure administration of the proper dose of the drug, the patient should be instructed by the physician or other health professional in the proper use of the DISKUS inhaler.

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 Warnings and Precautions and Adverse Reactions). Overdosage may cause tachycardia, cardiac arrhythmia, hypokalemia, hypertension 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. There is insufficient evidence to determine if dialysis is beneficial for overdosage of VENTOLIN DISKUS inhalation powder.

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 fibres. This action is manifested by an improvement in pulmonary function as demonstrated by spirometric measurements. Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects. At therapeutic doses, salbutamol has little action on the $beta_1$-adrenergic receptors in cardiac muscle.

A measurable decrease in airway resistance is typically observed within 5 to 15 minutes after inhalation of salbutamol. The maximum improvement in pulmonary function usually occurs 60 to 90 minutes after salbutamol treatment, and significant bronchodilator activity has been observed to persist for 3 to 6 hours.

Pharmacokinetics

After inhalation of recommended doses of salbutamol, plasma drug levels are very low. When 100 mcg of titrated salbutamol aerosol was administered to two normal volunteers, plasma levels of drug-radioactivity were insignificant at 10, 20 and 30 minutes following inhalation. The plasma concentration of salbutamol may be even less, as the amount of plasma drug-radioactivity does not differentiate salbutamol from its principal metabolite, a sulfate ester. In a separate study, plasma salbutamol levels ranged from less than 0.5 ng/mL to 1.6 ng/mL in ten asthmatic children one hour after inhalation of 200 mcg of salbutamol.

Approximately 10% of an inhaled salbutamol dose is deposited in the lungs. Eighty-five percent of the remaining salbutamol administered from a metered-dose inhaler is swallowed, however, since the dose is low (100 to 200 mcg), the absolute amount swallowed is too small to be of clinical significance. Salbutamol is only weakly bound to plasma proteins. Results of animal studies indicate that following systemic administration, salbutamol does not cross the blood-brain barrier but does cross the placenta using an *in vitro* perfused isolated human placenta model. It has been found that between 2% and 3% of salbutamol was transferred from the maternal side to the fetal side of the placenta.

Salbutamol is metabolized in the liver. The principal metabolite in humans is salbutamol-o-sulfate, which has negligible pharmacologic activity. Salbutamol may also be metabolized by oxidative deamination and/or conjugation with glucuronide.

Salbutamol is longer acting than isoprenaline in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-O-methyl transferase. Salbutamol and its metabolites are excreted in the urine (>80%) and the feces (5% to 10%). Plasma levels are insignificant after administration of aerosolized salbutamol; the plasma half-life ranges from 3.8 to 7.1 hours.

STORAGE AND STABILITY

Keep out of the sight and reach of children. Do not store above 30°C. Keep in a dry place. Protect from frost and light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

VENTOLIN DISKUS inhalation powder is a disposable blue-coloured plastic inhaler device containing a foil strip with 60 blisters. Each blister contains 200 mcg of salbutamol (as sulfate) as active ingredient. It also contains lactose (milk sugar), including milk protein, which acts as the 'carrier'.

VENTOLIN DISKUS inhalation powder is a dry powder inhaler that delivers 200 mcg of salbutamol (as sulfate) per inhalation.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

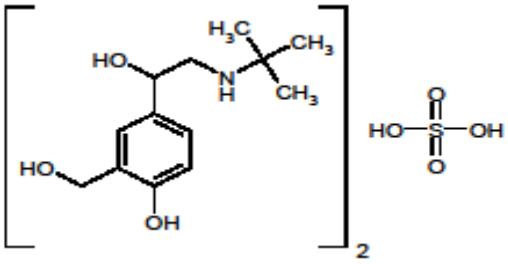
Drug Substance

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: $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$, 576.7

Structural formula:



Physicochemical properties:

Physical Form: White to almost white powder.

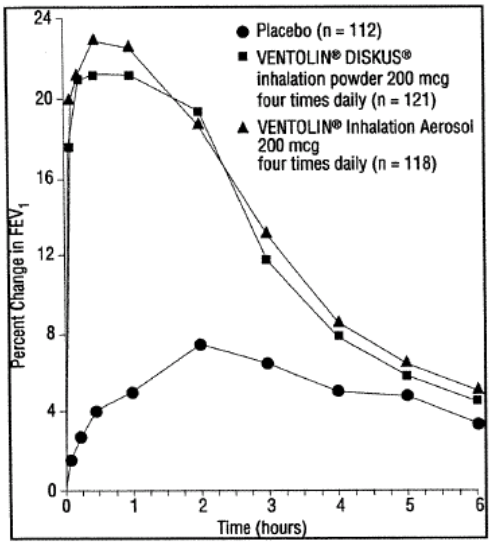
Solubility: Soluble in water and slightly soluble in ethanol.

CLINICAL TRIALS

In separate 4-week, randomized, double-blind, active and placebo-controlled trials, 142 asthma patients 4 to 11 years of age and 268 asthma patients 12 to 75 years of age were evaluated for the bronchodilator efficacy of VENTOLIN (salbutamol sulfate) DISKUS inhalation powder 200 mcg four times daily (49 pediatric and 90 adolescent/adult patients) in comparison to VENTOLIN (salbutamol sulfate) Inhalation Aerosol 200 mcg four times daily (48 pediatric and 87 adult/adolescent patients) and placebo (45 pediatric and 91 adolescent/adult patients). Thirty-seven percent of pediatric patients and 47% of adolescent/adults were taking concurrent inhaled corticosteroids. On Treatment Day 1 and at Treatment Week 4, serial FEV_1 measurements in patients ≥6 years of age (shown below as percent change from test-day baseline at Treatment Week 4) and serial peak expiratory flow rate (PEFR) measurements in patients 4 to 11 years of age demonstrated that one inhalation of VENTOLIN DISKUS inhalation powder produced significantly greater improvement in pulmonary function than placebo. There was no gender- or age-related differences in safety or efficacy of VENTOLIN DISKUS inhalation powder as compared to placebo.

Compared to two inhalations of VENTOLIN Inhalation Aerosol, one inhalation of VENTOLIN DISKUS inhalation powder produced significantly comparable improvements in pulmonary function. In children, VENTOLIN DISKUS inhalation powder appeared to provide slightly better results, while in adolescent /adults, VENTOLIN Inhalation Aerosol appeared to provide slightly better results. Therefore, while VENTOLIN DISKUS inhalation powder was comparable to VENTOLIN Inhalation Aerosol in clinical studies, it should not be assumed that VENTOLIN Inhalation Aerosol and VENTOLIN DISKUS inhalation powder will produce clinically equivalent outcomes in all patients.

Percent Change From Same Day Baseline in FEV_1 From Two 4-Week Clinical Trials in Patients ≥6 Years of Age: Treatment Week 4



In both adolescent /adult and pediatric studies, the majority of patients achieved ≥15% increase in FEV_1 (or PEFR) within 15 minutes after inhalation of VENTOLIN DISKUS inhalation powder 200 mcg. Additional analyses were performed on all patients who responded within 30 minutes. For these patients, the median onset of effect ranged from 3 to 3.6 minutes, and the median duration of effect ranged from 2.9 to 4.9 hours. In some patients, duration of effect was as long as 6 hours. Greater than 90% of both adolescent/adult and pediatric patients complied with the dosing instructions of VENTOLIN DISKUS inhalation powder.

Similarly, the majority of patients in both the adolescent/adult and pediatric studies achieved ≥15% increase in FEV_1 (or PEFR) within 15 minutes after inhalation of VENTOLIN Inhalation Aerosol 200 mcg. Additional analyses were performed on all patients who responded within 30 minutes. For these patients, the median onset of effect ranged from 3 to 4.2 minutes, and the median duration of effect ranged from 1.7 to 5.8 hours. In some patients, duration of effect was as long as 6 hours.

A single dose crossover trial compared 200 and 400 mcg VENTOLIN DISKUS inhalation powder with 100, 200, and 400 mcg VENTOLIN Inhalation Aerosol and placebo in patients 4 to 11 years of age with asthma. All treatments were significantly better than placebo in improving pulmonary function. Results of serial PEFR testing demonstrated that the peak effect within 30 minutes of dosing, expressed as percent change from test-day baseline, was 23.6% for VENTOLIN DISKUS inhalation powder 200 mcg, compared with 19.9% for VENTOLIN Inhalation Aerosol 200 mcg. In this single dose study, the majority of patients achieved ≥15% increase in PEFR within 30 minutes after inhalation of VENTOLIN DISKUS inhalation powder 200 mcg. For these patients, the median onset of effect was 3.6 minutes, and the median duration of effect was 5 hours. In some patients, duration of effect was as long as 6 hours.

A single dose crossover trial compared VENTOLIN DISKUS inhalation powder 200 mcg with VENTOLIN Inhalation Aerosol 200 mcg and placebo in patients 18 years of age and older with exercise-induced bronchospasm (EIB). Both treatments were comparable and significantly better than placebo in maintaining pulmonary function and protecting against EIB.

DETAILED PHARMACOLOGY

Animal

In vitro studies and *in vivo* pharmacologic studies have demonstrated that salbutamol has a preferential effect on $beta_2$-adrenergic receptors compared with isoprenaline. While it is recognized that $beta_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that there is a population of $beta_2$-receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these, however, is not yet established.

The pharmacologic effects of beta-adrenergic agonist drugs, including salbutamol, are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cAMP). Increased cAMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

The muscle-relaxing effect of salbutamol was found to be more prolonged than when the effect was induced by isoprenaline. As suggested from the results of experiments in isolated animal tissues, salbutamol has been shown to produce a substantial bronchodilator effect in the intact animal. In the anaesthetised guinea pig, salbutamol completely prevents acetylcholine-induced bronchospasm at the dose of 100 mcg/kg intravenously.

Administration of salbutamol aerosol at a dose of 250 mcg/mL for one minute to guinea pigs prevented acetylcholine-induced bronchospasm without any chronotropic effect. A prolonged bronchodilator effect of salbutamol compared to isoprenaline (in terms of mean times to dyspnea following acetylcholine challenge) was observed following oral administration of salbutamol to conscious guinea pigs. The protective action of salbutamol in this case persisted for up to six hours.

In anaesthetised 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 $beta_1$-adrenergic receptors in the heart is minimal.

In a number of studies using guinea pig atria, it was found that on a weight-to-weight basis, salbutamol was from 2,000 to 2,500 times less active in terms of inotropic effect and 500 times less active in terms of chronotropic effect than isoprenaline. Compared to

orciprenaline, salbutamol was about 40 times less active in terms of inotropic effect and four times less potent in terms of chronotropic effect. Salbutamol has been shown to be one-fifth as potent a vasodilator in skeletal muscle as isoprenaline, as measured by effects on hind limb blood flow in the anaesthetised dog. In the perfused rabbit ear, salbutamol was shown to possess only one-tenth the activity of isoprenaline in terms of vasodilating effect. In dogs, salbutamol was shown to increase coronary blood flow, which was subsequently shown to be the result of a direct coronary vasodilating effect of salbutamol.

In six dogs with right-sided cardiac bypass, salbutamol, given at the dose of 25 mcg/kg, improved left ventricular efficiency and increased coronary blood flow. Recent studies in minipigs, rodents, and dogs recorded the occurrence of cardiac arrhythmias and sudden death (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.

Animal studies show that salbutamol does not pass the blood brain barrier.

TOXICOLOGY

Acute Toxicity

Species (n)	Oral LD_{50}	Intravenous LD_{50}
Mouse (10)	> 2000 mg/kg	72 mg/kg
Rat (10)	> 2000 mg/kg	60 mg/kg

Rat (n)	Intraperitoneal LD_{50}
Newborn (155)	216 mg/kg
Weanling (100)	524 mg/kg
2 week old (90)	437 mg/kg

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 drug administration.

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

Intermediate (Four Months) Toxicity

Rats received salbutamol twice daily, in oral doses from 0.5 to 25 mg/kg, on an increasing scale. The only significant hematological changes were a small increase in hemoglobin and packed cell volume. BUN and SGOT values were elevated while blood glucose and plasma protein levels remained unchanged. Pituitaries had increased amount of PAS-positive material in the cleft at the higher dose levels.

Salbutamol was given to dogs twice daily, in oral doses from 0.05 to 12.5 mg/kg, on an increasing scale. The rate of increase of hemoglobin and packed cell volume was

depressed, particularly at higher doses. Leukocyte count decreased after sixteen weeks of treatment at each dose level. Platelet count was increased after eight weeks at the highest dose. No significant biochemical effects were observed. The only significant histological change was the appearance of corpora amylacea in the stomach which was attributed to altered mucus secretion. Inhalation of 1000 mcg of salbutamol aerosol twice daily for three months did not produce any morphological changes in the lungs, trachea, lymph nodes, liver or heart.

Long-Term Toxicity

Fifty female, Charles River CD Albino rats received salbutamol orally at 2, 10 and 50 mg/kg/day for one hundred and four weeks; fifty female Charles River CD Sprague-Dawley-derived rats received 20 mg/kg/day salbutamol orally for fifty weeks, and fifty female Charles River Long-Evans rats received 20 mg/kg/day salbutamol orally for ninety-six weeks. These rat 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-administration 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

Salbutamol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human aerosol dose; when given subcutaneously 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%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. No cleft palates were observed at a dose of 0.025 mg/kg salbutamol. Cleft palate occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoprenaline (positive control).

In rats, salbutamol treatment given orally at 0.5. 2.32, 10.75 and 50 mg/kg/day throughout pregnancy resulted in no significant fetal abnormalities. However, at the highest dose level there was an increase in neonatal mortality. Reproduction studies in rats revealed no evidence of impaired fertility.

Salbutamol had no adverse effect when given orally to Stride Dutch rabbits, at doses of 0.5, 2.32 and 10.75 mg/kg/day throughout pregnancy. At a dose of 50 mg/kg/day, which

represents 2800 times the maximum human inhalation dose, cranioschisis was observed in 7 of 19 (37%) fetuses.

A reproduction study in New Zealand White rabbits using salbutamol sulfate/HFA-134a formulation, revealed enlargement of the frontal portion of the fontanelles in 6 of 95 (6%) and 15 of 107 (14%) fetuses at 28 and 149 mcg/kg, respectively (approximately 2/5 and 2 times, respectively, the maximum recommended human daily dose on a mg/m^2 basis), giving plasma levels of approximately 12 and 60 ng/mL, respectively.

PART III: CONSUMER INFORMATION

PrVENTOLIN DISKUS
salbutamol sulfate powder for oral inhalation

This leaflet is part III of a three-part "Product Monograph" for VENTOLIN DISKUS and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VENTOLIN DISKUS. Please read this leaflet carefully before you start to take your medicine or start administering it to a child. Contact your doctor or pharmacist if you have any questions about the drug. This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

ABOUT THIS MEDICATION

What the medication is used for:
VENTOLIN DISKUS is used in Adults and Children 4 years or older to:

- relieve bronchospasm
- prevent bronchospasm
- prevent bronchospasm caused by exercise

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

The safety and effectiveness of VENTOLIN DISKUS in children under the age of 4 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 DISKUS if you are allergic to it or any of the components of its formulation including lactose (milk sugar) or milk protein or for the treatment of preterm labour or miscarriage.

What the medicinal ingredient is:
Salbutamol sulfate

What the nonmedicinal ingredients are:
Lactose (milk sugar which includes milk protein).

What dosage forms it comes in:
VENTOLIN DISKUS inhalation powder is a disposable blue-coloured plastic inhaler device containing a foil strip with 60 blisters. Each blister contains 200 mcg of the active ingredient salbutamol (as the sulfate salt). The blisters protect the powder for inhalation from effects of the atmosphere. It cannot be refilled.

WARNINGS AND PRECAUTIONS

Before you use VENTOLIN DISKUS talk to your doctor or pharmacist if:

- You have ever had to stop taking other medicines for this illness because you were allergic to them or they caused problems.
- You are having treatment for a thyroid condition.
- You are having treatment for high blood pressure or a heart problem.
- You have been told that you are allergic to lactose (milk sugar) or milk protein.
- You have diabetes.
- You have a past history of seizures.
- You 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)
- You are pregnant or intend to become pregnant. Taking VENTOLIN DISKUS 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 DISKUS while you're pregnant
- You are breastfeeding. It is not known if VENTOLIN DISKUS passes into breast milk

If the relief of wheezing or chest tightness is not as good as usual, or the effect lasts for less than three hours, tell your doctor as soon as possible. If you notice a sudden worsening of your shortness of breath and wheeze shortly after taking your medicine, 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.

You should always carry your VENTOLIN DISKUS with you to use immediately in case you experience an asthma attack.

Effects on Children:
Children may experience:

- Changes in sleep patterns
- changes in behaviour such as restlessness, excitability (hyperactivity)
- seeing or hearing things that are not there

INTERACTIONS WITH THIS MEDICATION

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 DISKUS:

- Anti-depressants
- Allergy medication
- Blood pressure-lowering drugs, including propranolol
- 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 DISKUS **should only be inhaled**. Do not swallow.

If You Are Also Using an Inhaled Corticosteroid:

- Always use VENTOLIN DISKUS first
- Wait a few minutes
- Then use your inhaled corticosteroid.

Your doctor may prescribe VENTOLIN DISKUS regularly every day, or only for when you are wheezy or short of breath, or before you exercise. Use VENTOLIN DISKUS only as directed by your doctor.

The action of VENTOLIN DISKUS may last up to 6 hours and should last at least 4 hours.

You should call your doctor immediately if:

- the effects of one dose last less than 3 hours;
- you notice a sudden worsening of your shortness of breath
- your symptoms gets worse;
- your usual dose does not provide relief of wheezing or chest tightness;
- you need to use VENTOLIN DISKUS more often than before

These may be signs that your asthma or chest condition is getting worse. Your doctor may want to reassess your treatment plan.

Do not increase the dose or the number of times you use your medicine without asking your doctor, as this may make you feel worse.

If you have to go to hospital for an operation, take VENTOLIN DISKUS with you and tell the doctor what medicine(s) you are taking.

Usual dose:

Adults and Children 4 years or older

- **To relieve bronchospasm:** 1 inhalation as needed. If you have a more severe attack, you can repeat the dose every 4 to 6 hours, and immediately consult your doctor or the nearest hospital

- **To prevent bronchospasm:** 1 inhalation repeated every 4 to 6 hours up to a maximum three or four times a day as prescribed by your doctor

- **To prevent bronchospasm caused by exercise:** 1 inhalation 15 minutes before exercise

Maximum dose - 4 inhalations in a 24 hour period

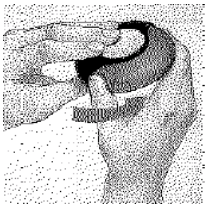
How to Use VENTOLIN DISKUS:

VENTOLIN DISKUS is closed when you first take it out of the box. It counts down from 60 to 1. **To show when the last five doses have been reached the numbers appear in red**.

Before you use VENTOLIN DISKUS read through this entire section carefully.

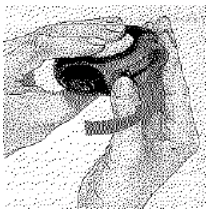
1. Open

To open your DISKUS inhaler hold the outer case in one hand and put the thumb of your other hand on the thumb grip. Push your thumb away from you as far as it will go.



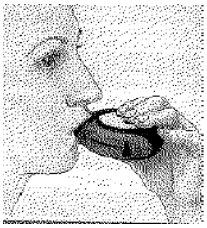
2. Slide

Hold your DISKUS inhaler with the mouthpiece towards you. Slide the lever away from you as far as it will go – until it clicks. Your DISKUS inhaler is now ready to use. Every time the lever is pushed back a dose is made available for inhaling. This is shown by the dose counter. Do not play with the lever as this releases dose which will be wasted.

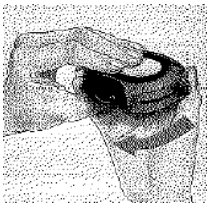


3. Inhale

- Hold the DISKUS inhaler away from your mouth. Breathe out as far as is comfortable. Remember – never breathe into your DISKUS inhaler.
- Put the mouthpiece to your lips. Breathe in steadily and deeply – through the DISKUS inhaler, not through your nose.
- Remove the DISKUS inhaler from your mouth.
- Hold your breath for about 10 seconds or for as long as is comfortable.
- Breathe out slowly.



4. Close



To close your DISKUS inhaler, put your thumb in the thumb grip, and slide the thumb grip back towards you, as far as it will go.

When you close the DISKUS inhaler, it clicks shut. The lever automatically returns to its original position and is reset. Your DISKUS inhaler is now ready for you to use again.

Remember:
Keep your DISKUS inhaler dry.
Keep it closed when not in use.
Only slide the lever when you are ready to take a dose.

Children - During inhalation, children should be assisted or supervised by an adult who knows the proper use of the inhaler.

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. Take this leaflet or your medication with you so that the hospital or poison control centre will know what you have taken.

If you accidentally take a **larger dose than prescribed**, you are more likely to get side effects like a faster heart beat, headaches and feeling shaky or restless. These effects usually wear off within a few hours, but you should tell your doctor as soon as possible.

Missed Dose:
If you forget to inhale a dose do not worry, just inhale the next dose when it is due or if you become wheezy. Your doctor may have told you to use your DISKUS inhaler regularly every day, or only when you are wheezy or short of breath.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

Effects on heart
- Hypertension

Effects on nervous system
- Headache
- Feeling a little shaky
- Feeling anxious or irritable
- Feeling tired or weak
- Trouble sleeping (insomnia)
- Hyperactivity in children
- Dizziness, vertigo
- Drowsiness

Effects on muscles and joints
- Muscle cramps
- Muscle pain

Other Effects
- Fever
- Respiratory infections and/or inflammation
- Nausea and vomiting
- Chest pain or discomfort
- Flushing
- Difficulty urinating
- Unusual taste in your mouth
- Dry or irritated throat

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	
Common	**Faster heart beat** than usual		✓	
Uncommon	**Irregular heart beat** (palpitations)		✓	
Rare	**Low Blood Potassium (hypokalemia):** muscle weakness and muscle spasms		✓	
	Hallucinations in Children: see or hear things that are not there		✓	
Very Rare	**Bronchospasm:** Sudden worsening of shortness of breath and wheezing shortly after using VENTOLIN DISKUS			✓
	Allergic Reactions: sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat.			✓
	Irregular Heart Beat (atrial fibrillation, supraventricular tachycardia, extrasystoles)		✓	

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

HOW TO STORE IT

Keep out of sight and reach of children.

Do not store VENTOLIN DISKUS inhalation powder above 30˚C. Keep in a dry place.

Protect from frost and light.

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 https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html**
- **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 1908C
    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 https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html.

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 found at:
http://www.gsk.ca
or by contacting the sponsor, GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
1-800-387-7374

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