Product Monograph

Including Patient Medication Information

[Pr] VENTOLIN DISKUS

salbutamol sulfate dry powder for inhalation

200 mcg salbutamol / blister

Bronchodilator

(beta$_2$-adrenergic agonist)

ATC Code: R03AC02

GlaxoSmithKline Inc.
100 Milverton Drive
Suite 800
Mississauga, Ontario
L5R 4H1
Canada

Date of Authorization:

2025-09-19

Control Number: 296330

Recent Major Label Changes

4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	2025-09
4 Dosage and Administration, 4.5 Missed Dose	2025-09
7 Warnings and Precautions, Respiratory	2025-09

Table of Contents

Certain sections (as indicated in section 2.1. of the PM Guidance) or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Recent Major Label Changes 2

Table of Contents 2

Part 1: Healthcare Professional Information 4

1 Indications 4

1.1 Pediatrics 4

2 CONTRAINDICATIONS 4

4 Dosage and Administration 4

4.1 Dosing Considerations 4

4.2 Recommended Dose and Dosage Adjustment 5

4.4 Administration 5

5 Overdosage 5

6 Dosage Forms, Strengths, Composition, and Packaging 6

7 Warnings and Precautions 6

7.1 Special Populations 8

7.1.1 Pregnancy 8

7.1.2 Breastfeeding 8

7.1.3 Pediatrics 8

7.1.4 Geriatrics 9

8 Adverse Reactions 9

8.1 Adverse Reaction Overview 9

8.2 Clinical Trial Adverse Reactions 9

9 DRUG INTERACTIONS 10

9.4 Drug-Drug Interactions 10

9.5 Drug-Food Interactions 11

9.6 Drug-Herb Interactions 11
9.7 Drug-Laboratory Test Interactions 12
10 Clinical Pharmacology 12
10.1 Mechanism of Action 12
10.3 Pharmacokinetics 12
11 Storage, Stability and Disposal 13
Part 2: Scientific Information 14
13 Pharmaceutical Information 14
14 Clinical Trials 14
14.1 Clinical Trials by Indication 14
15 Microbiology 16
16 Non-Clinical Toxicology 16
Patient Medication Information 19

Part 1: Healthcare Professional Information

1 Indications

Adults and Children (4 years and older):
VENTOLIN DISKUS (salbutamol sulfate) 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.

1.1 Pediatrics

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

2 Contraindications

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container (see 6 Dosage Forms, Strengths, 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.

4 Dosage and Administration

4.1 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 physicians or the nearest hospital.

4.2 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 to 6 hours, as needed, 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 physicians or the nearest hospital.

** Patients who are taking VENTOLIN DISKUS more than twice a week on an "as needed" basis may be at risk for overuse of VENTOLIN DISKUS A reassessment of the patient's therapy plan may be required. Bronchodilators should not be the only or main treatment in patients with persistent asthma.

4.4 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 healthcare professional on the proper use of the DISKUS inhaler.

5 Overdosage

Symptoms and Signs

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events (see 7 Warnings and Precautions and 8.1 Adverse Reaction Overview). 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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral Inhalation	Powder for inhalation / 200 mcg / salbutamol	Lactose (which contains milk protein)

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.

7 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 physician should be consulted immediately.

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.

Immune

- **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.

Monitoring and Laboratory Tests

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

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 8.1 Adverse Reaction Overview).

- **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 by a physician.

Patients who are taking VENTOLIN DISKUS more than twice a week on an “as needed” basis, not counting prophylactic use prior to a known trigger should be re-evaluated (i.e., daytime symptoms, nighttime awakening, and activity limitation due to asthma) for proper treatment adjustment as these patients are at risk for overuse of VENTOLIN DISKUS. A reassessment of the patient's therapy plan may be required.

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 physician 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 4.1 Dosing Considerations).

Overuse of short-acting beta-agonists may mask the progression of the underlying disease and contribute to deteriorating asthma control, leading to an increased risk of severe asthma exacerbations and mortality.

Patients who are prescribed regular asthma anti-inflammatory therapy (e.g., inhaled corticosteroids) should be advised to continue taking their anti-inflammatory medication even when symptoms improve, and they no longer require VENTOLIN DISKUS.

- **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 VENTOLIN DISKUS 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 instructs the patient on the need for further evaluation if the patient's asthma becomes worse (see 4 Dosage and Administration).

7.1 Special Populations

7.1.1 Pregnancy

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 16 Non-Clinical 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.

7.1.2 Breastfeeding

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.

7.1.3 Pediatrics

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.

7.1.4 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.

8 Adverse Reactions

8.1 Adverse 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 beta$_2$-agonist therapy, primarily from parenteral and nebulised routes of administration (see 7 Warnings and Precautions, Endocrine and Metabolism, Metabolic Effects).

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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Clinical trials with VENTOLIN DISKUS (salbutamol sulfate) 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 2 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.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 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: CS = Case Study

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 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.

10.3 Pharmacokinetics

After inhalation of recommended doses of salbutamol, plasma drug levels are very low. When 100 mcg of tritiated 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.

11 Storage, Stability and Disposal

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.

Part 2: Scientific Information

13 Pharmaceutical Information

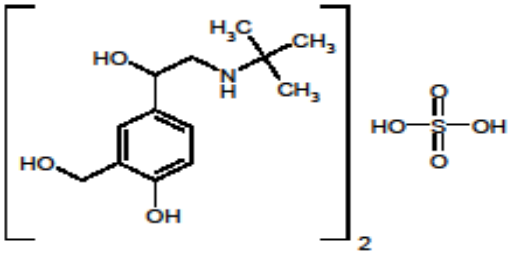
Drug Substance

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.

14 Clinical Trials

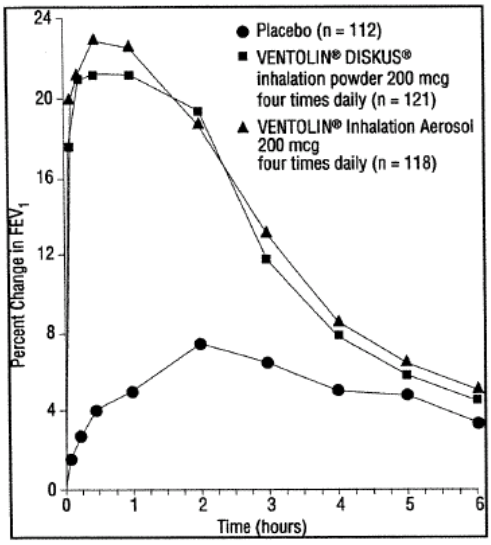
14.1 Clinical Trials by Indication

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 DISKUS (salbutamol sulfate) 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.

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

Animal Pharmacology

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.

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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] VENTOLIN DISKUS salbutamol sulfate powder for oral inhalation

This Patient Medication Information is written for the person who will be taking **VENTOLIN DISKUS**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **VENTOLIN DISKUS**, talk to a healthcare professional.

What VENTOLIN DISKUS is used for:

VENTOLIN DISKUS is used in adults and children (4 years or older) to:

- relieve and prevent worsening breathing problems (bronchospasm) due to chronic bronchitis (inflammation of the airways of the lungs with mucus production), bronchial asthma (inflammation of the airways of the lungs) and other problems with the airways of the lungs.
- prevent breathing problems caused by exercise.

The safety and effectiveness of VENTOLIN DISKUS in children under the age of 4 are not known.

How VENTOLIN DISKUS works:

Salbutamol belongs to a group of medicines knowns as “bronchodilators”. Salbutamol relaxes the muscles in the walls of the small air passages in the lungs. This helps to open up the airways of the lungs making it easier to breathe.

The ingredients in VENTOLIN DISKUS are:

Medicinal ingredients: Salbutamol sulfate

Non-medicinal ingredients: Lactose

VENTOLIN DISKUS comes in the following dosage forms:

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.

Do not use VENTOLIN DISKUS if:

- you are allergic to salbutamol sulphate or any of the other ingredients in VENTOLIN DISKUS. This includes lactose (which contains milk protein) and milk.
- for the treatment of preterm labour or miscarriage.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VENTOLIN DISKUS. Talk about any health conditions or problems you may have, including if you:

- Have ever had to stop taking other medicines for this illness because you were allergic to them or they caused problems.
- Have thyroid problems.
- Have a heart problem.
- Have high blood pressure.
- Have diabetes.
- Have seizures or a past history of seizures.
- Have low levels of potassium in your blood (hypokalemia), especially if you are taking:
  - Medicines known as xanthine derivatives (such as theophylline)
  - Steroids to treat asthma
  - Diuretics also known as “water pills”, used to lower fluid levels and treat high blood pressure
- Are pregnant or plan to become pregnant. Taking VENTOLIN DISKUS during pregnancy may cause harm to your baby. Your healthcare professional will consider the benefit to you and the risk to your baby of taking VENTOLIN DISKUS while you're pregnant.
- Are breastfeeding. It is not known if VENTOLIN DISKUS passes into breast milk.

Other warnings you should know about:

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

Monitoring: Your healthcare professional might monitor your health throughout your treatment with VENTOLIN DISKUS. This can include monitoring your lungs, the level of potassium in your blood and how you respond to VENTOLIN DISKUS.

Overuse: If you are using VENTOLIN DISKUS more than twice a week to treat your asthma symptoms (not including before or after exercise or other triggers) talk to your healthcare professional. This may be a sign that your asthma is not well controlled and may increase the risk of severe asthma attacks. Your healthcare professional may need to reassess your treatment.

Paradoxical bronchospasm: If you feel tightness of the chest, coughing, wheezing or breathlessness right after using VENTOLIN DISKUS, you may have a serious condition called “paradoxical bronchospasm” (an unexpected closing of your airways). Stop using VENTOLIN DISKUS and seek medical help right away.

Tell your healthcare professional about all the medicines you take, including any, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VENTOLIN DISKUS:

- anti-depressants, medicines used to treat depression (such as monoamine oxidase inhibitors, and tricyclic antidepressants).
- medicines used to treat allergies.
- beta-blockers, medicines used to lower blood pressure (such as propranolol).
- diuretics also known as “water pills”, medicines used to lower fluid levels and treat high blood pressure.
- other bronchodilators, medicines used to open the airway (such as asthma medicines such as ipratropium bromide).
- epinephrine, a medicine that can be used to treat allergic reactions or sudden asthma attacks.
- digoxin, a medicine used to treat certain heart problems.

How to take VENTOLIN DISKUS:

- Take VENTOLIN DISKUS exactly as directed by your healthcare professional.
- It is important that you use your VENTOLIN DISKUS properly. This will ensure that you receive the prescribed dose of your medicine. Make sure you know how, when, and how much you should use. Follow your healthcare professional’s instructions carefully. If you are not sure, ask your healthcare professional.
- VENTOLIN DISKUS should only be inhaled. Do not swallow.
- If you are using an asthma anti-inflammatory medicine daily (such as an inhaled corticosteroid) continue using it regularly, even if you feel better.
- If you are using an inhaled corticosteroid:
    - Always use VENTOLIN DISKUS first.
    - Wait a few minutes and then use your inhaled corticosteroid.
- If you have to go into hospital for an operation, take your inhaler with you and tell the healthcare professional what medicine(s) you are taking.

Salbutamol has a duration of action of 4 to 6 hours in most patients.

You should call your healthcare professional immediately if:

- the effects of one dose last less than 3 hours;
- you notice a sudden worsening of your shortness of breath;
- your symptoms get~~s~~ worse (for example you have frequent symptoms or flare ups such as breathlessness, cough, wheezing, tight chest, night-time awakening or limited physical ability);
- 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 healthcare professional may want to reassess your treatment plan.

Instructions for Use of 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 inhaler hold the outer case in one hand and put the thumb of your other hand on the thumb grip (see Figure 1).

Push your thumb away from you as far as it will go.

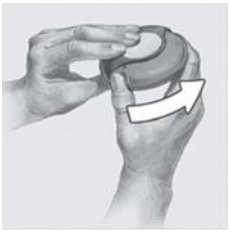


Figure 1

2. Slide

- Hold your inhaler with the mouthpiece towards you. Slide the lever away from you as far as it will go – until it clicks. Your 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 a dose which will be wasted.

Figure 2

3. Inhale

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

Figure 3

4. Close

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

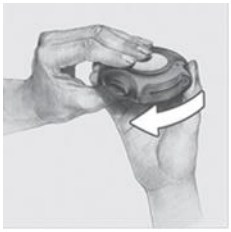


Figure 4

Remember:

- Keep your 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.

Usual dose:

Your healthcare professional will decide your dose of VENTOLIN DISKUS. This may depend on your condition, your age, and how you react to VENTOLIN DISKUS. Your dose may be repeated every 4 to 6 hours as directed. Do not increase the dose or the number of times you use your medicine without asking your healthcare professional, as this may make you feel worse.

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 healthcare professional or the nearest hospital.
- **To prevent bronchospasm:** 1 inhalation repeated every 4 to 6 hours up, as needed, to a maximum three or four times a day as prescribed by your healthcare professional.
- **To prevent bronchospasm caused by exercise:** 1 inhalation 15 minutes before exercise.

Maximum dose: 4 inhalations in a 24 hour period.

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

Overdose:

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 healthcare professional as soon as possible.

If you think you, or a person you are caring for, have taken too much VENTOLIN DISKUS, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Possible side effects from using VENTOLIN DISKUS:

These are not all the possible side effects you may have when taking VENTOLIN DISKUS. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Headache
- Feeling a little shaky
- Feeling anxious or irritable
- Feeling tired or weak
- Trouble sleeping (insomnia)
- Hyperactivity in children
- Dizziness, vertigo
- Drowsiness
- Muscle cramps

- Muscle pain
- 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 and what to do about them

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Common			
Tachycardia (heart rate that exceeds the normal resting rate): heart beating faster than usual		✓	
Uncommon			
Palpitation (sensation of rapid or irregular heart rate): irregular heart beat		✓	
Rare			
Hallucinations in Children: see or hear things that are not there		✓	
Hypokalemia (low level of potassium in the blood): muscle weakness, muscle spasms, cramping, constipation, feeling of skipped heart beats or palpitations, fatigue, tingling or numbness		✓	
Very Rare			
Allergic Reactions: difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			✓
Arrhythmia (abnormal heart rhythms): rapid, slow or irregular heartbeat		✓	
Bronchospasm (when there is a sudden narrowing of the airway): : increased wheezing, tightness in the chest, or difficulty in breathing (can happen after taking your dose)			✓

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Unknown			
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness, chest pain, or swelling in your ankles and legs		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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

If you want more information about VENTOLIN DISKUS:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.gsk.ca, or by calling 1-800-387-7374.

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

This leaflet was prepared by GlaxoSmithKline Inc.

Date of Authorization: 2025-09-19