

PRODUCT MONOGRAPH

PrSEREVENT® DISKHALER® Disk
salmeterol xinafoate dry powder for inhalation

50 mcg salmeterol (as the xinafoate salt)/blister

PrSEREVENT® DISKUS®
salmeterol xinafoate dry powder for inhalation

50 mcg salmeterol (as the xinafoate salt)/blister

Bronchodilator
(beta₂-adrenergic stimulant)

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
www.gsk.ca

Date of Revision:
October 16, 2013

Submission Control No: 166378

© 2013 GlaxoSmithKline Inc. All Rights Reserved

®SEREVENT, DISKHALER and DISKUS are registered trademarks, used under license by GlaxoSmithKline Inc.

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS	4
WARNINGS AND PRECAUTIONS.....	5
ADVERSE REACTIONS.....	11
DRUG INTERACTIONS	17
DOSAGE AND ADMINISTRATION.....	19
OVERDOSAGE	21
ACTION AND CLINICAL PHARMACOLOGY	22
STORAGE AND STABILITY	23
DOSAGE FORMS, COMPOSITION AND PACKAGING	24
PART II: SCIENTIFIC INFORMATION.....	25
PHARMACEUTICAL INFORMATION.....	25
CLINICAL TRIALS.....	26
DETAILED PHARMACOLOGY	30
TOXICOLOGY	34
REFERENCES	37
PART III: CONSUMER INFORMATION.....	39
PART III: CONSUMER INFORMATION.....	45

PrSEREVENT® DISKHALER® Disk
salmeterol xinafoate dry powder for inhalation

PrSEREVENT® DISKUS®
salmeterol xinafoate dry powder for inhalation

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral Inhalation	Dry powder for inhalation/50 mcg salmeterol/blister	Lactose and milk protein

INDICATIONS AND CLINICAL USE

Asthma

SEREVENT® (salmeterol xinafoate) is indicated for the treatment of asthma only as add-on therapy to an inhaled corticosteroid; a long-term asthma control medication; in patients 4 years of age and older with reversible obstructive airway disease, including patients with nocturnal asthma.

Corticosteroids should not be stopped because salmeterol is prescribed.

Long-acting beta₂-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT® DISKUS® and SEREVENT® DISKHALER® Disk, increase the risk of asthma-related death (see WARNINGS AND PRECAUTIONS). Use of SEREVENT® DISKUS® or SEREVENT® DISKHALER® Disk for the treatment of asthma without concomitant use of an inhaled corticosteroid; a long-term asthma control medication; is contraindicated (see CONTRAINDICATIONS). Use SEREVENT® DISKUS® or SEREVENT® DISKHALER® Disk only as add-on therapy for patients with asthma who are currently taking but are inadequately controlled on an inhaled corticosteroid.

Once asthma control is achieved and maintained, assess the patient at regular intervals. If possible without loss of asthma control, discontinue SEREVENT® DISKUS® or SEREVENT® DISKHALER® Disk and maintain the patient on an inhaled corticosteroid; a long-term asthma control medication. Do not use SEREVENT® DISKUS® or SEREVENT® DISKHALER® Disk for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

SEREVENT® is a slow onset, long-acting, beta₂-agonist and should not be used as a rescue medication. To relieve acute asthmatic symptoms, a rapid onset, short duration inhaled bronchodilator (e.g. salbutamol) should be used.

Pediatrics and Adolescent Patients:

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients (see WARNINGS AND PRECAUTIONS). For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate inhaled corticosteroid and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.

Chronic Obstructive Pulmonary Disease (COPD)

SEREVENT® is indicated for:

- long term, twice daily (morning and evening) administration in the maintenance treatment of bronchospasm and relief of dyspnea associated with COPD, including chronic bronchitis and emphysema.

Geriatrics:

There is no need to adjust the dose in otherwise healthy elderly patients.

Pediatrics (< 4 years of age):

At present, there is insufficient clinical data to recommend the use of salmeterol xinafoate in children younger than 4 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container and to adrenergic compounds. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Patients with cardiac tachyarrhythmias.
- SEREVENT® (salmeterol xinafoate) dry powder for inhalation (SEREVENT® DISKHALER® Disk and SEREVENT® DISKUS®) formulations contain lactose (which contains milk protein) and is therefore contraindicated in patients with an allergy to lactose or milk.
- Patients with a history of anaphylactic shock, anaphylactic reaction or angioedema associated with salmeterol xinafoate or any component of this drug.
- Because of the risk of asthma-related death and hospitalization, use of SEREVENT® DISKUS® or SEREVENT® DISKHALER® Disk for the treatment of asthma without concomitant use of an inhaled corticosteroid; a long-term asthma control medication; is contraindicated (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

ASTHMA RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT® DISKUS® and SEREVENT® DISKHALER® Disk, increase the risk of asthma-related death. Data from a large placebo controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to patients usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13, 176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13, 179 patients on placebo). Post-hoc analysis of the SMART trial data suggests that the risks may be lower in patients who were using inhaled corticosteroids (ICS) at study entry. However, these post-hoc analysis results are not conclusive (see CLINICAL TRIALS: Salmeterol Multi-center Asthma Research Trial (SMART)). Currently available clinical data are inadequate to determine whether concurrent use of inhaled corticosteroids mitigates the increased risk of asthma-related death from LABA.

Because of this risk, use of SEREVENT® DISKUS® or SEREVENT® DISKHALER® Disk for the treatment of asthma without concomitant use of an inhaled corticosteroid; a long-term asthma control medication; is contraindicated (see CONTRAINDICATION).

Use SEREVENT® DISKUS® or SEREVENT® DISKHALER Disk only as add-on therapy for patients with asthma who are currently taking but are inadequately controlled on an inhaled corticosteroid.

Once asthma control is achieved and maintained, assess the patient at regular intervals. If possible without loss of asthma control, discontinue SEREVENT® DISKUS® or SEREVENT® DISKHALER® Disk and maintain the patient on an inhaled corticosteroid; a long-term asthma control medication. Do not use SEREVENT® DISKUS® or SEREVENT® DISKHALER® Disk for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids (see DOSAGE AND ADMINISTRATION).

Pediatric and Adolescent Patients

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be considered to ensure adherence with both drugs. In cases where use of a separate inhaled corticosteroid and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended (see DOSAGE AND ADMINISTRATION).

Use in Asthma

Important Information

SEREVENT® (salmeterol xinafoate) should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition. Serious acute respiratory events, including fatalities, have been reported worldwide, when SEREVENT® has been initiated in this situation.

Although it is not possible from these reports to determine whether SEREVENT® contributed to these events or simply failed to relieve the deteriorating asthma, the use of SEREVENT® in this setting is inappropriate.

In most cases these reports have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications, increasing need for inhaled rapid onset, short duration beta₂-agonists, increasing need for systemic corticosteroids, significant increase in symptoms, recent emergency room visits, sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. There are no data demonstrating that SEREVENT® provides greater efficacy than or additional efficacy to rapid onset, short duration, inhaled beta₂-agonists in patients with worsening asthma.

General

SEREVENT® is not a substitute for inhaled or oral corticosteroids

All asthma patients should be advised that they must also use corticosteroids if they are taking SEREVENT®. Corticosteroid therapy should not be stopped or reduced when SEREVENT® is initiated.

There are no data demonstrating that SEREVENT® has a clinical anti-inflammatory effect and could be expected to take the place of, or reduce the dose of, corticosteroids. Asthmatic patients must be warned not to stop or reduce corticosteroid therapy even if they feel better as a result of initiating SEREVENT®. Any change in corticosteroid dosage should be made ONLY after clinical evaluation.

In the treatment of COPD, the role of inhaled corticosteroid therapy is less well established and SEREVENT® could be used with or without concomitant corticosteroids. The use of oral or inhaled corticosteroids should be determined by the treating physician.

SEREVENT® should not be used to treat acute asthma or COPD symptoms

It is crucial to inform patients of this and prescribe a rapid onset, short duration, inhaled bronchodilator to relieve acute symptoms. The use of bronchodilator should be determined by the treating physician.

The role of long-acting beta₂-agonists in the Management of Asthma and COPD

The management of asthma should normally follow a stepwise programme, and *patient response should be monitored clinically and by lung function tests*. Sudden or progressive deterioration in asthma control is potentially life-threatening; treatment plan must be re-evaluated, and consideration be given to increasing corticosteroid therapy. *In patients at risk, daily peak flow monitoring with precise instructions for acceptable variation limits should be considered.*

Increased use of inhaled, rapid onset, short duration beta₂-agonists is a marker of destabilization of asthma and requires re-evaluation of the patient and consideration of alternative treatment regimens, especially inhaled or systemic corticosteroids.

Long-acting beta₂-agonists are an alternative additional therapy for patients with moderate asthma with unsatisfactory symptom control despite an optimal dose of inhaled steroids particularly when there are nocturnal symptoms.

Before introducing long-acting beta₂-agonists, adequate education should be provided to the patient on how to use the drug and what to do if asthma flares up.

Long-acting beta₂-agonists are an additional therapy for COPD patients requiring long-acting control of symptoms.

Use with rapid onset, short duration bronchodilators

When asthmatic patients begin treatment with SEREVENT®, those who have been taking rapid onset, short duration, inhaled beta₂-agonists on a regular daily basis should be advised to discontinue their regular daily-dosing regimen and should be clearly instructed to use rapid onset, short duration, inhaled beta₂-agonists only for symptomatic relief if they develop asthma symptoms while taking SEREVENT®.

When beginning treatment with SEREVENT®, COPD patients should be instructed to use their rapid onset, short duration bronchodilators as determined by their treating physician, at the lowest dose to relieve their symptoms. The regular twice daily administration of SEREVENT® should reduce the excessive use of rapid onset, short duration inhaled bronchodilators.

Cardiovascular Effects

The pharmacological side-effects of beta₂-agonist treatment, such as palpitations have been reported, but tend to be transient and to reduce with regular therapy (see ADVERSE REACTIONS). A small increase in QTc interval has been reported at therapeutic doses. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Fatalities have been reported following excessive use of aerosol preparations containing sympathomimetic amines, the exact cause of which is unknown. Cardiac arrest was reported in several instances.

In a very large scale post-marketing surveillance study in the UK, involving over twenty-four thousand patients comparing safety of salmeterol and salbutamol in the treatment of asthma, the overall cardiovascular deaths on salmeterol treatment were 0.17% vs. 0.12% on salbutamol ($p=0.308$). The subdivision of these deaths into groups dependent on asthma severity was as follows:

Investigator Assessment of Severity of Asthma			
	Mild (%)	Moderate (%)	Severe (%)
Salmeterol	0.04	0.11	0.55
Salbutamol	0.14	0.07	0.27

Test for interaction $p=0.233$

In individual patients any beta₂-adrenergic agonist may have a clinically significant cardiac effect.

Cardiovascular effects such as increased blood pressure and heart rate may occasionally be seen with all sympathomimetic drugs, especially at higher than therapeutic doses.

Occurrence of cardiovascular effects may require discontinuation of the drug.

Salmeterol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in systolic and/or diastolic blood pressure, pulse rate, and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with salmeterol.

Central Nervous System

Central nervous system effects (e.g., agitation) can occur after the use of SEREVENT®. Occurrence of central nervous system effects may require discontinuation of the drug.

The pharmacological side-effects of beta₂-agonist treatment, such as tremor and headache have been reported, but tend to be transient and to reduce with regular therapy.

Salmeterol, like all sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

Ear/Nose/Throat

Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported rarely in patients receiving SEREVENT®.

Systemic Effects

The results of a drug interaction study conducted in healthy subjects indicated that concomitant use of systemic ketoconazole (a strong cytochrome P450 3A4 inhibitor) increased exposure to salmeterol in some subjects. This increase in plasma salmeterol exposure may lead to prolongation in the QTc interval. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with ketoconazole is not recommended (see DRUG INTERACTIONS, and ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics). Caution should also be exercised when other CYP3A4 inhibitors are co-administered with salmeterol (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin).

Endocrine and Metabolism

Metabolic Effects

Similar to other beta-adrenergic agents, salmeterol can induce reversible metabolic changes (e.g. hyperglycemia, hypokalemia). There have been very rare reports of increases in blood glucose levels (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions) and this should be considered when prescribing to patients with a history of diabetes mellitus.

Doses of the related beta₂-adrenoceptor agonist salbutamol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. Administration of beta₂-adrenoceptor agonists may cause a decrease in serum potassium, possibly through intracellular shunting, which has the potential to increase the likelihood of arrhythmias. The effect is usually seen at higher therapeutic doses and the decrease is usually transient, not requiring supplementation. Therefore, salmeterol should be used with caution in patients predisposed to low levels of serum potassium.

Hypersensitivity

Immediate hypersensitivity reactions may occur after administration of SEREVENT[®], as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and very rare cases of anaphylactic shock, or anaphylactic reaction.

Respiratory

As with other inhalation therapy, paradoxical bronchospasm, characterized by an immediate increase in wheezing after dosing may occur with SEREVENT[®]. This should be treated immediately with a rapid onset, short duration inhaled bronchodilator (e.g. salbutamol) to relieve acute asthmatic symptoms. SEREVENT[®] should be discontinued immediately, the patient assessed, and if necessary, alternative therapy instituted (see ADVERSE REACTIONS).

Special Populations

Pregnant Women

In animal studies, some effects on the fetus, typical for a beta-agonist occurred at exposure levels substantially higher than those that occur with therapeutic use. Extensive use of other beta-agonists has provided no evidence that effects in animals are relevant to human use.

There are no adequate and well-controlled studies with SEREVENT® in pregnant women. SEREVENT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labour and Delivery

There are no well-controlled human studies that have investigated effects of salmeterol on preterm labour or labour at term. Because of the potential for beta-agonist interference with uterine contractility, use of SEREVENT® during labour should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Women

Plasma levels of salmeterol after inhaled therapeutic doses are very low (85 to 200 pg/mL) in humans and therefore levels in milk should be correspondingly low. Studies in lactating animals indicate that salmeterol is likely to be secreted in only very small amounts in breast milk. However, since there is no experience with use of SEREVENT® by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when salmeterol xinafoate is administered to a nursing woman.

Pediatrics (< 4 years of age)

The safety and efficacy of SEREVENT® in children younger than 4 years of age have not been established.

Pediatrics (4-11 years of age)

The safety and efficacy of salmeterol in children 4-11 years old with asthma have been evaluated in controlled clinical trials for up to 1 year.

Geriatrics

No apparent differences in the efficacy and safety of SEREVENT® were observed when geriatric patients were compared with younger patients in asthma and COPD clinical trials. As with other beta₂-agonists, however, special caution should be observed when using SEREVENT® in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug.

Monitoring and Laboratory Tests

Monitoring Control of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's rapid onset, short duration inhaled beta₂-agonist becomes less effective or the patient needs more inhalation than usual, this may be a marker of destabilization of asthma. In this setting, the patient requires immediate re-evaluation with reassessment of the treatment regimen. Increasing the daily dosage of SEREVENT® in this situation is not appropriate. SEREVENT® should not be used more frequently than twice daily (morning and evening) at the recommended dose.

Use in Adolescents/Children and Asthma Severity Reassessment

In adolescents and children, the severity of asthma may be variable with age and periodic reassessment should be considered to determine if continued maintenance therapy with SEREVENT® is still indicated. Compliance, especially neglect of anti-inflammatory therapy and overuse of rapid onset, short duration beta₂-agonists, should be carefully followed in adolescents/children receiving long-acting beta₂-agonists.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

As with other 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.

Adverse reactions to SEREVENT® (salmeterol xinafoate) are similar in nature to reactions to other selective beta₂-adrenoceptor agonists, i.e. palpitation; immediate hypersensitivity reactions, including urticaria, rash, bronchospasm, edema, angioedema, and anaphylactic shock or anaphylactic reaction; headache; tremor; nervousness; oropharyngeal irritation, and paradoxical bronchospasm. There have also been reports of arthralgia and muscle cramps.

Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) have been reported, usually in susceptible patients.

Clinically significant changes in blood glucose and/or serum potassium were seen rarely during clinical studies with long-term administration of SEREVENT® at recommended doses.

Asthma

Long-acting beta₂-adrenergic agonists (LABA), including salmeterol, the active ingredient in SEREVENT® DISKUS® and SEREVENT® DISKHALER® Disk, increase the risk of asthma-related death. Data from a large, 28-week, placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or

placebo added to usual asthma therapy showed an increase in asthma-related death in patients receiving salmeterol. Post-hoc analysis of the SMART trial data suggests that the risks may be lower in patients who were using inhaled corticosteroids (ICS) at study entry. However, these post-hoc analysis results are not conclusive (see CLINICAL TRIALS: Salmeterol Multi-center Asthma Research Trial (SMART)).

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients (see WARNINGS AND PRECAUTIONS, and CLINICAL TRIALS: Salmeterol Multi-center Asthma Research Trial (SMART)).

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.

Use in Adolescents and Adults

In controlled, multidose clinical trials involving almost 2000 patients, the most frequently occurring adverse events were headache, tremor and palpitations (see Table 1 below), which are pharmacologically predictable effects of beta₂-adrenoceptor agonists. Tremor tended to be transient, dose-related and reduced with regular therapy. Headache and palpitations were reported but the incidence was not significantly different from placebo.

Table 1 Number (and percentage) of patients with adverse events

Adverse Event	SEREVENT® (50 mcg bid) n= 1462 (%)	placebo n= 195 (%)
Headache	62 (4.2)	5 (2.6)
Palpitations	22 (1.5)	4 (2.1)
Tremor	20 (1.4)	4 (2.1)

In a subsequent controlled clinical trial patients received either salmeterol in combination with beclomethasone dipropionate (BDP) or BDP alone. A rapid onset, short duration inhaled beta₂- adrenergic drug was also provided to all patients for use on an as-needed basis. The incidence of pharmacologically predictable adverse events was similar in all groups except for tremor which was significantly higher in the salmeterol 100 mcg group compared with the other two groups (see Table 2 below).

Table 2 Number (and percentage) of patients with drug-related adverse events

Adverse Event	Salmeterol 50 mcg bid + BDP* 500 mcg bid n= 243 (%)	Salmeterol 100 mcg bid ¹ + BDP* 500 mcg bid n= 244 (%)	BDP* 1000 mcg n= 251 (%)
Headache	26 (11)	38 (16)	42 (17)
Tremors	6 (2)	19 (8)	2 (<1)
Palpitations	4 (2)	6 (2)	4 (2)
Tachycardia	4 (2)	5 (2)	2 (<1)

BDP* = beclomethasone dipropionate

¹ = 100 mcg bid is not a recommended dose

Use in Children

Two multicenter, randomized, double-blind studies have compared twice daily administration of SEREVENT® 25 mcg and 50 mcg versus salbutamol in patients aged 4 to 16 years with asthma. Adverse events that occurred with an incidence of $\geq 3\%$ in the salmeterol groups, irrespective of the relationship to treatment, are summarized in Table 3 below.

Table 3 Number (and percentage) of patients with adverse events (incidence $\geq 3\%$) in two large 12-month pediatric clinical trials.

Adverse Event		SEREVENT® 25 mcg bid n= 251 (%)	SEREVENT® 50 mcg bid n= 277 (%)	Salbutamol 200 mcg bid (n= 255) (%)
Ear/Nose/Throat	Upper Resp. Tract Infection (URTI)	48	49	53
	Sore Throat	23	19	20
	Ear Infection	10	19	5
	Nasal Symptoms	5	3	4
Eye	Conjunctivitis	7	6	5
	Eye Infection	3	0	1
Gastrointestinal	Nausea & Vomiting	6	6	5
	Gastric Upset	4	4	3
	Gastroenteritis	4	5	1
	Abdominal Pain	3	4	4
Hypersensitivity	Allergic Rhinitis	8	10	7
Miscellaneous	Fever	8	12	10
	Influenza	10	6	9
	Viral Infections	5	5	3
	Chicken Pox	3	1	3
	Injuries	3	2	2
Neurological	Headaches	14	14	13
Respiratory	Asthma	50	56	47
	Cough	18	23	18
	Chest Infection	10	12	13
	Bronchitis	7	10	9
Skin	Eczema	5	5	3

The studies did not reveal any unexpected or clinically important differences between treatment with salmeterol 25 mcg bid or 50 mcg bid and salbutamol 200 mcg bid. There was no evidence to suggest that children of a younger age were more at risk than those in the older age groups.

Other Asthma Clinical Trial Adverse Drug Reactions

In US clinical trials, other events occurring in the SEREVENT® treatment group at a frequency of 1% to 3% were:

Ear/Nose/Throat: laryngitis, rhinitis

Gastrointestinal: abdominal pain, dental pain, diarrhea, nausea and vomiting, viral gastroenteritis

Hypersensitivity: urticaria

Musculoskeletal: back pain, muscle cramp/contraction, muscular soreness, myalgia/myositis, pain in joints

Neurological: malaise/fatigue, nervousness

Respiratory: bronchitis/tracheitis

Skin: rash/skin eruption

Urogenital: dysmenorrhea

In small dose-response studies, tremor, nervousness, and palpitations appeared to be dose related.

COPD

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT® inhalation aerosol in patients with COPD. In clinical trials, SEREVENT® was generally well tolerated over chronic dosing periods. The most frequently reported adverse events with SEREVENT® 50 mcg twice daily were headache, upper respiratory tract infection and sore throat.

Table 4 below includes all events (whether considered drug-related or non-drug-related by the investigator) that occurred at a rate of over 3% in the SEREVENT® inhalation aerosol treatment group and were more common in the SEREVENT® inhalation aerosol group than in the placebo group.

Table 4 Adverse experience incidence (>3%) in two large 12-week COPD clinical trials

Adverse Event		SEREVENT® 50 mcg bid n= 267	Placebo n= 278	Ipratropium 40 mcg qid n= 271
		(%)	(%)	(%)
Ear/Nose/Throat	Upper Resp. Tract Infection (URTI)	9	7	9
	Sore Throat	8	3	6
	Nasal Sinus Infection	4	1	2
Gastrointestinal	Diarrhea	5	3	4
Musculoskeletal	Back Pain	4	3	3
Neurological	Headache	12	10	8
Respiratory	Chest Congestion	4	3	3

Common cold, rhinorrhea, bronchitis, cough, exacerbation of chest congestion, chest pain, and dizziness occurred at 3% or more but were equally common on placebo.

Electrocardiographic Monitoring in Patients with COPD

Continuous electrocardiographic (Holter) monitoring was performed on 284 patients in two large COPD clinical trials during five 24-hour periods. No significant increase in the incidence of ventricular and supraventricular ectopic events was observed between SEREVENT® and placebo. No cases of sustained ventricular tachycardia were observed. At baseline, non-sustained, asymptomatic ventricular tachycardia was recorded for 7 (7.1%), 8 (9.4%), and 3 (3.0%) patients in the placebo, SEREVENT®, and ipratropium groups, respectively. During treatment, non-sustained, asymptomatic ventricular tachycardia that represented a clinically significant change from baseline was reported for 11 (11.6%), 15 (18.3%), and 20 (20.8%) patients receiving placebo, SEREVENT®, and ipratropium, respectively. Four of these cases of ventricular tachycardia were reported as adverse events (1 placebo, 3 SEREVENT®) by one investigator based upon review of Holter data. One case of ventricular tachycardia was observed during ECG evaluation of chest pain (ipratropium) and reported as an adverse event.

Other COPD Clinical Trial Adverse Drug Reactions

Other events occurring in the SEREVENT® inhalation aerosol treatment group at a frequency of 1% to 3% were:

Ear/Nose/Throat: cold symptoms, earache, epistaxis, nasal congestion, nasal sinus congestion, sinus headache, sneezing

Gastrointestinal: abdominal pain, constipation, dyspepsia, gastric pain, gastric upset, heartburn, nausea, oral candidiasis, surgical removal of tooth, vomiting, xerostomia

Musculoskeletal: leg cramps, muscle injury of neck, myalgia, neck pain, pain in arm, shoulder pain

Neurological: insomnia

Non Site Specific: discomfort in chest, fatigue, fever, pain in body

Respiratory: acute bronchitis, dyspnea, influenza, lower respiratory tract infection, pneumonia, respiratory tract infection, shortness of breath

Urogenital: urinary tract infection

Post-Market Adverse Drug Reactions

In addition to adverse events reported from clinical trials, the following events have been identified during worldwide use of any formulation of SEREVENT® or ADVAIR® (fluticasone propionate and salmeterol), regardless of indication. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to SEREVENT® or ADVAIR® or a combination of these factors.

Cardiac Disorders

Very rare: Hypertension and arrhythmias (including atrial fibrillation, supraventricular tachycardia, and extrasystoles).

Immune System Disorders

Immediate hypersensitivity reactions:

Rare: Urticaria, angiodema, rash, and bronchospasm.

Very rare: Anaphylactic shock or anaphylactic reaction.

Metabolism and Nutrition Disorders

Very rare: Hyperglycemia.

Respiratory, Thoracic and Mediastinal Disorders

Rare: Upper airway symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking.

Very rare: Oropharyngeal irritation and paradoxical bronchospasm (see WARNINGS AND PRECAUTIONS).

In extensive worldwide postmarketing experience, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS AND PRECAUTIONS), but they have occurred in a few patients with less severe asthma as well. It was not possible from these reports

to determine whether SEREVENT[®] contributed to these events or simply failed to relieve the deteriorating asthma.

DRUG INTERACTIONS

Overview

Use SEREVENT[®] (salmeterol xinafoate) with caution in patients receiving other medications causing hypokalemia and/or increased QTc interval (diuretics, high dose steroids, antiarrhythmics) and monoamine oxidase inhibitors or tricyclic antidepressants, since cardiac and vascular effects may be potentiated.

Inhibitors of cytochrome P450 3A4: Co-administration of repeat dose ketoconazole (a cytochrome P450 3A4 inhibitor) and salmeterol in healthy subjects resulted in a significant increase in plasma salmeterol exposure (1.4-fold increase in C_{max} and 15-fold increase in AUC). This increase in plasma salmeterol exposure may cause a prolongation of the QTc interval (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics).

Cromoglycate: In clinical trials, inhaled cromolyn sodium did not alter the safety profile of SEREVENT[®] when administered concurrently.

Ipratropium Bromide: In COPD trials, ipratropium bromide did not alter the safety profile of SEREVENT[®] when administered concurrently.

Drug-Drug Interactions

Table 5 Established or Potential Drug-Drug Interactions

Drug type	Ref	Effect	Clinical comment
Sympathomimetic agents	CT	May lead to deleterious cardiovascular effects.	Aerosol bronchodilators of the rapid onset, short duration adrenergic stimulant type may be used for relief of breakthrough symptoms while using salmeterol for asthma. However, increasing use of such preparations to control symptoms indicates deterioration of asthma control and the patient's therapy plan should be reassessed. The regular, concomitant use of salmeterol and other sympathomimetic agents is not recommended.
Monoamine Oxidase Inhibitors or Tricyclic Antidepressants	CS	Action of salmeterol on vascular system may be potentiated.	Salmeterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents.
Methylxanthines	CT	Unknown	The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving salmeterol has not been completely evaluated.
Beta-Blockers	CS	May antagonise the bronchodilating action of salmeterol.	Non-selective beta-blocking drugs, should never be prescribed in combination with salmeterol. Cardioselective beta-blocking drugs should be used with caution in patients using medications for bronchodilation.
Inhibitors of cytochrome P450 3A4	CT	Increased systemic exposure to salmeterol xinafoate.	Caution is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole) (See "DRUG INTERACTIONS", "WARNINGS AND PRECAUTIONS", and "ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics")

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

DOSAGE AND ADMINISTRATION

Dosing Considerations, Asthma

Long-acting beta₂-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT® DISKUS® and SEREVENT® DISKHALER® Disk, increase the risk of asthma-related death (see WARNINGS AND PRECAUTIONS). **Because of this risk, use of SEREVENT® DISKUS® or SEREVENT® DISKHALER® Disk for the treatment of asthma without concomitant use of an inhaled corticosteroid, a long-term asthma control medication, is contraindicated** (see CONTRAINDICATIONS). Use SEREVENT® DISKUS® and SEREVENT® DISKHALER® Disk only as add-on therapy for patients with asthma who are currently taking but are inadequately controlled on an inhaled corticosteroid.

Once asthma control is achieved and maintained, assess the patient at regular intervals. If possible without loss of asthma control, discontinue SEREVENT® DISKUS® or SEREVENT® DISKHALER® Disk and maintain the patient on an inhaled corticosteroid, a long-term asthma control medication. Do not use SEREVENT® DISKUS® or SEREVENT® DISKHALER® Disk for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids (see WARNINGS AND PRECAUTIONS).

Pediatric and Adolescent Patients (4 to 17 years of age): Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For patients with asthma less than 18 years of age who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure adherence with both drug. In cases where use of a separate inhaled corticosteroid and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended (see WARNINGS AND PRECAUTIONS).

General Considerations for Asthma and COPD

The dosage or frequency of SEREVENT® administration should not be increased since there may be serious adverse effects associated with excessive dosing. SEREVENT® should not be used more than twice daily.

Elderly and patients with impaired renal or hepatic function: There is no need to adjust the dose in the otherwise healthy elderly or in patients with impaired renal function. Because salmeterol is predominantly cleared by hepatic metabolism, patients with hepatic disease should be closely monitored.

Asthma

SEREVENT® (salmeterol xinafoate) should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition (see WARNINGS AND PRECAUTIONS).

SEREVENT® is not a replacement for inhaled or oral corticosteroid therapy; its use is complementary to it. Patients must be warned not to stop or reduce anti-inflammatory therapy (see CONTRAINDICATIONS).

SEREVENT® should not be used to treat acute symptoms. It is crucial to inform patients of this and prescribe a rapid onset, short duration beta₂-agonist for this purpose. The need for additional symptomatic bronchodilator therapy is usually reduced with SEREVENT® (see WARNINGS AND PRECAUTIONS section). Medical attention should be sought if patients find that rapid onset, short duration relief bronchodilator treatment becomes less effective or if they need more inhalations than usual.

Bronchodilators should not be the only or the main treatment in patients with moderate to severe or unstable asthma. Patients with severe asthma require regular medical assessment since death may occur. These patients will require high dose inhaled or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under medical supervision.

As twice-daily regular treatment, SEREVENT® provides 24-hour bronchodilation and can replace regular use of a rapid onset, short duration (4 hour) inhaled or oral bronchodilator (e.g. salbutamol) when optimum corticosteroid therapy is being used.

For full therapeutic benefit, regular usage of SEREVENT® is recommended in the treatment of reversible airways obstruction.

Adolescents/Children: At present, there are insufficient clinical data to recommend the use of salmeterol xinafoate in children younger than 4 years of age. Based on available data, no adjustment of salmeterol dosage in pediatric patients is warranted. In adolescents/children the severity of asthma may be variable with age and periodic reassessment should be considered to determine if continued maintenance therapy with SEREVENT® is still indicated.

COPD

Counselling on smoking cessation should be the first step in treating patients with COPD. Smoking cessation produces symptomatic benefits and has been shown to confer a survival advantage by slowing or stopping the progression of chronic bronchitis and emphysema.

Use with Rapid Onset, Short Duration Bronchodilators: When beginning treatment with SEREVENT®, COPD patients should be instructed to use their rapid onset, short duration bronchodilators as determined by their treating physician, at the lowest dose to relieve their symptoms. The regular twice-daily administration of SEREVENT® should reduce the excessive use of rapid onset, short duration, inhaled bronchodilators.

Recommended Dose - Asthma

Maintenance Therapy

SEREVENT® DISKHALER® Disk:

SEREVENT® DISKHALER® Disks are for use with a SEREVENT® DISKHALER® device only.

Patients 4 years of age and older: One blister [50 micrograms of salmeterol (as the xinafoate)] twice daily.

SEREVENT® DISKUS®:

Patients 4 years of age and older: One blister [50 micrograms of salmeterol (as the xinafoate)] twice daily.

Recommended Dose - COPD

SEREVENT® DISKHALER® Disk:

One blister [50 micrograms of salmeterol (as the xinafoate)] twice daily.

SEREVENT® DISKUS®:

One blister [50 micrograms of salmeterol (as the xinafoate)] twice daily.

Missed Dose

If a patient forgets to inhale a dose, instruct the patient to inhale another as soon as they remember **unless** it is near the time for their next dose. If so the patient should wait until the next dose and resume the regular dosing schedule. Do not double dose.

Administration

SEREVENT® is administered by the inhaled route only.

OVERDOSAGE

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

Do Not Exceed Recommended Dosage: As with other inhaled beta₂-adrenergic drugs, SEREVENT® should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias (see WARNING AND PRECAUTIONS, Cardiovascular).

The expected signs and symptoms of salmeterol overdosage are those typical of excessive beta₂ adrenergic stimulation including tremor, headache, tachycardia, increases in systolic blood pressure, cardiac arrhythmias, hypokalemia, hypertension, or hypotension, metabolic acidosis (in rare cases) and, in extreme cases, sudden death. There is no specific treatment for an overdose of salmeterol. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm.

Fatalities have been reported following excessive use of aerosol preparations containing sympathomimetic amines, the exact cause of which is unknown. Cardiac arrest was reported in several instances.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

SEREVENT® (salmeterol xinafoate) is a selective, long-acting (12 hours), slow onset (10-20 minutes) beta₂- adrenoceptor agonist with a long side-chain which binds to the exo-site of the receptor.

Salmeterol offers more effective protection against histamine-induced bronchoconstriction and produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional rapid onset, short duration beta₂-agonists.

In contrast to conventional rapid onset, short duration beta₂-agonists, the onset of the bronchodilator effect of salmeterol usually occurs in 10-20 minutes. However, the full benefits only become apparent after the first or second dose of the drug. Regular dosing produces sustained improvement in lung function thereby reducing symptoms of airways obstruction.

In vitro tests on human lung, have shown salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes and prostaglandin D₂.

In man, salmeterol inhibits the early and late phase response to inhaled allergen. The late phase response is inhibited for over 30 hours after a single dose, when the bronchodilator effect is no longer evident. The full clinical significance of these findings is not yet clear. The mechanism is different from the anti-inflammatory effect of corticosteroids.

Pharmacodynamics

In patients, salmeterol by both pressurised and powder inhalers in single doses of 25 mcg or greater has been shown to produce bronchodilation lasting for approximately 12 hours. This long duration of action has been confirmed by challenge studies using exercise, histamine and methacholine as bronchoconstrictor agents. Salmeterol has also been

shown to abolish both the early and late phase bronchoconstrictor response to inhaled allergen, the clinical significance of which has not been established.

Pharmacokinetics

Salmeterol acts locally in the lung; plasma levels therefore do not predict therapeutic effect. Because of the low therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (50 mcg twice daily).

Salmeterol is predominantly cleared by hepatic metabolism; liver function impairment may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

An *in vitro* study showed that salmeterol is extensively metabolised to α -hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4). A repeat dose study with salmeterol and erythromycin in healthy volunteers showed no clinically significant changes in pharmacodynamic effects at 500 mg three times daily doses of erythromycin. However, a salmeterol-ketoconazole interaction study resulted in a significant increase in plasma salmeterol exposure (see WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS).

In a placebo-controlled, crossover drug interaction study in 15 healthy subjects, co-administration of salmeterol (50 mcg twice daily inhaled) and the cytochrome P450 3A4 (CYP3A4) inhibitor, ketoconazole (400 mg once daily orally), for 7 days, resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). There was no increase in salmeterol accumulation with repeat dosing. Three subjects were withdrawn from salmeterol and ketoconazole co-administration due to QTc prolongation or palpitations with sinus tachycardia. In the remaining 12 subjects, co-administration of salmeterol and ketoconazole did not result in a clinically significant effect on heart rate, blood potassium or QTc duration (see WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS).

STORAGE AND STABILITY

SEREVENT® DISKHALER® Disk should not be exposed to extremes of temperature, and should be stored below 25° C and protected from humidity.

A SEREVENT® DISKHALER® Disk may be kept in the DISKHALER® at all times but a blister should only be pierced immediately prior to use. Failure to observe this instruction will affect operation of the DISKHALER®.

SEREVENT® DISKUS® should be stored below 30° C and in a dry place.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SEREVENT® DISKHALER® Disks

SEREVENT® DISKHALER® Disks are circular, double-foil blister packs with four regularly distributed blisters, each containing a dry powder blend of microfine salmeterol (as the xinafoate salt) and lactose (which contains milk protein). Each blister contains 50 mcg salmeterol. The disk blister packs are available in cartons of 15 disks (4 blisters/disk). SEREVENT® DISKHALER® Disks are available individually.

SEREVENT® DISKUS®

SEREVENT® DISKUS® is a novel dry powder presentation of microfine salmeterol (as the xinafoate salt) for inhalation. It also contains lactose (milk sugar), including milk protein, which acts as the ‘carrier’. The product consists of 60 doses, each containing the equivalent of 50 mcg of salmeterol per dose.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

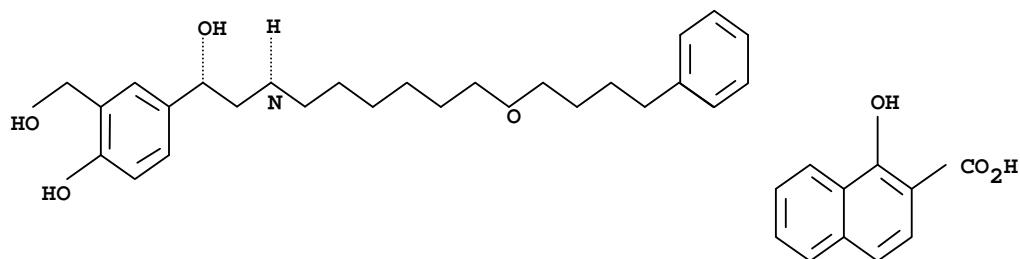
Drug Substance

Proper name: salmeterol xinafoate

Chemical name: 4-hydroxy- α^1 -[[[6-(4-phenylbutoxy) hexyl]amino]-methyl]-1, 3-benzenedimethanol, 1-hydroxy-2-naphthoate

Molecular formula and molecular mass: C₂₅H₃₇NO₄·C₁₁H₈O₃ 603.8

Structural formula:



Physicochemical properties:

Description: White to off-white crystalline powder with a melting point $\geq 123^\circ\text{C}$

Solubility:

- In water $\geq 0.07 \text{ mg/mL}$ ($\text{pH} \geq 8$)
- In saline $\geq 0.08 \text{ mg/mL}$ (0.9%w/v)
- In methanol $\geq 40 \text{ mg/mL}$
- In ethanol $\geq 7 \text{ mg/mL}$
- In chloroform $\geq 3 \text{ mg/mL}$
- In isopropanol $\geq 2 \text{ mg/mL}$

pKa and pH:

Salmeterol is amphoteric and is partially ionised in water over the whole pH range. The ionised species have a low solubility, thus accurate determination of the two macro-dissociation constants by potentiometric titration has not been possible. The apparent pKa for dissociation of the phenolic group (as determined by ultraviolet spectrophotometry) is 9.3. The four microconstants lie between 8.9 and 9.7.

The pH of a saturated aqueous solution of salmeterol xinafoate (0.07 mg/mL) is about 8.

Partition Coefficient:

The partition coefficient between n-octanol and water is pH-dependent and has been determined by an HPLC procedure.

$$\log D = 3.2 \text{ (pH 9.2)}$$

$$\log D = 2.0 \text{ (pH 7.4)}$$

$$\log D = 0.6 \text{ (pH 4.0)}$$

CLINICAL TRIALS

Asthma - Clinical Experience

Use in adolescents and adults

The efficacy of SEREVENT[®] (salmeterol xinafoate) was evaluated in controlled clinical studies using both the aerosol and dry powder formulations. The doses used in these studies were 50 mcg bid and 100 mcg bid for moderate to severe patients.

These studies involved over 1500 patients with mild, moderate and severe airways obstruction. In these trials, salmeterol demonstrated superior efficacy as compared with salbutamol 200 mcg (aerosol) and 400 mcg (powder) four times daily, and dose-titrated theophylline, twice daily.

In these trials, salmeterol treatment significantly improved lung function and reduced nocturnal and daytime symptoms and the requirement for additional rapid onset, short duration inhaled bronchodilators (e.g. salbutamol).

There were no significant differences between the aerosol and dry powder formulations with respect to any of the efficacy parameters.

SEREVENT[®] Nationwide Post-Marketing Surveillance Study

Subsequent to the completion of the clinical trial program, a large scale post-marketing surveillance study, involving 25,180 patients was carried out in the UK, to compare safety of salmeterol and salbutamol in treating asthma. This was a randomised, double blind, double-dummy, parallel group, 16-week study. Randomisation was 2 salmeterol patients: 1 salbutamol patient.

Medical withdrawals due to asthma were statistically significant, fewer with salmeterol than with salbutamol (2.91% vs. 3.79%, p=0.0002).

However there was a small increase in mortality in the group taking salmeterol for obstructive airways disease deaths [16 (0.10%) in salmeterol and 3 (0.04%) in salbutamol groups ($p=0.105$)] and cardiovascular deaths [29 (0.17%) in salmeterol and 10 (0.12%) in salbutamol ($p=0.308$)].

For both treatment groups the number of nonfatal adverse events was related to severity of asthma on entry.

Salmeterol Multi-center Asthma Research Trial (SMART)

The SMART study was a large US post-marketing study that compared the safety of SEREVENT® inhalation aerosol (salmeterol 50 mcg twice daily) and placebo, added to the usual asthma therapy for a 28-week treatment period. This study was prematurely terminated after a planned interim analysis in which a safety issue was identified. This analysis was performed on 26,355 patients, approximately half of the intended number for enrollment in this trial.

Analysis of the data available to date showed increased risk for asthma-related death and other serious respiratory-related outcomes in patients treated with SEREVENT® compared to those treated with placebo, in addition to their usual asthma therapy. The risk for the primary endpoint of combined respiratory-related death or life-threatening experience (i.e., intubation and/or mechanical ventilation) which includes the asthma-related outcomes, during the 28-week treatment period, was 40% higher in patients using salmeterol in addition to their usual asthma therapy compared to those using placebo in addition to their usual asthma therapy (50 in 13,176 vs 36 in 13,179; <1% in both cases; relative risk of 1.40 with 95% CI: 0.91, 2.14). When asthma-related death was analysed alone, a statistically significant increased risk of greater than four-fold was seen in patients who used salmeterol as compared to those who used placebo in addition to their usual asthma therapy (13 in 13,176 vs 3 in 13,179; <1% in both cases; relative risk of 4.37 with 95% CI: 1.25, 15.34). In addition, statistically significant increased risks were observed for the outcomes of combined asthma-related death or life-threatening experience (37 vs 22; relative risk of 1.71 with 95% CI: 1.01, 2.89) and respiratory-related death (24 vs 11; relative risk of 2.16 with 95% CI: 1.06, 4.41). These statistically significant increased risks were observed at interim analysis when enrollment was half the planned number, and the power relatively low.

Post-hoc subgroup analyses suggest that the risk for these serious events may be greater in the African-American population. In this subgroup, the relative risks after the 28-week treatment period were: 4.10 for the primary endpoint (20 out of 2,366 vs 5 out of 2,319; 95% CI: 1.54, 10.90) in patients using salmeterol in addition to their usual asthma therapy compared to those using placebo in addition to their usual asthma therapy, 7.26 for asthma-related death (7 vs 1; 95% CI: 0.89, 58.94), 4.92 for combined asthma-related death or life-threatening experience (19 vs 4; 95% CI: 1.68, 14.45), and 3.88 for respiratory-related death (8 vs 2; 95% CI: 0.83, 18.26). The relative risks in the Caucasian population were: 1.05 for the primary endpoint (29 out of 9,281 vs 28 out of 9,361; 95% CI: 0.62, 1.76) for patients using salmeterol in addition to their usual asthma therapy compared to those adding placebo, 5.82 for asthma-related death (6 vs 1; 95%

CI: 0.70, 48.37), 1.08 for combined asthma-related death or life-threatening experience (17 vs 16; 95% CI: 0.55, 2.14), and 2.29 for respiratory-related death (16 vs 7; 95% CI: 0.94, 5.56).

While not conclusive, a post-hoc analyses, of the data from the SMART trial suggested that the use of inhaled corticosteroids as reported at study entry, had a protective effect regarding asthma-related outcomes in patients taking SEREVENT®. For the primary endpoint of combined respiratory-related death or life-threatening experience, a relative risk of 1.60 (27 out of 7,049 vs 17 out of 7,041; 95% CI: 0.87, 2.93) was observed for patients not reporting inhaled corticosteroid use at study entry, while a relative risk of 1.21 (23 out of 6,127 vs 19 out of 6,138; 95% CI: 0.66, 2.23) was observed for those who did report ICS use. For asthma-related death alone, the relative risks were: 18.98* (9 vs 0; with 95% CI: 1.10, 326.15) for those without baseline ICS use, and 1.35 (4 vs 3; 95% CI: 0.30, 6.04) for those reporting ICS use. For asthma-related death or life-threatening experience, the relative risks were: 2.39 (21 vs 9; 95% CI: 1.10, 5.22) for those without baseline ICS use, and 1.24 (16 vs 13; 95% CI: 0.60, 2.58) for those reporting ICS use; and, for respiratory-related death: 2.28 (14 vs 6; 95% CI: 0.88, 5.94) for those without baseline ICS use, and 2.00 (10 vs 5; 95% CI: 0.69, 5.86) for those reporting ICS use. Hence, the apparent protective effect was most notable for asthma-related outcomes. When ICS effect was further analysed by ethnicity, risks of asthma-related outcomes were diminished for the African-American subgroup with ICS use (as reported at study entry), but contrary to the Caucasian subgroup, these risks were not extinguished, although the data for this analysis were sparse. It is to be noted that the SMART study data do not include information regarding the continued use of ICS after study entry, nor information regarding the dose(s) of ICS used throughout the treatment period of 28 weeks.

A number of limitations are noted in the clinical trial's design and conduct, such as the ascertainment and enumeration of events, collection of covariate information (i.e., continued concurrent ICS use) and confounding factors, which may make the interpretation of the results problematic. In addition, post-hoc subgroup analyses may be unstable and/or easily influenced by small changes in covariates or additional events.

The findings from SMART are similar to the Salmeterol Nationwide Surveillance study conducted in the UK, where increased asthma-related deaths were observed for patients treated with salmeterol as compared to salbutamol over a 16-week period.

Given the similar basic mechanisms of action of β_2 -agonists, it is possible that the findings seen in this study may be consistent with a class effect.

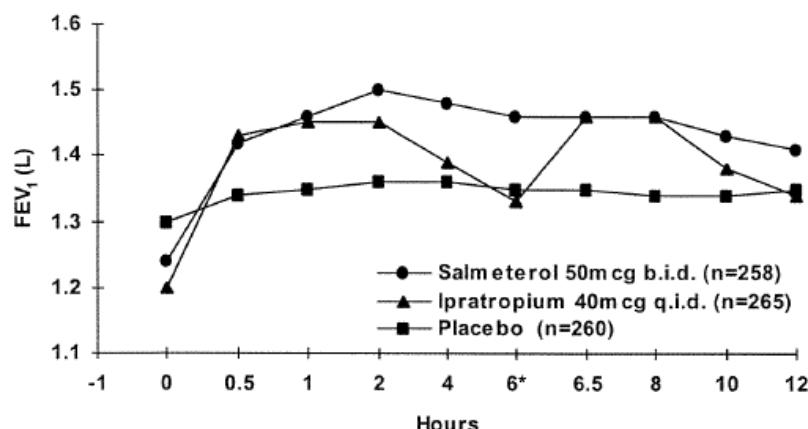
*Estimated by adding .5 to each cell of the treatment by event occurrence table.

(See WARNINGS AND PRECAUTIONS)

Chronic Obstructive Pulmonary Disease (COPD) – Clinical Experience

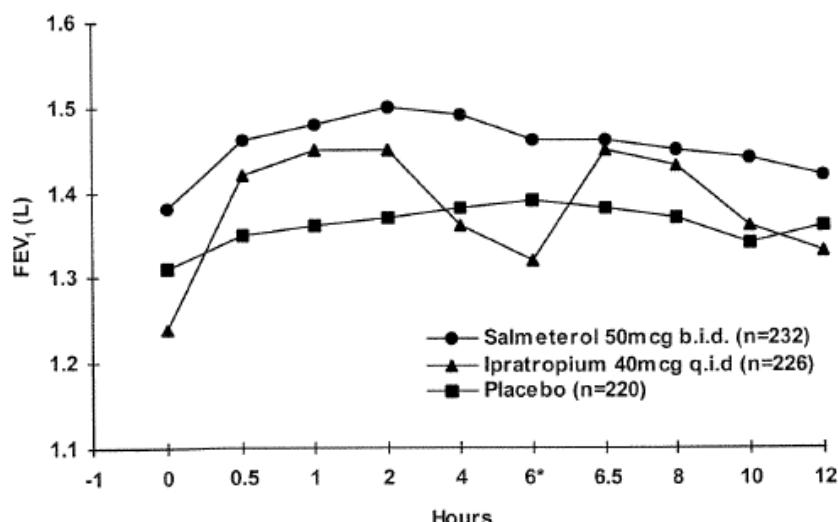
In two large randomized, double-blind studies, SEREVENT® inhalation aerosol was compared with placebo and ipratropium bromide in patients with COPD (emphysema and chronic bronchitis), including patients who were reversible ($\geq 12\%$ and ≥ 200 mL increase in baseline FEV₁ after salbutamol treatment) and non-reversible to salbutamol. After a single 50 mcg dose of SEREVENT®, significant improvement in pulmonary function (mean FEV₁ increase of 12% or more) occurred within 30 minutes, reached a peak within 4 hours on average and persisted for 12 hours with no loss in effectiveness observed over a 12-week treatment period. Serial 12 hour measurements of FEV₁ from these two 12-week trials are shown below for both the first (Figure 1) and last treatment (Figure 2) days.

Figure 1 FEV₁ From Two Large 12-Week Clinical Trials: First Treatment Day.



* ipratropium (or matching placebo) administered immediately following hour 6 assessment.

Figure 2 FEV₁ From Two Large 12-Week Clinical Trials: Last Treatment Day (Week 12).



* ipratropium (or matching placebo) administered immediately following hour 6 assessment.

FEV₁ area under the curve (FEV₁ over time) was consistently greater with SEREVENT® as compared to ipratropium in the total population and in patients reversible to salbutamol. SEREVENT® and ipratropium had a similar treatment response in patients that were non-reversible to salbutamol. Results similar to those shown above were seen in the groups reversible and non-reversible to salbutamol. However, the magnitude of response was greater in the group of patients reversible to salbutamol. In addition, improvement in dyspnea as measured using the Baseline Dyspnea Index and Transitional Dyspnea Index occurred within 2 weeks of treatment. Improvement in dyspnea was sustained over 12 weeks of treatment. No clinically significant age or gender related differences in efficacy were observed. Improvement in disease specific quality of life was assessed using the Chronic Respiratory Disease Questionnaire. In patients using SEREVENT® a significantly greater percentage of patients showed improvement in global quality of life scores (46%) as compared to patients receiving placebo (32%).

DETAILED PHARMACOLOGY

Animals

Salmeterol is a potent, selective beta₂-agonist in respiratory smooth muscle and on lung mast cells. Salmeterol is virtually devoid of beta₁-adrenoceptor activity with only weak agonist activity at beta₃-adrenoceptors.

In vitro Studies

In the isolated, electrically-stimulated guinea pig trachea, salmeterol was 7-fold more potent than isoprenaline and 20-fold more potent than salbutamol. In the PGF2 α -contracted guinea pig tracheal strip, salmeterol was equipotent with isoprenaline and twice as potent as salbutamol (EC₅₀ 3.5nM salmeterol, and 6.4nM salbutamol).

Salmeterol xinafoate was an extremely weak partial agonist in the electrically-driven left atrium of the rat, a beta₁-adrenoceptor containing preparation.

In the isolated guinea pig fundus preparation, salmeterol xinafoate produced smooth muscle relaxation. The concentration required to cause relaxation of guinea pig fundus, containing beta₃-adrenoceptors, was at least 1000 times higher than that required to activate beta₂-adrenoceptors in airways smooth muscle.

Salmeterol has a significantly longer duration of action than salbutamol (12 minutes and 2-4 minutes, respectively). This was confirmed in the electrically-stimulated guinea pig trachea where there was less than 50% recovery from the inhibitory responses to even submaximally effective concentrations of salmeterol xinafoate for periods in excess of 8 hours, despite continuous superfusion of the tissue without drug. The persistent action of the drug could be fully reversed by the beta₁- and beta₂-adrenoceptor blocker, sotalol, but when the antagonist was washed out, the activity of salmeterol was reasserted. In contrast, salbutamol and isoprenaline exhibited shorter durations of action (2-3 minutes and 11.4 minutes respectively).

Despite the sustained agonist action, no tolerance or tachyphylaxis has been observed with salmeterol in respiratory smooth muscle.

Binding studies in rats have shown evidence of slow dissociation of the drug from its receptor site.

The long duration of effect of salmeterol is due to a unique method of action whereby a portion of the molecule binds with high affinity to non-polar domains or exosites from where the rest of the molecule can interact freely with the active site of the beta₂-adrenoceptor.

In vivo Studies

The potency and duration of action of the bronchodilator activity of salmeterol was determined in conscious guinea-pigs following inhaled and oral administration.

Nebulised aerosols of (0.012-12 μ M, equivalent to 5-5000 mcg/mL) caused dose-related inhibition of histamine-induced bronchoconstriction, with bronchodilator activity being similar to salbutamol. There were no clear differences between the durations of action of salmeterol and salbutamol by the oral route.

However, following inhaled administration, the duration of action of salmeterol was substantially longer, exceeding 6 hours, at concentrations of 50 mcg/mL and above, compared with 1.5-3 hours for salbutamol (478 mcg/mL).

Nebulised aerosols of salmeterol (0.001-1mg/mL) caused a dose-related inhibition of plasma protein extravasation (PPE) induced by histamine. Both salmeterol and salbutamol had an ED₅₀ of approximately 0.01 mg/mL, but the duration of action of salmeterol was substantially longer, being 6-8 hours compared with less than 2 hours for salbutamol. Orally administered salmeterol (0.01-1 mg/kg) also reduced histamine-induced PPE in a dose-related manner with an ED₅₀ of 0.02 mg/kg.

Prior treatment of animals with propranolol abolished the inhibition of PPE, indicating that these effects were mediated by beta-adrenoceptors, probably at the level of the vascular endothelium.

The effects of salmeterol (as either the base or the xinafoate salt) on behaviour, muscle tone, reflexes and autonomic function were investigated following intravenous dosing in the dog and acute oral administration in conscious rat and dog. These effects were consistent with the known pharmacology of beta₂-adrenoceptor agonists. Salmeterol base (0.1-1.0 mg/kg i.v.) in the dog caused marked tachycardia. At 0.3 mg/kg, there was slight vasodilation and vomiting. Animals receiving 1 mg/kg showed signs of subdued behaviour. Salmeterol (25-100 mg/kg p.o.) reduced general activity in the rat. In the dog, oral salmeterol (1, 3 and 10 mg/kg) induced persistent tachycardia and cutaneous vasodilation, with some lacrimation occurring at 3 and 10 mg/kg. Salmeterol caused no overt effects on gastrointestinal function following oral administration, producing no emetic or defaecatory effects in dogs over the dose range 1-10 mg/kg and no effects on defaecatory activity in rats at doses of 25-100 mg/kg. However, emesis was observed in the dog following intravenous doses of 0.3 and 1 mg/kg.

In conscious cynomolgus monkey, oral salmeterol (1 and 10 mg/kg) had only minor cardiovascular effects, causing small increases in heart rate which were not clearly dose-related. There was no evidence of dysrhythmia or of significant changes in the electrocardiogram at either dose level.

Salmeterol did not affect pentobarbitone-induced sleeping time in mice suggesting it is unlikely to interfere with hepatic drug metabolism.

Pharmacokinetics

Salmeterol is extensively absorbed across the GI tract in both rat and dog following oral administration. However, the clearance of salmeterol is about three times higher in rat than in dog indicating that hepatic extraction is also higher in the rat.

In radiolabelled studies in rat, dog, mouse and pregnant rabbit, peak plasma levels were attained within 1 hour of dosing and were much lower than the mean peak concentrations of total drug-related material indicating extensive metabolism. However, salmeterol represented a much higher proportion of the circulating radioactivity in the dog than in the rat. This is consistent with the oral bioavailability of salmeterol being lower in rat (<15%) than in dog (approx. 60%).

The maximum concentrations of salmeterol detected in plasma from animals in repeat-dose, combined oral/inhalation toxicity studies exceeds by several hundred-fold the maximum concentrations (200 pg/mL) determined after the standard therapeutic dose in humans. The species used in toxicological studies were subjected to a systemic exposure of salmeterol of up to 1800-fold greater than that resulting from the therapeutic dosage in humans.

The distribution of salmeterol xinafoate in body tissues is consistent with that expected of a highly lipophilic base. At least 93% of the salmeterol distributed between erythrocytes and plasma is reversibly bound to the plasma proteins, beta₁-acid glycoprotein and albumin, in the mouse, rat, rabbit, dog, and in man. The high plasma clearance of salmeterol indicates that changes in the degree of protein binding are unlikely to influence the rate of elimination.

In all species, salmeterol and its metabolites are excreted predominantly in the bile. Enterohepatic circulation of salmeterol has been demonstrated in the rat; however, no enterohepatic circulation of drug-related material occurs in the dog.

Glucuronidation of salmeterol is the major metabolic pathway in the rat, rabbit and mouse, but not in the dog. The major metabolite of salmeterol in humans, hydroxylated on the butyl chain, is only a minor metabolite in the rat. However, exposure to this metabolite during rat toxicology studies was 100-fold greater than in humans.

The pharmacokinetics of hydroxynaphthoic acid (HNA), a xenobiotic, has been extensively investigated in both animal and human studies. Tissue distribution studies in rat have shown that HNA is rapidly absorbed in the blood and widely distributed following administration.

With the exception of the rabbit, HNA accumulates on repeat dosing in animals. Accumulation was also observed in humans, but the steady-state concentrations (100 NG/mL) in humans were 1000-fold lower than those seen in species used in toxicology testing. It is likely that the major metabolite of HNA in humans is the same as that in rats. HNA and its metabolites are excreted predominantly via urine.

Human

Pharmacology

Salmeterol caused a concentration-related inhibition of mediators such as histamine, leukotrienes C4/D4 and PGD2 in sensitized human lung tissue and was significantly more potent than salbutamol. Inhibition of mediator release induced by salbutamol was of short duration of action (<2 hours) whereas significant activity was observed with salmeterol after 20 hours.

The pharmacodynamics of salmeterol has been investigated in healthy subjects and in patients with reversible airways obstruction. In healthy subjects, there were pharmacologically predictable extra-pulmonary effects on pulse rate, tremor and metabolic parameters. These effects, however, became clinically significant only at doses of 200 mcg and greater.

The onset of bronchodilator action of salmeterol (10-20 minutes) is slower than that seen with salbutamol (5-15 minutes). There was no evidence of tachyphylaxis in the bronchodilator effects of salmeterol.

Pharmacokinetics

Following inhalation of a single dose of 50 mcg salmeterol, plasma concentrations of approximately 200 pg/mL were detected. Since salmeterol acts locally in the lung, plasma levels are not predictive of therapeutic effect.

TOXICOLOGY

Animals

Acute Toxicity

Extremely high levels of salmeterol xinafoate, relative to the therapeutic dose, were tolerated irrespective of the route of administration or species employed. At the maximum achievable or maximum non-lethal dosages, clinical signs were generally non-specific or were expected consequences of the pharmacological activity of salmeterol (e.g. vasodilation and tachycardia in dogs). There were no findings indicative of specific target organ toxicity and salmeterol was well tolerated in the respiratory tract.

Species	Approx. LD ₅₀ (mg/kg)	Maximum Non-Lethal Dose [MNLD] (mg/kg)	MNLD as a Multiple of Therapeutic Dose
Mouse	>150; \geq 500	\geq 150	>75,000
Rat	>600	\geq 1000	>500,000
Rat (juv.)	>300	\geq 300	>150,000
Rat	>2.9	\geq 2.9	>1400
Dog	>0.7	\geq 0.7	>350

Long-term Toxicity

Subacute toxicity studies of up to 13 weeks in rats, at doses up to 0.7 mg/kg/day by inhalation and/or 2.0 mg/kg/day orally were conducted. No significant treatment-induced changes were seen. Findings included reductions in the number of platelets, decreased plasma glucose, increased urea and creatinine, increased urine volume associated with decreased specific gravity, increased heart and lung weights, and decreased liver and kidney weights. These regressed following a 4-week recovery period and were considered to be a consequence of the pharmacological activity of salmeterol.

Slight increases in serum transaminases and bilirubin concentration were considered to reflect metabolic adaptation by the liver to high circulating concentrations of salmeterol and regressed fully during the recovery period.

In dog studies up to 13 weeks, reductions in mean cell volume and mean cell hemoglobin, and increases in anisocytosis and hypochromia were found to occur at doses greater than 0.05 mg/kg/day orally and 0.07 mg/kg/day by inhalation. In two female dogs treated at these dosages, histological changes were observed in the papillary muscle of the heart in common with known effects of other adrenoceptor agonists.

Chronic toxicity studies were carried out for up to 18 months in rats and up to 12 months in dogs. Repeated high exposures to salmeterol xinafoate were tolerated well by rats and dogs, both locally within the respiratory tract, and systemically. Minor laryngeal changes occurred only after prolonged exposure to high inhaled doses (≥ 0.18 mg/kg/day) and were confined to the rat, a species known to be especially sensitive. Other findings were a consequence of excessive pharmacological activity or expected metabolic adjustments in response to high circulating plasma levels of salmeterol. No effects attributable to hydroxynaphthoic acid were observed in any study.

A slight, work-induced increase in heart weight was found to occur in rats treated with inhaled salmeterol xinafoate. Cardiovascular effects in dogs dosed orally at 0.1-10.0 mg/kg/day included slight to marked transient reflex tachycardia as a consequence of peripheral vasodilation and occasional areas of focal papillary muscle necrosis as a consequence of tachycardia.

Skeletal muscle hypertrophy was evident in rats and dogs treated orally or by inhalation. In rats, the effect diminished with extended treatment and reversed over 18 months. Small increases in plasma urea and creatinine in some rat and dog studies were concluded to be associated with skeletal muscle hypertrophy; no renal pathology was detected.

Minor fluctuations in serum enzyme activity levels occurred in some rat studies without significant histopathological changes and were attributed to slight metabolic adjustments by the liver to high circulating salmeterol levels. Mild, transient reductions in some erythrocyte measurements occurred in some dogs treated orally at doses of 1 mg/kg/day or more of salmeterol. The effects regressed despite continued treatment.

Carcinogenicity

In an 18-month oral carcinogenicity study in CD-mice, salmeterol xinafoate caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, and leiomyomas of the uterus and a dose-related increase in the incidence of cysts in the ovaries. A higher incidence of leiomyosarcomas was not statistically significant; tumor findings were observed at oral doses of 1.4 and 10 mg/kg, which gave 9 and 63 times, respectively, the human exposure based on rodent:human AUC comparisons.

Salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts in Sprague Dawley rats in a 24-month inhalation/oral carcinogenicity study. Tumors were observed in rats receiving doses of 0.68 and 2.58 mg/kg per day (about 55 and 215 times the recommended clinical dose [mg/m²]). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

No significant effects occurred in mice at 0.2 mg/kg (1.3 times the recommended clinical dose based on comparisons of the AUCs) and in rats at 0.21 mg/kg (15 times the recommended clinical dose on a mg/m² basis).

Mutagenicity

Salmeterol xinafoate produced no detectable or reproducible increases in microbial and mammalian gene mutation *in vitro*. No blastogenic activity occurred *in vitro* in human lymphocytes or *in vivo* in a rat micronucleus test. No effects on fertility were identified in male and female rats treated orally with salmeterol xinafoate at doses up to 2 mg/kg orally (about 160 times the recommended clinical dose on a mg/m² basis).

Reproduction and Teratology

No significant effects of maternal exposure to oral salmeterol xinafoate occurred in the rat at doses up to the equivalent of about 160 times the recommended clinical dose on a mg/m² basis. Dutch rabbit fetuses exposed to salmeterol xinafoate *in utero* exhibited effects characteristically resulting from beta-adrenoceptor stimulation; these included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at 0.6 mg/kg given orally (12 times the recommended clinical dose based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at 10mg/kg given orally (approximately 1,600 times the recommended clinical dose on a mg/m² basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to use in humans.

Irritancy and Local Tolerance

In an eye irritation study, 4 puffs (100 mg/puff) of salmeterol aerosol suspension were administered to the right eyes of female New Zealand White rabbits. The left eyes served as controls. No signs of iritis or irritant reaction of the cornea were seen over the 24-hour period following the administration of salmeterol xinafoate aerosol.

REFERENCES

1. Britton M. Salmeterol and salbutamol: large multicentre studies. *Eur Resp Rev* 1991; 1(4):288-292.
2. Britton MG, Earnshaw JS, Palmer JB. A twelve month comparison of salmeterol with salbutamol in asthmatic patients. European Study Group. *Eur Respir J* 1992; 5(9):1062-1067.
3. Brogden RN, Faulds D. Salmeterol xinafoate. A review of its pharmacological properties and therapeutic potential in reversible obstructive airways disease. *Drugs* 1991; 42(5):895-912.
4. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993; 306(6884):1034-1037.
5. Cheung D, Timmers MC, Zwinderman AH, Bel EH, Dijkman JH, Sterk PJ. Long-term effects of a long-acting beta 2-adrenoceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. *N Engl J Med* 1992; 327(17):1198-1203.
6. Fitzpatrick MF, Mackay T, Driver H, Douglas NJ. Salmeterol in nocturnal asthma: a double blind, placebo controlled trial of a long acting inhaled beta 2 agonist. *BMJ* 1990; 301(6765):1365-1368.
7. Holgate ST. Allergen challenge studies. *Eur Resp Review* 1991; (1)(4):268-271.
8. Lofdahl CG, Chung KF. Long-acting beta 2-adrenoceptor agonists: a new perspective in the treatment of asthma. *Eur Respir J* 1991; 4(2):218-226.
9. Lotvall J, Lunde H, Ullman A, Tornqvist H, Svedmyr N. Twelve months, treatment with inhaled salmeterol in asthmatic patients. Effects on beta 2-receptor function and inflammatory cells. *Allergy* 1992; 47(5):477-483.
10. Lundback B, Rawlinson DW, Palmer JB. Twelve month comparison of salmeterol and salbutamol as dry powder formulations in asthmatic patients. European Study Group. *Thorax* 1993; 48(2):148-153.
11. Malo JL, Ghezzo H, Trudeau C, L'Archeveque J, Cartier A. Salmeterol, a new inhaled beta 2-adrenergic agonist, has a longer blocking effect than albuterol on hyperventilation-induced bronchoconstriction. *J Allergy Clin Immunol* 1992; 89(2):567-574.
12. Pauwels R, Derom E. Salmeterol's early clinical development and challenge studies. *Eur Resp Rev* 1991;(4):261-264.

13. Pearlman DS, Chervinsky P, LaForce C, Seltzer JM, Southern DL, Kemp JP et al. A comparison of salmeterol with albuterol in the treatment of mild-to-moderate asthma. *N Engl J Med* 1992; 327(20):1420-1425.
14. Sears MR, Taylor DR, Print CG, Lake DC, Li QQ, Flannery EM et al. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990; 336(8728):1391-1396.
15. Simons FE, Soni NR, Watson WT, Becker AB. Bronchodilator and bronchoprotective effects of salmeterol in young patients with asthma. *J Allergy Clin Immunol* 1992; 90(5):840-846.
16. Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992; 326(8):501-506.
17. Twentyman OP, Finnerty JP, Harris A, Palmer J, Holgate ST. Protection against allergen-induced asthma by salmeterol. *Lancet* 1990; 336(8727):1338-1342.
18. Ullman A, Svedmyr N. Salmeterol, a new long acting inhaled beta 2 adrenoceptor agonist: comparison with salbutamol in adult asthmatic patients. *Thorax* 1988; 43(9):674-678.
19. Ullman A, Hedner J, Svedmyr N. Inhaled salmeterol and salbutamol in asthmatic patients. An evaluation of asthma symptoms and the possible development of tachyphylaxis. *Am Rev Respir Dis* 1990; 142(3):571-575.

PART III: CONSUMER INFORMATION

PrSEREVENT® DISKHALER® Disk
salmeterol xinafoate dry powder for inhalation

This leaflet is part III of a three-part "Product Monograph" for SEREVENT® DISKHALER® Disk and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SEREVENT® DISKHALER® Disk. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:****Asthma (patients 4 years old and older):**

Asthma is a chronic inflammatory disease of the lungs characterized by episodes of difficulty in breathing. People with asthma have extra sensitive or "twitchy" airways. During an asthma attack, the airways react by narrowing making it more difficult for the air to flow in and out of the lungs.

Control of asthma requires avoiding irritants that cause asthma attacks and taking the appropriate medications. For example, patients should avoid exposure to house dust mites, mold, pets, tobacco smoke and pollens.

SEREVENT® DISKHALER® Disk helps to prevent breathlessness and wheezing from happening due to asthma. SEREVENT® DISKHALER® Disk is used **only as an add-on therapy to an inhaled corticosteroid** when an inhaled corticosteroid by itself is not adequate to control your asthma symptoms.

Note to Parents: It is extremely important to make sure that children 4 to 18 years take both SEREVENT® DISKHALER® Disk **and** an inhaled corticosteroid together. If this cannot be **guaranteed**, speak to your doctor. A single combination product, containing both a bronchodilator and an inhaled corticosteroid, may be required.

Chronic Obstructive Pulmonary Disease (COPD):

COPD is a type of lung disease in which there is a permanent narrowing of the airways, leading to breathing difficulties. In many patients, this narrowing of the airways is a result of many years of cigarette smoking. If you suffer from COPD, you must stop smoking to prevent further lung damage. Please contact your physician or other health care provider for help in smoking cessation.

SEREVENT® DISKHALER® Disk is to be used for the long-term control of symptoms due to COPD and to prevent wheezing in adults with COPD.

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.

What it does:

SEREVENT® DISKHALER® Disk is a bronchodilator. It works by relieving spasm or narrowing in the small air passages in the lungs. This helps to open up the airways and makes it easier for air to get in and out of the lungs. The effects of SEREVENT® DISKHALER® Disk last for at least 12 hours. When it is taken regularly for the treatment of COPD or in combination with an inhaled corticosteroid for the treatment of asthma, it helps the small air passages to stay open.

When it should not be used:

SEREVENT® DISKHALER® Disk does not act quickly enough to provide relief from a sudden attack of breathlessness or wheezing due to asthma or COPD. A fast acting 'reliever' medicine, such as salbutamol (e.g., VENTOLIN®) should be used for any sudden attacks of breathlessness or wheezing (e.g., asthma attacks).

Remember:

If you are being treated for asthma, you should always be given an inhaled corticosteroid for use together with SEREVENT® DISKHALER® Disk. The inhaled corticosteroid decreases the inflammation in your lungs while SEREVENT® DISKHALER® Disk opens the airways.

Do not use SEREVENT® DISKHALER® Disk:

- Without an inhaled corticosteroid if you are being treated for asthma
- If you are allergic or have had an allergic reaction (swelling, anaphylactic reaction) to salmeterol or any of the ingredients
- If you have a medical history of cardiac tachyarrhythmias (problems of your heart beating fast and/or irregularly)
- If you are allergic to lactose (milk sugar) or milk protein

What the medicinal ingredient is:

salmeterol xinafoate.

What the nonmedicinal ingredients are:

lactose (milk sugar) and milk protein.

What dosage forms it comes in:

SEREVENT® DISKHALER® Disks are circular foil disks each having four blisters around the edge. Each blister contains 50 mcg of salmeterol.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS FOR ASTHMA PATIENTS TAKING SEREVENT® DISKHALER® Disk

SEREVENT® DISKHALER® Disk increases the risk of asthma-related death. SEREVENT® DISKHALER® Disk may increase the risk of asthma-related hospitalizations in patients 4 to 18 years old. Therefore, SEREVENT® DISKHALER® Disk:

- must **only** be used as an **add-on** therapy when your inhaled corticosteroid does not adequately control your asthma symptoms.
- must be used together with an inhaled corticosteroid.
- may be discontinued by your doctor when your asthma is assessed as adequately under control.

For any concerns regarding the use of SEREVENT® DISKHALER® Disk, consult with your doctor.

SEREVENT® DISKHALER® Disk is not for the treatment of acute asthma attacks or sudden increase of breathlessness and wheezing in COPD. If you get a sudden attack of wheezing and breathlessness between your doses of SEREVENT® DISKHALER® Disk and inhaled corticosteroid, you should use your fast acting 'reliever' medicine, such as salbutamol (e.g. VENTOLIN®) which your doctor has prescribed to you. Use the medication as directed by your doctor.

Before and while you use SEREVENT® DISKHALER® Disk talk to your doctor or pharmacist if the following situations apply to you so that they can determine whether you should start or continue taking this medication:

- Had to stop taking another medication for your breathing problems because you were allergic to it or it caused problems.
- Have been told that you are allergic to lactose (milk sugar) or milk protein.
- Are receiving treatment for a thyroid condition.
- Have diabetes.
- Have raised blood pressure.
- Have a heart problem.
- Are pregnant, planning to become pregnant or breastfeeding.
- Are taking a medicine called ketoconazole, used to treat fungal infection.
- If you have a past history of seizures.

SEREVENT® DISKHALER® Disk can increase your blood sugar levels. Diabetic patients may need their blood sugar monitored more often. If you notice changes, discuss this with your doctor. Your diabetes medication may need a dosage adjustment.

Asthma:

You should have your asthma assessed at regular intervals as agreed upon with your doctor. Once control of your asthma is achieved and maintained, your doctor may discontinue your SEREVENT® DISKHALER® Disk. Do not stop taking your SEREVENT® DISKHALER® Disk unless your doctor has advised you to do so.

If you notice the following warning signs, you should contact your doctor as soon as possible or go to the nearest hospital:

- A sudden worsening of your shortness of breath and wheezing shortly after using your fast acting 'reliever' medicine or after using SEREVENT® DISKHALER® Disk and inhaled corticosteroid.
- You do not feel relief within 10 minutes after using your fast acting 'reliever' medicine or the relief does not last for at least 3 hours.
- Measurement from your peak flow meter indicates a value less than 60 percent of predicted or personal best.
- You are breathless at rest.
- Your pulse is more than 120 beats per minute.

The following warning signs indicate that your asthma condition may be worsening and that your treatment needs to be reassessed by your doctor.

- A change in your symptoms such as more coughing, attacks of wheezing, chest tightness, or an unusual increase in the severity of the breathlessness.
- You wake up at night with chest tightness, wheezing or shortness of breath.
- You use increasing amounts of your fast acting 'reliever' medicine.
- Measurement from your peak flow meter indicates a value between 60 and 80 percent of predicted or personal best.

COPD:

If you have COPD, it is very important that even mild chest infections be treated right away. If you think you have an infection, see your doctor immediately.

People with COPD are more likely to get the flu (influenza). You should ask your doctor about flu vaccination.

The following warning signs indicate that your COPD condition may be worsening. You should contact your doctor as soon as possible if you notice:

- An unusual increase or decrease in the amount of phlegm.

IMPORTANT: PLEASE READ

- An unusual increase in the consistency and stickiness of the phlegm.
- The presence of blood in phlegm.
- A change in the colour of the phlegm to either brown, yellow or green.
- An unusual increase in the severity of the breathlessness.
- The necessity to increase the number of pillows in order to sleep in comfort.
- Symptoms of a cold (e.g., sore throat).
- Unexplained tiredness or fever.
- Chest tightness.
- Unexplained swelling.

instructions.

Adolescents/Children with Asthma (4 to 18 years of age):

SEREVENT® DISKHALER® Disk is suitable for children 4 years of age and older. The severity of asthma changes with age. Your child should therefore be periodically re-examined by a doctor. It is important to make sure that he/she understands and properly follows the asthma therapies that have been prescribed. These will include in addition to SEREVENT® DISKHALER® Disk, a drug which reduces the inflammation in the lung due to asthma (also known as an inhaled corticosteroid or controller medication) and a rapid onset, short duration bronchodilator (also known as a fast acting ‘reliever’ medicine).

It is extremely important to make sure that children 4 to 18 years take both SEREVENT® DISKHALER® Disk **and** an inhaled corticosteroid together. If this cannot be **guaranteed**, speak to your doctor. A single combination product, containing both a bronchodilator and an inhaled corticosteroid, may be required.

Usual COPD Dose:

The usual dose is 1 inhalation twice daily (1 inhalation in the morning and 1 inhalation in the evening).

COPD:

If you are troubled with mucus, try to clear your chest as completely as possible by coughing before you use SEREVENT® DISKHALER® Disk. This will allow SEREVENT® DISKHALER® Disk to pass more deeply into your lungs.

Even if you feel much better after starting to use SEREVENT® DISKHALER® Disk, you must continue to use your other COPD medication(s) according to your doctor’s instructions.

Overdose:

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

If you accidentally take a **larger dose than recommended**, you may notice that your heart is beating faster than usual and that you feel shaky. Other symptoms you may experience include headache, muscle weakness and aching joints. Tell your doctor as soon as possible or contact your hospital emergency department.

Excessive use of SEREVENT® DISKHALER® Disk can be extremely dangerous. If you have used a larger than allowed recommended dose of SEREVENT® DISKHALER® Disk for a long period of time (months or years), you should talk to your doctor or pharmacist for advice. A gradual reduction of

INTERACTIONS WITH THIS MEDICATION

Make sure that your doctor knows what other medicines you are taking such as those for allergies, nervousness, depression, migraine, other airway-opening medications (e.g. other asthma medications), high blood pressure, heart problems, water pills (diuretics) and azole antifungals (e.g. ketoconazole), including those you can buy without a prescription as well as herbal and alternative medicines.

PROPER USE OF THIS MEDICATION

It is very important that you use SEREVENT® DISKHALER® Disk twice a day, even if you have no symptoms. Use it once in the morning and again in the evening. When used for the treatment of COPD or together with an inhaled corticosteroid for the treatment of asthma, SEREVENT® DISKHALER® Disk will help protect you against breakthrough symptoms throughout the day and during the night. **You should not use it more than twice a day.** SEREVENT® DISKHALER® Disk does not replace your fast acting ‘reliever’ medicine, such as salbutamol (e.g., VENTOLIN®) or inhaled corticosteroid therapy, such as fluticasone propionate (e.g., FLOVENT®). The overuse of SEREVENT® DISKHALER® Disk can cause serious side effects.

After you have started taking SEREVENT® DISKHALER® Disk it is likely that you will not need to use the fast acting ‘reliever’ medicine as often. If you have more than one medicine be careful not to confuse them.

If your doctor decides to stop treatment, do not keep any left-over medicine unless your doctor tells you to.

Usual Asthma Dose:

The usual dose is 1 inhalation twice daily (1 inhalation in the morning and 1 inhalation in the evening).

Even if you feel much better after starting to use SEREVENT® DISKHALER® Disk, you must continue to use an inhaled corticosteroid for your asthma according to your doctor's

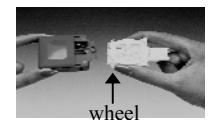
IMPORTANT: PLEASE READ

your dose may be needed. Do not stop taking the medication suddenly.

Missed Dose:

It is very important that you use SEREVENT®

DISKHALER® Disk regularly. If you forget to inhale a dose do not worry, inhale another as soon as you remember **but** if it is near to the time for the next dose, wait until this is due. Do not take a double dose. Then go on as before.



How to use your SEREVENT® DISKHALER® Disk properly:

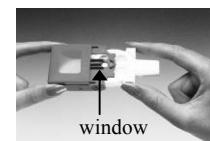
Remember the medicine in SEREVENT® DISKHALER® Disk blisters should only be inhaled using a special kind of inhaler called a DISKHALER® inhalation device. Make sure that you have one and can use it properly. Follow the instructions shown. If you have any difficulties or do not understand this information, ask your doctor or pharmacist.



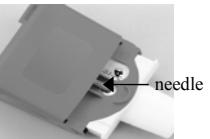
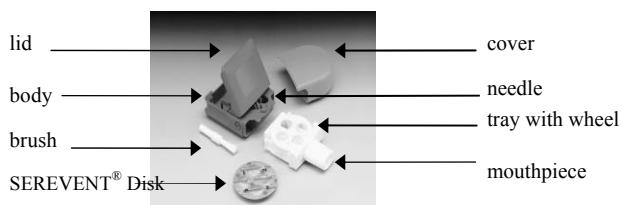
The SEREVENT® DISKHALER® device is used together with a SEREVENT® DISKHALER® Disk, for inhaling the medication.

The DISKHALER® device consists of:

- an outer coloured body with a hinged lid and piercing needle.
- a cleaning brush contained at the rear of the body.
- a coloured mouthpiece cover.
- a white sliding tray with mouthpiece.
- a white wheel to support the disk.



The SEREVENT® Disk consists of 4 blisters. Each blister contains a measured dose of dry powder medication.

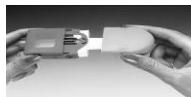


Warning: do not puncture any disk blister until loaded into the DISKHALER® device.

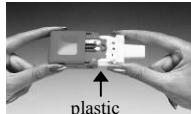


To load the SEREVENT® Disk into the DISKHALER® device.

1. Remove the mouthpiece cover and check inside and outside to ensure that the mouthpiece is clean.



2. Hold the corners of the white tray and pull out gently until you can see all the plastic ridges on the sides of the tray.



3. Put your finger and thumb on the ridges, squeeze inwards and gently pull the tray out of the DISKHALER® body.



4. Place the disk on the wheel with the numbers facing up. Then slide the tray back fully into the DISKHALER® body.

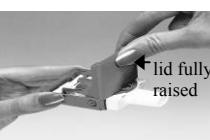
To rotate the Disk to the first dose

5. Hold the corners of the tray and rotate the disk by gently pulling the tray out and pushing it in until the number '4' appears in the indicator hole. The DISKHALER® is now ready for use.

The indicator hole always shows the number of doses remaining in the DISKHALER®.

To pierce the blister in the SEREVENT® DISKHALER®

6. Raise the lid as far as it will go into the fully upright position. Both surfaces of the blister must be pierced. Some resistance will be felt as the upper, and especially the lower surfaces of the blister, are pierced. Then close the lid.



Warning: Do not try to lift the lid unless the tray is positioned fully within the body of the DISKHALER® device or is completely removed, e.g. when cleaning the DISKHALER® device.

To inhale from the DISKHALER®

7. Breathe out as far as is comfortable. Keeping the DISKHALER® device level, raise it to your mouth and gently place the mouthpiece between your teeth and lips but do not bite the mouthpiece. Do not cover the air inlets on either side of the mouthpiece. Breathe in through your mouth steadily and as deeply as you can. Hold your breath and remove the DISKHALER® device from your mouth. Continue to hold your breath for as long as is comfortable.

To prepare for the next inhalation

8. Rotate the SEREVENT® Disk to the next blister by gently pulling the tray out once and in again. Do not pierce the blister until immediately before inhalation.

9. Always replace the mouthpiece cover after use.

IMPORTANT: PLEASE READ

To replace the SEREVENT® Disk

10. Each disk consists of 4 blisters containing medication. When the number '4' reappears in the indicator hole, the disk is empty and should be replaced with a new disk by repeating steps 2 to 5.

Warning: do not throw the wheel away with the empty disk.

Care of the DISKHALER®

A brush is provided at the rear of the DISKHALER® body to clean any remaining powder from the DISKHALER® device. This should be done with the tray and wheel removed from the DISKHALER® body before inserting a new disk.

You may need to replace your DISKHALER® device after about 6 months of use.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- pain in joints
- muscle cramps
- headache
- feeling a little shaky (tremor)
- disturbed sleep
- upper respiratory tract infection
- cough
- fever
- throat irritation
- feeling tired
- diarrhea
- nausea
- vomiting

SEREVENT® DISKHALER® Disk can cause abnormal blood test results including increased blood sugar. Your doctor will decide when to perform blood tests and will interpret the results.

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 seek immediate emergency medical attention
	Only if severe	In all cases	
Uncommon	Allergic reactions: lumpy skin rash or hives anywhere in the body.		✓
	Fast or irregular heartbeat that does not go away on its own.	✓	
Rare	Low blood potassium: muscle weakness, and muscle spasms.	✓	
	Increased amount of sugar in blood: excessive thirst, frequent urination, dry skin, blurred vision and fatigue.	✓	
Very rare	Allergic reactions: sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat.		✓
	Bronchospasm: Sudden worsening of shortness of breath and wheezing shortly after using SEREVENT® DISKHALER® Disk.		✓
	Mouth, throat becomes unusually irritated causing high pitched wheezing and choking.	✓	
	High Blood Pressure: headache and dizziness.		✓

IMPORTANT: PLEASE READ

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 seek immediate emergency medical attention
	Only if severe	In all cases	
Unknown	Worsening of lung symptoms such as increased shortness of breath, wheezing, cough and chest tightness accompanied by fever and more phlegm.		✓
	Increased Excitement: Feeling anxious, nervous, or agitated.	✓	

This is not a complete list of side effects. For any unexpected effects while taking SEREVENT® DISKHALER® Disk, contact your doctor or pharmacist.

HOW TO STORE IT

Keep your medicine in a safe place where children cannot reach it. Your medicine may harm them.

Keep SEREVENT® DISKHALER® Disks away from direct heat or sunlight and protect them from high temperatures (above 25°C or 77°F). Keep them in a dry place.

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

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

MORE INFORMATION

You may need to read this package insert 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., at: 1-800-387-7374.

7333 Mississauga Rd.
Mississauga, Ontario
Canada L5N 6L4

This leaflet was prepared by GlaxoSmithKline Inc.

Last revised: October 16, 2013

© 2013 GlaxoSmithKline Inc. All Rights Reserved

®SEREVENT, VENTOLIN, FLOVENT and DISKHALER are registered trademarks, used under license by GlaxoSmithKline Inc.

PART III: CONSUMER INFORMATION

Pr SEREVENT® DISKUS®
salmeterol xinafoate dry powder for inhalation

This leaflet is part III of a three-part "Product Monograph" for SEREVENT® DISKUS® and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SEREVENT® DISKUS®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:****Asthma (patients 4 years old and older):**

Asthma is a chronic inflammatory disease of the lungs characterized by episodes of difficulty in breathing. People with asthma have extra sensitive or "twitchy" airways. During an asthma attack, the airways react by narrowing making it more difficult for the air to flow in and out of the lungs.

Control of asthma requires avoiding irritants that cause asthma attacks and taking the appropriate medications. For example, patients should avoid exposure to house dust mites, mold, pets, tobacco smoke and pollens.

SEREVENT® DISKUS® helps to prevent breathlessness and wheezing from happening due to asthma. SEREVENT® DISKUS® is used **only as an add-on therapy to an inhaled corticosteroid** when an inhaled corticosteroid by itself is not adequate to control your asthma symptoms.

Note to Parents: It is extremely important to make sure that children 4 to 18 years take both SEREVENT® DISKUS® and an inhaled corticosteroid together. If this cannot be **guaranteed**, speak to your doctor. A single combination product, containing both a bronchodilator and an inhaled corticosteroid, may be required.

Chronic Obstructive Pulmonary Disease (COPD):

COPD is a type of lung disease in which there is a permanent narrowing of the airways, leading to breathing difficulties. In many patients, this narrowing of the airways is a result of many years of cigarette smoking. If you suffer from COPD, you must stop smoking to prevent further lung damage. Please contact your physician or other health care provider for help in smoking cessation.

SEREVENT® DISKUS® is to be used for the long-term control of symptoms due to COPD and to prevent wheezing in adults with COPD.

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.

What it does:

SEREVENT® DISKUS® is a bronchodilator. It works by relieving spasm or narrowing in the small air passages in the lungs. This helps to open up the airways and makes it easier for air to get in and out of the lungs. The effects of SEREVENT® DISKUS® last for at least 12 hours. When it is taken regularly for the treatment of COPD or in combination with an inhaled corticosteroid for the treatment of asthma, it helps the small air passages to stay open.

When it should not be used:

SEREVENT® DISKUS® does not act quickly enough to provide relief from a sudden attack of breathlessness or wheezing due to asthma or COPD. A fast acting 'reliever' medicine, such as salbutamol (e.g., VENTOLIN®) should be used for any sudden attacks of breathlessness or wheezing (e.g., asthma attacks).

Remember:

If you are being treated for asthma, you should always be given an inhaled corticosteroid for use together with SEREVENT® DISKUS®. The inhaled corticosteroid decreases the inflammation in your lungs while SEREVENT® DISKUS® opens the airways.

Do not take SEREVENT® DISKUS®:

- Without an inhaled corticosteroid if you are being treated for asthma
- If you are allergic or have had an allergic reaction (swelling, anaphylactic reaction) to salmeterol or any of the ingredients
- If you have a medical history of cardiac tachyarrhythmias (problems of your heart beating fast and/or irregularly)
- If you are allergic to lactose (milk sugar) or milk protein

What the medicinal ingredient is:

salmeterol xinafoate.

What the nonmedicinal ingredients are:

lactose (milk sugar) and milk protein.

What dosage forms it comes in:

SEREVENT® DISKUS® is a dry powder administered through a plastic inhaler device containing a foil strip with 60 blisters. Each blister contains 50 mcg of salmeterol.

WARNINGS AND PRECAUTIONS**SERIOUS WARNINGS FOR ASTHMA PATIENTS TAKING SEREVENT® DISKUS®**

SEREVENT® DISKUS® increases the risk of asthma-related death. SEREVENT® DISKUS® may increase the risk of asthma-related hospitalizations in patients 4 to 18 years old. Therefore, SEREVENT® DISKUS®:

- must **only** be used as an **add-on** therapy when your inhaled corticosteroid does not adequately control your asthma symptoms.
- must be used together with an inhaled corticosteroid.
- may be discontinued by your doctor when your asthma is assessed as adequately under control.

For any concerns regarding the use of SEREVENT® DISKUS®, consult with your doctor.

SEREVENT® DISKUS® is not for the treatment of acute asthma attacks or sudden increase of breathlessness and wheezing in COPD. If you get a sudden attack of wheezing and breathlessness between your doses of SEREVENT® DISKUS® and inhaled corticosteroid, you should use your fast acting ‘reliever’ medicine, such as salbutamol (e.g. VENTOLIN®) which your doctor has prescribed to you. Use the medication as directed by your doctor.

Before and while you use SEREVENT® DISKUS® talk to your doctor or pharmacist if the following situations apply to you so that they can determine whether you should start or continue taking this medication:

- Had to stop taking another medication for your breathing problems because you were allergic to it or it caused problems.
- Have been told that you are allergic to lactose (milk sugar) or milk protein.
- Are receiving treatment for a thyroid condition.
- Have diabetes.
- Have raised blood pressure.
- Have a heart problem.
- Are pregnant, planning to become pregnant or breastfeeding.
- Are taking a medicine called ketoconazole, used to treat fungal infection.
- If you have a past history of seizures.

SEREVENT® DISKUS® can increase your blood sugar levels. Diabetic patients may need their blood sugar monitored more often. If you notice changes, discuss this with your doctor. Your diabetes medication may need a dosage adjustment.

Asthma:

You should have your asthma assessed at regular intervals as agreed upon with your doctor. Once control of your asthma is achieved and maintained, your doctor may discontinue your SEREVENT® DISKUS®. Do not stop taking your SEREVENT® DISKUS® unless your doctor has advised you to do so.

If you notice the following warning signs, you should contact your doctor as soon as possible or go to the nearest hospital:

- A sudden worsening of your shortness of breath and wheezing shortly after using your fast acting ‘reliever’ medicine or after using SEREVENT® DISKUS® and inhaled corticosteroid.
- You do not feel relief within 10 minutes after using your fast acting ‘reliever’ medicine or the relief does not last for at least 3 hours.
- Measurement from your peak flow meter indicates a value less than 60 percent of predicted or personal best.
- You are breathless at rest.
- Your pulse is more than 120 beats per minute.

The following warning signs indicate that your asthma condition may be worsening and that your treatment needs to be reassessed by your doctor.

- A change in your symptoms such as more coughing, attacks of wheezing, chest tightness, or an unusual increase in the severity of the breathlessness.
- You wake up at night with chest tightness, wheezing or shortness of breath.
- You use increasing amounts of your fast acting ‘reliever’ medicine.
- Measurement from your peak flow meter indicates a value between 60 and 80 percent of predicted or personal best.

COPD:

If you have COPD, it is very important that even mild chest infections be treated right away. If you think you have an infection, see your doctor immediately.

People with COPD are more likely to get the flu (influenza). You should ask your doctor about flu vaccination.

The following warning signs indicate that your COPD condition may be worsening. You should contact your doctor as soon as possible if you notice:

- An unusual increase or decrease in the amount of phlegm.
- An unusual increase in the consistency and stickiness of the phlegm.

IMPORTANT: PLEASE READ

- The presence of blood in phlegm.
- A change in the colour of the phlegm to either brown, yellow or green.
- An unusual increase in the severity of the breathlessness.
- The necessity to increase the number of pillows in order to sleep in comfort.
- Symptoms of a cold (e.g., sore throat).
- Unexplained tiredness or fever.
- Chest tightness.
- Unexplained swelling.

INTERACTIONS WITH THIS MEDICATION

Make sure that your doctor knows what other medicines you are taking such as those for allergies, nervousness, depression, migraine, other airway-opening medications (e.g. other asthma medications), high blood pressure, heart problems, water pills (diuretics) and azole antifungals (e.g. ketoconazole), including those you can buy without a prescription as well as herbal and alternative medicines.

PROPER USE OF THIS MEDICATION

It is very important that you use SEREVENT® DISKUS® twice a day, even if you have no symptoms. Use it once in the morning and again in the evening. When used for the treatment of COPD or together with an inhaled corticosteroid for the treatment of asthma, SEREVENT® DISKUS® will help protect you against breakthrough symptoms throughout the day and during the night. **You should not use it more than twice a day.** SEREVENT® DISKUS® does not replace your fast acting ‘reliever’ medicine, such as salbutamol (e.g. VENTOLIN®) or inhaled corticosteroid therapy such as fluticasone propionate (e.g., FLOVENT®). The overuse of SEREVENT® DISKUS® can cause serious side effects.

After you have started taking SEREVENT® DISKUS® it is likely that you will not need to use the fast acting ‘reliever’ medicine as often. If you have more than one medicine be careful not to confuse them.

If your doctor decides to stop treatment, do not keep any left-over medicine unless your doctor tells you to.

Usual Asthma Dose:

The usual dose is 1 inhalation twice daily (1 inhalation in the morning and 1 inhalation in the evening).

Even if you feel much better after starting to use SEREVENT® DISKUS®, you must continue to use an inhaled corticosteroid for your asthma according to your doctor's instructions.

Adolescents/Children with Asthma (4 to 18 years of age):
SEREVENT® DISKUS® is suitable for children 4 years of age and older. The severity of asthma changes with age. Your

child should therefore be periodically re-examined by a doctor. It is important to make sure that he/she understands and properly follows the asthma therapies that have been prescribed. These will include in addition to SEREVENT® DISKUS®, a drug which reduces the inflammation in the lung due to asthma (also known as an inhaled corticosteroid or ‘controller’ medication) and a rapid onset, short duration bronchodilator (also known as a fast acting ‘reliever’ medicine).

It is extremely important to make sure that children 4 to 18 years take both SEREVENT® DISKUS® **and** an inhaled corticosteroid together. If this cannot be **guaranteed**, speak to your doctor. A single combination product, containing both a bronchodilator and an inhaled corticosteroid, may be required.

Usual COPD Dose:

The usual dose is 1 inhalation twice daily (1 inhalation in the morning and 1 inhalation in the evening).

COPD:

If you are troubled with mucus, try to clear your chest as completely as possible by coughing before you use SEREVENT® DISKUS®. This will allow SEREVENT® DISKUS® to pass more deeply into your lungs.

Even if you feel much better after starting to use SEREVENT® DISKUS®, you must continue to use your other COPD medication(s) according to your doctor's instructions.

Overdose:

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

If you accidentally take a **larger dose than recommended**, you may notice that your heart is beating faster than usual and that you feel shaky. Other symptoms you may experience include headache, muscle weakness and aching joints. Tell your doctor as soon as possible or contact your hospital emergency department.

Excessive use of SEREVENT® DISKUS® can be extremely dangerous. If you have used a larger than allowed recommended dose of SEREVENT® DISKUS® for a long period of time (months or years), you should talk to your doctor or pharmacist for advice. A gradual reduction of your dose may be needed. Do not stop taking the medication suddenly.

Missed Dose:

It is **very important that you use SEREVENT® DISKUS® regularly.** If you forget to inhale a dose do not worry, inhale another as soon as you remember **but** if it is near to the time for the next dose, wait until this is due. Do not take a double

IMPORTANT: PLEASE READ

dose. Then go on as before.

About your SEREVENT® DISKUS®:

The blisters protect the powder for inhalation from the effects of the atmosphere.

When you take your SEREVENT® DISKUS® out of its box, it will be in the **closed position**.

A new DISKUS® contains 60 individually protected doses of your medicine, in powder form. The device has a dose counter which tells you the number of doses remaining. It counts down from 60 to 1. **To show when the last five doses have been reached the numbers appear red.**

Each dose is accurately measured and hygienically protected. It requires no maintenance, and no refilling.

How to use your SEREVENT® DISKUS® properly:

It is important that you take each dose as instructed by your doctor, nurse, or pharmacist.

The DISKUS® is easy to use. When you need a dose, just follow the six simple steps illustrated:

1. Open, 2. Slide, 3. Exhale, 4. Inhale, 5. Close, 6. Rinse.

Sliding the lever of your DISKUS® opens a small hole in the mouthpiece and unwraps a dose ready for you to inhale it. When you close the DISKUS®, the lever automatically moves back to its original position ready for your next dose when you need it. The outer case protects your DISKUS® when it is not in use.

1. Open

To open your DISKUS® hold the outer case in one hand and put the thumb of your other hand on the thumb grip. Push the thumb grip away from you, until you hear it click into place.



2. Slide

Hold your DISKUS® with the mouthpiece towards you. Slide the lever away until you hear another click. Your DISKUS® 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 doses which will be wasted.

3. Exhale

Hold the DISKUS® away from your mouth. Breath out as far as is comfortable. Remember – never exhale into your DISKUS®.



4. Inhale

Before you start to inhale the dose, read through this section carefully.

Once you have fully exhaled, place the mouthpiece to your mouth and close your lips around it. Breathe in steadily and deeply through your mouth until a full breath is taken.



Remove the DISKUS® from your mouth. Hold your breath for about 10 seconds or as long as is comfortable. **Breathe out slowly.**

5. Close

To close your DISKUS®, put your thumb in the thumb grip, and slide it back until you hear a click. The lever is now automatically reset for your next use. The counter on the DISKUS® indicates how many doses are remaining.



6. Rinse

Rinse out your mouth and gargle with water after each dose. Do not swallow the water.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- pain in joints
- muscle cramps
- headache
- feeling a little shaky (tremor)
- disturbed sleep
- upper respiratory tract infection
- cough
- fever
- throat irritation
- feeling tired
- diarrhea
- nausea
- vomiting

SEREVENT® DISKUS® can cause abnormal blood test results including increased blood sugar. Your doctor will decide when to perform blood tests and will interpret the results.

IMPORTANT: PLEASE READ

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 seek immediate emergency medical attention
	Only if severe	In all cases	
Uncommon	Allergic reactions: lumpy skin rash or hives anywhere in the body.		✓
	Fast or irregular heartbeat that does not go away on its own.	✓	
Rare	Low blood potassium: muscle weakness, and muscle spasms.	✓	
	Increased amount of sugar in blood: excessive thirst, frequent urination, dry skin, blurred vision and fatigue.	✓	
Very rare	Allergic reactions: sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat.		✓
	Bronchospasm: Sudden worsening of shortness of breath and wheezing shortly after using SEREVENT® DISKUS®.		✓
	Mouth, throat becomes unusually irritated causing high pitched wheezing and choking.	✓	
	High Blood Pressure: headache and dizziness.		✓

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 seek immediate emergency medical attention
	Only if severe	In all cases	
Unknown	Worsening of lung symptoms such as increased shortness of breath, wheezing, cough and chest tightness accompanied by fever and more phlegm.		✓
	Increased Excitement: Feeling anxious, nervous, or agitated.	✓	

This is not a complete list of side effects. For any unexpected effects while taking SEREVENT® DISKUS®, contact your doctor or pharmacist.

HOW TO STORE IT

Keep your medicine in a safe place where children cannot reach it. Your medicine may harm them.

Keep SEREVENT® DISKUS® below 30°C and in a dry place.

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

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

MORE INFORMATION

You may need to read this package insert 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., at:
1-800-387-7374.

7333 Mississauga Rd.
Mississauga, Ontario
Canada L5N 6L4

This leaflet was prepared by GlaxoSmithKline Inc.

Last revised: October 16, 2013

© 2013 GlaxoSmithKline Inc. All Rights Reserved

®SEREVENT, VENTOLIN, FLOVENT and DISKUS are registered trademarks, used under license by GlaxoSmithKline Inc.