PRODUCT MONOGRAPH

PrSEREVENT®

salmeterol xinafoate inhalation aerosol

25 mcg salmeterol (as the xinafoate salt)/metered dose

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
(β_2-adrenergic stimulant)

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Date of Preparation:
August 27, 2001

Date of Revision:
March 2, 2006

Submission Control No: 102588

Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral Inhalation	Dry powder for inhalation/50 mcg salmeterol/blister	Lactose and milk protein
	Inhalation Aerosol/ 25 mcg salmeterol/ metered dose	Dichlorodifluoromethane, soya lecithin, and trichlorofluoromethane

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

INDICATIONS AND CLINICAL USE

Asthma
SEREVENT® (salmeterol xinafoate) is indicated for:

- long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma in patients 4 years of age and older with reversible obstructive airway disease, including patients with nocturnal asthma, who are using optimal corticosteroid treatment and experiencing breakthrough symptoms requiring regular use of a rapid onset, short duration bronchodilator.

It should not be used in patients whose asthma can be managed by occasional use of rapid onset, short duration, inhaled β_2-agonists.

Corticosteroids should not be stopped because salmeterol is prescribed.

SEREVENT® is a slow onset, long-acting, β_2-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.

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.
- Patients with an allergy to lecithin, soya or related products such as soybeans.
- 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.

WARNINGS AND PRECAUTIONS

SERIOUS WARNING

SEREVENT® (salmeterol xinafoate) is not recommended for use in patients with asthma who are not also using optimal doses of inhaled corticosteroids (ICS).

Health care providers are advised of the results from an interim analysis of a large US clinical trial (Salmeterol Multi-center Asthma Research Trial - SMART Study) which showed increased risks of asthma-related death and other serious respiratory-related outcomes in patients who used SEREVENT® in addition to their usual asthma therapy as compared to those who used placebo in addition to their usual asthma therapy. These results applied particularly to patients who did not report using concomitant ICS at study entry. Further, the data suggest that the risks may be greater in African-American patients. Consequently, the SMART study was prematurely terminated after enrollment of half the intended number of patients.

For the total population studied (N= 26, 355 patients), the risk for the primary endpoint, combined respiratory-related death and life-threatening experience (which included asthma-related outcomes), was 40% higher in the SEREVENT® group compared to placebo (50 out of 13,176 vs 36 out of 13,179; <1% in both cases; relative risk of 1.40 with 95% Cl: 0.91, 2.14), and the risk for asthma-related death was increased more than four-fold (13 vs 3; <1% in both cases; relative risk of 4.37 with 95% CI: 1.25, 15.34) during the 28-week randomized treatment period. Increased risks were also observed regarding other respiratory-related outcomes, i.e. respiratory-related death and combined asthma-related death or life-threatening experience. Subgroup analysis suggested that the risk for these serious events may be greater in the African-American population. Furthermore, in patients who did not report taking inhaled corticosteroids (ICS) as part of their usual asthma therapy at study entry, there were more asthma related deaths: 9 out of 7,049 (SEREVENT®) vs 0 out of 7,041 (placebo) as compared to 4 out of 6,127 (SEREVENT®) vs 3 out of 6,138 (placebo) for those who did report taking inhaled corticosteroids. Overall, these results suggest a protective effect of concomitant ICS use as reported at study entry. Although the data were limited, ICS use at study entry did not completely extinguish the risk for African Americans.

(See the SMART study description under Pharmacology, Human, Asthma - Clinical Experience section.)

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 β_2-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 β_2-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 β_2-Agonist 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 β_2-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 β_2-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 β_2-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 β_2-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 β_2-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 β_2-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.

<u>Cardiovascular And Other Effects</u>
Although clinically not significant, a small increase in QTc intervals have been reported at therapeutic doses. It is not known if this becomes clinically significant when concomitant medications causing similar effects are prescribed and/or in the presence of heart diseases, hypokalemia, or hypoxia.

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. 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 were 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 β_2-adrenergic agonist may have a clinically significant cardiac effect.

No clinically significant effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol in recommended doses. Cardiovascular effects such as increased blood pressure and heart rate may occasionally be seen with all sympathomimetic drugs, especially at higher than therapeutic doses. Central nervous system effects (increased excitement) can occur after the use of SEREVENT®. Occurrence of cardiovascular or central nervous system 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; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other β-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.

Ear/Nose/Throat

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

Endocrine and Metabolism

Metabolic Effects

In common with other β-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, Postmarketing Experience) and this should be considered when prescribing to patients with a history of diabetes mellitus.

Doses of the related β_2-adrenoceptor agonist salbutamol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. Administration of β_2-adrenoceptor agonists may cause a decrease in serum potassium, possibly through intracellular shunting, which has the potential to increase the likelihood of arrythmias. 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 inhaled medications, paradoxical bronchospasm (which can be life threatening) has been reported following the use of SEREVENT® inhalation aerosol. If it occurs, treatment with SEREVENT® inhalation aerosol should be discontinued immediately and alternative therapy instituted.

Special Populations

Pregnant Women

In animal studies, some effects on the fetus, typical for a β-agonist occurred at exposure levels substantially higher than those that occur with therapeutic use. Extensive use of other β-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 β-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 has 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 β_2-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 β_2-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 β_2-agonists, should be carefully followed in adolescents/children receiving long-acting β_2-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 β_2-adrenoceptor agonists, i.e. palpitation; immediate hypersensitivity reactions, including urticaria, rash, bronchospasm, edema, angioedema, and anaphylactic shock or anaphylactic reaction; headache; tremor; nervousness 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.

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*.

Asthma

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 β_2-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 β_2- 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 100mcg 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® 25mcg and 50mcg 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 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 25mcg bid or 50mcg bid and salbutamol 200mcg 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
Neurologica	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 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 section), 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.

Postmarketing experience includes rare reports of upper airway symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking. Hypertension and arrhythmias (including atrial fibrillation, supraventricular tachycardia, and extrasystoles) have been reported. There have also been reports of oropharyneal irritation and very rare reports of hyperglycemia. Immediate hypersensitivity reactions have also been reported after administration of SEREVENT®, as demonstrated by rare cases of urticaria, angiodema, rash, and bronchospasm, and very rare cases of anaphylactic shock or anaphylactic reaction. Because these events are voluntarily reported from a population of unknown size, estimates of frequency cannot be made.

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, anti-arrhythmics, astemizole, terfenadine) and monoamine oxidase inhibitors or tricyclic anti-depressants, since cardiac and vascular effects may be potentiated.

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

Proper name	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. But increasing use of such preparations to control symptoms indicate 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.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

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 section).

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 without medical advice, even if they feel better on SEREVENT®.

SEREVENT® should not be used to treat acute symptoms. It is crucial to inform patients of this and prescribe a rapid onset, short duration β_2-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 corticosteroids dosage which should be administered under medical supervision.

As twice-daily regular treatment, SEREVENT® provides twenty-four 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 chronic obstructive pulmonary disease. 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® Inhalation Aerosol:
Patients 4 years of age and older: Two inhalations [2 x 25 micrograms of salmeterol (as the xinafoate)] twice daily.

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

For maintenance treatment of bronchospasm and relief of dyspnea associated with COPD (including chronic bronchitis and emphysema), the usual dosage is 50 micrograms of salmeterol (as the xinafoate) twice daily.

SEREVENT® Inhalation Aerosol:
Two inhalations [2 x 25 micrograms of salmeterol (as the xinafoate)] twice daily.

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

Do Not Exceed Recommended Dosage: As with other inhaled β_2-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 section).

The expected signs and symptoms of salmeterol overdosage are those typical of excessive β_2 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. Treatment should be symptomatic; cardiac and respiratory function should be monitored and support provided if necessary. The preferred antidote for overdosage with salmeterol is the judicious use of a cardioselective β-blocking agent. Cardioselective β-blocking drugs should be used with caution, bearing in mind the danger of inducing an asthmatic attack. Serum potassium level should be monitored.

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) β_2- 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 β_2-agonists.

In contrast to conventional rapid onset, short duration β_2-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 D_2.

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 25mcg 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.

STORAGE AND STABILITY

SEREVENT® inhalation aerosol should be stored between 15° and 30° C and protected from frost and direct sunlight.

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.

SPECIAL HANDLING INSTRUCTIONS

SEREVENT® Inhalation Aerosol
Important - contents under pressure. The canister should not be broken, punctured or burnt, even when apparently empty.

As with most inhaled medications in pressurized metered-dose inhalers, the therapeutic effect of this medication may decrease when the canister is cold.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SEREVENT® Inhalation Aerosol
SEREVENT® inhalation aerosol is a pressurised metered-dose inhaler presentation containing a non-aqueous suspension of microfine salmeterol (as the xinafoate salt), soya lecithin, dichlorodifluoromethane, and trichlorofluoromethane. SEREVENT® is available in 60 and 120 metered dose (25 mcg salmeterol/actuation) formats.

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

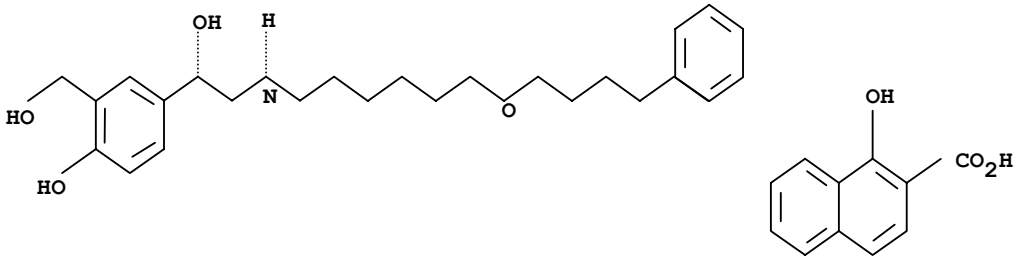
Drug Substance

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: $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$ 603.8

Structural formula:



Physicochemical properties:

Description: White to off-white crystalline powder with a melting point ≥ 123°C

Solubility:

In water ≥ 0.07 mg/mL (pH ≥ 8)
In saline ≥ 0.08 mg/mL (0.9%w/v)
In methanol ≥ 40 mg/mL
In ethanol ≥ 7 mg/mL
In chloroform ≥ 3 mg/mL
In isopropanol ≥ 2 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 (pH 9.2)
log D = 2.0 (pH 7.4)
log D = 0.6 (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 50mcg bid and 100mcg 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 200mcg (aerosol) and 400mcg (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 non fatal adverse events was related to severity of asthma on entry.

Salmeterol Multi-center Research Trial (SMART)

The SMART study was a large US post-marketing study that compared the safety of SEREVENT® inhalation aerosol (salmeterol 50mcg 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).

From post-hoc analyses, the data from the SMART trial suggest that the use of inhaled corticosteroids as reported at study entry, has 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 $beta_2$-agonists, it is possible that the findings seen in this study may be consistent with a class effect.

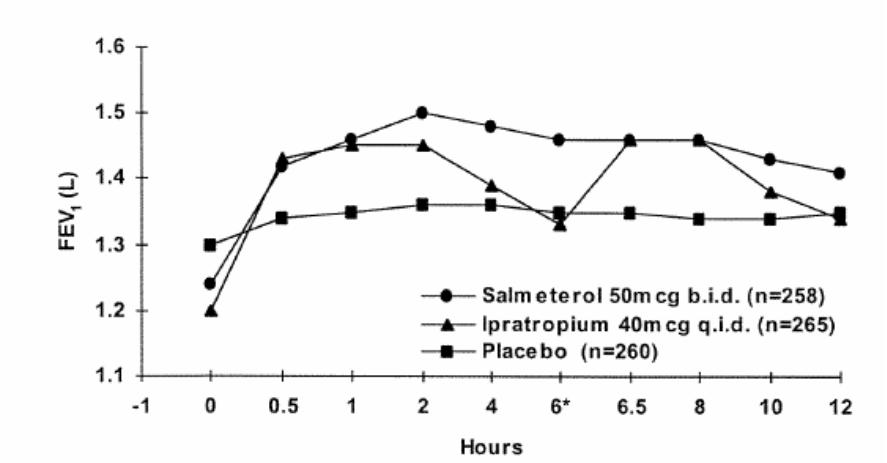
*Estimated by adding .5 to each cell of the treatment by event occurrence table.

(See Warnings.)

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 (≥ 12% and ≥ 200 mL increase in baseline FEV_1 after salbutamol treatment) and non-reversible to salbutamol. After a single 50mcg dose of SEREVENT®, significant improvement in pulmonary function (mean FEV_1 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

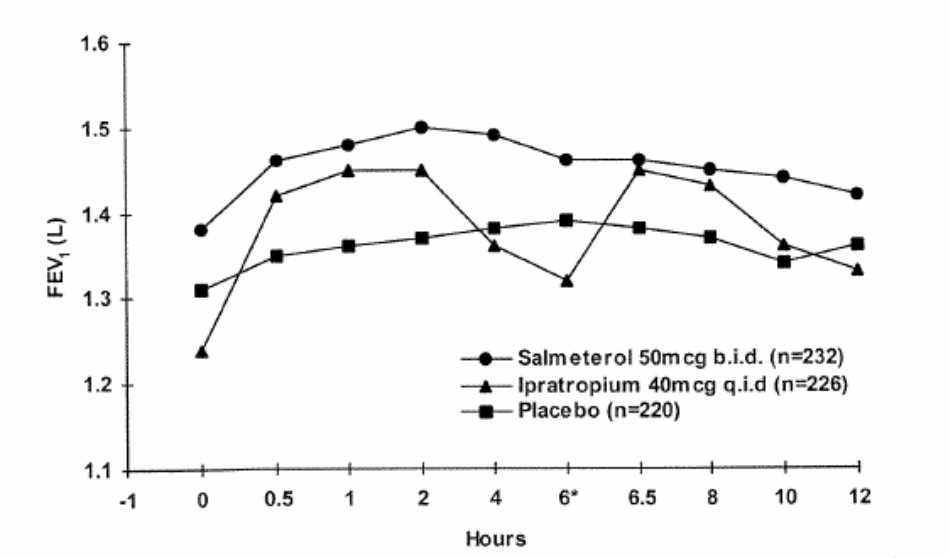
observed over a 12-week treatment period. Serial 12 hour measurements of FEV_1 from these two 12 week trials are shown below for both the first (Figure 1) and last treatment (Figure 2) days.

Figure 1: FEV_1 From Two Large 12 Week Clinical Trials: First Treatment Day.



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

Figure 2: FEV_1 From Two Large 12 Week Clinical Trials: Last Treatment Day (Week 12).



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

FEV_1 area under the curve (FEV_1 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 β_2-agonist in respiratory smooth muscle and on lung mast cells. Salmeterol is virtually devoid of β_1-adrenoceptor activity with only weak agonist activity at β_3-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 (EC_{50} 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 β_1-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 β_3-adrenoceptors, was at least 1000-times higher than that required to activate β_2-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 β_1 and β_2-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 β_2-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 (0.012-12μM, equivalent to 5-5000mcg/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 50mcg/mL and above, compared with 1.5-3 hours for salbutamol (478mcg/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 ED_{50} of approximately 0.01mg/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 (0.01-1mg/kg) also reduced histamine-induced PPE in a dose-related manner with an ED_{50} of 0.02mg/kg.

Prior treatment of animals with propranolol abolished the inhibition of PPE, indicating that these effects were mediated by β-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 β_2-adrenoceptor agonists. Salmeterol base (0.1-1.0mg/kg i.v.) in the dog caused marked tachycardia. At 0.3mg/kg, there was slight vasodilation and vomiting. Animals receiving 1mg/kg showed signs of subdued behaviour. Salmeterol (25-100mg/kg p.o.) reduced general activity in the rat. In the dog, oral salmeterol (1, 3 and 10mg/kg) induced persistent tachycardia and cutaneous vasodilation, with some lacrimation occurring at 3 and 10mg/kg. Salmeterol caused no overt effects on gastrointestinal function following oral administration, producing no emetic or defaecatory effects in dogs over the dose range 1-10mg/kg and no effects on defaecatory activity in rats at doses of 25-100mg/kg.

However, emesis was observed in the dog following intravenous doses of 0.3 and 1mg/kg.

In conscious cynomolgus monkey, oral salmeterol (1 and 10mg/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 (200pg/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, β_1-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 (100NG/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 sensitised 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 200mcg 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 50mcg salmeterol, plasma concentrations of approximately 200pg/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; ≥500	≥150	>75,000
Rate	>600	≥1000	>500,000
Rat (juv.)	>300	≥300	>150,000
Rat	>2.9	≥2.9	>1400
Dog	>0.7	≥0.7	>350

Longterm Toxicity

Subacute toxicity studies of up to 13 weeks in rats, at doses up to 0.7mg/kg/day by inhalation and/or 2.0mg/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 haemoglobin, and increases in anisocytosis and hypochromia were found to occur at doses greater than 0.05mg/kg/day orally and 0.07mg/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 (≥0.18mg/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 0.1-10.0mg/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 1mg/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 10mg/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 2.58mg/kg per day (about 55 and 215 times the recommended clinical dose [mg/m^2]). 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 0.2mg/kg (1.3 times the recommended clinical dose based on comparisons of the AUCs) and in rats at 0.21mg/kg (15 times the recommended clinical dose on a mg/m^2 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 2mg/kg orally (about 160 times the recommended clinical dose on a mg/m^2 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/m^2 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 0.6mg/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/m^2 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 (100mg/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.

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PART III: CONSUMER INFORMATION
Pr SEREVENT®
salmeterol xinafoate inhalation aerosol

This leaflet is part III of a three-part "Product Monograph" for SEREVENT® inhalation aerosol and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SEREVENT® inhalation aerosol. Contact your doctor or pharmacist if you have any questions about the drug. This medicine is for **you**. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

ABOUT THIS MEDICATION

What the medication is used for:
SEREVENT® inhalation aerosol is a medicine which your doctor will have chosen to suit you and your condition. SEREVENT® is used to help breathing problems in asthma and other chest illnesses such as chronic obstructive pulmonary disease (COPD) which includes chronic bronchitis and emphysema.

Asthma
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.

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.

What it does:
SEREVENT® is one of a group of medicines called bronchodilators. It works by relieving spasm or narrowing in the small air passages in the lungs causing chest tightness and wheezing. This helps to open up the airways and makes it easier for air to get in and out of the lungs. The effects of salmeterol xinafoate last for at least 12 hours. When it is taken regularly, it helps the small air passages to stay open.

When it should not be used:
SEREVENT® does not act quickly enough to be used as a relief medication. SEREVENT® should not be used to provide relief for a sudden attack of breathlessness.

- Do not use if you are allergic or have had an allergic reaction (swelling, anaphylactic reaction) to salmeterol or any of the ingredients in this medication (see what the important non medicinal ingredients are).
- Do not use if you have heart problems.
- Do not use if you are allergic to lecithin, soya or related food products such as soybeans.

What the medicinal ingredient is:
SEREVENT® inhalation aerosol contains salmeterol xinafoate.

What the important nonmedicinal ingredients are:
SEREVENT® inhalation aerosol contains dichlorodifluoromethane, soya lecithin and trichlorofluoromethane.

What dosage forms it comes in:
SEREVENT® inhalation aerosol is a pressurised metered-dose inhaler available in 60 and 120 metered dose (25 mcg salmeterol/actuation) formats.

WARNINGS AND PRECAUTIONS

SERIOUS WARNING FOR ASTHMA PATIENTS TAKING SEREVENT®
You are advised of the results of a large US clinical trial which showed an increased risk of asthma-related death and other serious respiratory-related outcomes in patients who used salmeterol in addition to their usual asthma therapy as compared to those who used placebo in addition to their usual asthma therapy. This risk was lower in patients who reported taking inhaled corticosteroids at study entry.
Therefore,

- If you or your child suffers from asthma, an inhaled corticosteroid must also be used if you or your child is using SEREVENT®;
- You or your child should not stop or reduce the inhaled corticosteroid dosage without consulting with your physician; and,
- For any concerns regarding the use of SEREVENT®, you should consult with your physician.

Before you use SEREVENT® inhalation aerosol talk to your doctor or pharmacist if:

- You had to stop taking another medication for your breathing problems because you were allergic to it or it caused problems.
- You have been told that you are allergic to lecithin, soya or related food products such as soybeans.
- You are receiving treatment for a thyroid condition, diabetes, raised blood pressure, or a heart problem.
- You are pregnant or breastfeeding.

Asthma:
All asthma patients are advised that they must also use corticosteroids (e.g. an inhaled corticosteroid such as fluticasone propionate) if they are using SEREVENT®. If you are already using such anti-inflammatory medicines, you must continue to take them regularly to treat your chest condition. These act together with SEREVENT® to give the best treatment to control or prevent you getting breathless or wheezy. It is important that you continue taking these regularly and do not stop or reduce the dose unless your doctor tells you, even if you feel much better.

If you get a sudden attack of wheezing and breathlessness between your doses of SEREVENT®, you should use your rapid onset, short duration relief medication (e.g. salbutamol) which your doctor has given you, and use it as directed by your doctor.

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

- **A sudden worsening of your shortness of breath and wheezing shortly after using your rapid onset, short duration relief medication or after using SEREVENT®.**
- **You do not feel relief within 10 minutes after using your rapid onset, short duration medication 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 is getting worse and that your treatment needs to be reassessed by your physician.

- 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 rapid onset short duration relief medication.
- Measurement from your peak flow meter indicates a value between 60 and 80 percent of predicted or personal best.

COPD:
The following warning signs indicate that your chest condition is worsening. You should contact your physician 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.
- 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.

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 physician about flu vaccination.

INTERACTIONS WITH THIS MEDICATION

Make sure that your doctor knows what other medicines you are taking (such as those for allergies, nervousness, depression, migraine etc.), 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® twice a day, in the morning and again in the evening. This 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® does not replace your fast-acting asthma relief medication (e.g. salbutamol) or inhaled anti-inflammatory therapy (e.g. beclomethasone dipropionate or fluticasone propionate). Its overuse can be serious.

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

Adolescents/Children with Asthma:
SEREVENT® 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 physician. 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®, a drug which reduces the inflammation in the lung due to asthma (also known as a preventive medication) and a rapid onset short duration bronchodilator (also known as a quick reliever).

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

Usual dose:
Patients ≥ 4 years of age
The usual dose is 2 puffs (2 x 25 micrograms) twice daily (2 puffs in the morning and 2 puffs in the evening).

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

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

Overdose:
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.

In the event of an excessive overdose tell your doctor without delay or contact your hospital emergency department or nearest poison control centre.

Missed Dose:
It is **very important that you use SEREVENT® inhalation aerosol 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® inhalation aerosol properly
Follow the instructions shown. It is important that you inhale each dose as instructed by your doctor. If you have any problems taking this medicine, tell your doctor or pharmacist.

Before you use your new SEREVENT® inhalation aerosol for the first time release the first two puffs into the air.

1. Remove the cap from the mouthpiece; the strap on the cap will stay attached to the actuator. Check the mouthpiece inside and outside to ensure that it is clean.

2. Shake the inhaler well.

3. Hold the inhaler upright between fingers and thumb with your thumb on the base, below the mouthpiece. Breathe out as far as comfortable.

4. For the next step there are two alternatives (4a or 4b) depending on the technique preferred by your physician.

4a. Place the mouthpiece in your mouth between your teeth and close your lips around it, but do not bite it. Just after starting to breathe in through your mouth, press down on the top of the inhaler to release the drug while still breathing in steadily and deeply.

Or

4b. Place the inhaler two finger widths directly in front of the mouth as shown. Begin a slow deep inward breath through the wide open mouth, at the same time pressing the canister down firmly into the inhaler.

5. While holding your breath, take the inhaler from your mouth and take your finger from the top of the inhaler. Continue holding your breath for about 10 seconds or for as long as is comfortable.

6. If you are to take a further puff, keep the inhaler upright and wait about half a minute before repeating steps 2 through 5.

7. After use, always snap the mouthpiece cover back into position to keep out dust and lint.

Important
Do not rush steps 4 and 5. It is important that you start to breathe in as slowly as possible just before operating your inhaler. Practice in front of a mirror for the first few times. If you see "mist" coming from the top of your inhaler or the sides of your mouth you should start again from step 2. (Applicable to Step 4a only).

If your doctor has given you different instructions for using your inhaler, please follow them carefully.

Cleaning
Your inhaler should be cleaned at least once a week.

1. Pull the metal canister out of the plastic casing of the inhaler.
2. Rinse the plastic casing and mouthpiece cover in warm water. A mild detergent may be added to the water (your pharmacist will advise you). Then rinse thoroughly with clean water before drying. **Do not put the metal canister into water.**
3. Leave the casing and mouthpiece cover to dry in a warm place. Avoid excessive heat.
4. Replace the canister and mouthpiece.
5. After cleaning release one puff into the air to make sure it works.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Very occasionally some people feel a little shaky or have a headache or notice that their heart is beating faster than usual. These effects usually wear off with continued treatment. Tell your doctor but do not stop using the medicine unless told to do so.

The treatment may cause an increase in the amount of sugar (glucose) in your blood. If you have diabetes, this may cause an upset in your blood sugar control. More frequent blood sugar monitoring and possibly adjustment of your usual diabetes treatment may be required.

Medicines affect different people in different ways. Just because side effects have occurred in other patients does not mean you will get them. If any side effects bother you, please contact your doctor.

Also tell the doctor if you have any of the following symptoms: headache, muscle cramps, pains in joints, skin rash or trembling, increase in pulse rate, mouth or throat irritation.

This is not a complete list of side effects. For any unexpected effects or if you feel unwell or have any symptoms that you do not understand while taking SEREVENT®, contact your doctor or pharmacist.

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

If you notice a sudden worsening of your shortness of breath and wheeze shortly after using your inhaler, tell your doctor as soon as possible.

Some people can be allergic to medicines. If you have any of the following symptoms soon after taking SEREVENT®, **stop** taking this medication and seek immediate medical attention.

- Feel faint
- Sudden wheeziness and chest pain or tightness.
- Swelling of eyelids, face or lips.
- Lumpy skin rash or "hives" anywhere on the body.

HOW TO STORE IT

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

Store between 15°C and 30°C. Protect from frost, direct sunlight and high temperatures (above 30°C or 86°F).

If the aerosol inhaler becomes very cold, remove the metal canister and warm **in your hand** for a few minutes before use. **Never** use other forms of heat.

Warning – The metal canister is pressurized. Do not puncture it or burn even when empty.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone:	866-234-2345
toll-free fax	866-678-6789
By email:	cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

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. North
Mississauga, Ontario
Canada L5N 6L4

This leaflet was prepared by GlaxoSmithKline Inc.
Last revised:

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. This medicine is for **you**. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

ABOUT THIS MEDICATION

What the medication is used for:
SEREVENT® DISKHALER® Disk is a medicine which your doctor will have chosen to suit you and your condition. SEREVENT® is used to help breathing problems in asthma and other chest illnesses such as chronic obstructive pulmonary disease (COPD) which includes chronic bronchitis and emphysema.

Asthma
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.

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.

What it does:
SEREVENT® is one of a group of medicines called bronchodilators. It works by relieving spasm or narrowing in the small air passages in the lungs causing chest tightness and wheezing. This helps to open up the airways and makes it easier for air to get in and out of the lungs. The effects of salmeterol xinafoate last for at least 12 hours. When it is taken regularly, it helps the small air passages to stay open.

When it should not be used:
SEREVENT® does not act quickly enough to be used as a relief medication. SEREVENT® should not be used to provide relief for a sudden attack of breathlessness.

- Do not use if you are allergic or have had an allergic reaction (swelling, anaphylactic reaction) to salmeterol or any of the ingredients in this medication (see what the important non medicinal ingredients are).
- Do not use if you have heart problems.
- Do not use if you are allergic to lactose (milk sugar) or milk protein.

What the medicinal ingredient is:
SEREVENT® DISKHALER® Disks contain salmeterol xinafoate.

What the important nonmedicinal ingredients are:
SEREVENT® DISKHALER® Disks contains lactose (milk sugar) and milk protein, which acts as the "carrier".

What dosage forms it comes in:
SEREVENT® Disks are circular foil disks each having four blisters around the edge. Each blister contains 50 mcg of salmeterol.

WARNINGS AND PRECAUTIONS

SERIOUS WARNING FOR ASTHMA PATIENTS TAKING SEREVENT®
You are advised of the results of a large US clinical trial which showed an increased risk of asthma-related death and other serious respiratory-related outcomes in patients who used salmeterol in addition to their usual asthma therapy as compared to those who used placebo in addition to their usual asthma therapy. This risk was lower in patients who reported taking inhaled corticosteroids at study entry.
Therefore,

- If you or your child suffers from asthma, an inhaled corticosteroid must also be used if you or your child is using SEREVENT®;
- You or your child should not stop or reduce the inhaled corticosteroid dosage without consulting with your physician; and,
- For any concerns regarding the use of SEREVENT®, you should consult with your physician.

Before you use SEREVENT® DISKHALER® Disk talk to your doctor or pharmacist if:

- You had to stop taking another medication for your breathing problems because you were allergic to it or it caused problems.
- You have been told that you are allergic to lactose (milk sugar) or milk protein.
- You are receiving treatment for a thyroid condition, diabetes, raised blood pressure, or a heart problem.
- You are pregnant or breastfeeding.

Asthma:
All asthma patients are advised that they must also use corticosteroids (e.g. an inhaled corticosteroid such as fluticasone propionate) if they are using SEREVENT®. If you are already using such anti-inflammatory medicines, you must continue to take them regularly to treat your chest condition. These act together with SEREVENT® to give the best treatment to control or prevent you getting breathless or wheezy. It is important that you continue taking these regularly and do not stop or reduce the dose unless your doctor tells you, even if you feel much better.

If you get a sudden attack of wheezing and breathlessness between your doses of SEREVENT®, you should use your rapid onset, short duration relief medication (e.g. salbutamol) which your doctor has given you, and use it as directed by your doctor.

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

- **A sudden worsening of your shortness of breath and wheezing shortly after using your rapid onset, short duration relief medication or after using SEREVENT®.**
- **You do not feel relief within 10 minutes after using your rapid onset, short duration medication 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 is getting worse and that your treatment needs to be reassessed by your physician.

- 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 rapid onset, short duration relief medication.
- Measurement from your peak flow meter indicates a value between 60 and 80 percent of predicted or personal best.

COPD:
The following warning signs indicate that your chest condition is worsening. You should contact your physician 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.
- 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.

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 physician about flu vaccination.

INTERACTIONS WITH THIS MEDICATION

Make sure that your doctor knows what other medicines you are taking (such as those for allergies, nervousness, depression, migraine etc.), 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® twice a day, in the morning and again in the evening. This 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® does not replace your fast-acting asthma relief medication (e.g. salbutamol) or inhaled anti-inflammatory therapy (e.g. beclomethasone dipropionate or fluticasone propionate). Its overuse can be serious.

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

Adolescents/Children with Asthma:
SEREVENT® 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 physician. 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®, a drug which reduces the inflammation in the lung due to asthma (also known as a preventive medication) and a rapid onset, short duration bronchodilator (also known as a quick reliever).

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

Usual dose:
Patients ≥ 4 years of age
The usual dose is 1 blister (1 x 50 micrograms) twice daily (1 blister in the morning and 1 blister in the evening).

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

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

Overdose:
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.

In the event of an excessive overdose tell your doctor without delay or contact your hospital emergency department or nearest poison control centre.

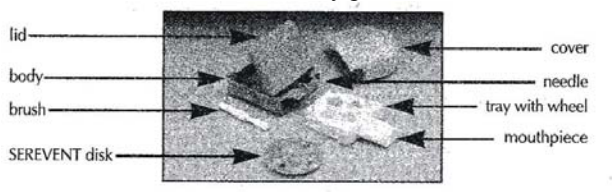
Missed Dose:
It is **very important that you use SEREVENT® DISKHALER® dry powder for inhalation regularly.** If you forget to inhale a dose do not worry, inhale another as soon as you remember **but** if it is near to the time for the next dose, wait until this is due. Do not take a double dose. Then go on as before.

How to use your SEREVENT® DISKHALER® properly
Remember the medicine in SEREVENT® 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® Disk, for inhaling medication.

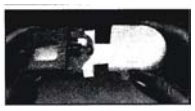
The DISKHALER® device consists of:
- an outer coloured body with a hinged lid and piercing needle.
- a cleaning brush contained at the rear of the body.
- a coloured mouthpiece cover.
- a white sliding tray with mouthpiece.
- a white wheel to support the disk.

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.

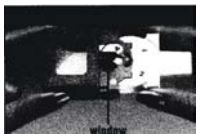


2. Hold the corners of the white tray and pull out gently until you can see all the plastic ridges on the sides of the tray.

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.

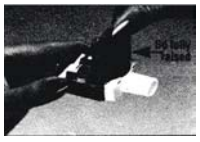
To rotate the Disk to the first dose



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.

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

Very occasionally some people feel a little shaky or have a headache or notice that their heart is beating faster than usual. These effects usually wear off with continued treatment. Tell your doctor but do not stop using the medicine unless told to do so.

The treatment may cause an increase in the amount of sugar (glucose) in your blood. If you have diabetes, this may cause an upset in your blood sugar control. More frequent blood sugar monitoring and possibly adjustment of your usual diabetes treatment may be required.

Medicines affect different people in different ways. Just because side effects have occurred in other patients does not mean you will get them. If any side effects bother you, please contact your doctor.

Also tell the doctor if you have any of the following symptoms: headache, muscle cramps, pains in joints, skin rash or trembling, increase in pulse rate, mouth or throat irritation.

This is not a complete list of side effects. For any unexpected effects or if you feel unwell or have any symptoms that you do not understand while taking SEREVENT®, contact your doctor or pharmacist.

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

If you notice a sudden worsening of your shortness of breath and wheeze shortly after using your inhaler, tell your doctor as soon as possible.

Some people can be allergic to medicines. If you have any of the following symptoms soon after taking SEREVENT®, **stop** taking this medication and seek immediate medical attention.

- Feel faint
- Sudden wheeziness and chest pain or tightness.
- Swelling of eyelids, face or lips.
- Lumpy skin rash or “hives” anywhere on the body.

HOW TO STORE IT

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

Keep SEREVENT® 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
To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone:	866-234-2345
toll-free fax	866-678-6789
By email:	cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney’s Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

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. North
Mississauga, Ontario
Canada L5N 6L4

This leaflet was prepared by GlaxoSmithKline Inc.
Last revised:

PART III: CONSUMER INFORMATION
PrSEREVENT® 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. This medicine is for **you**. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

ABOUT THIS MEDICATION

What the medication is used for:
SEREVENT® DISKUS® is a medicine which your doctor will have chosen to suit you and your condition. SEREVENT® is used to help breathing problems in asthma and other chest illnesses such as chronic obstructive pulmonary disease (COPD) which includes chronic bronchitis and emphysema.

Asthma
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.

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.

What it does:
SEREVENT® is one of a group of medicines called bronchodilators. It works by relieving spasm or narrowing in the small air passages in the lungs causing chest tightness and wheezing. This helps to open up the airways and makes it easier for air to get in and out of the lungs. The effects of salmeterol xinafoate last for at least 12 hours. When it is taken regularly, it helps the small air passages to stay open.

When it should not be used:
SEREVENT® does not act quickly enough to be used as a relief medication. SEREVENT® should not be used to provide relief for a sudden attack of breathlessness.

- Do not use if you are allergic or have had an allergic reaction (swelling, anaphylactic reaction) to salmeterol or any of the ingredients in this medication (see what the important non medicinal ingredients are).
- Do not use if you have heart problems.
- Do not use if you are allergic to lactose (milk sugar) or milk protein.

What the medicinal ingredient is:
SEREVENT® DISKUS® contains salmeterol xinafoate.

What the important nonmedicinal ingredients are:
SEREVENT® DISKUS® contains lactose (milk sugar) and milk protein, which acts as the "carrier".

What dosage forms it comes in:
SEREVENT® DISKUS® is a plastic inhaler device containing a foil strip with 60 blisters. Each blister contains 50 mcg of salmeterol.

WARNINGS AND PRECAUTIONS

SERIOUS WARNING FOR ASTHMA PATIENTS TAKING SEREVENT®
You are advised of the results of a large US clinical trial which showed an increased risk of asthma-related death and other serious respiratory-related outcomes in patients who used salmeterol in addition to their usual asthma therapy as compared to those who used placebo in addition to their usual asthma therapy. This risk was lower in patients who reported taking inhaled corticosteroids at study entry.
Therefore,

- If you or your child suffers from asthma, an inhaled corticosteroid must also be used if you or your child is using SEREVENT®;
- You or your child should not stop or reduce the inhaled corticosteroid dosage without consulting with your physician; and,
- For any concerns regarding the use of SEREVENT®, you should consult with your physician.

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

- You had to stop taking another medication for your breathing problems because you were allergic to it or it caused problems.
- You have been told that you are allergic to lactose (milk sugar) or milk protein.
- You are receiving treatment for a thyroid condition, diabetes, raised blood pressure, or a heart problem.
- You are pregnant or breastfeeding.

Asthma:
All asthma patients are advised that they must also use corticosteroids (e.g. an inhaled corticosteroid such as fluticasone propionate) if they are using SEREVENT®. If you are already using such anti-inflammatory medicines, you must continue to take them regularly to treat your chest condition. These act together with SEREVENT® to give the best treatment to control or prevent you getting breathless or wheezy. It is important that you continue taking these regularly and do not stop or reduce the dose unless your doctor tells you, even if you feel much better.

If you get a sudden attack of wheezing and breathlessness between your doses of SEREVENT®, you should use your rapid onset, short duration relief medication (e.g. salbutamol) which your doctor has given you, and use it as directed by your doctor.

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

- **A sudden worsening of your shortness of breath and wheezing shortly after using your rapid onset, short duration relief medication or after using SEREVENT®.**
- **You do not feel relief within 10 minutes after using your rapid onset, short duration medication 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 is getting worse and that your treatment needs to be reassessed by your physician.

- 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 rapid onset, short duration relief medication.
- Measurement from your peak flow meter indicates a value between 60 and 80 percent of predicted or personal best.

COPD:
The following warning signs indicate that your chest condition is worsening. You should contact your physician 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.
- 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.

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 physician about flu vaccination.

INTERACTIONS WITH THIS MEDICATION

Make sure that your doctor knows what other medicines you are taking (such as those for allergies, nervousness, depression, migraine etc.), 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® twice a day, in the morning and again in the evening. This 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® does not replace your fast-acting asthma relief medication (e.g. salbutamol) or inhaled anti-inflammatory therapy (e.g. beclomethasone dipropionate or fluticasone propionate). Its overuse can be serious.

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

Adolescents/Children with Asthma:
SEREVENT® 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 physician. 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®, a drug which reduces the inflammation in the lung due to asthma (also known as a preventive medication) and a rapid onset, short duration bronchodilator (also known as a quick reliever).

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

Usual dose:
Patients ≥ 4 years of age
The usual dose is 1 blister (1 x 50 micrograms) twice daily (1 blister in the morning and 1 blister in the evening).

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

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

Overdose:
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.

In the event of an excessive overdose tell your doctor without delay or contact your hospital emergency department or nearest poison control centre.

Missed Dose:
It is **very important that you use SEREVENT® DISKUS® dry powder for inhalation 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® DISKUS® properly
Follow the instructions shown. It is important that you inhale each dose as instructed by your doctor. If you have any problems taking this medicine, tell your doctor or pharmacist.

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**.

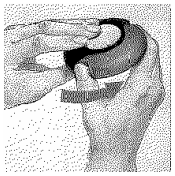
A new DISKUS® contains 60 individually protected doses of your medicine, in powder form. The device has a dose counter which tells you the number of doses remaining. It counts down from 60 to 1. **To show when the last five doses have been reached the numbers appear red.**

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

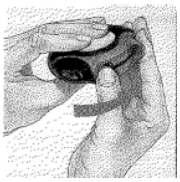
How your SEREVENT® DISKUS® works
The DISKUS® is easy to use. When you need a dose, just follow the four simple steps illustrated:
1.Open, 2. Slide, 3. Inhale, 4. Close.

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

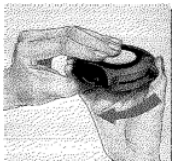


2. Slide
Hold your DISKUS® with the mouthpiece towards you. Slide the lever away from you as far as it will go - until it clicks. Your DISKUS® is now ready to use. Every time the lever is pushed back a dose is made available for inhaling. This is shown by the dose counter. Do not play with the lever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



3. Inhale
Before you start to inhale the dose, read through this section carefully.
Hold the DISKUS® away from your mouth.
Breathe out as far as is comfortable.
Remember - never breathe into your DISKUS®.
Put the mouthpiece to your lips. Breathe in steadily and deeply – through the DISKUS®, not through your nose.
Remove the DISKUS® from your mouth.
Hold your breath for about 10 seconds or for as long as is comfortable.
Breathe out slowly.

4. Close
To close your DISKUS®, put your thumb in the thumb grip, and slide the thumb grip back towards you, as far as it will go.
When you close the DISKUS®, it clicks shut. The lever automatically returns to its original position and is reset. Your DISKUS® is now ready for you to use again.



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Very occasionally some people feel a little shaky or have a headache or notice that their heart is beating faster than usual. These effects usually wear off with continued treatment. Tell your doctor but do not stop using the medicine unless told to do so.

The treatment may cause an increase in the amount of sugar (glucose) in your blood. If you have diabetes, this may cause an upset in your blood sugar control. More frequent blood sugar monitoring and possibly adjustment of your usual diabetes treatment may be required.

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This is not a complete list of side effects. For any unexpected effects of if you feel unwell or have any symptoms that you don not understand while taking SEREVENT®, contact your doctor or pharmacist.

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

If you notice a sudden worsening of your shortness of breath and wheeze shortly after using your device, tell your doctor as soon as possible.

Some people can be allergic to medicines. If you have any of the following symptoms soon after taking SEREVENT®, **stop** taking this medication and seek immediate medical attention.

- Feel faint
- Sudden wheeziness and chest pain or tightness.
- Swelling of eyelids, face or lips.
- Lumpy skin rash or "hives" anywhere on the body.

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

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone:	866-234-2345
toll-free fax	866-678-6789
By email:	cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

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. North
Mississauga, Ontario
Canada L5N 6L4

This leaflet was prepared by GlaxoSmithKline Inc.
Last revised: March 2, 2006