PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]SEREVENT DISKUS

salmeterol xinafoate dry powder for inhalation

50 mcg salmeterol (as the xinafoate salt)/blister

Bronchodilator
(beta2-adrenergic stimulant)

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Asthma

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

Corticosteroids should not be stopped because salmeterol is prescribed.

Long-acting beta$_2$-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death (see WARNINGS AND PRECAUTIONS). Use of SEREVENT DISKUS for the treatment of asthma without concomitant use of an inhaled corticosteroid; a long-term asthma control medication; is contraindicated (see CONTRAINDICATIONS). Use SEREVENT DISKUS only as add-on therapy for patients with asthma who are currently taking but are inadequately controlled on an inhaled corticosteroid.

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

SEREVENT DISKUS is a slow onset, long-acting, beta$_2$-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.

Pediatrics and Adolescent Patients:

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

Chronic Obstructive Pulmonary Disease (COPD)

SEREVENT DISKUS 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.

SEREVENT DISKUS should not be used as a rescue medication.

1.1 Pediatrics

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.

1.2 Geriatrics

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

2 CONTRAINDICATIONS

- SEREVENT DISKUS is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container and to adrenergic compounds. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with cardiac tachyarrhythmias.
- SEREVENT DISKUS (salmeterol xinafoate) dry powder for inhalation formulation contains lactose (which contains milk protein) and is therefore contraindicated in patients with an allergy to lactose or milk.
- Patients with a history of anaphylactic shock, anaphylactic reaction or angioedema associated with salmeterol xinafoate or any component of this drug.
- Because of the risk of asthma-related death and hospitalization, use of SEREVENT DISKUS for the treatment of asthma without concomitant use of an inhaled corticosteroid; a long-term asthma control medication; is contraindicated (see WARNINGS AND PRECAUTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

ASTHMA RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death. Data from a large placebo controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to patients usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Post-hoc analysis of the SMART trial data suggests that the risks may be lower in patients who were using inhaled corticosteroids (ICS) at study entry. However, these post-hoc analysis results are not conclusive (see 14 CLINICAL TRIALS: Salmeterol Multi-center Asthma Research Trial (SMART)). Currently available clinical data are inadequate to determine whether concurrent use of inhaled corticosteroids mitigates the increased risk of asthma-related death from LABA.

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

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

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

Pediatric and Adolescent Patients

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Asthma
Long-acting beta$_2$-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death (see WARNINGS AND PRECAUTIONS). **Because of this risk, use of SEREVENT DISKUS for the treatment of asthma without concomitant use of an inhaled corticosteroid, a long-term asthma control medication, is contraindicated** (see CONTRAINDICATIONS). Use SEREVENT DISKUS only as add-on therapy for patients with asthma who are currently taking but are inadequately controlled on an inhaled corticosteroid.

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

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

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 DISKUS is still indicated.

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

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

SEREVENT DISKUS should not be used to treat acute symptoms. It is crucial to inform patients of this and prescribe a rapid onset, short duration beta$_2$-agonist for this purpose. The need for additional symptomatic bronchodilator therapy is usually reduced with SEREVENT DISKUS (see WARNINGS AND PRECAUTIONS section). Medical attention should be sought if patients find that rapid onset, short duration relief bronchodilator treatment becomes less effective or if they need more inhalations than usual.

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

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

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

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

Use with Rapid Onset, Short Duration Bronchodilators: When beginning treatment with SEREVENT DISKUS, 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 DISKUS should reduce the excessive use of rapid onset, short duration, inhaled bronchodilators.

General Considerations for Asthma and COPD
The dosage or frequency of SEREVENT DISKUS administration should not be increased since there may be serious adverse effects associated with excessive dosing. SEREVENT DISKUS 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.

4.2 Recommended Dose and Dosage Adjustment

Asthma

Maintenance Therapy

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

COPD

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

4.4 Administration

SEREVENT DISKUS is administered by the inhaled route only.

4.5 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.

5 OVERDOSAGE

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

Do Not Exceed Recommended Dosage: As with other inhaled beta$_2$-adrenergic drugs, SEREVENT DISKUS 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 WARNINGS AND PRECAUTIONS, Cardiovascular).

The expected signs and symptoms of salmeterol overdosage are those typical of excessive beta$_2$ 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. There is no specific treatment for an overdose of salmeterol. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Route of Administration, Dosage Forms/Strengths and Nonmedicinal Ingredients.

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

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.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

Use in Asthma
Important Information

SEREVENT DISKUS (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 DISKUS 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 $beta_2$-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 DISKUS provides greater efficacy than or additional efficacy to rapid onset, short duration, inhaled $beta_2$-agonists in patients with worsening asthma.

General
SEREVENT DISKUS 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 DISKUS. Corticosteroid therapy should not be stopped or reduced when SEREVENT DISKUS 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 DISKUS. 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 DISKUS could be used with or without concomitant corticosteroids. The use of oral or inhaled corticosteroids should be determined by the treating physician.

SEREVENT DISKUS 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 $beta_2$-agonists in the Management of Asthma and COPD
The management of asthma should normally follow a stepwise programme, and *patient response should be monitored clinically and by lung function tests*. Sudden or progressive deterioration in asthma control is potentially life-threatening; treatment plan must be re-evaluated, and consideration be given to increasing corticosteroid therapy. *In patients at risk, daily peak flow monitoring with precise instructions for acceptable variation limits should be*

considered.

Increased use of inhaled, rapid onset, short duration beta$_2$-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 beta$_2$-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 beta$_2$-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 beta$_2$-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 DISKUS, those who have been taking rapid onset, short duration, inhaled beta$_2$-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 beta$_2$-agonists only for symptomatic relief if they develop asthma symptoms while taking SEREVENT DISKUS.

When beginning treatment with SEREVENT DISKUS, 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 DISKUS should reduce the excessive use of rapid onset, short duration inhaled bronchodilators.

Cardiovascular
The pharmacological side-effects of beta$_2$-agonist treatment, such as palpitations have been reported, but tend to be transient and to reduce with regular therapy (see ADVERSE REACTIONS). A small increase in QTc interval has been reported at therapeutic doses. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Fatalities have been reported following excessive use of aerosol preparations containing sympathomimetic amines, the exact cause of which is unknown. Cardiac arrest was reported in several instances.

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

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

Test for interaction p=0.233

In individual patients any beta$_2$-adrenergic agonist may have a clinically significant cardiac effect.

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

Occurrence of cardiovascular effects may require discontinuation of the drug.

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

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

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

The pharmacological side-effects of beta$_2$-agonist treatment, such as tremor and headache have been reported, but tend to be transient and to reduce with regular therapy.

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

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

Endocrine and Metabolism
Metabolic Effects
Similar to other beta-adrenergic agents, salmeterol can induce reversible metabolic changes (e.g. hyperglycemia, hypokalemia). There have been very rare reports of increases in blood glucose levels (see ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions) and this should be considered when prescribing to patients with a history of diabetes mellitus.

Doses of the related beta$_2$-adrenoceptor agonist salbutamol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. Administration of beta$_2$-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.

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 beta$_2$-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 DISKUS in this situation is not appropriate. SEREVENT DISKUS 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 DISKUS is still indicated. Compliance, especially neglect of anti-inflammatory therapy and overuse of rapid onset, short duration beta$_2$-agonists, should be carefully followed in adolescents/children receiving long-acting beta$_2$-agonists.

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

Systemic Effects
The results of a drug interaction study conducted in healthy subjects indicated that concomitant use of systemic ketoconazole (a strong cytochrome P450 3A4 inhibitor) increased exposure to salmeterol in some subjects. This increase in plasma salmeterol exposure may lead to prolongation in the QTc interval. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with ketoconazole is not recommended (see 9 DRUG INTERACTIONS, Drug-Drug Interactions). Caution should also be exercised when other CYP3A4 inhibitors are co-administered with salmeterol (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin).

7.1 Special Populations

7.1.1 Pregnant Women

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

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

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

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Pediatrics (< *4 years of age*): The safety and efficacy of SEREVENT in children younger than 4 years of age have not been established.

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

7.1.4 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 beta$_2$-agonists, however, special caution should be observed when using SEREVENT DISKUS in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

As with other 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 beta$_2$-adrenoceptor agonists, i.e. palpitation; immediate hypersensitivity reactions, including urticaria, rash, bronchospasm, edema, angioedema, and anaphylactic shock or anaphylactic reaction; headache; tremor; nervousness; oropharyngeal irritation, and paradoxical bronchospasm. There have also been reports of arthralgia and muscle cramps.

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

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

Asthma
Long-acting beta$_2$-adrenergic agonists (LABA), including salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death. Data from a large, 28-week, placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related death in patients receiving salmeterol. Post-hoc analysis of the SMART trial data suggests that the risks may be lower in patients who were using inhaled corticosteroids (ICS) at study entry. However, these post-hoc analysis results are not conclusive (see 14 CLINICAL TRIALS: Salmeterol Multi-center Asthma Research Trial (SMART)).

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients (see WARNINGS AND PRECAUTIONS, and 14 CLINICAL TRIALS: Salmeterol Multi-center Asthma Research Trial (SMART)).

8.2 Clinical Trial Adverse 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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Asthma

Use in Adolescents and Adults (18 years of age and above)
In controlled, multidose clinical trials (treatment period of up to 1 year) involving almost 2000 patients (≥18 years old), the most frequently occurring adverse events were headache, tremor and palpitations (see Table 2 below), which are pharmacologically predictable effects of beta$_2$-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 2 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 24 week controlled clinical trial, 738 patients (≥18 years old) received either salmeterol in combination with beclomethasone dipropionate (BDP) or BDP alone. A rapid onset, short duration inhaled beta$_2$-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 100 mcg group compared with the other two groups (see Table 3 below).

Table 3 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

Chronic Obstructive Pulmonary Disease (COPD)

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT inhalation aerosol in patients (≥35 years old) with COPD. In clinical trials, SEREVENT was generally well tolerated over chronic dosing periods. The most frequently reported adverse events with SEREVENT 50 mcg twice daily were headache, upper respiratory tract infection and sore throat.

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

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

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

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

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

Other Asthma Clinical Trial Adverse Drug Reactions

Asthma

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.

Chronic Obstructive Pulmonary Disease (COPD)

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

8.2.1 Clinical Trial Adverse Reactions (Pediatrics)

Asthma

Two multicenter, randomized, double-blind studies have compared twice daily administration of SEREVENT 25 mcg and 50 mcg versus salbutamol in patients aged 4 to 16 years with asthma. Adverse events that occurred with an incidence of ≥3% in the salmeterol groups, irrespective of the relationship to treatment, are summarized in Table 5 below.

Table 5 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 25 mcg bid or 50 mcg bid and salbutamol 200 mcg bid. There was no evidence to suggest that children of a younger age were more at risk than those in the older age groups.

8.5 Post-Market Adverse Reactions

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

Cardiac Disorders

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

Immune System Disorders

Immediate hypersensitivity reactions:
Rare: Urticaria, angiodema, rash, and bronchospasm.

Very rare: Anaphylactic shock or anaphylactic reaction.

Metabolism and Nutrition Disorders

Very rare: Hyperglycemia.

Respiratory, Thoracic and Mediastinal Disorders

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

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

In extensive worldwide post-marketing experience, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS AND PRECAUTIONS), but they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether SEREVENT contributed to these events or simply failed to relieve the deteriorating asthma.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

Inhibitors of cytochrome P450 3A4: Co-administration of repeat dose ketoconazole (a cytochrome P450 3A4 inhibitor) and salmeterol in healthy subjects resulted in a significant increase in plasma salmeterol exposure (1.4-fold increase in C_{max} and 15-fold increase in AUC). This increase in plasma salmeterol exposure may cause a prolongation of the QTc interval (see WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY: 10.3 Pharmacokinetics).

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

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

9.4 Drug-Drug Interactions

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

Table 6 Established or Potential Drug-Drug Interactions

Drug type	Ref	Effect	Clinical comment
Sympathomimetic agents	CT	May lead to deleterious cardiovascular effects.	Aerosol bronchodilators of the rapid onset, short duration adrenergic stimulant type may be used for relief of breakthrough symptoms while using salmeterol for asthma. However, increasing use of such preparations to control symptoms indicates deterioration of asthma control and the patient's therapy plan should be reassessed. The regular, concomitant use of salmeterol and other sympathomimetic agents is not recommended.
Monoamine Oxidase Inhibitors or Tricyclic Antidepressants	CS	Action of salmeterol on vascular system may be potentiated.	Salmeterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents.
Methylxanthines	CT	Unknown	The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving salmeterol has not been completely evaluated.
Beta-Blockers	CS	May antagonise the bronchodilating action of salmeterol.	Non-selective beta-blocking drugs, should never be prescribed in combination with salmeterol. Cardioselective beta-blocking drugs should be used with caution in patients using medications for bronchodilation.
Inhibitors of cytochrome P450 3A4	CT	Increased systemic exposure to salmeterol xinafoate.	Caution is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole) (See "DRUG INTERACTIONS", "WARNINGS AND PRECAUTIONS ", and "CLINICAL PHARMACOLOGY: 10.3 Pharmacokinetics")

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

A repeat dose study with salmeterol and erythromycin in healthy volunteers showed no clinically significant changes in pharmacodynamic effects at 500 mg three times daily doses of erythromycin. However, a salmeterol-ketoconazole interaction study resulted in a significant increase in plasma salmeterol exposure (see WARNINGS AND PRECAUTIONS).

In a placebo-controlled, crossover drug interaction study in 15 healthy subjects, co-administration of salmeterol (50 mcg twice daily inhaled) and the cytochrome P450 3A4 (CYP3A4) inhibitor, ketoconazole (400 mg once daily orally), for 7 days, resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). There was no increase in salmeterol accumulation with repeat dosing. Three subjects were withdrawn from salmeterol and ketoconazole co-administration due to QTc prolongation or palpitations with sinus

tachycardia. In the remaining 12 subjects, co-administration of salmeterol and ketoconazole did not result in a clinically significant effect on heart rate, blood potassium or QTc duration (see WARNINGS AND PRECAUTIONS).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

SEREVENT (salmeterol xinafoate) is a selective, long-acting (12 hours), slow onset (10-20 minutes) $beta_2$- adrenoceptor agonist with a long side-chain which binds to the exo-site of the receptor.

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 $beta_2$-adrenoceptor.

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 $beta_2$-agonists.

In contrast to conventional rapid onset, short duration $beta_2$-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.

10.2 Pharmacodynamics

In patients, salmeterol by both pressurised and powder inhalers in single doses of 25 mcg or greater has been shown to produce bronchodilation lasting for approximately 12 hours. This long duration of action has been confirmed by challenge studies using exercise, histamine and methacholine as bronchoconstrictor agents. Salmeterol has also been shown to abolish both the early and late phase bronchoconstrictor response to inhaled allergen, the clinical significance of which has not been established.

Pharmacology

Salmeterol is a potent, selective $beta_2$-agonist in respiratory smooth muscle and on lung mast cells. Salmeterol is virtually devoid of $beta_1$-adrenoceptor activity with only weak agonist activity at $beta_3$-adrenoceptors. Salmeterol xinafoate was an extremely weak partial agonist in the

electrically-driven left atrium of the rat, a $beta_1$-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 $beta_3$-adrenoceptors, was at least 1000 times higher than that required to activate $beta_2$-adrenoceptors in airways smooth muscle.

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

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

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

10.3 Pharmacokinetics

Salmeterol xinafoate is an ionic salt that dissociates in solution so that salmeterol and 1-hypdroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized and excreted independently.

Absorption: 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). Following inhalation of a single dose of 50 mcg salmeterol, plasma concentrations of approximately 200 pg/mL were detected.

Distribution: At least 93% of the salmeterol distributed between erythrocytes and plasma is reversibly bound to the plasma proteins, $beta_1$-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.

Metabolism: Salmeterol is predominantly cleared by hepatic metabolism; liver function impairment may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored. An *in vitro* study showed that salmeterol is extensively metabolised to α-hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4).

Elimination: Following oral administration of radiolabelled salmeterol approximately 25% and 60% of the dose was recovered in the urine and feces, respectively. Excretion was predominantly as metabolites with no significant amount of unchanged salmeterol detected.

Hydroxynapthoic acid:

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.

Accumulation was observed in humans, but the steady-state concentrations (100 ng/mL, determined with 50 mcg of salmeterol xinafoate, administered by inhalation, twice daily for 12 months) 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.

11 STORAGE, STABILITY AND DISPOSAL

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

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

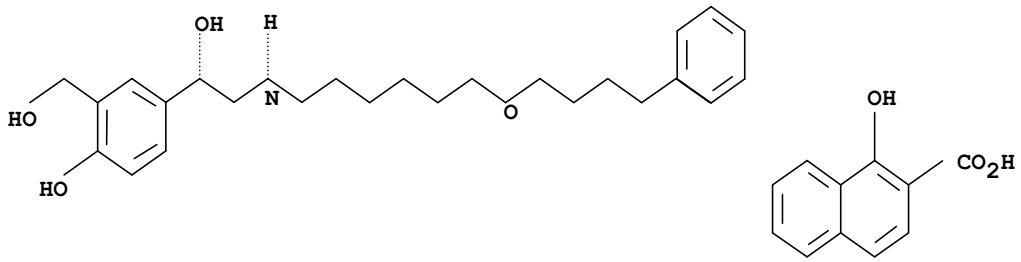
Drug Substance

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)

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Patient demographics for clinical trials in asthma and COPD are presented in Tables 7-8 below.

Asthma

Table 7 Summary of patient demographics for clinical trials in asthma (Adults and Adolescents aged 18 years and older)

Study #	Trial Design	Dosage, route of administration and duration	Study Subjects (n)	Mean age (Range)	Sex M/F
SLGT02 (GRP/89/072)	Multicentre, Randomized, Double Blind, Parallel Group	Salmeterol MDI 50 mcg BID Salbutamol MDI 200 mcg QID Oral Inhalation 3 months	334 333	49 (18 to 81 years) 49 (18 to 79 years)	151/183 181/152
SLGT06 (GRP/89/076)	Multicentre, Randomized, Double Blind, Parallel Group	Salmeterol DPI 50 mcg BID Salbutamol DPI 400 mcg QID Oral inhalation 3 Months	190 198	43 (19 to 79 years) 46.5 (18 to 78 years)	89/101 100/98
SLGT04 (GRP/89/073)	Multicentre, Randomized, Double Blind, Parallel Group	Salmeterol MDI 50 mcg BID Salmeterol MDI 100 mcg BID Oral Inhalation 3 Months	146 137	56 (20 to 80 years) 58 (26 to 79 years)	91/55 83/54
SLGT05 (GRP/89/075)	Multicentre, Randomized, Double Blind, Parallel Group	Salmeterol MDI 50 mcg BID Salmeterol DPI 50 mcg BID Oral inhalation 2 Weeks	69 69	48 (19 to 75 years) 49 (18 to 79 years)	37/32 32/37

Study #	Trial Design	Dosage, route of administration and duration	Study Subjects (n)	Mean age (Range)	Sex M/F
SLGT03 (GRP/89/074)	Multicentre, Randomized, Double Blind, Double Dummy, Crossover	Salmeterol MDI 50 mcg BID Oral inhalation	72	51 (22 to 75 years)	43/29
		Theophylline Individualized BID dosing to maintain serum levels of 10-20 mcg/mL Capsules 150 mg Oral administration	69	50 (18 to 72 years)	37/32
		2 Weeks			

DPI = Dry powder inhaler; MDI = metered-dose inhaler; QID = four times a day; BID = twice daily.

Key Inclusion/Exclusion criteria:

SLGT02, SLGT06 and SLGT05: Subjects were eligible if they had mild to moderate reversible airways obstruction defined by FEV_1 or daily PEFR ≥50% of predicted values.

SLGT04: Subjects were eligible if they had moderate to severe reversible airways obstruction defined by FEV_1 or PEFR ≤50% of predicted values.

In all studies, subjects were also required to demonstrate ≥15% reversibility in FEV_1 after salbutamol 200 mcg, or if this criterion was not met, ≥20% reversibility in FEV_1 after a further 400 mcg dose of salbutamol. In addition, subjects had to have either asthma symptom scores ≥2 or diurnal variation in PEFR ≥15%. Subjects were excluded if they required a maintenance dose of oral prednisolone >20 mg/day, or, in the previous 14 or 28 days, they a) had a lower respiratory tract infection, b) required hospitalisation for any aspect of their reversible airways disease, or c) required a booster course of prednisolone >20 mg/day.

SLGT03: Subjects were eligible if they had a clinical requirement for theophylline treatment, were receiving corticosteroids (inhaled or oral doses up to the equivalent of prednisolone 20 mg/day), and who demonstrated a PEFR ≥50 % of predicted values and ≥15% reversibility in FEV_1 after salbutamol 200 mcg, or if this criterion was not met, ≥20% reversibility in FEV_1 after a further 400 mcg dose of salbutamol. In addition, subjects had to have either asthma symptom scores ≥2 or diurnal variation in PEFR ≥15%. Subjects were excluded if they required a maintenance dose of oral prednisolone >20 mg/day, or, in the previous 28 days, they a) had a lower respiratory tract infection, b) required hospitalisation for any aspect of their reversible airways disease, or c) required a booster course of prednisolone >20 mg/day.

Chronic Obstructive Pulmonary Disease (COPD)

Table 8 Summary of patient demographics for clinical trials in COPD (Adults)

Study #	Trial Design	Dosage, route of administration and duration	Study Subjects (n)	Mean age (Range)	Sex M/F
SLGA4004 (RM1996/00370/00)	Multicentre, Stratified, Randomized, Double Blind, Double Dummy, Placebo Controlled, Parallel Group	Salmeterol 50 mcg BID	132	63.85 (aged 35 to 87 years)	81/51
		Ipratropium 40 mcg QID	138	61.72 (aged 37 to 85 years)	89/49
		Placebo	135	63.70 (aged 35 to 82 years)	87/48
		Oral Inhalation 12 Weeks			

Study #	Trial Design	Dosage, route of administration and duration	Study Subjects (n)	Mean age (Range)	Sex M/F
SLGA4005 (RM1996/00364/00)	Multicentre, Stratified, Randomized, Double Blind, Double Dummy, Placebo Controlled, Parallel Group	Salmeterol 50 mcg BID	135	63.21 (aged 41 to 85 years)	97/38
		Ipratropium 40 mcg QID	133	64.02 (aged 36 to 80 years)	97/36
		Placebo	143	63.19 (aged 40 to 80 years)	109/34
		Oral Inhalation 12 Weeks			

MDI = metered-dose inhaler; QID = four times a day; BID = twice daily.

Key Inclusion/Exclusion criteria (SLGA4004 and SLGA4005): Subjects aged ≥35 years were eligible if they had a diagnosis of COPD (defined as emphysema or chronic bronchitis), an FEV_1 >0.70 L and ≤65% of predicted values or <0.70 L and ≥40% predicted, a FEV_1/FVC ratio ≤0.70, a past or current history of smoking for ≥10 pack-years, and a Modified Medical Research Council (MMRC) dyspnea score of >1 (using a 0 to 4 scale where 0=not troubled with breathlessness except with strenuous exercise and 4=too breathless to leave the house or breathless when dressing or undressing). Subjects were excluded if they had a bacterial pulmonary infection within 4 weeks of screening, or a primary diagnosis of asthma. The concurrent use of inhaled corticosteroids and oral steroids was allowed provided the daily dose of oral corticosteroids was <10 mg per day.

14.2 Study Results

Asthma - Clinical Experience

Use in adolescents and adults

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

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

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

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

Table 9 Results summary for asthma studies in patients ≥18 years of age (SLGT02, SLGT06, SLGT04, SLGT05)

	SLGT02 (GRP/89/072)		SLGT06 (GRP/89/076)		SLGT04 (GRP/89/073)		SLGT05 (GRP/89/075)	
	Study Product and Dosage							
	Salmeterol 50 mcg BID	Salbutamol 200 mcg QID	Salmeterol 50 mcg BID	Salbutamol 400 mcg QID	Salmeterol 50 mcg BID	Salmeterol 100 mcg BID	Salmeterol 50 mcg DPI BID	Salmeterol 50 mcg MDI BID
Morning PEFR (L/min) (Total Population, Total Data Set)								
Adjusted Mean Weeks 1 to 12	386	355	397	376	305	316		
Adjusted Mean Weeks 1 to 2							355	356
Adjusted Mean Difference (Salmeterol – Salbutamol) (Salmeterol 100 mcg - 50 mcg) (Salmeterol DPI – MDI)	30		21		11		-1	
95% CI	24, 37		12, 31		0, 22		-13, 10	
p-value	<0.001		<0.001		0.047		0.802	
Evening PEFR (L/min) (Total Population, Total Data Set)								
Adjusted Mean Weeks 1 to 12	398	387	410	408	323	335		
Adjusted Mean Weeks 1 to 2							368	367
Adjusted Mean Difference (Salmeterol – Salbutamol) (Salmeterol 100 mcg - 50 mcg) (Salmeterol DPI – MDI)	11		2		12		1	
95% CI	5, 17		-6, 11		2, 22		-11, 13	
p-value	<0.001		0.559		0.023		0.840	
Morning-Evening PEFR Decrease (L/min) (Total Population, Total Data Set)								
Adjusted Mean Weeks 1 to 12	12	31	11	32	18	16		
Adjusted Mean Weeks 1 to 2							12	13
Adjusted Mean Difference (Salmeterol – Salbutamol) (Salmeterol 100 mcg - 50 mcg) (Salmeterol DPI – MDI)	-19		-21		-1		-1	
95% CI	-22, -15		-27, -16		-7, 4		-7, 6	
p-value	<0.001		<0.001		0.637		0.869	

DPI = Dry powder inhaler; MDI = metered-dose inhaler; QID = four times a day; BID = twice daily.

Table 10 Results summary for asthma studies in adults (SLGT03)

	SLGT03 (GRP/89/074)					
	Study Product and Treatment Sequence					
	Theophylline Strata: Naïve and Tolerant		Theophylline Strata: Naïve		Theophylline Strata: Tolerant	
	Salmeterol followed by Theophylline	Theophylline followed by Salmeterol	Salmeterol followed by Theophylline	Theophylline followed by Salmeterol	Salmeterol followed by Theophylline	Theophylline followed by Salmeterol
Morning PEFR (L/min) (Total Population, Total Data Set)						
Mean PEFR Period 1	357	373	385	382	337	367
Mean PEFR Period 2	347	394	369	419	331	375
Difference (Period 1– Period 2)	10	-20	16	-37	7	-8
Mean Difference (Salmeterol – Theophylline)	16		27		8	
95% CI	8, 24		15, 39		-2, 18	
p-value	<0.001		<0.001		0.113	
Evening PEFR (L/min) (Total Population, Total Data Set)						
Mean PEFR Period 1	376	388	403	397	356	383
Mean PEFR Period 2	364	407	383	426	351	393
Difference (Period 1– Period 2)	11	-18	20	-29	5	-10
Mean Difference (Salmeterol – Theophylline)	15		24		8	
95% CI	7, 22		13, 36		-2, 17	
p-value	<0.001		<0.001		0.114	
Morning-Evening PEFR Decrease (L/min) (Total Population, Total Data Set)						
Mean PEFR Period 1	19	15	19	14	19	15
Mean PEFR Period 2	18	13	15	6	21	18
Difference (Period 1– Period 2)	1	2	4	8	-1	-3
Mean Difference (Salmeterol – Theophylline)	-1		-2		0	
95% CI	-6, 4		-10, 6		-6, 7	
p-value	0.813		0.628		0.917	

SEREVENT Nationwide Post-Marketing Surveillance Study

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

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

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

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

Salmeterol Multi-center Asthma Research Trial (SMART)

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

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

Post-hoc subgroup analyses suggest that the risk for these serious events may be greater in the African-American population. In this subgroup, the relative risks after the 28-week treatment period were: 4.10 for the primary endpoint (20 out of 2,366 vs 5 out of 2,319; 95% CI: 1.54, 10.90) in patients using salmeterol in addition to their usual asthma therapy compared to those using placebo in addition to their usual asthma therapy, 7.26 for asthma-related death (7 vs 1; 95% CI; 0.89, 58.94), 4.92 for combined asthma-related death or life-threatening experience (19 vs 4; 95% CI: 1.68, 14.45), and 3.88 for respiratory-related death (8 vs 2; 95% CI: 0.83, 18.26). The relative risks in the Caucasian population were: 1.05 for the primary endpoint (29 out of 9,281 vs 28 out of 9,361; 95% CI: 0.62, 1.76) for patients using salmeterol in addition to their usual asthma therapy compared to those adding placebo, 5.82 for asthma-related death (6 vs 1; 95% CI: 0.70, 48.37), 1.08 for combined asthma-related death or life-threatening experience (17 vs 16; 95% CI: 0.55, 2.14), and 2.29 for respiratory-related death (16 vs 7; 95% CI: 0.94, 5.56).

While not conclusive, a post-hoc analyses, of the data from the SMART trial suggested that the use of inhaled corticosteroids as reported at study entry, had a protective effect regarding asthma-related outcomes in patients taking SEREVENT. For the primary endpoint of combined respiratory-related death or life-threatening experience, a relative risk of 1.60 (27 out of 7,049 vs 17 out of 7,041; 95% CI: 0.87, 2.93) was observed for patients not reporting inhaled corticosteroid use at study entry, while a relative risk of 1.21 (23 out of 6,127 vs 19 out of 6,138; 95% CI: 0.66, 2.23) was observed for those who did report ICS use. For asthma-related death alone, the relative risks were: 18.98* (9 vs 0; with 95% CI: 1.10, 326.15) for those without baseline ICS use, and 1.35 (4 vs 3; 95% CI: 0.30, 6.04) for those reporting ICS use. For asthma-related death or life-threatening experience, the relative risks were: 2.39 (21 vs 9; 95%

CI: 1.10, 5.22) for those without baseline ICS use, and 1.24 (16 vs 13; 95% CI; 0.60, 2.58) for those reporting ICS use; and, for respiratory-related death: 2.28 (14 vs 6; 95% CI; 0.88, 5.94) for those without baseline ICS use, and 2.00 (10 vs 5; 95% CI: 0.69, 5.86) for those reporting ICS use. Hence, the apparent protective effect was most notable for asthma-related outcomes. When ICS effect was further analysed by ethnicity, risks of asthma-related outcomes were diminished for the African-American subgroup with ICS use (as reported at study entry), but contrary to the Caucasian subgroup, these risks were not extinguished, although the data for this analysis were sparse. It is to be noted that the SMART study data do not include information regarding the continued use of ICS after study entry, nor information regarding the dose(s) of ICS used throughout the treatment period of 28 weeks.

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

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

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

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

(See WARNINGS AND PRECAUTIONS)

Chronic Obstructive Pulmonary Disease (COPD) – Clinical Experience

In two large randomized, double-blind studies, SEREVENT inhalation aerosol was compared with placebo and ipratropium bromide in patients with COPD (emphysema and chronic bronchitis), including patients who were reversible (≥ 12% and ≥ 200 mL increase in baseline FEV_1 after salbutamol treatment) and non-reversible to salbutamol. After a single 50 mcg 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 (

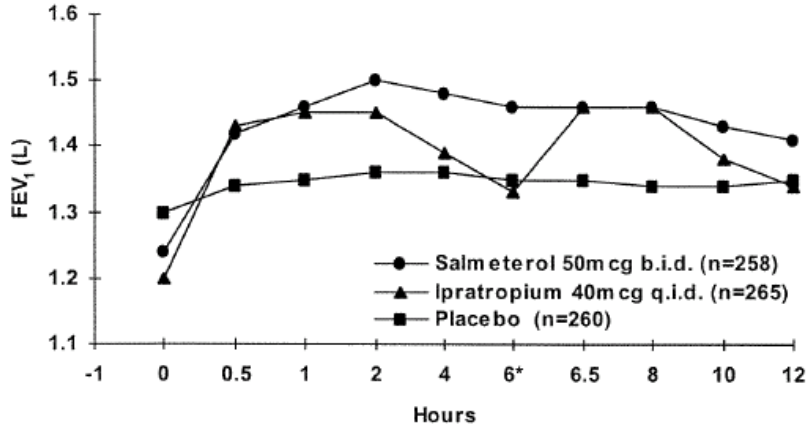
Figure 1) and last treatment (Figure 2) days.

Table 11 Results summary for COPD studies in adults (SLGA4004 and SLGA4005)

	SLGA4004 (RM1996/00370/00)			SLGA4005 (RM1996/00364/00)		
	Study Product and Dosage					
	Placebo	**Salmeterol 50 mcg BID**	**Ipratropium 40 mcg QID**	**Placebo**	**Salmeterol 50 mcg BID**	**Ipratropium 40 mcg QID**
Forced expiratory volume in 1-second (FEV_1) area under the curve (AUC)						
FEV_1 AUC (L), Week 12, n	103	107	113	113	122	112
Change From Baseline, Mean (SE)	-0.08 (0.33)	2.01 (0.32)	2.11 (0.28)	-0.74 (0.40)	2.45 (0.31)	1.77 (0.31)
Ipratropium vs. Placebo	p<0.001			p <0.001		
Salmeterol vs. Placebo	p<0.001			p <0.001		
Salmeterol vs. Ipratropium	p=0.662			p =0.070		
Transitional Dyspnea Index (TDI)						
Baseline BDI, n	135	132	138	143	135	132
Mean (SE)	6.01 (0.19)	5.96 (0.18)	6.27 (0.18)	6.29 (0.19)	5.87 (0.22)	6.04 (0.22)
TDI, Week 12, n	106	110	114	122	127	117
Mean (SE)	0.88 (0.23)	1.43 (0.25)	1.07 (0.23)	0.52 (0.25)	0.64 (0.25)	1.26 (0.26)
Ipratropium vs. Placebo	p=0.596			p=0.026		
Salmeterol vs. Placebo	p=0.135			p=0.602		
Salmeterol vs. Ipratropium	p=0.324			p=0.082		

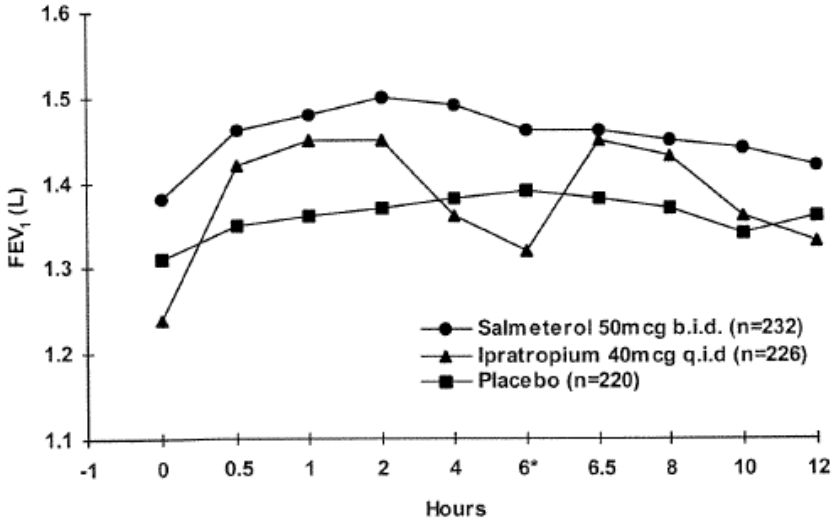
SE = standard error; n = number of subjects

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%).

16 NON-CLINICAL TOXICOLOGY

Safety Pharmacology

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 $beta_2$-adrenoceptor agonists. Salmeterol base (0.1-1.0 mg/kg i.v.) in the dog caused marked tachycardia. At 0.3 mg/kg, there was slight vasodilation and vomiting. Animals receiving 1 mg/kg showed signs of subdued behaviour. Salmeterol (25-100 mg/kg p.o.) reduced general activity in the rat. In the dog, oral salmeterol (1, 3 and 10 mg/kg) induced persistent tachycardia and cutaneous vasodilation, with some lacrimation occurring at 3 and 10 mg/kg. Salmeterol caused no overt effects on gastrointestinal function following oral administration, producing no emetic or defaecatory effects in dogs over the dose range 1-10 mg/kg and no effects on defaecatory activity in rats at doses of 25-100 mg/kg. However, emesis was observed in the dog following intravenous doses of 0.3 and 1 mg/kg.

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

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

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.

Table 12 Species comparison of single dose toxicity studies conducted with salmeterol xinafoate

Species (route)	Approx. LD_{50} (mg/kg)	Maximum Non-Lethal Dose [MNLD] (mg/kg)	MNLD as a Multiple of Therapeutic Dose
Mouse (oral)	>150	≥150	>75,000
Rat (oral)	>600	≥1000	>500,000
Rat (juvenile, oral)	>300	≥300	>150,000
Rat (inhaled)	>2.9	≥2.9	>1400
Dog(inhaled)	>0.7	≥0.7	>350

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

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

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

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

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

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

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

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

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

Salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts in Sprague Dawley rats in a 24-month inhalation/oral carcinogenicity study. Tumors were observed in rats receiving doses of 0.68 and 2.58 mg/kg per day (about 55 and 215 times the recommended clinical dose [mg/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 0.2 mg/kg (1.3 times the recommended clinical dose based on comparisons of the AUCs) and in rats at 0.21 mg/kg (15 times the recommended clinical dose on a mg/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 2 mg/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 0.6 mg/kg given orally (12 times the recommended clinical dose based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at 10mg/kg given orally (approximately 1,600 times the recommended clinical

dose on a mg/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 (100 mg/puff) of salmeterol aerosol suspension were administered to the right eyes of female New Zealand White rabbits. The left eyes served as controls. No signs of iritis or irritant reaction of the cornea were seen over the 24-hour period following the administration of salmeterol xinafoate aerosol.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrSEREVENT DISKUS
salmeterol xinafoate dry powder for inhalation

Read this carefully before you start taking SEREVENT DISKUS and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about SEREVENT DISKUS.

Serious Warnings and Precautions

SERIOUS WARNINGS FOR ASTHMA PATIENTS TAKING SEREVENT DISKUS

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

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

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

What is SEREVENT DISKUS used for?

Asthma (patients 4 years old and older):

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

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.

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

Chronic Obstructive Pulmonary Disease (COPD):

SEREVENT DISKUS is used for the long-term control of symptoms due to COPD and to prevent wheezing in adults with 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 healthcare professional for help in smoking cessation.

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

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

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

What are the ingredients in SEREVENT DISKUS?
Medicinal ingredients: salmeterol xinafoate.
Non-medicinal ingredients: lactose (milk sugar) and milk protein.

SEREVENT DISKUS comes in the following dosage forms:
SEREVENT DISKUS is a dry powder administered through a plastic inhaler device containing a foil strip with 60 blisters. Each blister contains 50 mcg of salmeterol.

Do not use SEREVENT DISKUS:
- Without an inhaled corticosteroid if you are being treated for asthma
- If you are allergic or have had an allergic reaction (swelling, anaphylactic reaction) to salmeterol or any of the ingredients in SEREVENT DISKUS
- If you have a past history of problems with the way your heart beats called cardiac tachyarrhythmias (heart beating fast and/or irregularly)
- If you are allergic to lactose (milk sugar) or milk protein

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SEREVENT DISKUS. Talk about any health conditions or problems you may have, including if you:
- Had to stop taking another medication for your breathing problems because you were allergic to it or it caused problems.
- Have been told that you are allergic to lactose (milk sugar) or milk protein.
- Are receiving treatment for a thyroid condition.
- Have diabetes.
- Have raised blood pressure.
- Have a heart problem.
- Are pregnant, planning to become pregnant or breastfeeding.
- Are taking a medicine called ketoconazole, used to treat fungal infection.

- Have a past history of seizures.

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

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

Blood Tests:
SEREVENT DISKUS can cause abnormal blood test results including increased blood sugar. Your healthcare professional will decide when to perform blood tests and will interpret the results.

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

If you notice the following warning signs, you should contact your healthcare professional as possible or go to the nearest hospital:
- **A sudden worsening of your shortness of breath and wheezing shortly after using your fast acting 'reliever' medicine or after using SEREVENT DISKUS and inhaled corticosteroid.**
- **You do not feel relief within 10 minutes after using your fast acting 'reliever' medicine or the relief does not last for at least 3 hours.**
- **Measurement from your peak flow meter indicates a value less than 60 percent of predicted or personal best.**
- **You are breathless at rest.**
- **Your pulse is more than 120 beats per minute.**

The following warning signs indicate that your asthma condition may be worsening and that your treatment needs to be reassessed by your doctor.
- A change in your symptoms such as more coughing, attacks of wheezing, chest tightness, or an unusual increase in the severity of the breathlessness.
- You wake up at night with chest tightness, wheezing or shortness of breath.
- You use increasing amounts of your fast acting 'reliever' medicine.
- Measurement from your peak flow meter indicates a value between 60 and 80 percent of predicted or personal best.

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

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

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

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

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

The following may interact with SEREVENT DISKUS:

- Medicines used to treat fungal infections, such as ketoconazole
- Medicines used to treat high blood pressure, such as diuretics, also called “water pills”
- Medicines used to treat heart problems, such as beta-blockers
- Medicines used to treat depression, such as monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants
- Other medicines to treat asthma and COPD

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

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

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

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

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

Adolescents/Children with Asthma (4 to 18 years of age):
SEREVENT DISKUS is suitable for children 4 years of age and older. The severity of asthma changes with age. Your child should therefore be periodically re-examined by a doctor. It is important to make sure that he/she understands and properly follows the asthma therapies that have been prescribed. These will include in addition to SEREVENT DISKUS, a drug which reduces the inflammation in the lung due to asthma (also known as an inhaled corticosteroid or 'controller' medication) and a rapid onset, short duration bronchodilator (also known as a fast acting 'reliever' medicine).

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

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

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

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

About your SEREVENT DISKUS:
The blisters protect the powder for inhalation from the effects of the atmosphere.

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

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

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

How to use your SEREVENT DISKUS properly:
It is important that you take each dose as instructed by your doctor, nurse, or pharmacist.

The DISKUS is easy to use. When you need a dose, just follow the six simple steps illustrated: 1. Open, 2. Slide, 3. Exhale, 4. Inhale, 5. Close, 6. Rinse.

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

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

2. Slide
Hold your DISKUS with the mouthpiece towards you. Slide the lever away until you hear another click. Your DISKUS is now ready to use.

Every time the lever is pushed back a dose is made available for inhaling. This is shown by the dose counter. Do not play with the lever as this releases doses which will be wasted.

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

4. Inhale
Before you start to inhale the dose, read through this section carefully.
Once you have fully exhaled, place the mouthpiece to your mouth and close your lips around it. Breathe in steadily and deeply through your mouth until a full breath is taken.

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

You may not be able to taste or feel the powder on your tongue, even if you have used the DISKUS correctly.

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

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

Overdose:

If you think you have taken too much SEREVENT DISKUS, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

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

Excessive use of SEREVENT DISKUS can be extremely dangerous. If you have used a larger

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

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

What are possible side effects from using SEREVENT DISKUS?
These are not all the possible side effects you may feel when taking SEREVENT DISKUS. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

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

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
UNCOMMON	**Allergic reactions**: lumpy skin rash or hives anywhere in the body.			√
	Heart problems: fast or irregular heartbeat that does not go away on its own.		√	
RARE	**Low blood potassium**: muscle weakness, and muscle spasms.		√	
	Increased amount of sugar in blood: excessive thirst, frequent urination, dry skin, blurred vision and fatigue.		√	
VERY RARE	**Allergic reactions**: sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat.			√
	Bronchospasm: sudden worsening of shortness of breath and wheezing shortly after using SEREVENT DISKUS.			√
	Mouth, throat becomes unusually irritated causing high pitched wheezing and choking.		√	

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
	High blood pressure: headache and dizziness.			√
UNKNOWN	**Worsening of lung symptoms:** increased shortness of breath, wheezing, cough and chest tightness accompanied by fever and more phlegm.		√	
	Increased excitement: feeling anxious, nervous, or agitated.	√		

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

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:
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.

If you want more information about SEREVENT DISKUS:
- Talk to your healthcare professional

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

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