

Pr **ADVAIR[®] DISKUS[®]**

salmeterol xinafoate/fluticasone propionate dry powder for inhalation

Pr **ADVAIR[®] 100 DISKUS[®]**

50 mcg salmeterol (as the xinafoate salt) and 100 mcg fluticasone propionate

Pr **ADVAIR[®] 250 DISKUS[®]**

50 mcg salmeterol (as the xinafoate salt) and 250 mcg fluticasone propionate

Pr **ADVAIR[®] 500 DISKUS[®]**

50 mcg salmeterol (as the xinafoate salt) and 500 mcg fluticasone propionate

Pr **ADVAIR[®]**

salmeterol xinafoate/fluticasone propionate inhalation aerosol

Pr **ADVAIR[®] 50**

25 mcg salmeterol (as the xinafoate salt) and 50 mcg fluticasone propionate

Pr **ADVAIR[®] 125**

25 mcg salmeterol (as the xinafoate salt) and 125 mcg fluticasone propionate

Pr **ADVAIR[®] 250**

25 mcg salmeterol (as the xinafoate salt) and 250 mcg fluticasone propionate

Bronchodilator and Corticosteroid for Oral Inhalation

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salmeterol xinafoate/fluticasone propionate dry powder for inhalation

Pr **ADVAIR[®]**

salmeterol xinafoate/fluticasone propionate inhalation aerosol

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral Inhalation	Dry Powder for inhalation/ 50 mcg salmeterol/ 100, 250, 500 mcg fluticasone propionate/blister	Lactose and milk protein
Oral Inhalation	Inhalation aerosol/ 25 mcg salmeterol/ 50, 125, 250 mcg fluticasone propionate/metered dose	1,1,1,2-tetrafluoroethane (HFA-134a)

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

INDICATIONS AND CLINICAL USE

ASTHMA

ADVAIR[®] (salmeterol xinafoate/fluticasone propionate) is indicated for:

- the maintenance treatment of asthma in patients with reversible obstructive airways disease where the use of a combination product is considered to be appropriate.

When treating asthma patients, ADVAIR[®]/ADVAIR[®] DISKUS[®] should be used only in patients whose conditions are not adequately controlled using low- to medium-dose inhaled corticosteroids or the severity of whose disease clearly warrants the initiation of treatment with two maintenance therapies. ADVAIR[®]/ADVAIR[®] DISKUS[®] is **not** indicated for patients whose asthma can be managed by occasional use of a rapid onset, short duration, inhaled beta₂-agonist or for patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of a rapid onset, short duration, inhaled beta₂-agonist.

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

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

ADVAIR[®] 250 DISKUS[®] and ADVAIR[®] 500 DISKUS[®] are indicated for:

- the maintenance treatment of COPD, including emphysema and chronic bronchitis, in patients where the use of a combination product is considered appropriate.

ADVAIR[®] DISKUS[®] should not be used as a rescue medication.

Physicians should reassess patients several months after the initiation of ADVAIR[®] DISKUS[®] and if symptomatic improvement has not occurred, ADVAIR[®] DISKUS[®] should be discontinued.

Geriatrics:

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

Pediatrics (< 4 years of age):

At present, there is insufficient clinical data to recommend the use of ADVAIR[®] DISKUS[®] in children younger than 4 years of age and the use of ADVAIR[®] inhalation aerosol in children younger than 12 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Patients with IgE mediated allergic reactions to lactose (which contains milk protein) or milk (ADVAIR[®] DISKUS[®] users only).
- Patients with cardiac tachyarrhythmias.
- Patients with untreated fungal, bacterial or tuberculous infections of the respiratory tract.
- In the primary treatment of status asthmaticus or other acute episodes of asthma, or in patients with moderate to severe bronchiectasis.

WARNINGS AND PRECAUTIONS

General

Information concerning a study regarding salmeterol, a component of ADVAIR[®]/ADVAIR[®] DISKUS[®]

WARNING: Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR[®]/ADVAIR[®] DISKUS[®], may increase the risk of asthma-related death. When treating asthma patients, ADVAIR[®]/ADVAIR[®] DISKUS[®] should be used only in patients whose conditions are not adequately controlled using low- to medium- dose inhaled corticosteroids or the severity of whose disease clearly warrants the initiation of treatment with two maintenance therapies. Data from a large placebo-controlled US study (Salmeterol Multi-center Asthma Research Trial, also known as “SMART”) comparing the safety of salmeterol (SEREVENT[®] Inhalation Aerosol) to that of a placebo added to the original 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). Data from this study also suggested that African American patients may be at greater risk of serious respiratory-related events or deaths when using salmeterol compared to placebo. It is not known if this was due to pharmacogenetic or other factors (see CLINICAL TRIALS: CLINICAL STUDIES IN ASTHMA: Salmeterol Multi-center Asthma Research Trial).

ADVAIR[®] (salmeterol xinafoate/fluticasone propionate) should not be used to treat acute symptoms of asthma. It is crucial to inform patients of this and prescribe rapid onset, short duration inhaled bronchodilator (e.g., salbutamol) to relieve the acute symptoms of asthma. Patients should be clearly instructed to use rapid onset, short duration, inhaled beta₂-agonists only for symptomatic relief if they develop asthma symptoms while taking ADVAIR[®]. When beginning treatment with ADVAIR[®], patients who have been taking rapid onset, short duration, inhaled beta₂-agonists on a regular basis (e.g., q.i.d) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief if they develop acute symptoms of asthma while taking ADVAIR[®].

Discontinuance

Treatment with inhaled corticosteroids should not be stopped abruptly in patients with asthma due to risk of exacerbation. In this case, therapy should be titrated down gradually, under physician supervision. For patients with COPD, cessation of therapy may be associated with symptomatic decompensation and should be supervised by a physician.

Cardiovascular And Other Effects

Although clinically not significant, a small increase in QTc interval has been reported with therapeutic doses of salmeterol. It is not known if this becomes clinically significant when concomitant medications causing similar effects are prescribed and/or in the presence of heart diseases, hypokalemia, or hypoxia. 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.

No clinically significant effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol in recommended doses. Cardiovascular effects such as increased blood pressure and heart rate may occasionally be seen with all sympathomimetic drugs, especially at higher than therapeutic doses. Central nervous system effects (increased excitement) can occur after the use of salmeterol. Occurrence of cardiovascular or central nervous system effects may require discontinuation of the drug.

For this reason, salmeterol xinafoate/fluticasone propionate, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

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

Ear/Nose/Throat

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

Also see Immune, Candidiasis.

Endocrine And Metabolism

Systemic Steroid Replacement by Inhaled Steroid

Particular care is needed in patients who are transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer. For the transfer of patients being treated with oral corticosteroids, inhaled corticosteroids should first be added to the existing oral steroid therapy which is then gradually withdrawn.

Patients with adrenocortical suppression should be monitored regularly and the oral steroid reduced cautiously. Some patients transferred from other inhaled steroids or oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled fluticasone propionate.

After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although inhaled fluticasone propionate may provide control of asthmatic symptoms during these episodes, it does not provide the systemic steroid which is necessary for coping with these emergencies. The physician may consider supplying oral steroids for use in times of stress (e.g. worsening asthma attacks, chest infections, and surgery).

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning and evening cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal only if it falls at or near the normal mean level.

Systemic Effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods; these effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, and adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density (BMD), cataract and glaucoma. It is important therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained (see Monitoring and Laboratory Tests).

The long-term effects of fluticasone propionate in human subjects are still unknown. The local effect of the drug on developmental or immunologic processes in the mouth, pharynx, trachea, and lungs is unknown. There is also no information about the possible long-term systemic effects of the agent (see Monitoring and Laboratory Tests).

Long-term use of orally inhaled corticosteroids may affect normal bone metabolism resulting in a loss of bone mineral density. In patients with major risk factors for decreased bone mineral content, such as chronic alcohol use, tobacco use, age, sedentary lifestyle, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), ADVAIR[®] may pose an additional risk.

Effects of treatment with ADVAIR[®] DISKUS[®] 50/500 mcg, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on BMD was evaluated in a subset of 658 patients (females and males 40 to 80 years of age) with COPD in a 3 year study (SCO30003). BMD evaluations were conducted at baseline and at 48, 108 and 158 weeks. There were no significant differences between any of the treatment groups at 3 years. A slight reduction in BMD measured at the hip was observed in all treatment groups (ADVAIR[®] DISKUS[®] -3.2%, fluticasone propionate -2.9%, salmeterol -1.7%, placebo -3.1%). Fracture risk was estimated for the entire population of patients with COPD in study SCO30003 (N = 6,184). There were no significant differences between any of the treatment groups. The probability of a fracture over 3 years was 6.3% for ADVAIR[®] DISKUS[®], 5.4% for fluticasone propionate, 5.1% for salmeterol, and 5.1% for placebo.

During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects (see DRUG INTERACTIONS).

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

Metabolic Effects

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

salmeterol/fluticasone propionate should be used with caution in patients predisposed to low levels of serum potassium.

The possibility of impaired adrenal response should always be borne in mind in emergency and elective situations likely to produce stress and appropriate corticosteroid treatment must be considered.

Certain individuals can show greater susceptibility to the effects of inhaled corticosteroid than do most patients.

In common with other beta-adrenergic agents, salmeterol can induce reversible metabolic changes (hyperglycemia, hypokalemia). There have been very rare reports of increases in blood glucose levels and this should be considered when prescribing to patients with a history of diabetes mellitus.

There is an enhanced effect of corticosteroids on patients with hypothyroidism.

Hematologic

Eosinophilic Conditions

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alerted to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established.

Hepatic/Biliary/Pancreatic

There is an enhanced effect of corticosteroids on patients with cirrhosis.

Hypersensitivity

Immediate hypersensitivity reactions may occur after administration of salmeterol, as demonstrated by rare cases of urticaria, angioedema, rash and bronchospasm, and very rare cases of anaphylactic reactions, anaphylactic shock.

Immune

Candidiasis

Therapeutic dosages of fluticasone propionate frequently cause the appearance of Candida albicans (thrush) in the mouth and throat. The development of pharyngeal and laryngeal candidiasis is a cause for concern because the extent of its penetration into the respiratory tract is unknown. Patients may find it helpful to rinse the mouth and gargle

with water after using ADVAIR[®]. Symptomatic candidiasis can be treated with topical anti-fungal therapy while continuing to use ADVAIR[®].

Infection

Corticosteroids may mask some signs of infection and new infections may appear. A decreased resistance to localised infection has been observed during corticosteroid therapy. This may require treatment with appropriate therapy or stopping the administration of fluticasone propionate until the infection is eradicated. Patients who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with intramuscular pooled immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

For patients with asthma or COPD, consideration should be given to additional corticosteroid therapy and to antibiotics if an exacerbation is associated with an infection.

For COPD patients, it is important that even mild chest infections be treated immediately since these patients may be more susceptible to damaging lung infections than healthy individuals. Patients should be instructed to contact their physician as soon as possible if they suspect an infection.

Physicians should recommend that COPD patients receive an annual influenza vaccination.

In a 3 year study of 6,184 patients with COPD (SCO30003) there was an increased reporting of any adverse event of pneumonia in patients receiving ADVAIR[®] 50/500 mcg compared with placebo (16% on ADVAIR[®] DISKUS[®] 50/500 mcg, 14% on fluticasone propionate 500 mcg, 11% on salmeterol 50 mcg and 9% on placebo). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap (see CLINICAL TRIAL ADVERSE DRUG REACTIONS, COPD).

Ophthalmologic

For patients at risk, monitoring of ocular effects (cataract and glaucoma) should also be considered in patients receiving maintenance therapy with ADVAIR[®].

Effects of treatment with ADVAIR[®] DISKUS[®] 50/500 mcg, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on development of cataracts or glaucoma was evaluated in a subset of 658 patients with COPD in a 3 year (SCO30003) study. Ophthalmic examinations were conducted at baseline and at 48, 108 and 158 weeks. The

presence of cataracts and glaucoma at baseline was similar across treatment groups (61% to 71% and 5% to 8%, respectively). New cataracts were diagnosed in all treatment groups (26% on ADVAIR[®] DISKUS[®] 50/500 mcg, 17% on fluticasone propionate, 15% on salmeterol, and 21% on placebo). A few new cases of glaucoma were diagnosed (2% on ADVAIR[®] DISKUS[®] 50/500 mcg, 5% on fluticasone propionate, none on salmeterol, and 2% on placebo). There were no significant differences in the development of glaucoma or cataracts between any of the treatment groups.

Respiratory

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

Special Populations

Use In Women

Pregnant Women

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

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.

Like other glucocorticoids, fluticasone propionate is teratogenic to rodent species. Adverse effects typical of potent corticosteroids are only seen at high systemic exposure levels; administration by inhalation ensures minimal systemic exposure. The relevance of these findings to humans has not yet been established since well-controlled trials relating to fetal risk in humans are not available. Infants born of mothers who have received substantial doses of glucocorticoids during pregnancy should be carefully observed for hypoadrenalism.

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 ADVAIR[®] during labour should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Women

Plasma levels of salmeterol after inhaled therapeutic doses are very low (85 to 200 pg/mL) in humans and therefore levels in milk should be correspondingly low.

Studies in lactating animals indicate that salmeterol is likely to be secreted in only very small amounts in breast milk.

Glucocorticoids are excreted in human milk. The excretion of fluticasone propionate into human breast milk has not been investigated. When measurable plasma levels were obtained in lactating laboratory rats following subcutaneous administration, there was evidence of fluticasone propionate in the breast milk. However, plasma levels in patients following inhaled fluticasone propionate at recommended doses are likely to be low.

Since there is no experience with use of ADVAIR[®] 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.

Pediatrics: (≥ 4 years of age): In adolescents and children, the severity of asthma may vary with age and periodic reassessment should be considered to determine if continued maintenance therapy with ADVAIR[®] is still indicated.

Also see Monitoring and Laboratory Tests.

The safety and efficacy of ADVAIR[®] DISKUS[®] in children younger than 4 years of age have not been established.

The safety and efficacy of ADVAIR[®] inhalation aerosol in children younger than 12 years of age have not been established.

Geriatrics: As with other beta₂-agonists, special caution should be observed when using salmeterol in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Based on available data, no adjustment of salmeterol dosage in geriatric patients is warranted.

Monitoring And Laboratory Tests

Monitoring Control of Asthma or COPD

ADVAIR[®] should not be introduced in acutely deteriorating asthma or COPD, which is a potentially life threatening condition. Increasing use of rapid onset, short duration inhaled bronchodilators to control symptoms indicates deterioration of asthma control. Sudden and progressive deterioration in asthma control is potentially life-threatening and the treatment plan should be re-evaluated. Also, where current dosage of ADVAIR[®] has failed to give adequate control of reversible obstructive airways disease the patient should be reviewed by a physician. Before introducing ADVAIR[®], adequate education should be provided to the patient on how to use the drug and what to do if asthma flares up.

During long-term therapy, HPA axis function and haematological status should be assessed periodically. For patients at risk, monitoring of bone and ocular effects (cataract and glaucoma) should also be considered in patients receiving maintenance therapy with

ADVAIR[®]. It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a rapid onset, short duration inhaled bronchodilator. ADVAIR[®] (salmeterol xinafoate/fluticasone propionate) should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

The type and severity of adverse reactions associated with salmeterol xinafoate and fluticasone propionate may be expected with ADVAIR[®]. There is no incidence of additional adverse events following combined administration of the two compounds.

Salmeterol Xinafoate

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

Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) may occur in some patients.

There have been reports of arthralgia and hypersensitivity reactions, including rash, urticaria, bronchospasm, edema, angioedema, anaphylactic reaction and anaphylactic shock.

There have been reports of oropharyngeal irritations as well as common reports of muscle cramps.

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

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

Fluticasone Propionate

In general, inhaled corticosteroid therapy may be associated with dose dependent increases in the incidence of ocular complications, reduced bone density, suppression of HPA axis responsiveness to stress, and inhibition of growth velocity in children. Such events have been reported rarely in clinical trials with fluticasone propionate.

Possible systemic effects include Cushing's syndrome, Cushingoid features and adrenal suppression.

Glaucoma may be exacerbated by inhaled corticosteroid treatment. In patients with established glaucoma who require long-term inhaled corticosteroid treatment, it is prudent to measure intraocular pressure before commencing the inhaled corticosteroid and to monitor it subsequently. In patients without established glaucoma, but with a potential for developing intraocular hypertension (e.g. the elderly), intraocular pressure should be monitored at appropriate intervals.

In elderly patients treated with inhaled corticosteroids, the prevalence of posterior subcapsular and nuclear cataracts is probably low but increases in relation to the daily and cumulative lifetime dose. Cofactors such as smoking, ultraviolet B exposure, or diabetes may increase the risk. Children may be less susceptible.

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if any child's or adolescent's growth appears slowed.

Osteoporosis and fracture are the major complications of long-term treatment with parenteral or oral steroids. Inhaled corticosteroid therapy is also associated with dose-dependent bone loss although the degree of risk is very much less than with oral steroid. This risk may be offset by estrogen replacement in post-menopausal women, and by titrating the daily dose of inhaled steroid to the minimum required to maintain optimal control of respiratory symptoms. It is not yet known whether the peak bone density achieved during youth is adversely affected if substantial amounts of inhaled corticosteroid are administered prior to 30 years of age.

Failure to achieve maximal bone density during youth could increase the risk of osteoporotic fracture when those individuals reach 60 years of age and older.

Hoarseness and candidiasis (thrush) of the mouth and throat can occur in some patients receiving inhaled fluticasone propionate. These may be relieved by rinsing the mouth and gargling with water after use of ADVAIR[®]. Symptomatic candidiasis can be treated with topical anti-fungal therapy while still continuing with ADVAIR[®] (see WARNINGS AND PRECAUTIONS, Drug Interactions).

There have been uncommon reports of cutaneous hypersensitivity reactions. There have also been rare reports of hypersensitivity reactions manifesting as angioedema (mainly facial and oropharyngeal edema), respiratory symptoms (dyspnea and/or bronchospasm) and very rarely, anaphylactic reactions.

There have been very rare reports of anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children and adolescents).

Eosinophilic Conditions

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alerted to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established.

Asthma

Data from a large placebo-controlled US study comparing the safety of salmeterol to that of a placebo added to the original asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. Data from this study also suggested that African American patients may be at greater risk of serious respiratory-related events or deaths when using salmeterol compared to placebo. It is not known if this was due to pharmacogenetic or other factors (see CLINICAL TRIALS: CLINICAL STUDIES IN ASTHMA: Salmeterol Multi-center Asthma Research Trial (SMART)).

Clinical Trial Adverse Drug Reactions

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

Asthma

Use in adolescents and adults

There have been very rare reports of anxiety, sleep disorders and behavioural changes including hyperactivity and irritability (predominantly in children and adolescents).

There have been uncommon reports of contusions (skin bruising).

ADVAIR[®] DISKUS[®]

In clinical trials involving 1824 adult and adolescent patients, the most commonly reported adverse events with the combination salmeterol xinafoate/fluticasone propionate

DISKUS[®] were: hoarseness/dysphonia, throat irritation, headache, candidiasis of mouth and throat and palpitations as detailed in the table below:

Table 1 Number (and percentage) of patients with drug-related adverse events (incidence $\geq 1\%$ ¹) (Safety Population)

Adverse events	Salmeterol xinafoate/fluticasone propionate combination product	Salmeterol xinafoate and Fluticasone propionate concurrent therapy	Fluticasone propionate alone	Salmeterol xinafoate alone	Placebo
Number of patients	644	486	339	180	175
Any event	110 (17%)	81 (17%)	50 (15%)	9 (5%)	5 (3%)
Hoarseness/dysphonia	15 (2%)	11 (2%)	8 (2%)	1 (<1%)	0
Throat irritation	14 (2%)	10 (2%)	8 (2%)	1 (<1%)	1 (<1%)
Candidiasis of mouth and throat	15 (2%)	9 (2%)	5 (1%)	0	0
Headaches	16 (2%)	11 (2%)	3 (<1%)	0	0
Asthma ²	9 (1%)	11 (2%)	3 (<1%)	0	0
Palpitations	7 (1%)	4 (<1%)	2 (<1%)	1 (<1%)	0
Cough	6 (<1%)	2 (<1%)	5 (1%)	1 (<1%)	0
Breathing disorders	6 (<1%)	2 (<1%)	4 (1%)	0	0
Candidiasis-unspecified site	6 (<1%)	3 (<1%)	4 (1%)	0	2 (1%)
Upper respiratory tract infection	5 (<1%)	5 (1%)	2 (<1%)	0	0

¹ in any integrated treatment group
² asthma was not recorded as an adverse event in those studies which included treatment with salmeterol xinafoate alone or placebo (unless it was a serious adverse event)

In the ADVAIR[®] DISKUS[®] group, there was no apparent relationship to fluticasone propionate dose for drug-related adverse events (15% with 50/100 mcg, 19% with 50/250 mcg and 17% with 50/500 mcg).

ADVAIR[®] Inhalation Aerosol

In clinical trials, the most commonly reported adverse events with the combination salmeterol xinafoate/fluticasone propionate inhalation aerosol were: hoarseness/dysphonia, throat irritation and headache. All other adverse events with a reasonable possibility of being related to study drug were reported in $\leq 1\%$ of subjects.

Table 2 Number (and percentage) of patients with drug-related adverse events (incidence $\geq 1\%$ ¹) (Safety Population)

Adverse events	Salmeterol xinafoate/fluticasone propionate MDI combination product	Fluticasone propionate alone	Salmeterol xinafoate alone	Placebo
Number of patients	622	614	274	176
Any event	67 (11 %)	71 (11 %)	29 (11%)	9 (5%)
Hoarseness/dysphonia	13 (2 %)	7 (1 %)	3 (2 %)	0 (0 %)
Throat irritation	13 (2 %)	14 (2 %)	10 (4 %)	3 (2 %)
Candidiasis of mouth and throat	8 (1 %)	8 (1 %)	0 (0 %)	1 (<1 %)
Headaches	11 (2 %)	11 (2 %)	5 (2 %)	3 (2 %)
Cough	3 (<1 %)	3 (<1 %)	6 (2%)	1 (<1 %)
Hyposalivation	6 (1 %)	2 (<1 %)	1 (<1 %)	0 (0 %)

¹ in any integrated treatment group
MDI = metered dose inhaler

The incidence of drug-related adverse events for the MDI combination product groups was similar to the individual components.

Use in children

A total of 257 pediatric patients participated in the clinical development programme and received either the combination 50 mcg salmeterol xinafoate/100 mcg fluticasone propionate DISKUS[®] or concurrent therapy (with salmeterol and fluticasone propionate administered via separate inhalers). Only one drug-related adverse event, candidiasis, was reported with an incidence of 2% or more in the ADVAIR[®] group. The combination product was generally well tolerated and the safety profile was comparable to that observed in the concurrent therapy group.

There have been very rare reports of anxiety, sleep disorders and behavioural changes including hyperactivity and irritability (predominantly in children and adolescents).

COPD

Clinical trial adverse drug reaction data is provided for two 24-week studies, a 52-week study and a 3-year study.

24-week studies

In clinical trials involving 2054 adults, the most commonly reported adverse events with ADVAIR[®] DISKUS[®] after 24 weeks were: upper respiratory tract infection, throat irritation, headache and musculoskeletal pain as detailed in the table below. These adverse reactions were mostly mild to moderate in severity.

The following table includes all events (whether considered drug-related or non drug-related by the investigator) that occurred at a rate of 3% or greater in either of the groups receiving ADVAIR[®] DISKUS[®] and were more common than in the placebo group.

Table 3 Overall adverse experiences with $\geq 3\%$ incidence in controlled clinical trials with ADVAIR[®] DISKUS[®] in patients with COPD

Adverse Event	ADVAIR [®] DISKUS [®] 50/500 mcg (n = 169) %	ADVAIR [®] DISKUS [®] 50/250 mcg (n = 178) %	Fluticasone propionate 500 mcg (n = 391) %	Fluticasone propionate 250 mcg (n = 399) %	Salmeterol 50 mcg (n = 341) %	Placebo (n = 576) %
Any event	78	70	80	74	68	69
Ear, nose, and throat						
Upper respiratory tract infection	17	12	18	16	11	15
Nasal congestion/blockage	4	3	7	4	4	3
Throat irritation	11	8	9	9	7	6
Upper respiratory inflammation	9	2	7	5	5	5
Sinusitis	3	3	3	6	4	2
Sinusitis/sinus infection	4	2	2	2	1	2
Hoarseness/dysphonia	3	5	5	5	<1	1
Candidiasis mouth/throat	7	10	12	6	2	<1
Lower respiratory						
Viral respiratory infections	8	6	9	5	5	4
Neurology						
Dizziness	3	4	2	2	4	2
Headaches	18	16	17	13	14	11
Gastrointestinal						
Nausea & vomiting	4	2	4	4	3	3
Non-site specific						
Fever	4	4	3	3	1	3
Musculoskeletal						
Malaise & fatigue	4	3	3	3	2	3
Muscle cramps & spasms	8	3	2	2	3	1
Muscle pain	4	0	3	2	1	<1
Musculoskeletal pain	12	9	9	10	12	10

Other COPD Clinical Trial Adverse Drug Reactions (1-3%)

Cardiovascular: arrhythmias, hypertension, palpitations

Drug Interaction, Overdose and Trauma: contusions, fractures, hematomas, lacerations and wounds

Ear/Nose/Throat: ear/nose/throat infections, ear/nose/throat signs and symptoms, ear signs and symptoms, epistaxis, laryngitis, nasal sinus disorders, pharyngitis/throat infections, rhinorrhea/post nasal drip, sputum abnormalities

Endocrine and Metabolism: diabetes mellitus, hypothyroidism

Gastrointestinal: constipation, dental discomfort and pain, diverticulosis, dyspeptic symptoms, gastrointestinal infections, gum signs and symptoms, hyposalivation, oral discomfort and pain; oral lesions, regurgitation and reflux

Hepatic/Biliary/Pancreatic: abnormal liver function tests

Immune: bacterial infections, candidiasis unspecified site, viral infections

Neurologic: anxiety, situational disorders, sleep disorders, syncope, tremors, vertigo

Non-Site Specific: bone and skeletal pain, edema and swelling, non-site specific pain, non-specific condition, soft tissue injuries

Ophthalmologic: dry eyes, eye infections, lacrimal disorders, ocular pressure disorders, visual disturbances

Per-Operative Considerations: postoperative complications

Respiratory: breathing disorders, bronchitis, lower respiratory hemorrhage, lower respiratory signs and symptoms, pneumonia

Skin: fungal skin infections and skin infections

52-week study

After 52 weeks of treatment with ADVAIR[®] DISKUS[®] (50/500 mcg), fluticasone propionate 500 mcg, salmeterol 50 mcg and placebo in 1465 patients with COPD, the most commonly reported drug related adverse event was candidiasis of the mouth and throat (ADVAIR[®] DISKUS[®] 50/500 mcg, 6%; fluticasone propionate 500 mcg, 6%; salmeterol 50 mcg, 1%; placebo, 1%).

3-year study

Study SCO30003 provided safety data on 6,184 patients with moderate to severe COPD who were randomised and received at least one dose of study medication and treated for up to 3 years; defined as the Safety population. The safety profile of ADVAIR[®] over the three-year treatment period was comparable to that seen in previous studies of shorter duration, confirming the long-term tolerability of ADVAIR[®]. All three active treatments were well tolerated and the adverse events reported were generally those expected based on clinical experience with these treatments, with the exception of pneumonia. The estimated 3 year probability of having pneumonia reported as an adverse event was 12.3% for placebo, 13.3% for salmeterol, 18.3% for fluticasone propionate and 19.6% for ADVAIR[®] (Hazard ratio for ADVAIR[®] vs placebo: 1.64, 95% CI: 1.33 to 2.01, $p < 0.001$). There was no increase in pneumonia related deaths for ADVAIR[®]; deaths while on treatment that were adjudicated as primarily due to pneumonia were 7 for placebo, 9 for salmeterol, 13 for fluticasone propionate and 8 for ADVAIR[®]. There was no significant difference in probability of bone fracture (5.1% placebo, 5.1% salmeterol, 5.4% fluticasone propionate and 6.3% ADVAIR[®]; Hazard ratio for ADVAIR[®] versus placebo: 1.22, 95% CI: 0.87 to 1.72, $p=0.248$). The incidence of adverse events of eye disorders, bone disorders, and HPA axis disorders was low and there was no difference observed between treatments. There was no evidence of an increase in cardiac events for ADVAIR[®], salmeterol, and fluticasone propionate.

Post-Market Adverse Drug Reactions

There have been uncommon reports of cutaneous hypersensitivity reactions. There have also been rare reports of hypersensitivity reactions manifesting as angioedema (mainly facial and oropharyngeal edema), respiratory symptoms (dyspnea and/or bronchospasm) and very rarely, anaphylactic reactions, anaphylactic shock.

There have been very rare reports of anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children and adolescents). Very rarely, hyperglycemia and hypertension have been reported.

DRUG INTERACTIONS

Overview

Use ADVAIR[®] (salmeterol xinafoate/fluticasone propionate) with caution in patients receiving other medications causing hypokalemia and/or increased QTc interval (diuretics, high dose steroids, anti-arrhythmics, astemizole, terfenadine) since cardiac and vascular effects may be potentiated.

Salmeterol Xinafoate

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

Fluticasone Propionate

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions involving fluticasone propionate are unlikely.

A drug interaction study of intranasal fluticasone propionate in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects.

This study has shown that other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. However, there have been a few case reports during world-wide post-market use of adrenal cortisol suppression associated with concomitant use ofazole anti-fungals and inhaled fluticasone propionate. Therefore, care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole) as there is potential for increased systemic exposure to fluticasone propionate.

Drug-Drug Interactions

Table 5 **Established or Potential Drug-Drug Interactions**

Proper name	Ref	Effect	Clinical comment
Sympathomimetic agents	CT	May lead to deleterious cardiovascular effects.	Aerosol bronchodilators of the rapid onset, short duration adrenergic stimulant type may be used for relief of breakthrough symptoms while using salmeterol for asthma. Increasing use of such preparations to control symptoms indicates deterioration of disease control and the patient's therapy plan should be reassessed. The regular, concomitant use of salmeterol and other sympathomimetic agents is not recommended.
Mono amine 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 asthma or COPD. Cardioselective beta-blocking drugs should be used with caution in patients with asthma or COPD.
Acetylsalicylic acid	T		Use with caution in conjunction with corticosteroids in hypoprothrombinemia.
Ritonavir	CT & post-marketing	Systemic effects including Cushings syndrome and adrenal suppression.	Concomitant use of fluticasone propionate and ritonavir should be avoided. (See DRUG INTERACTIONS, Overview)
Other inhibitors of cytochrome P450 3A4	CT	Increased systemic exposure to salmeterol xinafoate and fluticasone propionate.	Caution is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole). (See DRUG INTERACTIONS, Overview, WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics)

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

When treating asthma patients, ADVAIR[®]/ADVAIR[®] DISKUS[®] should be used only in patients whose conditions are not adequately controlled using low- to medium-dose inhaled corticosteroids or the severity of whose disease clearly warrants the initiation of treatment with two maintenance therapies. ADVAIR[®]/ADVAIR[®] DISKUS[®] is **not** indicated for patients whose asthma can be managed by occasional use of a rapid onset, short duration, inhaled beta₂-agonist or for patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of a rapid onset, short duration, inhaled beta₂-agonist.

ADVAIR[®] (salmeterol xinafoate/fluticasone propionate) should not be used to treat acute symptoms of asthma or COPD. It is crucial to inform patients of this.

For asthma, a rapid onset, short duration beta₂-agonist should be prescribed for this purpose. 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. Sudden worsening of symptoms may require increased corticosteroid dosage, which should be administered under medical supervision.

As twice-daily regular treatment, ADVAIR[®] provides twenty-four hour bronchodilation and can replace regular use of a rapid onset, short duration (4 hour) inhaled or oral bronchodilator (e.g. salbutamol). Rapid onset, short duration beta₂-agonists should be used only to relieve acute symptoms of asthma (see WARNINGS AND PRECAUTIONS).

Patients should be regularly reassessed so that the strength of ADVAIR[®] they are receiving remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose of fluticasone propionate at which effective control of symptoms is maintained.

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.

Recommended Dose And Dosage Adjustment

ADVAIR[®] DISKUS[®]

	Asthma		COPD	
	Children 4-11 years of age	Adults and adolescents ≥12 years of age	Adults ≥18 years of age	
ADVAIR [®] 100 DISKUS [®]	One inhalation twice daily	One inhalation twice daily	--	OR
ADVAIR [®] 250 DISKUS [®]	--	One inhalation twice daily	One inhalation twice daily	OR
ADVAIR [®] 500 DISKUS [®]	--	One inhalation twice daily	One inhalation twice daily	

ADVAIR[®] Inhalation Aerosol

	Asthma	
	Adults and adolescents ≥12 years of age	
ADVAIR [®] 50*	Two inhalations twice daily	OR
ADVAIR [®] 125	Two inhalations twice daily	OR
ADVAIR [®] 250	Two inhalations twice daily	

*ADVAIR[®] 50 is not available in Canada

Use with Spacer Devices

Spacer devices may be used in patients who have difficulty coordinating the actuation of a metered dose inhaler (MDI) with inhalation. The dosage of ADVAIR[®] inhalation aerosol should be adjusted according to individual response. For patients whose asthma has been stabilized without the use of a spacer device, continuation of therapy with a spacer may require a dosage adjustment.

Two small single dose pharmacokinetic studies were conducted in subjects with asthma to investigate the performance of various spacer devices. The studies showed that following the administration of ADVAIR[®] inhalation aerosol, the exposure to both fluticasone propionate (FP) and salmeterol xinafoate (SAL) was significantly higher (up to 4 fold) when used with the AeroChamber Max spacer, compared to the MDI alone. Exposure to FP and SAL was also increased with the use of the AeroChamber Plus and Ventahaler spacers, but to a lesser degree than that seen with the AeroChamber Max spacer. The long term safety and clinical effect of using a spacer device with ADVAIR[®] inhalation aerosol was not evaluated in these studies.

Missed Dose

If a single dose is missed, instruct the patient to take the next dose when it is due.

Administration

ADVAIR[®] is to be administered by oral inhalation only.

The patient should be made aware that for optimum benefit ADVAIR[®] should be taken regularly, even when asymptomatic.

As a general rule, rinsing the mouth and gargling with water after each inhalation can help in preventing the occurrence of candidiasis. Cleansing dentures has the same effect.

OVERDOSAGE

ADVAIR[®] (salmeterol xinafoate/fluticasone propionate) should not be used more frequently than twice daily (morning and evening) at the recommended dose. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs (See WARNINGS AND PRECAUTIONS). 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.

There are no data available from clinical trials on overdose with ADVAIR[®] (salmeterol xinafoate/fluticasone propionate), however data on overdose with individual drugs is given below.

The expected signs and symptoms of salmeterol overdose are those typical of excessive beta₂-adrenergic stimulation, including tremor, headache, tachycardia, increases in systolic blood pressure, cardiac arrhythmias, hypokalemia, hypertension and, in extreme cases, sudden death. Treatment should be symptomatic; cardiac and respiratory function should be monitored and support provided if necessary. The preferred antidote is the judicious use of a cardioselective beta-blocking agent. Cardioselective beta-blocking drugs should be used with caution, bearing in mind the danger of inducing an asthmatic attack. Serum potassium level should be monitored. If ADVAIR[®] therapy has to be withdrawn due to overdose of the beta-agonist component of the drug; provision of appropriate replacement steroid therapy should be considered.

Acute inhalation of fluticasone propionate doses in excess of those approved may lead to temporary suppression of the hypothalamic-pituitary-adrenal axis. This does not usually require emergency action, as normal adrenal function typically recovers within a few days.

If higher than approved doses are continued over prolonged periods, significant adrenocortical suppression is possible. There have been very rare reports of acute adrenal crisis occurring in children exposed to higher than approved dosages (typically 1000 mcg daily and above), over prolonged periods (several months or years); observed features included hypoglycemia and sequelae of decreased consciousness and/or convulsions. Situations which would potentially trigger acute adrenal crisis include exposure to trauma, surgery or infection or any rapid reduction in dosage. Patients receiving higher than approved dosages should be managed closely and the dose reduced gradually.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism Of Action

ADVAIR[®] (salmeterol xinafoate/fluticasone propionate) contains salmeterol xinafoate and fluticasone propionate which have differing modes of action for the treatment of COPD and reversible obstructive airways disease, including asthma. Salmeterol is a long-acting bronchodilator that prevents breakthrough symptoms of wheezing and chest tightness; fluticasone propionate is an inhaled anti-inflammatory agent that reduces airways irritability. ADVAIR[®] can offer a more convenient regime for patients requiring concurrent long-acting beta₂-agonists and inhaled corticosteroid therapy. ADVAIR[®] is designed to produce a greater improvement in pulmonary function and symptom control than either fluticasone propionate or salmeterol used alone at their recommended dosages. The respective mechanisms of action of both drugs are discussed below:

Salmeterol is a selective, long-acting (12 hours), slow onset (10-20 minutes) beta₂-adrenoceptor agonist with a long side-chain which binds to the exo-site of the receptor. Salmeterol offers more effective protection against histamine-induced bronchoconstriction and produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional rapid onset, short duration beta₂-agonists.

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

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

Fluticasone propionate is a highly potent glucocorticoid anti-inflammatory steroid. When administered by inhalation at therapeutic dosages, it has a direct potent anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, and less adverse effects than systemically administered corticosteroids.

In comparisons with beclomethasone dipropionate, fluticasone propionate has demonstrated greater topical potency.

Pharmacodynamics

The pharmacodynamic effects and pharmacokinetics of the combination product in the DISKUS[®] powder inhaler were investigated in healthy adult male and female volunteers after single and repeat-dose administration.

Those studies showed that the systemic pharmacodynamic effects of salmeterol xinafoate and fluticasone propionate are essentially unchanged when the two drugs are administered in combination, when compared with the component drugs given alone or concurrently.

There was no evidence that the systemic exposure to salmeterol was altered by concomitant exposure to fluticasone propionate. In one study, the salmeterol plasma C_{max} and T_{max} were not significantly different when compared between the groups receiving salmeterol xinafoate 100 mcg and fluticasone propionate 500 mcg twice daily in the combination product (C_{max} 0.23 ng/mL) or salmeterol xinafoate 100 mcg twice daily as a single agent (C_{max} 0.22 ng/mL).

When fluticasone propionate alone or the salmeterol xinafoate/fluticasone propionate product are administered at the same dosage, there is similar systemic exposure to fluticasone propionate.

Pharmacokinetics

There is no evidence in animal or human subjects that the administration of salmeterol xinafoate and fluticasone propionate together by the inhaled route affects the pharmacokinetics of either component. For pharmacokinetic purposes therefore each component can be considered separately.

Salmeterol Xinafoate

Salmeterol acts locally in the lung; therefore, plasma levels are not an indication of therapeutic effect. Because of the low therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (50 mcg twice daily). Salmeterol is predominantly cleared by hepatic metabolism; liver function impairment may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

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

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

Fluticasone Propionate

Following intravenous administration, the pharmacokinetics of fluticasone propionate are proportional to the dose. Fluticasone propionate is extensively distributed within the body. The volume of distribution at steady state is approximately 300 litres and has a very high clearance which is estimated to be 1.1 litre/minute indicating extensive hepatic extraction.

Peak plasma fluticasone propionate concentrations are reduced by approximately 98% within 3-4 hours and only low plasma concentrations are associated with the terminal half-life, which is approximately 8 hours.

Following oral administration of fluticasone propionate, 87-100% of the dose is excreted in the faeces. Following doses of either 1 or 16 mg, up to 20% and 75% respectively, is excreted in the faeces as the parent compound. There is a non-active major metabolite. Absolute oral bioavailability is negligible (< 1%) due to a combination of incomplete absorption from the gastrointestinal tract and extensive first-pass metabolism.

Following inhaled dosing in healthy volunteers, absolute systemic bioavailability of fluticasone propionate varies between approximately 10-30% of the nominal dose depending on the inhalation device used. Systemic absorption of fluticasone propionate occurs mainly through the lungs, and is initially rapid, then prolonged.

The plasma protein binding of fluticasone propionate is 91%. Fluticasone propionate is extensively metabolised by CYP3A4 enzyme to an inactive carboxylic acid derivative.

STORAGE AND STABILITY

ADVAIR[®] DISKUS[®]

Do not store ADVAIR[®] DISKUS[®] above 25°C. Keep in a dry place.

ADVAIR[®] inhalation aerosol

Replace the mouthpiece cover firmly and snap it into position. Store ADVAIR[®] inhalation aerosol between 15°C and 25°C. Protect from frost and direct sunlight.

SPECIAL HANDLING INSTRUCTIONS

ADVAIR[®] inhalation aerosol

Contents under pressure. Container may explode if heated. Do not place in hot water or near radiators, stoves, or other sources of heat. Even when apparently empty, do not puncture or incinerate container or store at temperatures over 25°C.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

ADVAIR[®] DISKUS[®]

ADVAIR[®] DISKUS[®] (salmeterol xinafoate/fluticasone propionate) is a dry powder plastic inhaler device containing a foil strip with 28 or 60 regularly placed blisters each containing 50 mcg of salmeterol (as the xinafoate salt), and 100, 250 or 500 mcg of fluticasone propionate per inhalation. It also contains lactose (milk sugar), including milk protein, which acts as the “carrier”.

ADVAIR[®] inhalation aerosol

ADVAIR[®] inhalation aerosol is a pressurized metered-dose inhaler (MDI) consisting of an aluminum canister fitted with a metering valve. Each canister is fitted into the supplied purple actuator/adaptor. A dust cap is fitted over the actuator’s mouthpiece when not in use.

ADVAIR[®] inhalation aerosol comprises a suspension of salmeterol and fluticasone propionate in the propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no excipients. ADVAIR[®] inhalation aerosol delivers 25 mcg of salmeterol and 50*, 125 or 250 mcg of fluticasone propionate per actuation.

Available in 120 dose formats.

**ADVAIR[®] 50 is not available in Canada*

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

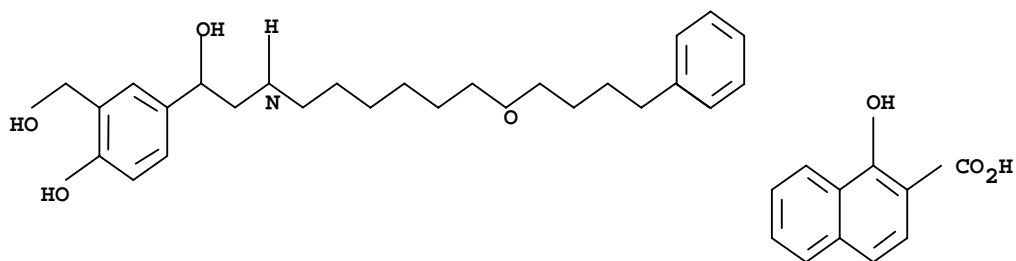
Drug Substance

Proper name: salmeterol xinafoate

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

Molecular formula and molecular mass: $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$ 603.8

Structural formula:



Physicochemical properties:

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

Solubility:

In water ~ 0.07 mg/mL (pH = 8)
In saline ~ 0.08 mg/mL (0.9%w/v)
In methanol ~ 40 mg/mL
In ethanol ~ 7 mg/mL
In chloroform ~ 3 mg/mL
In isopropanol ~ 2 mg/mL

pKa and pH:

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

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

Partition Coefficient:

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

log D = 3.2 (pH 9.2)

log D = 2.0 (pH 7.4)

log D = 0.6 (pH 4.0)

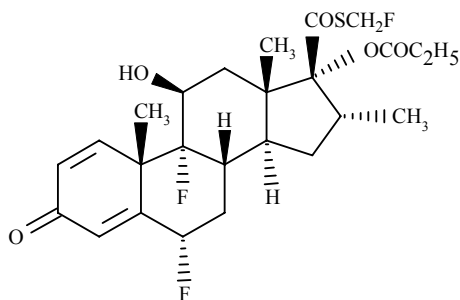
Drug Substance

Proper name: fluticasone propionate

Chemical name: s-fluoromethyl 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

Molecular formula and molecular mass: C₂₅H₃₁F₃O₅S 500.6

Structural formula:



Physicochemical properties:

Description: Fluticasone propionate is a white to off-white powder. It is freely soluble in dimethyl sulfoxide and dimethylformamide, sparingly soluble in acetone, dichloromethane, ethyl acetate and chloroform, slightly soluble in methanol and 95% ethanol, and practically insoluble in water. Fluticasone propionate decomposes without melting. Onset of decomposition occurs at about 225°C.

CLINICAL TRIALS

Clinical Studies in Asthma

There have been very rare reports of anxiety, sleep disorders and behavioural changes including hyperactivity and irritability (predominantly in children and adolescents).

ADVAIR[®] DISKUS[®]

Use in adolescents and adults

Clinical studies in patients 12 years of age and older showed that the combination product was significantly more effective than placebo or salmeterol alone in all primary efficacy comparisons. It was significantly more effective than fluticasone propionate alone in all primary efficacy comparisons ($p < 0.001$) except in one study for probability of remaining in the study ($p = 0.084$).

In clinical studies comparing the efficacy and safety of the combination product versus concurrent therapy with fluticasone propionate and salmeterol administered via separate inhalers, results for the primary efficacy variable, mean morning PEFr during weeks 1-12, in the Intent-to-Treat Population met the criterion for clinical equivalence (90% confidence limits for the difference between treatments contained within +15L/min) in two studies. Results were similar when the 95% confidence limits were considered rather than 90%. In the study using the 50/100 mcg dose, equivalence was not demonstrated, with treatment differences indicating a slightly greater efficacy for the combination product.

In randomized, double-blind, placebo-controlled trials involving 700 patients aged 12 years and over, treatment with 50/100 mcg or 50/250 mcg salmeterol xinafoate/fluticasone propionate DISKUS[®] produced clinically significant improvements in quality of life as assessed by the Asthma Quality of Life Questionnaire (AQLQ). There were significant differences in quality of life between the combination product and salmeterol xinafoate 50 mcg alone, fluticasone propionate 100 mcg or 250 mcg alone, or placebo. Differences between the combination product and salmeterol or placebo were clinically significant. In these 2 studies, survival analysis revealed that patients treated with 50/100 mcg or 50/250 mcg salmeterol xinafoate/fluticasone propionate DISKUS[®] also had a significantly greater probability of remaining in the study over time without being withdrawn because of worsening asthma than did those in the salmeterol or fluticasone treatment groups. ($p \leq 0.020$ and $p \leq 0.002$ respectively). In both studies, statistically significantly fewer patients receiving the salmeterol/fluticasone combination were withdrawn from the study due to worsening asthma (3% and 4%) compared with fluticasone (11% and 22%), salmeterol (35% and 38%) and placebo (49% and 62%). The combination product significantly reduced symptom scores and supplemental salbutamol use compared with the other treatments. In the first study, regardless of baseline asthma therapy (inhaled corticosteroids or salmeterol), greater improvements in asthma control were observed with the combination as compared to the individual agents. In both studies, the mean change from baseline in pre-dose FEV₁ at the Week 12 endpoint was

significantly greater in the combination group ($p < 0.001$ and $p = 0.003$ respectively) compared to fluticasone propionate alone with no apparent diminution in the 12-hour bronchodilator effect following 12 weeks of therapy.

At the Week 12 endpoint, patients treated with the combination had a 25% and 23% improvement from baseline in FEV₁ respectively.

In a randomized, double-blind, active-controlled trial involving 267 patients aged 12 years and over, who were uncontrolled on short-acting beta₂-agonist therapy, treatment with 50/100 mcg salmeterol xinafoate/fluticasone propionate DISKUS[®] demonstrated superior efficacy and comparable safety compared with salmeterol (50 mcg) or fluticasone propionate (100 mcg) alone. ADVAIR[®] DISKUS[®] 50/100 mcg was proven to be significantly more efficacious than salmeterol alone for the mean change from baseline in morning pre-dose FEV₁ at endpoint ($p = 0.036$). In addition, ADVAIR[®] DISKUS[®] achieved significantly better results than fluticasone propionate alone for area under the serial FEV₁ curve at treatment week 12 relative to baseline ($p = 0.021$). Lung function parameters, asthma symptoms, and VENTOLIN[®] use all showed statistically significant and clinically relevant improvements with the combination product compared with its individual components.

Two, randomized, double-dummy, parallel-group, 12-week comparative trials of ADVAIR[®] DISKUS[®] 50/100 mcg versus oral montelukast 10 mg once-daily were conducted. 855 patients 15 years and older with persistent asthma inadequately controlled with scheduled or as needed short-acting beta₂-agonists alone were enrolled. In both trials, ADVAIR[®] DISKUS[®] was significantly more efficacious ($p < 0.001$, morning pre-dose FEV₁) and has a similar tolerability and adverse event profile compared to the once-daily montelukast.

Use in children

The efficacy of ADVAIR[®] DISKUS[®] 50/100 mcg was compared to concurrent therapy with salmeterol xinafoate and fluticasone propionate administered via separate inhalers in children 4-11 years old. The adjusted mean change in morning PEF_R from baseline for Weeks 1-12 were 33L/min for the combination product and 28L/min for concurrent therapy. Patients responded similarly in both treatment groups with marked reduction of asthma symptoms and VENTOLIN[®] use during the study.

ADVAIR[®] Inhalation Aerosol

Use in adolescents and adults

In clinical trials comparing ADVAIR[®] inhalation aerosol with individual components, improvements in most efficacy endpoints were greater with ADVAIR[®] inhalation aerosol than with the use of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed comparable results between ADVAIR[®] inhalation aerosol and ADVAIR[®] DISKUS[®].

When compared to salmeterol alone, ADVAIR[®] inhalation aerosol was significantly more efficacious in terms of asthma stability (probability of remaining in the study and change from baseline at endpoint in morning predose FEV₁). ADVAIR[®] inhalation aerosol was comparable or superior to salmeterol in area under the 12-hour serial FEV₁ curve relative to baseline [AUC(bl)] at Treatment Week 1 and Treatment Week 12, respectively.

When compared to fluticasone propionate alone, patients receiving ADVAIR[®] inhalation aerosol had significantly greater increases from baseline at endpoint in morning predose FEV₁ and serial FEV₁ results relative to baseline [AUC(bl)] at Treatment Week 1 and Treatment Week 12, respectively.

Patients' perceptions of the impact of asthma on their quality of life were assessed with the Asthma Quality of Life Questionnaire (AQLQ). Patients receiving ADVAIR[®] inhalation aerosol 25/50 mcg had statistically significant ($p \leq 0.006$) and clinically meaningful (≥ 0.5 point difference between groups in mean overall AQLQ score change from baseline) improvements in overall asthma-related quality of life (mean of 4 AQLQ domain scores: activity limitation, asthma symptoms, emotional function, and environmental stimuli) compared with placebo, fluticasone propionate 50 mcg and salmeterol.

In a one-year study, evaluating the safety of ADVAIR[®] inhalation aerosol 25/50 mcg, 25/125 mcg and 25/250 mcg, improvements in FEV₁ (0.17 to 0.35L at 4 weeks) were seen across all 3-treatment groups and were sustained throughout the 52-week treatment period. Few patients (3%) were withdrawn due to worsening asthma over 1 year.

The onset of action and progression of improvement in asthma control were evaluated in 3 studies. Following the first dose, the median time to onset of clinically significant bronchodilation ($\geq 15\%$ improvement in FEV₁) in most patients was seen within 30 to 60 minutes. Maximum improvement in FEV₁ occurred within 4 hours, and clinically significant improvement was maintained for 12 hours. Additionally, significant improvement in morning PEF, asthma symptom scores, and VENTOLIN[®] use were observed within 1 day and in evening PEF within 12 hours after initiating treatment with the ADVAIR[®] inhalation aerosol. Improvement continued over the weeks of therapy in all 3 studies.

Following the initial dose, predose FEV₁ relative to day 1 baseline improved markedly over the first week of treatment and continued to improve over the 12 weeks of treatment in all 3 studies.

Fluticasone Propionate

A 2-year study of patients with asthma receiving CFC-propelled fluticasone propionate inhalation aerosol (100 and 500 mcg twice daily) demonstrated no statistically significant changes in bone mineral density at any time point (24, 52, 76, and 104 weeks of double blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar region L1 and L4.

Salmeterol Xinafoate

Salmeterol Multi-center Research Trial (SMART)

The SMART study was a large US post-marketing study that compared the safety of SEREVENT[®] inhalation aerosol (salmeterol 50 mcg twice daily; a component of ADVAIR[®]/ADVAIR[®] DISKUS[®]) 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.

ADVAIR[®]/ADVAIR[®] DISKUS[®] are combination products of salmeterol and fluticasone propionate. However, since the SMART study did not assess the inhaled corticosteroid (ICS) dosages actually used by the patients, and may be different from those in the ADVAIR[®] combination products, it cannot be concluded that the increased risks observed with SEREVENT[®] use do not also apply to ADVAIR[®]/ADVAIR[®] DISKUS[®] therapy.

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 or 1.40 with 95% CI: 0.91, 2.14). When asthma-related death was analysed alone, a statistically significant increased risk of greater than four fold was seen in patients who used salmeterol as compared to those who used placebo in addition to their usual asthma therapy (13 in 13,176 vs 3 in 13,179; < 1% in both cases; relative risk of 4.37 with 95% CI: 1.25, 15.34). In addition, statistically significant increased risks were observed for the outcomes of combined asthma-related death or life-threatening experience (37 vs 22; relative risk of 1.71 with 95% CI: 1.01 2.89) and respiratory-related death (24 vs 11; relative risk of 2.16 with 95% CI: 1.06, 4.41). These statistically significant increased risks were observed at interim analysis when enrollment was half the planned number and the power relatively low.

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

From post-hoc analyses, the data from the SMART trial suggest that the use of inhaled corticosteroids as reported at study entry has a protective effect regarding asthma-related outcomes in patients taking SEREVENT[®]. For the primary endpoint of combined respiratory-related death or life-threatening experience, a relative risk of 1.60 (27 out of 7,049 vs 17 out of 7,041; 95% CI: 0.87, 2.93) was observed for patients not reporting ICS 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 beta₂-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.

Additional Clinical Study in Asthma

Use in adolescents and adults

The objective of study SAM40027, also known as the GOAL study (The Gaining Optimal Asthma Control study), was to determine whether patients could achieve asthma control based upon definitions derived from internationally accepted guidelines (Global Initiative for Asthma/National Institute of Health - GINA/NIH), by comparing the efficacy of an escalated dose of fluticasone propionate alone or in combination with the long acting beta₂-agonist salmeterol.

Study Demographics and Trial Design

Table 6 Summary of patient demographics for clinical trials in asthma

Study #	Trial design (Duration)	Dosage (mcg), route of administration	Study subjects (n=number)	Mean age (Range)	Gender
SAM40027 GOAL (Bateman et. al., 2004)	Stratified, randomized, double blind, parallel group, step-up, multicentre study Phase 1: 12-36 weeks Phase 2: 16-40 weeks Phase 1 & 2: 52-weeks	ADVAIR [®] DISKUS [®] 50/100, 50/250, 50/500 BID FP ¹ DISKUS [®] 100, 250, 500 BID Oral inhalation	3416	40 (9-83)	1428M/1988F

¹ fluticasone propionate

In SAM40027, the two treatment groups were well matched for all demographic characteristics. The study was divided into two phases, Phase 1: treatment step-up in which treatment was stepped-up every 12 weeks until “Total Control” was achieved or the highest dose of study drug was reached and Phase 2: treatment at constant dose. A broad range of subjects were included in the study and were stratified into 3 groups according to baseline asthma therapy over the 6 months prior to randomization; Stratum 1: ICS naïve or no ICS in last 6 months; Stratum 2: using low doses of inhaled corticosteroid (ICS) in the previous 6 months (≤500mcg BDP daily or equivalent, i.e. ≤250mcg of FP); Stratum 3: using moderate doses of ICS in the previous 6 months (>500mcg-1000mcg BDP daily or equivalent, i.e. >250-500mcg of FP).

SAM40027 assessed two pre-defined levels of asthma control: “Well-Controlled” (primary efficacy endpoint) and “Total Control”.

“Well-controlled” was defined as two or more of the following 3 criteria:

- Symptom score* of >1 allowed on ≤2 days per week only
- ≤ 2 days and up to 4 occasions of rescue medication use
- ≥80% predicted morning PEF every day

And all of the following criteria:

- no night-time awakenings,
- no exacerbations[#],
- no side effects enforcing a change in therapy.

“Total Control” was defined as:

- no symptoms, no rescue medication use,
- ≥80% predicted morning PEF every day,
- no night-time awakenings,
- no exacerbations[#] and
- no side effects enforcing a change in therapy.

Control needed to be sustained, during weeks 5-12, 17-24, or 29-36 in Phase 1, for at least 6 out of the last 7, or 7 out of the last 8 weeks of treatment to reach the composite endpoints defined above. Direct measurements of airway inflammation and/or hyper-responsiveness were not included in these composite endpoints.

Study Results

In each Stratum, more patients receiving ADVAIR[®] achieved “Well-Controlled” asthma versus inhaled FP alone at the end of Phase I (see Table 7, below).

Table 7 Proportion of patients who achieved “Well-Controlled” asthma in study SAM40027

Primary Endpoint	Associated value and statistical significance for ADVAIR [®] vs. FP	Number of Subjects ²
Proportion of subjects who achieved “Well-Controlled” asthma with ADVAIR [®] compared with FP alone in dose titration phase (Phase I, 12-36 weeks)	Stratum 1: 71% vs. 65% (p=0.039) ¹	1083
	Stratum 2: 69% vs. 52% (p<0.001)	1160
	Stratum 3: 51% vs. 33% (p<0.001)	1135

¹ Results for Stratum 1 did not meet the predefined 10% difference between treatments used to indicate a clinically important difference and are presented for completeness only.

² Excludes subjects with missing covariates (baseline FEV₁). Subject whose control status was missing or unevaluable were assessed as ‘not controlled’.

* Symptom score: 1 was defined as “symptoms for one short period during the day”.

Overall scale: 0(none) –5 (severe).

[#] Exacerbations defined as deterioration in asthma requiring treatment with an oral corticosteroid or an emergency department visit or hospitalization.

In Stratum 1 (ICS naïve or no ICS in last 6 months) the results for the primary endpoint did not meet the predetermined 10% difference used in the study to indicate a clinically important difference (6% treatment difference was achieved). This observation is consistent with the recommended use of LABA-containing drugs such as ADVAIR[®], which should not be introduced as initial therapy in these patients. ADVAIR[®] should be used only in patients whose conditions are not adequately controlled using low- to medium-dose inhaled corticosteroids or the severity of whose disease clearly warrants the initiation of treatment with two maintenance therapies.

Table 8 below displays the observed likelihood of achieving “Well-Controlled” asthma and the absolute difference for achieving “Well-Controlled” asthma, when comparing ADVAIR[®] with FP alone.

Table 8 Likelihood of achieving “Well-Controlled” asthma in study SAM40027

Stratum	Likelihood of achieving “Well-Controlled” asthma (ADVAIR[®] compared with FP alone)	Absolute difference for achieving “Well-Controlled” asthma (ADVAIR[®] compared with FP alone)
Stratum 1 ⁺	9% (95%CI: 0%-18%)	6% (95%CI: 0%-11%)
Stratum 2	31% (95%CI: 19%-44%)	16% (95%CI: 10%-22%)
Stratum 3	51% (95%CI: 31%-74%)	17% (95%CI: 11%-23%)

⁺ Stratum 1 results did not meet the predetermined 10% difference used to indicate a clinically important difference for the primary endpoint of achieving “Well-Controlled” asthma

Similar results were observed with “Total Control” of asthma, where more patients receiving ADVAIR[®] achieved “Total Control” of asthma versus inhaled FP alone at the end of Phase I for each individual Stratum⁺ (p<0.001). Table 9 below displays the observed likelihood of achieving “Total Control” of asthma and the absolute difference for achieving “Total Control” of asthma, when comparing ADVAIR[®] with FP alone.

Table 9 Likelihood of achieving “Total Control” of asthma in study SAM40027

Stratum	Likelihood of achieving “Total Control” of asthma (ADVAIR[®] compared with FP alone)	Absolute difference for achieving “Total Control” of asthma (ADVAIR[®] compared with FP alone)
Stratum 1 ⁺	34% (95%CI: 14%-58%)	11% (95%CI: 5%-16%)
Stratum 2	65% (95%CI: 35%-101%)	13% (95%CI: 8%-18%)
Stratum 3	124% (95%CI: 63%-209%)	10% (95%CI: 6%-14%)

⁺ Stratum 1 results did not meet the predetermined 10% difference used to indicate a clinically important difference for the primary endpoint of achieving “Well-Controlled” asthma

In general, these effects were observed earlier with ADVAIR[®] compared to FP alone and at a lower ICS dose. In those patients achieving ‘Well-controlled’ asthma or ‘Total control’ of asthma, across all Strata⁺, the time to achieve the first ‘Well-Controlled’ or ‘Total Control’ week during Weeks 1-12 was faster with ADVAIR[®] compared to FP alone (p≤0.002).

Attaining "Well-Controlled" asthma and "Total Control" of asthma resulted in an improved Quality of Life (QoL) as measured by the Asthma Quality of Life Questionnaire (AQLQ). In Stratum 2 (Week 52), 64% and 53% of patients reported minimal or no impairment on QoL after treatment with ADVAIR and FP alone, respectively, compared to 10% and 8% at baseline. In Stratum 3 (Week 52), 57% and 45% of patients reported minimal or no impairment on QoL after treatment with ADVAIR[®] and FP alone, respectively, compared to 8% and 9% at baseline. Sustained and continuous treatment for 52 weeks also resulted in significantly greater mean FEV₁ at each of the clinic visits in patients receiving ADVAIR[®] compared to those receiving FP alone (p<0.001). Differences between blinded treatments ranged from 0.13L to 0.16L in Stratum 2, and 0.11L to 0.15L in Stratum 3 in favour of ADVAIR[®].

In SAM40027, an adverse event was defined as any untoward medical occurrence in a subject and did not necessarily have a causal relationship with any treatment. During the blinded treatment period, the percentage of patients who had an adverse event was similar between treatment groups for each Strata: 56% in the FP group and 55% in the ADVAIR[®] group for Stratum 1, 57% FP and 60% ADVAIR[®] for Stratum 2, and 67% FP and 69% ADVAIR[®] in Stratum 3. Drug-related adverse events that were reported by at least 1% of subjects in either treatment group (all Strata combined) were: hoarseness (2% FP vs. 3% ADVAIR[®]), oral candidiasis (2% FP vs. 2% ADVAIR[®]) and pharyngolaryngeal pain (1% FP vs. <1% ADVAIR[®]). There was a greater number of subjects experiencing myocardial infarction and unstable angina or angina pectoris in ADVAIR[®] (n=8) compared with FP alone (n=3); however, none of these events were considered by the investigator to be related to the study medication.

Clinical Studies in COPD

Clinical study data is provided for a 52-week study.

⁺ Stratum 1 results did not meet the predetermined 10% difference used to indicate a clinically important difference for the primary endpoint of achieving ‘Well-Controlled’ asthma

52-week study

A long term (52 week) clinical study in 1465 COPD patients evaluated the safety and efficacy of ADVAIR[®] DISKUS[®] 50/500 (salmeterol xinafoate/fluticasone propionate) versus placebo and the individual components (salmeterol 50 mcg and fluticasone 500 mcg), all taken twice daily via the DISKUS[®] inhalation device. Patients who had an established clinical history of COPD with a pre-bronchodilator FEV₁ of ≥ 25 to $\leq 70\%$ of predicted normal, poor reversibility of airflow obstruction (defined as an increase of $< 10\%$ of the predicted normal FEV₁ value following the administration of 400 mcg salbutamol), and pre-bronchodilator FEV₁/FVC ratio of $\leq 70\%$ were included in the study. Patients who had respiratory disorders other than COPD, those requiring long term oxygen or those who received inhaled or systemic corticosteroids or antibiotic therapy in the 4 weeks prior to study start were excluded.

The primary measure of efficacy was pre-bronchodilator FEV₁.

Pre-bronchodilator FEV₁ in the ADVAIR[®] DISKUS[®] 50/500 group was 133mL higher than the placebo group ($p < 0.001$), 73mL higher than the salmeterol 50 mcg group ($p < 0.001$) and 95 mL higher than the fluticasone 500 mcg group ($p < 0.001$) throughout the treatment period.

Disease-specific quality of life was assessed with the St. George's Respiratory Questionnaire (SGRQ). With ADVAIR[®] DISKUS[®] 50/500, the raw mean changes in Total Score ranged from -2.4 at Week 2 to -4.5 at Week 52. A clinically meaningful change of > 4.0 was achieved as early as 8 weeks with ADVAIR[®] DISKUS[®] 50/500 but not with placebo, salmeterol 50 mcg or fluticasone 500 mcg.

The overall incidence of adverse events and COPD-related adverse events was similar across the four groups during the treatment period. Most commonly reported drug-related adverse event was candidiasis of the mouth and throat (ADVAIR[®] DISKUS[®] 50/500 mcg, 6%; fluticasone 500 mcg, 6%; salmeterol 50 mcg, 1%; placebo, 1%). Lower respiratory tract infections and pneumonia occurred in 7% of patients in the placebo and salmeterol groups compared to 12% and 14% in the fluticasone propionate 500 mcg and ADVAIR[®] DISKUS[®] 50/500 mcg groups respectively.

No clinically significant effects were observed following any treatment on ECG findings, vital signs or bruise count.

Bone density and fracture rates were not assessed in this study.

DETAILED PHARMACOLOGY

Note: For complete information on the pharmacology of the individual compounds salmeterol xinafoate and fluticasone propionate, please refer to the SEREVENT[®] and FLOVENT[®] Product Monographs.

Animals

A safety pharmacology study was performed to determine the potential interaction of subcutaneously administered fluticasone propionate with the cardiovascular and respiratory effects of intravenously administered salmeterol xinafoate in anaesthetised guinea-pigs. Fluticasone propionate (10 mg/kg, sc) or vehicle control was administered as two doses at 24 hours and 3 hours prior to dosing with salmeterol xinafoate.

Salmeterol at intravenous doses of 0.01 – 100 mcg/kg (including and exceeding those required for pharmacological effects or amounts likely to be absorbed clinically after inhalation), had no effects other than those consistent with the known pharmacological profile of the compound (decreases in blood pressure and increases in heart rate). These effects were not exacerbated by pre-treatment with fluticasone propionate.

Pharmacokinetics

Plasma concentrations of salmeterol xinafoate and fluticasone propionate administered concomitantly were determined in single dose inhalation studies in the rat and dog. Plasma levels at the lowest dose levels used in the studies (28/73 mcg/kg in the rat, and 48/50 mcg/animal in the dog) were about 30-fold and 26-fold greater in rat and 13-fold and 3- to 5-fold greater in dog than the peak levels likely to occur in man for salmeterol xinafoate and fluticasone propionate.

Repeat dose pharmacokinetics of salmeterol xinafoate and fluticasone propionate has been obtained by monitoring plasma concentrations in inhalation toxicity studies in the rat and dog.

In both species, plasma levels of fluticasone propionate were not affected by salmeterol administered concurrently and plasma levels of salmeterol were not affected by co-administration with fluticasone propionate.

Human

The pharmacodynamic effects and pharmacokinetics of the combination product in the DISKUS[®] powder inhaler were investigated in healthy adult male and female volunteers after single and repeat-dose administration.

Those studies showed that the systemic pharmacodynamic effects of salmeterol xinafoate and fluticasone propionate are essentially unchanged when the two drugs are administered in combination, when compared with the component drugs given alone or concurrently.

There was no evidence that the systemic exposure to salmeterol was altered by concomitant exposure to fluticasone propionate. In one study, the salmeterol plasma C_{\max} and T_{\max} were not significantly different when compared between the groups receiving salmeterol xinafoate 100 mcg and fluticasone propionate 500 mcg twice daily in the combination product (C_{\max} 0.23 ng/mL) or salmeterol xinafoate 100 mcg twice daily as a single agent (C_{\max} 0.22 ng/mL).

When fluticasone propionate alone or the salmeterol xinafoate/ fluticasone propionate product are administered at the same dosage, there is similar systemic exposure to fluticasone propionate.

Long-Term Outcomes in the Management of COPD

SCO30003 was a 3 year study to assess the effect of treatment with ADVAIR[®] DISKUS[®] 50/500 mcg twice daily, fluticasone propionate 500 mcg twice daily, salmeterol 50 mcg twice daily or placebo on all-cause mortality in 6,112 patients with COPD; defined as the Intent-to-Treat-Efficacy (ITT) population. The patients were 40 to 80 years of age with moderate to severe COPD, with a baseline (pre-bronchodilator) $FEV_1 < 60\%$ of predicted at study entry, and $< 10\%$ of predicted reversibility and were randomised to double-blind medication. During the study, patients were permitted usual COPD therapy with the exception of other inhaled corticosteroids, long-acting bronchodilators and long-term systemic corticosteroids. Survival status at 3 years was determined for all patients regardless of withdrawal from study medication.

The primary endpoint of study SCO30003 was the effect of ADVAIR[®] DISKUS[®] 50/500 mcg twice daily versus placebo on all-cause mortality at 3 years. After three years, 15.2% and 12.6% of patients died in the placebo and ADVAIR[®] DISKUS[®] 50/500 mcg treatment groups respectively, equating to an absolute risk reduction of 2.6%. Based on the results of this study, the hazard ratio for ADVAIR[®] DISKUS[®] 50/500 mcg versus placebo was 0.825 (95% CI 0.68, 1.00, $p = 0.052$), all adjusted for two pre-specified interim analyses. There was a trend towards improved survival in patients treated with ADVAIR[®] DISKUS[®] 50/500 mcg compared with placebo over 3 years however this did not achieve the pre-specified statistical significance level of $p \leq 0.05$.

In study SCO30003, ADVAIR[®] DISKUS[®] 50/500 mcg reduced the rate of moderate to severe exacerbations by 25% compared with placebo (95% CI: 19% to 31%; $p < 0.001$). ADVAIR[®] reduced the exacerbation rate by 9% compared with fluticasone propionate (95% CI: 1% to 16%; $p = 0.024$) and 12% compared with salmeterol (95% CI: 5% to 19%; $p = 0.002$).

Health Related Quality of Life, as measured by the St. George's Respiratory Questionnaire (SGRQ) was also improved by all active treatments in comparison with placebo in study SCO30003. An adjusted mean change of -4.3 unit decrease was seen at week 48 with ADVAIR[®] DISKUS[®] 50/500 mcg. The average improvement over three years for ADVAIR[®] DISKUS[®] compared with placebo was -3.1 units (95% CI: -4.1 to -2.1; $p < 0.001$), compared with salmeterol was -2.2 units ($p < 0.001$) and compared with fluticasone propionate was -1.2 units ($p = 0.017$).

Over the 3 year treatment period of study SCO30003, FEV₁ values were also higher in patients treated with ADVAIR[®] DISKUS[®] 50/500 mcg than for those treated with placebo (average difference over 3 years 92 mL, 95% CI: 75 to 108 mL; p < 0.001). ADVAIR[®] DISKUS[®] was also more effective than salmeterol or fluticasone propionate in improving FEV₁ (average difference over 3 years 50 mL, p < 0.001 for salmeterol and 44 mL, p < 0.001 for fluticasone propionate). Averaged over the 3 years of the study, patients treated with ADVAIR[®] DISKUS[®] showed a +29 mL increase from baseline in post-bronchodilator FEV₁ while the placebo, salmeterol and fluticasone propionate groups demonstrated a decline of -62 mL, -21 mL, and -15 mL, respectively.

TOXICOLOGY

Note: For complete information on the toxicology of the individual compounds salmeterol xinafoate and fluticasone propionate, please refer to the SEREVENT[®] and FLOVENT[®] Product Monographs.

Acute Toxicity

The experimental details of single dose studies are presented below:

Species (strain)	Route of Administration	Nominal Exposure Concentrations (mcg/L) (Salmeterol xinafoate: Fluticasone propionate)	Initial Group		Duration of Treatment (Days)
			M	F	
Rat (Wistar)	Inhalation (dry powder)	0:0	10	10	1
		75:40	10	10	
		0:0	5	5	
		10:20	5	5	
		20:40	5	5	
Rat (Wistar)	Inhalation (dry powder)	0:0	7	7	1
		1:2	7	7	
		2:4	7	7	
		5:10	7	7	
		10:20	7	7	
		20:40	7	7	
Rat (Wistar)	Inhalation (dry powder)	0:0	10	0	1
		75:0	10	0	
		75:40	10	0	

High single inhaled doses of combinations of salmeterol xinafoate and fluticasone propionate were well-tolerated by rats. With one exception (mild atrial myocarditis), all findings were expected at the doses of salmeterol xinafoate and fluticasone propionate administered.

Mild atrial myocarditis occurred at combination doses of 28 mcg/kg salmeterol with 73 mcg/kg fluticasone propionate, or higher, at which plasma drug concentrations were at least 30 times (salmeterol) or 26 times (fluticasone propionate) greater than peak levels in man. The change was characterized by degeneration, mononuclear cell infiltration and a predilection for localisation within the left atrium. This change was not observed in earlier studies when the drugs were administered alone.

The lesion was present 48 hours after a single exposure, but had resolved completely and was absent after 14 days. There were no associated rises in plasma enzyme activities (aspartate aminotransferase, lactate dehydrogenase or creatine phosphokinase) 48 hours after exposure. There were no large differences in heart rate or rhythm between rats given salmeterol alone or in combination with fluticasone propionate, although animals exposed to the combination showed slightly larger and more prolonged falls in blood pressure. No atrial lesions occurred in repeat dose studies in rats.

This is considered unlikely to be of relevance to man because it has been reported in rats after co-administration of other commonly used and clinically well-tolerated beta₂-agonists and corticosteroids.

Long-Term Toxicity

Findings from repeat dose inhalation toxicity studies of up to 13 weeks duration in rats and dogs were generally as expected for the doses of salmeterol xinafoate and fluticasone propionate administered, most being typical of beta₂-agonist or corticosteroid excess.

The experimental details of long-term toxicity studies are provided below:

Species (strain)	Route of Administration	Nominal Exposure Concentrations (mcg/L) (Salmeterol xinafoate: Fluticasone propionate)	Initial Group		Duration of Treatment (Weeks)
			M	F	
Rat (Wistar)	Inhalation	0:0	6	6	2
		2:0.2	7	7	
		20:2	7	7	
Rat (Sprague-Dawley and Wistar)	Inhalation	0:0	5	5	2
		0:2	5	5	
		20:0	5	5	
		20:0.02	5	5	
		20:0.2	5	5	
		20:2	5	5	
Rat (Wistar)	Inhalation	0:0	26	26	2 or 5
		2:4	21	21	
		2:10	21	21	
		4:20	26	26	
		10:20	26	26	
Rat (Wistar)	Inhalation	0:0	41	41	13
		3:0	31	31	
		0:6	31	31	
		0.6:6	31	31	
		3:6	41	41	
Dog (Beagle)	Inhalation	0:0	2	2	2
		15:15	2	2	
		150:150	2	2	
Dog (Beagle)	Inhalation	0:0	2	2	2
		5:0	2	2	
		15:0	2	2	
		5:10	2	2	
		5:25	2	2	
		15:30	2	2	
		15:75	2	2	
Dog (Beagle)	Inhalation	0:0	6	6	13
		15:0	4	4	
		0:30	4	4	
		3:30	4	4	
		15:30	6	6	

Focal coronary arteritis was the only finding not reported in earlier studies when salmeterol xinafoate and fluticasone propionate were administered alone.

Focal coronary arteritis occurred transiently and sporadically in Wistar rats exposed daily to salmeterol xinafoate and fluticasone propionate combinations for 2 weeks. The lesion was short-lived, resolving fully even with continued treatment, always being absent in studies of 5 and 13 weeks duration. It showed both species and strain specificity, being absent in dogs and Sprague-Dawley rats.

In 2 week inhalation studies in dogs, salmeterol-related pulse rate increases were slightly more marked in groups given the combination compared with those given salmeterol alone. However, there were no significant effects of the combination on ECG or on cardiac histopathology in this species.

Reproduction

Co-administration of high-doses of oral salmeterol and subcutaneous fluticasone propionate did not alter the incidence of any minor or major abnormality in rats or mice compared with studies in which the drugs were administered alone. The incidence of two variants, transposed (left) umbilical artery and incomplete ossification of the occipital bone, were increased in rats at the highest combination dose (10 mg/kg:100 mcg/kg, salmeterol xinafoate:fluticasone propionate).

Exposure at the no-effect dose for both variants of 1 mg/kg: 30 mcg/kg (salmeterol xinafoate:fluticasone propionate) was approximately 12 times (salmeterol) and 4 times (fluticasone propionate) greater than peak exposure in man after a standard 50:50 mcg dose (salmeterol xinafoate:fluticasone propionate).

Mutagenicity

Mutagenicity studies conducted with salmeterol xinafoate or fluticasone propionate alone did not show evidence of genotoxicity.

Genetic toxicity studies with the combination product were not conducted.

Carcinogenicity

In long-term studies, salmeterol xinafoate induced benign tumours of smooth muscle on the mesovarium of rats and the uterus of mice. These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human is unknown.

No treatment-related effects were observed on the type or incidence of neoplasia in an 18 month oral (gavage) study in mice administered fluticasone propionate at dose levels of up to 1 mg/kg/day. In a lifetime (2 years) snout-only inhalation study in rats, at dose levels of up to 57 mcg/kg/day, there was an increase in the incidence of tumours in the mammary gland, liver and pancreas. These were not considered as evidence of tumorigenic effect of fluticasone propionate based on the absence of statistical support of an increase in incidence and the historical tumour incidence data.

Salmeterol xinafoate/fluticasone propionate combination product was not tested in carcinogenicity studies.

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PART III: CONSUMER INFORMATION

Pr ADVAIR[®] DISKUS[®]
salmeterol xinafoate/fluticasone propionate
dry powder for inhalation

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

ABOUT THIS MEDICATION**What the medication is used for:**

Your doctor has chosen this medicine to suit you and your condition. ADVAIR[®] DISKUS[®] is used to help with breathing problems in people 4 years of age or older who need regular treatment.

Asthma

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

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

Unless advised by your doctor, ADVAIR[®] DISKUS[®] should not be the first asthma medication you use. It is only used when a regular inhaled corticosteroid medicine along with an as needed rapid onset, short duration, relief medication (e.g. VENTOLIN[®]) are not adequately helping you with your breathing problems. ADVAIR[®] DISKUS[®] should not be used as a relief medication for a sudden attack of breathlessness.

Chronic Obstructive Pulmonary Disease (COPD)

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

What it does:

ADVAIR[®] DISKUS[®] contains two medicinal ingredients, salmeterol xinafoate and fluticasone propionate.

Salmeterol xinafoate is one of a group of medicines called bronchodilators. It relaxes the muscles in the walls of the small air passages in the lungs. This helps to open the airways and makes it easier for air to get in and out of the lungs. The effects of salmeterol xinafoate last for at least 12 hours. When it is taken regularly it helps the small air passages to remain open.

Fluticasone propionate is one of a group of medicines called corticosteroids. Corticosteroids are used to treat breathing problems because they have an anti-inflammatory action. They reduce the swelling and irritation in the walls of the small air passages in the lungs and so ease breathing problems.

Corticosteroids also help to prevent attacks of asthma. When you take these two ingredients together regularly they will both help to control your breathing difficulties.

When it should not be used:

ADVAIR[®] DISKUS[®] does **not** act quickly enough to be used as a relief medication (e.g. VENTOLIN[®]). ADVAIR[®] DISKUS[®] should **not** be used to provide relief for a sudden attack of breathlessness.

ADVAIR[®] should not be used if you have had an allergic reaction to salmeterol xinafoate, fluticasone propionate, or any of the non-medicinal ingredients, including lactose (see What the important non-medicinal ingredients are).

Do NOT use this medication during pregnancy and breastfeeding without first discussing this with your doctor.

What the medicinal ingredient is:

ADVAIR[®] DISKUS[®] contains two active ingredients, salmeterol xinafoate and fluticasone propionate.

What the important nonmedicinal ingredients are:

ADVAIR[®] DISKUS[®] contains lactose (milk sugar), and milk protein, which acts as the 'carrier'.

What dosage forms it comes in:

ADVAIR[®] DISKUS[®] is a dry powder plastic inhaler device containing a foil strip with 28 or 60 regularly placed blisters each containing 50 mcg of salmeterol, and 100, 250 or 500 mcg of fluticasone propionate per inhalation.

WARNINGS AND PRECAUTIONS

**SERIOUS WARNING FOR ASTHMA PATIENTS
TAKING ADVAIR® DISKUS®**

A large US clinical trial showed an increased risk of asthma-related death and other serious respiratory-related outcomes in patients who used salmeterol in addition to their usual asthma therapy as compared to those who used placebo in addition to their usual asthma therapy. This risk was lower in patients who reported taking inhaled corticosteroids when they started the study.

ADVAIR® DISKUS® is a combination of salmeterol xinafoate and fluticasone propionate (an inhaled corticosteroid). Unless advised by your doctor, ADVAIR® DISKUS® should not be the first asthma medication you use. It is only used when a regular inhaled corticosteroid medicine along with an as needed rapid onset, short duration, relief medication (e.g. VENTOLIN®) are not adequately helping you with your breathing problems.

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

- you are suffering from any chest infection (cold, bronchitis).
- you have ever had to stop taking another medication for your breathing problems because you were allergic to it or it caused problems.
- you have been told you are allergic to lactose (milk sugar) or milk protein.
- you ever had thrush in your mouth.
- you are having treatment for a thyroid condition, diabetes, raised blood pressure, or heart problem.
- you have any history of tuberculosis (TB) infections.
- you are taking other “steroids” by mouth or by inhalation.
- you are pregnant or breastfeeding.
- you are taking a medicine called ketoconazole, used to treat fungal infection.

Asthma

If you get a sudden attack of wheezing and breathlessness between your doses of ADVAIR® DISKUS®, you should use your rapid onset, short duration relief medication (e.g. VENTOLIN® HFA) which your doctor has given you. Use the medication as directed by your doctor.

After you start taking ADVAIR® DISKUS®, your doctor may change the dosages of your other asthma medicines. Rarely, this may make a patient feel worse rather than better. This especially applies to oral corticosteroids (sometimes referred to as steroids), including prednisone. If your doctor decreases your oral steroid dose, and you become unwell, tell your doctor immediately.

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

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

The following warning signs indicate that your asthma is getting worse and that your treatment needs to be reassessed by your physician.

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

COPD

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

The following warning signs indicate that your chest condition is worsening. You should contact your physician as soon as possible if you notice:

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

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

You should avoid close contact with people who have colds or the flu (influenza). You should ask your physician about flu vaccination.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ADVAIR[®] DISKUS[®] include: Ritonavir (a medicine used to treat HIV infection or AIDS); and azole antifungals (e.g. ketoconazole). Make sure that your doctor knows what other medicines you are taking (such as those for allergies, nervousness, depression, migraine, etc.), including those you can buy without a prescription as well as herbal and alternative medicines.

PROPER USE OF THIS MEDICATION

It is very important that you use your ADVAIR[®] DISKUS[®] every day, twice a day. This will help you to keep free of symptoms throughout the day and night. **You should not use it more than twice a day.** If you take more than one inhaled medicine, make sure you understand the purpose for taking each medication and when you should use them.

Remember

Never exhale into your DISKUS[®]. Only slide the lever when you are ready to take a dose.

Usual dose:

Do not stop taking ADVAIR[®] DISKUS[®] suddenly – even if you feel better. Your doctor can provide you with information about how to slowly stop the medication if necessary. Do not change your dose unless told to by your doctor. If you have to go into hospital for an operation, take your ADVAIR[®] DISKUS[®] with you and tell the doctor what medicine(s) you are taking. If your doctor decides to stop the treatment, do not keep any left-over medicine unless your doctor tells you to.

For treatment of asthma

For patients 12 years of age and older, the usual dose is:
 One inhalation ADVAIR[®] 100 DISKUS[®] twice daily
 or One inhalation ADVAIR[®] 250 DISKUS[®] twice daily
 or One inhalation ADVAIR[®] 500 DISKUS[®] twice daily.
 For children 4 to 11 years of age the usual dose is one inhalation ADVAIR[®] 100 DISKUS[®] twice daily.

At present, there are insufficient clinical data to recommend the use of ADVAIR[®] DISKUS[®] in children younger than 4 years of age.

For treatment of COPD

The usual dose for adults (18 years and older) is:

One inhalation ADVAIR[®] 250 DISKUS[®] twice daily
 or One inhalation ADVAIR[®] 500 DISKUS[®] twice daily

Overdose:

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

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

Missed Dose:

It is **very important that you use ADVAIR[®] 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 it is due. Do not take a double dose. Then go on as before.

About your DISKUS[®]

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

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

A new DISKUS[®] contains 28 or 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 28 or 60 to 1. **To show when the last five doses have been reached the numbers appear in red.**

Each dose is accurately measured and hygienically protected. The DISKUS[®] requires no maintenance, and no refilling.

How your DISKUS[®] works

It is important that you take each dose as instructed by your doctor, nurse, or pharmacist. Your doctor will decide which strength of DISKUS[®] you should use.

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

1. Open, 2. Slide, 3. Inhale, 4. Close.

Sliding the lever of your DISKUS[®] opens a small hole in the mouthpiece and unwraps a dose ready for you to inhale it.

When you close the DISKUS[®], the lever automatically moves back to its original position ready for your next dose when you need it. The outer case protects your DISKUS[®] when it is not in use.

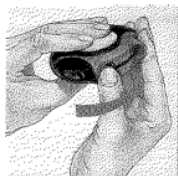
1. Open

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



2. Slide

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



3. Inhale

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



Breathe out slowly.

4. Close

To close your DISKUS[®], put your thumb in the thumb grip, and slide the thumb grip back towards you, as far as it will go. When you close the DISKUS[®], it clicks shut. The lever automatically returns to its original position and is reset. Your DISKUS[®] is now ready for you to use again. Rinse out your mouth and gargle with water after each dose. Do not swallow the water after rinsing and gargling.



Some people find that their mouth, throat or tongue becomes sore after taking this medicine or that their voice becomes a little hoarse. In some people, a mild yeast infection of the mouth and throat called candidiasis (thrush) may occur. Tell your doctor but do not stop treatment unless told to do so. Rinsing your mouth and gargling with water immediately after taking each dose may help. Do not swallow the water after rinsing and gargling. Cleaning dentures may also help. It is possible that some patients, especially those taking higher doses of this type of medication, may very rarely suffer from the following side effects: rounded face, loss of bone density, eye problems and slowing of growth in children and adolescents.

These effects are much less likely to occur than with steroid tablets. Studies have shown that children whose asthma is not controlled do not grow as quickly as other children. It is very important that you use your medicine regularly to control your asthma.

Very rarely the person taking the medicine may feel anxious, have disturbed sleep or notice behavioural changes, including hyperactivity and irritability (mainly in children and adolescents). Some people may experience increased bruising.

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

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

Patients with COPD have a higher chance of getting pneumonia (a lung infection). ADVAIR[®] DISKUS[®] may increase the chance of getting pneumonia. You should contact your physician as soon as possible if you notice:

- An unusual increase in the amount of phlegm.
- A change in the colour of the phlegm.
- An unusual increase in the severity of the breathlessness, cough or wheeze.
- Fever.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Allergic reactions: lumpy skin rash or hives anywhere on the body.			√
Very rare	Allergic reactions: sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat.			√
	Sudden worsening of shortness of breath and wheezing shortly after using ADVAIR [®] DISKUS [®] .			√

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

HOW TO STORE IT

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

Do not store ADVAIR[®] DISKUS[®] above 25°C. Keep in a dry place.

Remember

Keep your DISKUS[®] dry.
Keep it closed when not in use.

REPORTING SUSPECTED SIDE EFFECTS

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

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ONK1A 0K9

Note: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

You may need to read this package insert again. **Please do not throw it away** until you have finished your medicine. This document plus the full product monograph, prepared for health professionals can be found at: <http://www.gsk.ca> or by contacting the sponsor, GlaxoSmithKline Inc., at: 7333 Mississauga Road, Mississauga, Ontario, Canada L5N 6L4, 1-800-387-7374

This leaflet was prepared by GlaxoSmithKline Inc.

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PART III: CONSUMER INFORMATION

Pr ADVAIR®
salmeterol xinafoate/fluticasone propionate
inhalation aerosol

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

ABOUT THIS MEDICATION**What the medication is used for:**

Your doctor has chosen this medicine to suit you and your condition. ADVAIR® inhalation aerosol is used to help with breathing problems in people 12 years of age or older who need regular treatment.

Asthma

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

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

Unless advised by your doctor, ADVAIR® should not be the first asthma medication you use. It is only used when a regular inhaled corticosteroid medicine along with an as needed rapid onset, short duration, relief medication (e.g. VENTOLIN®) are not adequately helping you with your breathing problems. ADVAIR® should not be used as a relief medication for a sudden attack of breathlessness.

What it does:

ADVAIR® contains two medicinal ingredients, salmeterol xinafoate and fluticasone propionate.

Salmeterol xinafoate is one of a group of medicines called bronchodilators. It relaxes the muscles in the walls of the small air passages in the lungs. This helps to open the airways and makes it easier for air to get in and out of the lungs. The effects of salmeterol xinafoate last for at least 12 hours. When it is taken regularly it helps the small air passages to remain open.

Fluticasone propionate is one of a group of medicines called corticosteroids. Corticosteroids are used to treat breathing problems because they have an anti-inflammatory action. They reduce the swelling and irritation in the walls of the small air passages in the lungs and so ease breathing problems.

Corticosteroids also help to prevent attacks of asthma. When you take these two ingredients together regularly they will both help to control your breathing difficulties.

When it should not be used:

ADVAIR® inhalation aerosol does **not** act quickly enough to be used as a relief medication (e.g. VENTOLIN®). ADVAIR® inhalation aerosol should **not** be used to provide relief for a sudden attack of breathlessness.

ADVAIR® should not be used if you have had an allergic reaction to salmeterol xinafoate, fluticasone propionate, or any of the non-medicinal ingredients (see What the important non-medicinal ingredients are).

Do NOT use this medication during pregnancy and breastfeeding without first discussing this with your doctor.

What the medicinal ingredient is:

ADVAIR® inhalation aerosol contains two active ingredients, salmeterol xinafoate and fluticasone propionate.

What the important nonmedicinal ingredients are:

ADVAIR® inhalation aerosol is suspended in a CFC-free propellant, HFA.

What dosage forms it comes in:

ADVAIR® inhalation aerosol is a pressurized metered dose inhaler containing 25 mcg of salmeterol, and 50*, 125 or 250 mcg of fluticasone propionate per inhalation.

**ADVAIR® 50 is not available in Canada*

WARNINGS AND PRECAUTIONS**SERIOUS WARNING FOR ASTHMA PATIENTS
TAKING ADVAIR®**

A large US clinical trial showed an increased risk of asthma-related death and other serious respiratory-related outcomes in patients who used salmeterol in addition to their usual asthma therapy as compared to those who used placebo in addition to their usual asthma therapy. This risk was lower in patients who reported taking inhaled corticosteroids when they started the study.

ADVAIR® is a combination of salmeterol xinafoate and fluticasone propionate (an inhaled corticosteroid). Unless advised by your doctor, ADVAIR® should not be the first asthma medication you use. It is only used when a regular inhaled corticosteroid medicine along with an as needed rapid onset, short duration, relief medication (e.g. VENTOLIN®) are not adequately helping you with your breathing problems.

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

- you are suffering from any chest infection (cold, bronchitis).
- you have ever had to stop taking another medication for your breathing problems because you were allergic to it or it caused problems.
- you ever had thrush in your mouth.
- you are having treatment for a thyroid condition, diabetes, raised blood pressure, or heart problem.
- you have any history of tuberculosis (TB) infections.
- you are taking other “steroids” by mouth or by inhalation.
- you are pregnant or breastfeeding.
- you are taking a medicine called ketoconazole, used to treat fungal infection.

Asthma

If you get a sudden attack of wheezing and breathlessness between your doses of ADVAIR® inhalation aerosol, you should use your rapid onset, short duration relief medication (e.g. VENTOLIN® HFA) which your doctor has given you. Use the medication as directed by your doctor.

After you start taking ADVAIR® inhalation aerosol, your doctor may change the dosages of your other asthma medicines. Rarely, this may make a patient feel worse rather than better. This especially applies to oral corticosteroids (sometimes referred to as steroids), including prednisone. If your doctor decreases your oral steroid dose, and you become unwell, tell your doctor immediately.

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

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

The following warning signs indicate that your asthma is getting worse and that your treatment needs to be reassessed by your physician.

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

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ADVAIR® inhalation aerosol include: Ritonavir (a medicine used to treat HIV infection or AIDS) ; and azole antifungals (e.g. ketoconazole). Make sure that your doctor knows what other medicines you are taking (such as those for allergies, nervousness, depression, migraine, etc.), including those you can buy without a prescription as well as herbal and alternative medicines.

PROPER USE OF THIS MEDICATION

It is very important that you use your ADVAIR® inhalation aerosol every day, twice a day. This will help you to keep free of symptoms throughout the day and night. **You should not use it more than twice a day.** If you take more than one inhaled medicine, make sure you understand the purpose for taking each medication and when you should use them.

Usual dose:

It is very important that you use ADVAIR® inhalation aerosol regularly every day. Do not stop taking ADVAIR® inhalation aerosol suddenly – even if you feel better. Your doctor can provide you with information about how to slowly stop the medication if necessary. Do not change your dose unless told to by your doctor. If you have to go into hospital for an operation, take your ADVAIR® inhalation aerosol with you and tell the doctor what medicine(s) you are taking. If your doctor decides to stop the treatment, do not keep any left-over medicine unless your doctor tells you to.

Spacer devices (holding chamber) may be used in patients who have difficulty coordinating the actuation of a metered dose inhaler with inhalation. Talk to your doctor before using ADVAIR® inhalation aerosol with a spacer device because your dose may need to be changed. If using a spacer device, follow the manufacturer’s instructions.

For treatment of asthma

For patients 12 years of age and older, the usual dose is:
 Two inhalations ADVAIR® 50 inhalation aerosol twice daily or
 Two inhalations ADVAIR® 125 inhalation aerosol twice daily or
 Two inhalations ADVAIR® 250 inhalation aerosol twice daily.
 At present, there are insufficient clinical data to recommend the use of ADVAIR® inhalation aerosol in children younger than 12 years of age.

Overdose:

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

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

Missed Dose:

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

How to use your ADVAIR® inhalation aerosol properly

It is important that you take each dose as instructed by your doctor, nurse, or pharmacist. Your doctor will decide which strength of ADVAIR® inhalation aerosol you should use.

Before you use your ADVAIR® inhalation aerosol for the first time, remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well and release a puff

into the air and repeat until the counter reads 120 to make sure that it works. If your inhaler has not been used for a week or more, remove the mouthpiece cover, shake the inhaler well and release a puff into the air; repeat for a second puff. Each time the inhaler is activated, the number on the counter will count down by one after each actuation. In some circumstances, dropping the inhaler may cause the counter to count down.

After use, always replace the mouthpiece cover immediately to keep out dust and fluff. **REPLACE MOUTHPIECE COVER FIRMLY AND PUSH INTO POSITION.**

The cover must be replaced in the correct orientation; otherwise, the cover will not fit properly. Do not force; the cover will click into position if it is replaced in the correct orientation. If the cover is upside down, it will not be possible to fully replace it. If this happens, remove the cover, rotate it and try again.



1. To remove the snap-on mouthpiece cover, hold between the thumb and forefinger, squeeze gently and pull apart as shown. Check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.



2. Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.



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



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



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



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

7. Replace the mouthpiece cover by firmly pushing and snapping the cap into position to keep out dust and lint.

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

Important

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

If your doctor has given you different instructions for using 6your inhaler, please follow them carefully. Tell your doctor if you have any difficulties.

You should get a replacement when the counter shows the number 020. The counter will stop at 000 when all of the recommended puffs have been used. Stop using the inhaler when the counter reads 000. Never try to alter the numbers on the counter or detach the counter from the metal can. The counter cannot be reset and is permanently attached to the can.



Children/Elderly

Some children may need help and an adult may need to operate the inhaler for them. Encourage the child to breathe out and operate the inhaler just after the child starts to breathe in. Practice the technique together. Children or people with weak hands should hold the inhaler with both hands. Put the two forefingers on top of the inhaler and both thumbs on the base below the mouthpiece.

Cleaning

To prevent your inhaler blocking up, it is important to clean it at least once a week, following the instructions below. If your inhaler does block up, the same cleaning instructions should be followed. If you notice a build up of medicine around the mouthpiece, do not attempt to unblock it with a sharp object, such as a pin.

To clean your inhaler:

1. Remove the mouthpiece cover.
2. Do not remove the canister from the plastic casing.
3. Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth, tissue or cotton swab. Do not put the metal canister into water.
4. Replace the mouthpiece cover.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

Some people find that their mouth, throat or tongue becomes sore after taking this medicine or that their voice becomes a little hoarse. In some people, a mild yeast infection of the mouth and throat called candidiasis (thrush) may occur. Tell your doctor but do not stop treatment unless told to do so. Rinsing your mouth and gargling with water immediately after taking each dose may help. Do not swallow the water after rinsing and gargling. Cleaning dentures may also help.

It is possible that some patients, especially those taking higher doses of this type of medication, may very rarely suffer from the following side effects: rounded face, loss of bone density, eye problems and slowing of growth in children and adolescents.

These effects are much less likely to occur than with steroid tablets. Studies have shown that children whose asthma is not controlled do not grow as quickly as other children. It is very important that you use your medicine regularly to control your asthma.

Very rarely the person taking the medicine may feel anxious, have disturbed sleep or notice behavioural changes, including hyperactivity and irritability (mainly in children and adolescents). Some people may experience increased bruising.

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

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

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

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Allergic reactions: lumpy skin rash or hives anywhere on the body.			√
Very rare	Allergic reactions: sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat.			√
	Sudden worsening of shortness of breath and wheezing shortly after using ADVAIR [®] inhalation aerosol.			√

This is not a complete list of side effects. For any unexpected effects while taking ADVAIR[®] inhalation aerosol, contact your doctor or pharmacist.

HOW TO STORE IT

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

After use, replace the mouthpiece cover firmly and snap it into position. Do not use excessive force.

Store ADVAIR[®] inhalation aerosol between 15°C and 25°C. Protect from frost and direct sunlight.

As with most inhaled medications in pressurized canisters, the therapeutic effect of this medication may decrease when the canister is cold. If the inhaler becomes very cold, remove the metal canister and warm **in your hand** for a few minutes. **Never** use other forms of heat.

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

REPORTING SUSPECTED SIDE EFFECTS

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

By toll-free telephone: 866-234-2345
 By toll-free fax: 866-678-6789
 Online: www.healthcanada.gc.ca/medeffect
 By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ONK1A 0K9

Note: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

You may need to read this package insert again. **Please do not throw it away** until you have finished your medicine. This document plus the full product monograph, prepared for health professionals can be found at: <http://www.gsk.ca> or by contacting the sponsor, GlaxoSmithKline Inc., at: 7333 Mississauga Road, Mississauga, Ontario, Canada L5N 6L4, 1-800-387-7374

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