

## **PrADVAIR DISKUS**

fluticasone propionate and salmeterol inhalation powder USP

### **PrADVAIR DISKUS 100**

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

### **PrADVAIR DISKUS 250**

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

### **PrADVAIR DISKUS 500**

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

## **PrADVAIR**

fluticasone propionate and salmeterol pressurised inhalation, suspension BP

### **PrADVAIR 125**

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

### **PrADVAIR 250**

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

Corticosteroid and Bronchodilator for Oral Inhalation

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## PrADVAIR DISKUS

fluticasone propionate and salmeterol inhalation powder USP

## PrADVAIR

fluticasone propionate and salmeterol pressurised inhalation, suspension BP

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

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

#### INDICATIONS AND CLINICAL USE

##### Asthma

ADVAIR/ADVAIR DISKUS (fluticasone propionate/salmeterol) is a combination of an inhaled corticosteroid (ICS) and a long-acting beta<sub>2</sub>-adrenergic agonist (LABA) indicated for the maintenance treatment of asthma, in patients with reversible obstructive airways disease.

ADVAIR/ADVAIR DISKUS should be prescribed for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants treatment with both an ICS and a LABA.

ADVAIR/ADVAIR DISKUS is **not** indicated for patients whose asthma can be managed by occasional use of a rapid onset, short duration, inhaled beta<sub>2</sub>-agonist, or for patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of a rapid onset, short duration, inhaled beta<sub>2</sub>-agonist.

ADVAIR/ADVAIR DISKUS 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 DISKUS 250 and ADVAIR DISKUS 500 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 pressurised inhalation, suspension 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.

## **WARNINGS AND PRECAUTIONS**

### **General**

#### ***Serious Asthma-Related Events – Hospitalizations, Intubations, Death***

Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death (see Salmeterol Multicenter Asthma Research Trial (SMART)). Available data from controlled clinical trials also suggest that use of LABA

as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy.

When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone (see Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta<sub>2</sub>-adrenergic Agonist Combination Products).

#### Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta<sub>2</sub>-adrenergic Agonist Combination Products

Four (4) large, 26-week, randomized, double-blind, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared with ICS alone in subjects with asthma. Three (3) trials included adult and adolescent subjects aged 12 years and older: 1 trial compared budesonide/formoterol with budesonide, 1 trial compared fluticasone propionate/salmeterol with fluticasone propionate (see CLINICAL TRIALS), and 1 trial compared mometasone furoate/formoterol with mometasone furoate. The fourth trial included pediatric subjects aged 4 to 11 years and compared fluticasone propionate/salmeterol with fluticasone propionate (see CLINICAL TRIALS). The primary safety endpoint for all 4 trials was serious asthma-related events (hospitalizations, intubations, death). A single, blinded, independent, joint adjudication committee determined whether events were asthma related.

The 3 adult and adolescent trials were designed to rule out a 2.0-fold increase in relative risk for ICS/LABA compared with ICS, and the pediatric trial was designed to rule out a 2.7-fold increase in this relative risk. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the 3 adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone ([Table 1](#)). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

**Table 1 Meta-analysis of Serious Asthma-Related Events in Subjects with Asthma Aged 12 Years and Older**

	ICS/LABA (n=17,537) <sup>a</sup>	ICS (n=17,552) <sup>a</sup>	ICS/LABA vs. ICS Hazard Ratio (95% CI) <sup>b</sup>
Serious asthma-related event <sup>c</sup>	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization (≥24-hour stay)	115	105	

ICS = Inhaled Corticosteroid; LABA = Long-acting Beta<sub>2</sub>-adrenergic Agonist.

<sup>a</sup> Randomized subjects who had taken at least 1 dose of study drug. Planned treatment used for analysis.

<sup>b</sup> Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials.

<sup>c</sup> Number of subjects with an event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Subjects may have had one or more events, but only the first event was counted for analysis. A single, blinded, independent joint adjudication committee determined whether events were asthma related.

The pediatric safety trial included 6,208 pediatric subjects aged 4 to 11 years who received ICS/LABA (fluticasone propionate/salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3,107 (0.9%) subjects randomized to ICS/LABA and 21/3,101 (0.7%) subjects randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significant increase in risk of a serious asthma-related event compared with ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27).

#### Salmeterol Multicenter Asthma Research Trial (SMART)

A 28-week, placebo-controlled, U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol versus 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

#### *Not for Acute Use*

**ADVAIR/ADVAIR DISKUS should not be used to treat acute symptoms of asthma or COPD.** 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 or COPD. Patients should be clearly instructed to use rapid onset, short duration, inhaled beta<sub>2</sub>-agonists only for symptomatic relief if they develop asthma or COPD symptoms while taking ADVAIR/ADVAIR DISKUS.

When beginning treatment with ADVAIR/ADVAIR DISKUS, patients who have been taking rapid onset, short duration, inhaled beta<sub>2</sub>-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 or COPD while taking ADVAIR/ADVAIR DISKUS.

### ***Excessive Use and Use with Other LABA Products***

ADVAIR/ADVAIR DISKUS should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ADVAIR/ADVAIR DISKUS should not use another medicine containing a LABA (e.g. formoterol fumarate, indacaterol, olodaterol, vilanterol) for any reason.

### **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 Effects**

Pharmacological side-effects of beta-2 agonist treatment, such as palpitations have been reported, but tend to be transient and to reduce with regular therapy (see ADVERSE REACTIONS). A small increase in QTc interval has been reported with therapeutic doses of salmeterol. Cardiovascular effects such as increased blood pressure and heart rate may occasionally be seen with all sympathomimetic drugs, especially at higher than therapeutic doses.

Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Fatalities have been reported following excessive use of aerosol preparations containing sympathomimetic amines, the exact cause of which is unknown. Cardiac arrest was reported in several instances.

In individual patients any beta<sub>2</sub>-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.

Fluticasone propionate/salmeterol xinafoate, like all products, containing 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.

Occurrence of cardiovascular effects may require discontinuation of the drug.

### **Central Nervous System Effects**

Central nervous system effects of beta<sub>2</sub>-agonist treatment such as tremor and headache have been reported, but tend to be transient and to reduce with regular therapy. Other central nervous system effects of beta<sub>2</sub>-agonist treatment, such as situational disorders, agitation, anxiety, irritability, sleep disorders, syncope, vertigo or dizziness can occur after the use of ADVAIR/ADVAIR DISKUS.

### **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, glaucoma and central serous chorioretinopathy. 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).

### ***Effects on Growth***

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.

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).

### ***Bone Metabolism***

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/ADVAIR DISKUS may pose an additional risk.

Effects of treatment with ADVAIR DISKUS 500/50 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.

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 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.

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 (CYP3A4) 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, cobicistat-containing products).

### **Metabolic Effects**

Doses of the related beta<sub>2</sub>-adrenoceptor agonist salbutamol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. Administration of beta<sub>2</sub>-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, fluticasone propionate/salmeterol xinafoate 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.

Similar to other beta-adrenergic agents, salmeterol can induce reversible metabolic changes (hyperglycemia, hypokalemia). Reports of hyperglycemia have been uncommon 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 eosinophilic granulomatosis with polyangiitis (EGPA) (formerly 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/ADVAIR DISKUS. Symptomatic candidiasis can be treated with topical anti-fungal therapy while continuing to use ADVAIR/ADVAIR DISKUS.

### **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.

### **Ophthalmologic**

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients following the long-term administration of inhaled corticosteroids. Long-term administration of inhaled corticosteroids may result in central serous chorioretinopathy (CSCR). For patients at risk, monitoring of ocular effects (cataract, glaucoma, and CSCR) should also be considered in patients receiving maintenance therapy with ADVAIR/ADVAIR DISKUS.

Reports of glaucoma have been rare but 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.

Reports of cataracts have been uncommon. 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.

Effects of treatment with ADVAIR DISKUS 500/50 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 500/50 mcg, 17% on fluticasone propionate, 15% on salmeterol, and 21% on placebo). A few new cases of glaucoma were diagnosed (2% on ADVAIR DISKUS 500/50 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**

#### ***Paradoxical Bronchospasm***

As with other inhalation therapy, paradoxical bronchospasm, characterized by an immediate increase in wheezing after dosing, may occur with ADVAIR/ADVAIR DISKUS. This should be treated immediately with a rapid onset, short duration inhaled bronchodilator (e.g. salbutamol) to relieve acute asthmatic symptoms.

ADVAIR/ADVAIR DISKUS should be discontinued immediately, the patient assessed, and if necessary, alternative therapy instituted.

### ***Pneumonia (COPD Patients)***

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 500/50 mcg compared with placebo (16% on ADVAIR DISKUS 500/50 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).

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.

## **Special Populations**

### **Use In Women**

#### ***Fertility***

There are no data on human fertility (see TOXICOLOGY, Reproduction).

#### ***Pregnant Women***

There are no adequate and well-controlled clinical trials with ADVAIR/ADVAIR DISKUS in pregnant women and the safety of ADVAIR/ADVAIR DISKUS in pregnancy has not been adequately established. ADVAIR/ADVAIR DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are limited data from an observational epidemiological study with ADVAIR/ADVAIR DISKUS in pregnant women.

Results from a retrospective epidemiological study based on the UK General Practice Research Database (GPRD), did not find an increased risk of major congenital malformations following exposure to fluticasone propionate when compared to other inhaled corticosteroids, during the first trimester of pregnancy (see DETAILED PHARMACOLOGY).

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/ADVAIR DISKUS 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/ADVAIR DISKUS 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:** ( $\geq 4$  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/ADVAIR DISKUS 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 in children younger than 12 years of age have not been established.

**Geriatrics:** As with other beta<sub>2</sub>-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/ADVAIR DISKUS 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 the current dosage of ADVAIR/ADVAIR DISKUS has failed to give adequate control of asthma (in patients with reversible obstructive airways disease) the patient should be reviewed by a physician. Before introducing ADVAIR/ADVAIR DISKUS, 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, glaucoma, and central serous chorioretinopathy) should also be considered in patients receiving maintenance therapy with ADVAIR/ADVAIR DISKUS. It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The type and severity of adverse reactions associated with fluticasone propionate and salmeterol xinafoate may be expected with ADVAIR/ADVAIR DISKUS. There are no additional adverse reactions attributed to the combination product when compared to the adverse event profiles of the individual components.

Adverse drug reactions based on the frequency of reported events from pooled clinical trial data (23 asthma and 7 COPD studies) are listed in [Table 2](#) below. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $<1/10$ ), uncommon ( $\geq 1/1000$  to  $<1/100$ ), rare ( $\geq 1/10,000$  to  $<1/1000$ ) and very rare ( $<1/10,000$ ). The frequency of adverse drug reactions based on spontaneous adverse event reporting data is presented separately (see Post-Market Adverse Drug Reactions).

**Table 2 Adverse Drug Reactions based on the frequency of reported events from pooled clinical trial data (23 asthma and 7 COPD studies)**

<b>MedDRA preferred term</b>	<b>Frequency</b>
<b>Cardiac disorders</b>	
Atrial fibrillation	uncommon
Tachycardia	uncommon
Palpitations	uncommon
Cardiac arrhythmia	rare
Supraventricular tachycardia	rare
Supraventricular extrasystoles	rare
Ventricular extrasystoles	rare
<b>Eye disorders</b>	
Cataract	uncommon
Glaucoma	rare
<b>Infections and Infestations</b>	
Oral candidiasis	common
Pneumonia	common (COPD patients)
<b>Immune system disorders</b>	
Cutaneous hypersensitivity reactions	uncommon
Dyspnoea	uncommon
Anaphylactic reaction	rare
<b>Metabolism and nutrition disorders</b>	
Hyperglycemia	uncommon
<b>Musculoskeletal and connective tissue disorders</b>	
Arthralgia	common
Muscle spasms	common
<b>Nervous system disorders</b>	
Headache (see Warnings and Precautions)	very common
Tremor (see Warnings and Precautions)	uncommon
<b>Psychiatric disorders</b>	
Anxiety	uncommon
Sleep disorder	uncommon
Psychomotor hyperactivity	rare
Irritability	rare
Abnormal behaviour	rare
<b>Respiratory, thoracic and mediastinal disorders</b>	
Dysphonia/Hoarseness	common
Throat irritation	uncommon
<b>Skin and subcutaneous tissue disorders</b>	
Contusion	uncommon

In addition to the pooled data above, symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported rarely in patients receiving salmeterol. Clinically significant hypokalemia has also been seen rarely during long-term administration of salmeterol at recommended doses.

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 EGPA, a condition that is often treated with systemic corticosteroid therapy (see WARNINGS AND PRECAUTIONS, Hematologic, Eosinophilic Conditions).

### **Clinical Trial Adverse Drug Reactions**

#### **By Indication**

*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 of LABA monotherapy increases the risk of serious asthma-related events (death, hospitalizations, and intubations) (see WARNINGS AND PRECAUTIONS, General).

#### ***ADVAIR DISKUS Inhalation Powder***

In clinical trials involving 1824 adult and adolescent patients with asthma, the most commonly reported adverse events with the combination fluticasone propionate/salmeterol xinafoate DISKUS were: hoarseness/dysphonia, throat irritation, headache, candidiasis of mouth and throat and palpitations as detailed in the table below:

**Table 3 Number (and percentage) of patients with drug-related adverse events (incidence  $\geq 1\%$ ) (Safety Population)**

Adverse events	Fluticasone propionate/ salmeterol xinafoate combination product	Fluticasone propionate and salmeterol xinafoate 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 <sup>2</sup>	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

<sup>1</sup> in any integrated treatment group

<sup>2</sup> 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 100/50 mcg, 19% with 250/50 mcg and 17% with 500/50 mcg).

### ***ADVAIR Pressurised Inhalation, Suspension***

In clinical trials, the most commonly reported adverse events with the combination fluticasone propionate/salmeterol xinafoate pressurised inhalation, suspension 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 4 Number (and percentage) of patients with drug-related adverse events (incidence  $\geq 1\%$ <sup>1</sup>) (Safety Population)**

Adverse events	Fluticasone propionate/ salmeterol xinafoate 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 %)

<sup>1</sup> 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 100 mcg fluticasone propionate/50 mcg salmeterol xinafoate DISKUS or concurrent therapy (with fluticasone propionate and salmeterol 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 with COPD, 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 5 Overall adverse experiences with  $\geq 3\%$  incidence in controlled clinical trials with ADVAIR DISKUS in patients with COPD**

Adverse Event	ADVAIR DISKUS 500/50 mcg (n = 169) %	ADVAIR DISKUS 250/50 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
Infections and Infestations						
Upper respiratory tract infection	17	12	18	16	11	15
Sinusitis	3	3	3	6	4	2
Sinusitis/sinus infection	4	2	2	2	1	2
Candidiasis mouth/throat	7	10	12	6	2	<1
Viral respiratory infections	8	6	9	5	5	4
Respiratory, thoracic and mediastinal disorders						
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
Hoarseness/dysphonia	3	5	5	5	<1	1
Nervous system disorders						
Dizziness	3	4	2	2	4	2
Headaches	18	16	17	13	14	11
General disorders						
Fever	4	4	3	3	1	3
Malaise & fatigue	4	3	3	3	2	3
Gastrointestinal disorders						
Nausea & vomiting	4	2	4	4	3	3
Musculoskeletal and connective tissue disorders						
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 (500/50 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 500/50 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 DISKUS

over the three-year treatment period was comparable to that seen in previous studies of shorter duration, confirming the long-term tolerability of ADVAIR DISKUS. 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 DISKUS (Hazard ratio for ADVAIR DISKUS vs placebo: 1.64, 95% CI: 1.33 to 2.01,  $p < 0.001$ ). There was no increase in pneumonia related deaths for ADVAIR DISKUS; 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 DISKUS.

There was no significant difference in probability of bone fracture (5.1% placebo, 5.1% salmeterol, 5.4% fluticasone propionate and 6.3% ADVAIR DISKUS; Hazard ratio for ADVAIR DISKUS 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 DISKUS, fluticasone propionate, and salmeterol.

### **Post-Market Adverse Drug Reactions**

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

#### **Vascular disorders**

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

#### **Endocrine disorders**

*Rare:* Cushing's syndrome, Cushingoid, adrenal suppression (including suppression of HPA axis responsiveness to stress), growth retardation (in children and adolescents), bone density decreased, cataract, glaucoma

#### **Infections and Infestations**

*Rare:* Esophageal candidiasis

#### **Immune system disorders**

*Uncommon:* Cutaneous hypersensitivity reactions

*Rare:* Urticaria, rash, bronchospasm, angioedema (mainly facial and oropharyngeal edema)

*Very rare:* Anaphylactic shock or anaphylactic reaction.

### **Musculoskeletal and connective tissue disorders**

*Very Rare:* osteonecrosis (particularly with previous or concurrent use of systemic steroids (e.g., IV or oral))

### **Respiratory, thoracic and mediastinal disorders**

*Rare:* bronchospasm paradoxical, upper airway symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking.

*Very rare:* Oropharyngeal irritation

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

### **Metabolism and Nutrition Disorders**

*Very rare:* Hyperglycemia.

### **Psychiatric Disorders**

*Very rare:* Anxiety, sleep disorders and behaviour changes, including hyperactivity and irritability (predominantly in children and adolescents).

## **DRUG INTERACTIONS**

### **Overview**

Use ADVAIR with caution in patients receiving other medications causing hypokalemia and/or increased QTc interval (diuretics, high dose steroids, anti-arrhythmics) since cardiac and vascular effects may be potentiated.

### **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 (CYP3A4) 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 CYP3A4 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 CYP3A4 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 CYP3A4 inhibitors (e.g. ketoconazole) as there is potential for increased systemic exposure to fluticasone propionate.

#### Salmeterol Xinafoate

Co-administration of repeat dose ketoconazole (a CYP3A4 inhibitor) and salmeterol in healthy subjects resulted in a significant increase in plasma salmeterol exposure (1.4-fold increase in C<sub>max</sub> and 15-fold increase in AUC). This increase in plasma salmeterol exposure may cause a prolongation of the QT<sub>c</sub> interval (See WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics).

## Drug-Drug Interactions

**Table 6 Established or Potential Drug-Drug Interactions**

<b>Drug Type</b>	<b>Ref</b>	<b>Effect</b>	<b>Clinical comment</b>
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 Cushing's 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 fluticasone propionate and salmeterol xinafoate.	Caution is advised when co-administering potent CYP3A4 inhibitors (e.g. ketoconazole, cobicistat-containing products). (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

#### *COPD and Asthma*

ADVAIR/ADVAIR DISKUS should not be used to treat acute symptoms of asthma or COPD. It is crucial to inform patients of this. Patients should be prescribed a rapid onset, short duration inhaled bronchodilator (e.g., salbutamol) to relieve the acute symptoms such as shortness of breath and advised to have this available for use at all times.

As twice-daily regular treatment, ADVAIR/ADVAIR DISKUS 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 beta<sub>2</sub>-agonists should be used only to relieve acute symptoms of asthma and COPD (See WARNINGS AND PRECAUTIONS).

Patients should be regularly reassessed so that the strength of ADVAIR/ADVAIR DISKUS 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.

#### *Asthma*

When treating patients with asthma, physicians should only prescribe ADVAIR/ADVAIR DISKUS for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants treatment with both an inhaled corticosteroid and LABA.

## **Recommended Dose And Dosage Adjustment**

### **ADVAIR DISKUS Inhalation Powder**

	<b>Asthma</b>		<b>COPD</b>	
	Children 4-11 years of age	Adults and adolescents $\geq 12$ years of age	Adults $\geq 18$ years of age	
ADVAIR DISKUS 100	One inhalation twice daily	One inhalation twice daily	--	OR
ADVAIR DISKUS 250	--	One inhalation twice daily	One inhalation twice daily	OR
ADVAIR DISKUS 500	--	One inhalation twice daily	One inhalation twice daily	

### **ADVAIR Pressurised Inhalation, Suspension**

	<b>Asthma</b>	
	Adults and adolescents $\geq 12$ years of age	
ADVAIR 125	Two inhalations twice daily	OR
ADVAIR 250	Two inhalations twice daily	

It is intended that each prescribed dose of ADVAIR Pressurised Inhalation, Suspension be given by a minimum of two inhalations twice daily. However, the prescribed dose of ADVAIR DISKUS Inhalation Powder may be given by a single inhalation twice daily.

### **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 pressurised inhalation, suspension 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 pressurised inhalation, suspension, 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 pressurised inhalation, suspension 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/ADVAIR DISKUS are to be administered by oral inhalation only.

The patient should be made aware that for optimum benefit ADVAIR/ADVAIR DISKUS 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/ADVAIR DISKUS 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 - **General**). 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/ADVAIR DISKUS, however data on overdose with individual drugs is given below.

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.

The expected signs and symptoms of salmeterol overdose are those typical of excessive beta<sub>2</sub>-adrenergic stimulation, including tremor, headache, tachycardia, increases in systolic blood pressure, cardiac arrhythmias, hypokalemia, hypertension and, in extreme cases, sudden death. There is no specific treatment for an overdose of fluticasone propionate and salmeterol. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm.

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/ADVAIR DISKUS contains fluticasone propionate and salmeterol xinafoate which have differing modes of action for the treatment of COPD and asthma (in patients with reversible obstructive airways disease). Fluticasone propionate is an inhaled anti-inflammatory agent that reduces airways irritability; salmeterol is a long-acting bronchodilator that prevents breakthrough symptoms of wheezing and chest tightness. ADVAIR/ADVAIR DISKUS can offer a more convenient regime for patients requiring concurrent long-acting beta<sub>2</sub>-agonists and inhaled corticosteroid therapy.

ADVAIR/ADVAIR DISKUS 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) beta<sub>2</sub>-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 beta<sub>2</sub>-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 D<sub>2</sub>.

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 inhalation powder were investigated in healthy adult male and female volunteers after single and repeat-dose administration.

Those studies showed that the systemic pharmacodynamic effects of fluticasone propionate and salmeterol xinafoate 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 fluticasone propionate 500 mcg and salmeterol xinafoate 100 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 fluticasone propionate/salmeterol xinafoate 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 fluticasone propionate and salmeterol xinafoate 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  $\alpha$ -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 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.

The absolute bioavailability of fluticasone propionate has been estimated from within study comparisons of inhaled and intravenous pharmacokinetic data. In healthy adult subjects the absolute systemic bioavailability of fluticasone propionate from fluticasone propionate-salmeterol pressurised inhalation, suspension and from fluticasone propionate-salmeterol inhalation powder was 5.3% and 5.5% respectively. Systemic absorption of fluticasone propionate occurs mainly through the lungs, and is initially rapid, then prolonged.

The percentage of fluticasone propionate bound to human plasma proteins averages 99%. Fluticasone propionate is extensively metabolised by CYP3A4 enzyme to an inactive carboxylic acid derivative.

## **STORAGE AND STABILITY**

### **ADVAIR DISKUS inhalation powder**

Do not store ADVAIR DISKUS above 25°C. Keep in a dry place, away from direct heat or sunlight.

ADVAIR DISKUS should be safely discarded when the dose counter reads “0” or 1 month after it was removed from the foil pouch, whichever comes first.

## **ADVAIR pressurised inhalation, suspension**

Replace the mouthpiece cover firmly and snap it into position. Store ADVAIR pressurised inhalation, suspension between 15°C and 25°C. Protect from frost and direct sunlight.

## **SPECIAL HANDLING INSTRUCTIONS**

### **ADVAIR DISKUS inhalation powder**

ADVAIR DISKUS should be stored inside the unopened moisture-protective foil pouch and only removed from the pouch immediately before initial use. Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads “0” (after all blisters have been used), whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler apart.

### **ADVAIR pressurised inhalation, suspension**

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 inhalation powder**

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

The inhaler is packaged in a plastic-coated, moisture-protective foil pouch.

### **ADVAIR pressurised inhalation, suspension**

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

Available in 120 dose formats.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

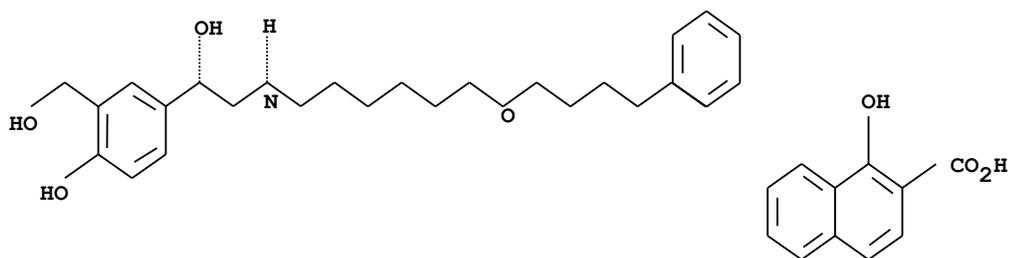
#### Drug Substance

Proper name: salmeterol xinafoate

Chemical name: 4-hydroxy- $\alpha^1$ -[[[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  $\sim 123$  °C

*Solubility:*

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

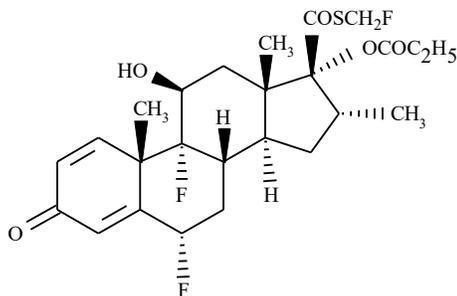
### Drug Substance

Proper name: fluticasone propionate

Chemical name: s-fluoromethyl 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-17 $\alpha$ -propionyloxyandrosta-1,4-diene-17 $\beta$ -carbothioate

Molecular formula and molecular mass: C<sub>25</sub>H<sub>31</sub>F<sub>3</sub>O<sub>5</sub>S 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 Fluticasone Propionate and Salmeterol Inhalation Powder**

#### *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 100/50 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 100/50 mcg or 250/50 mcg fluticasone propionate/salmeterol xinafoate 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 100/50 mcg or 250/50 mcg fluticasone propionate/salmeterol xinafoate 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 fluticasone/salmeterol 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 FEV<sub>1</sub> 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 FEV<sub>1</sub> respectively.

In a randomized, double-blind, active-controlled trial involving 267 patients aged 12 years and over, who were uncontrolled on short-acting beta<sub>2</sub>-agonist therapy, treatment with 100/50 mcg fluticasone propionate/salmeterol xinafoate DISKUS demonstrated superior efficacy and comparable safety compared with salmeterol (50 mcg) or fluticasone propionate (100 mcg) alone. ADVAIR DISKUS 100/50 mcg was proven to be significantly more efficacious than salmeterol alone for the mean change from baseline in morning pre-dose FEV<sub>1</sub> at endpoint ( $p = 0.036$ ). In addition, ADVAIR DISKUS achieved significantly better results than fluticasone propionate alone for area under the serial FEV<sub>1</sub> 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 100/50 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 beta<sub>2</sub>-agonists alone were enrolled. In both trials, ADVAIR DISKUS was significantly more efficacious ( $p < 0.001$ , morning pre-dose FEV<sub>1</sub>) and has a similar tolerability and adverse event profile compared to the once-daily montelukast.

### ***Use in children***

The efficacy of ADVAIR DISKUS 100/50 mcg was compared to concurrent therapy with fluticasone propionate and salmeterol xinafoate administered via separate inhalers in children 4-11 years old. The adjusted mean change in morning PEFr 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 Fluticasone Propionate and Salmeterol Pressurised Inhalation, Suspension**

### ***Use in adolescents and adults***

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

When compared to salmeterol alone, ADVAIR pressurised inhalation, suspension was significantly more efficacious in terms of asthma stability (probability of remaining in the

study and change from baseline at endpoint in morning predose FEV<sub>1</sub>). ADVAIR pressurised inhalation, suspension was comparable or superior to salmeterol in area under the 12-hour serial FEV<sub>1</sub> curve relative to baseline [AUC(bl)] at Treatment Week 1 and Treatment Week 12, respectively.

When compared to fluticasone propionate alone, patients receiving ADVAIR pressurised inhalation, suspension had significantly greater increases from baseline at endpoint in morning predose FEV<sub>1</sub> and serial FEV<sub>1</sub> 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 pressurised inhalation, suspension 125/25 mcg had 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 125 mcg and salmeterol 25 mcg. Clinically meaningful ( $\geq 0.5$  point differences between groups in mean overall AQLQ score change from baseline) improvements were seen in patients receiving ADVAIR pressurised inhalation, suspension 125/25 mcg compared with placebo, and salmeterol 25 mcg.

In a one-year study, evaluating the safety of ADVAIR pressurised inhalation, suspension 125/25 mcg and 250/25 mcg, improvements in FEV<sub>1</sub> (0.17 to 0.23L at 4 weeks) were seen across both treatment groups and were sustained throughout the 52-week treatment period. Few patients (4%) 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 FEV<sub>1</sub>) in most patients was seen within 30 to 60 minutes. Maximum improvement in FEV<sub>1</sub> 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 pressurised inhalation, suspension. Improvement continued over the weeks of therapy in all 3 studies.

Following the initial dose, predose FEV<sub>1</sub> 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.

## **Safety Studies in Asthma**

### ***Fluticasone Propionate***

A 2-year study of patients with asthma receiving CFC-propelled fluticasone propionate pressurised inhalation, suspension (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 – Serious asthma-related events***

### Salmeterol Multicenter Asthma Research Trial (SMART)

The Salmeterol Multicenter Asthma Research Trial (SMART) was a 28-week US post-marketing study that evaluated the safety of salmeterol (50 mcg twice daily) compared to placebo each added to usual asthma therapy in adult and adolescent subjects. The study showed a significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated with salmeterol versus 3 deaths out of 13,179 patients on placebo; relative risk of 4.37 [95% CI: 1.25, 15.34]). The study was not designed to assess the impact of concurrent inhaled corticosteroid use.

### Safety of ADVAIR DISKUS Compared With Inhaled Fluticasone Propionate Alone

Subsequent to the Salmeterol Multicenter Asthma Research Trial, two 26-week, randomized, double-blind, parallel-group, active-controlled, multicenter clinical safety trials, one in 11,679 adult and adolescent subjects aged 12 years and older (NCT01475721) and one in 6,208 pediatric subjects aged 4 to 11 years (NCT01462344) were conducted to evaluate the safety of ADVAIR DISKUS compared with inhaled fluticasone propionate alone.

The primary objective of both trials was to evaluate whether the addition of LABA to inhaled corticosteroid therapy (ADVAIR DISKUS) was non-inferior to inhaled corticosteroid therapy alone (fluticasone propionate) in terms of the risk of a serious asthma-related event (hospitalization, endotracheal intubation, and death). The adult and adolescent trial was designed to rule out a pre-specified risk margin for serious asthma-related events of 2.0 and the pediatric trial was designed to rule out a risk margin of 2.7. A blinded adjudication committee determined whether events were asthma related.

Adult and adolescent subjects enrolled in NCT01475721 had moderate to severe persistent asthma with a history of asthma-related hospitalization or at least 1 asthma exacerbation in the previous year treated with systemic corticosteroid. Subjects were randomized in a 1:1 ratio, within stratification groups based on previous asthma medication and asthma control, to receive ADVAIR DISKUS (100/50 mcg, 250/50 mcg or 500/50 mcg) twice daily or fluticasone propionate inhalation powder (100 mcg, 250 mcg or 500 mcg) twice daily. Pediatric subjects enrolled in NCT01462344 had a diagnosis of asthma and a history of at least 1 asthma exacerbation within the prior 12 months treated with systemic corticosteroid. Subjects were randomized in a 1:1 ratio, within stratification groups based on previous asthma medication, asthma control and number of asthma exacerbations in the prior year, to receive ADVAIR DISKUS (100/50 mcg or 250/50 mcg) twice daily or fluticasone propionate inhalation powder (100 mcg or 250 mcg) twice daily. Patients with life-threatening or unstable asthma were excluded from the 2 clinical trials.

For both trials, ADVAIR DISKUS was non-inferior to fluticasone propionate for time to first serious asthma-related events based on the pre-specified risk margins ([Table 7](#)). In

the pediatric trial, there was a higher number of asthma-related hospitalizations in the ADVAIR DISKUS group (27) compared to the fluticasone propionate group (21).

**Table 7 Serious Asthma-Related Events in the two 26-Week Safety Trials**

	NCT01475721		NCT01462344	
	Adults and adolescents (12 years and older)		Children (4-11 years)	
	ADVAIR DISKUS (n = 5,834)	Fluticasone Propionate (n = 5,845)	ADVAIR DISKUS (n = 3,107)	Fluticasone Propionate (n = 3,101)
Serious asthma-related event (hospitalization, endotracheal intubation, or death) <sup>a</sup>	34 (0.6%)	33 (0.6%)	27 (0.9%)	21 (0.7%)
ADVAIR DISKUS /Fluticasone Propionate Hazard ratio (95% CI)	1.03 (0.64-1.66) <sup>b</sup>		1.29 (0.73-2.27) <sup>b</sup>	
Asthma-related death	0	0	0	0
Asthma-related intubation (endotracheal)	0	2	0	0
Asthma-related hospitalization (≥24-hour stay)	34	33	27	21

<sup>a</sup> Number of subjects with an event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Subjects may have had one or more events, but only the first event was counted for analysis.

<sup>b</sup> The hazard ratio for time to first event was based on a Cox proportional hazards regression model with randomized treatment as a covariate and baseline hazards stratified by prior asthma medication and asthma control status. If the resulting upper 95% CI estimate for the relative risk was less than 2.0 (NCT01475721) or less than 2.7 (NCT01462344), then non-inferiority was concluded.

## 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 beta<sub>2</sub>-agonist salmeterol.

## Study Demographics and Trial Design

**Table 8 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 100/50, 250/50, 500/50 BID FP <sup>1</sup> DISKUS 100, 250, 500 BID Oral inhalation	3416	40 (9-83)	1428M/1988F

<sup>1</sup> 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 ( $\leq 500$ mcg BDP daily or equivalent, i.e.  $\leq 250$ mcg of FP); Stratum 3: using moderate doses of ICS in the previous 6 months ( $> 500$ mcg- $1000$ mcg BDP daily or equivalent, i.e.  $> 250$ - $500$ mcg 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  $\leq 2$  days per week only
- $\leq 2$  days and  $\leq 4$  occasions per week of rescue medication use
- $\geq 80\%$  predicted morning PEF every day

And all of the following criteria:

- no night-time awakenings,
- no exacerbations<sup>#</sup>,
- no side effects enforcing a change in therapy.

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

Overall scale: 0(none) –5 (severe).

<sup>#</sup> Exacerbations defined as deterioration in asthma requiring treatment with an oral corticosteroid or an emergency department visit or hospitalization.

“Total Control” was defined as:

- no symptoms, no rescue medication use,
- $\geq 80\%$  predicted morning PEF every day,
- no night-time awakenings,
- no exacerbations<sup>#</sup> 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 9](#), below).

**Table 9** 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 <sup>2</sup>
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) <sup>1</sup>	1083
	Stratum 2: 69% vs. 52% (p<0.001)	1160
	Stratum 3: 51% vs. 33% (p<0.001)	1135

<sup>1</sup>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.

<sup>2</sup>Excludes subjects with missing covariates (baseline FEV<sub>1</sub>). Subject whose control status was missing or unevaluable were assessed as ‘not controlled’.

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 10](#) 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 10 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 <sup>+</sup>	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%)

<sup>+</sup> 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<sup>+</sup> (p<0.001). Table 11 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 11 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 <sup>+</sup>	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%)

<sup>+</sup> 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<sup>+</sup>, 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 FEV<sub>1</sub> at each of the clinic visits in patients receiving ADVAIR compared to those receiving FP

<sup>+</sup> 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

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.

#### ***52-week study***

A long term (52 week) clinical study in 1465 COPD patients evaluated the safety and efficacy of ADVAIR DISKUS 500/50 (fluticasone propionate/salmeterol xinafoate) versus placebo and the individual components fluticasone propionate 500 mcg and salmeterol 50 mcg, all taken twice daily via the DISKUS inhalation device. Patients who had an established clinical history of COPD with a pre-bronchodilator FEV<sub>1</sub> of  $\geq 25$  to  $\leq 70\%$  of predicted normal, poor reversibility of airflow obstruction (defined as an increase of < 10% of the predicted normal FEV<sub>1</sub> value following the administration of 400 mcg salbutamol), and pre-bronchodilator FEV<sub>1</sub>/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 FEV<sub>1</sub>.

Pre-bronchodilator FEV<sub>1</sub> in the ADVAIR DISKUS 500/50 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 500/50, 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 500/50 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 500/50 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 500/50 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 fluticasone propionate and salmeterol xinafoate, 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 fluticasone propionate and salmeterol xinafoate 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 fluticasone propionate and salmeterol xinafoate.

Repeat dose pharmacokinetics of fluticasone propionate and salmeterol xinafoate 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 inhalation powder were investigated in healthy adult male and female volunteers after single and repeat-dose administration.

Those studies showed that the systemic pharmacodynamic effects of fluticasone propionate and salmeterol xinafoate 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 fluticasone propionate 500 mcg and salmeterol xinafoate 100 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 fluticasone propionate/salmeterol xinafoate 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 500/50 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 500/50 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 500/50 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 500/50 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 500/50 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 500/50 mcg reduced the rate of moderate to severe exacerbations by 25% compared with placebo (95% CI: 19% to 31%;  $p < 0.001$ ). ADVAIR DISKUS 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 500/50 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, FEV<sub>1</sub> values were also higher in patients treated with ADVAIR DISKUS 500/50 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 fluticasone propionate or salmeterol in improving FEV<sub>1</sub> (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 FEV<sub>1</sub> while the placebo, fluticasone propionate or salmeterol groups demonstrated a decline of -62 mL, -15 mL, and -21 mL, respectively.

### ***Fluticasone propionate containing medications in asthma during pregnancy***

An observational retrospective epidemiological cohort study utilising electronic health records from the United Kingdom was conducted to evaluate the risk of major congenital malformations following first trimester exposure to inhaled fluticasone propionate alone and fluticasone propionate -salmeterol combination relative to non- fluticasone propionate containing inhaled corticosteroids. No placebo comparator was included in this study given the disease being studied. As an epidemiologic study, biases may not have been controlled to the same extent as in a clinical trial.

Within the asthma cohort of 5362 first trimester inhaled corticosteroid-exposed pregnancies in which major congenital malformations were diagnosed by one year of age, 131 major congenital malformations were identified; in the 1612 (30%) pregnancies which were exposed to fluticasone propionate or fluticasone propionate -salmeterol, 42 diagnosed major congenital malformations were identified. In 3750 (70%) pregnancies which were exposed to non-FP inhaled corticosteroid (ICS), 89 diagnosed major congenital malformations were identified. The adjusted odds ratio for major congenital malformations diagnosed by 1 year was 1.1 (95% CI: 0.5 – 2.3) for fluticasone propionate exposed vs non- fluticasone propionate inhaled corticosteroid exposed women with moderate asthma and 1.2 (95% CI: 0.7 – 2.0) for women with considerable to severe asthma. No difference in the risk of major congenital malformations was identified following first trimester exposure to fluticasone propionate alone versus fluticasone propionate-salmeterol combination. Absolute risks of major congenital malformations

across the asthma severity strata ranged from 2.0 to 2.9 per 100 fluticasone propionate - exposed pregnancies.

## TOXICOLOGY

Note: For complete information on the toxicology of the individual compounds fluticasone propionate and salmeterol xinafoate, 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 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 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 powder	0:0	10	0	1
		75:0	10	0	
		75:40	10	0	

High single inhaled doses of combinations of fluticasone propionate and salmeterol xinafoate were well-tolerated by rats. With one exception (mild atrial myocarditis), all findings were expected at the doses of fluticasone propionate and salmeterol xinafoate 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 beta<sub>2</sub>-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 fluticasone propionate and salmeterol xinafoate administered, most being typical of beta<sub>2</sub>-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 2:0.2 20:2	6 7 7	6 7 7	2
Rat (Sprague-Dawley and Wistar)	Inhalation	0:0 0:2 20:0 20:0.02 20:0.2 20:2	5 5 5 5 5 5	5 5 5 5 5 5	2
Rat (Wistar)	Inhalation	0:0 2:4 2:10 4:20 10:20	26 21 21 26 26	26 21 21 26 26	2 or 5
Rat (Wistar)	Inhalation	0:0 3:0 0:6 0.6:6 3:6	41 31 31 31 41	41 31 31 31 41	13
Dog (Beagle)	Inhalation	0:0 15:15 150:150	2 2 2	2 2 2	2
Dog (Beagle)	Inhalation	0:0 5:0 15:0 5:10 5:25 15:30 15:75	2 2 2 2 2 2 2	2 2 2 2 2 2 2	2
Dog (Beagle)	Inhalation	0:0 15:0 0:30 3:30 15:30	6 4 4 4 6	6 4 4 4 6	13

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

Focal coronary arteritis occurred transiently and sporadically in Wistar rats exposed daily to fluticasone propionate and salmeterol xinafoate 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 subcutaneous fluticasone propionate and oral salmeterol 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 (100 mcg/kg: 10 mg/kg fluticasone propionate: salmeterol xinafoate).

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

### **Mutagenicity**

Mutagenicity studies conducted with fluticasone propionate and salmeterol xinafoate 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.

Fluticasone propionate/salmeterol xinafoate combination product was not tested in carcinogenicity studies.

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**PART III: CONSUMER INFORMATION****PrADVAIR DISKUS****fluticasone propionate and salmeterol inhalation powder USP**

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.

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

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

ADVAIR DISKUS should be used in patients:

- who have asthma that is not adequately controlled with a long-term asthma medication such as an inhaled corticosteroid (ICS) alone; or
- whose asthma severity requires treatment with both an ICS and long-acting beta<sub>2</sub> agonist (LABA).

ADVAIR DISKUS should not be the first asthma medication you use unless advised by your doctor. It is only used when a regular ICS medicine along with a fast acting 'reliever' medicine, such as salbutamol are not adequately helping you with your breathing problems. ADVAIR DISKUS helps to prevent breathlessness and wheezing from happening due to asthma.

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

**Chronic Obstructive Pulmonary Disease (COPD):**

COPD is a type of lung disease in which there is 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.

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

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

**What it does:**

ADVAIR DISKUS contains two medicinal ingredients, fluticasone propionate and salmeterol xinafoate. Fluticasone propionate is an inhaled corticosteroid. 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.

Salmeterol xinafoate is a LABA. 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 with an inhaled corticosteroid, it helps the small air passages to remain open.

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 provide relief from a sudden attack of breathlessness or wheezing due to asthma or COPD. A fast acting 'reliever' medicine, such as salbutamol should be used for any sudden attacks of breathlessness or wheezing (e.g., asthma attacks).**

**Remember:**

Do not use ADVAIR DISKUS if you:

- Are allergic or have had an allergic reaction to fluticasone propionate, salmeterol xinafoate.
- Are allergic to lactose (milk sugar) or milk protein.
- Have a medical history of cardiac tachyarrhythmias (problems of your heart beating fast and/or irregularly).
- Have an untreated fungal, bacterial or tuberculosis infection.

**What the medicinal ingredients are:**

fluticasone propionate and salmeterol xinafoate.

**What the nonmedicinal ingredients are:**

lactose (milk sugar) and milk protein.

**What dosage forms it comes in:**

ADVAIR DISKUS is an inhalation powder administered through a plastic inhaler device containing a foil strip with 28 or 60 blisters. Each blister contains 100, 250, or 500 mcg of fluticasone propionate and 50 mcg of salmeterol (as the xinafoate salt) per inhalation.

**WARNINGS AND PRECAUTIONS**

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

You may need to also take steroid tablets or syrup during a severe asthma attack, during other illnesses or during times of stress. Your doctor may give you some steroid tablets or syrup to carry with you as well as a steroid warning card, which will give you advice on when and how to use them.

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

- Have eye problems such as glaucoma, cataracts, blurry vision or other changes in vision.
- Are suffering from any chest infection (cold, bronchitis).
- Have ever had to stop taking another medication for your breathing problems because you were allergic to it or it caused problems.
- Have been told you are allergic to lactose (milk sugar) or milk protein.
- Ever had a yeast infection (thrush) in your mouth.
- Are having treatment for a thyroid condition.
- Have diabetes.
- Have high blood pressure.
- Have heart problems.
- Have had tuberculosis (TB) infections.
- Are taking other “steroids” by mouth or by inhalation.
- Are pregnant, planning to become pregnant or breastfeeding.
- Are taking a medicine called ketoconazole, used to treat fungal infection.
- Are taking medicines used to treat HIV infection (e.g. ritonavir, atazanavir, indinavir, nelfinavir, saquinavir and cobicistat containing products).
- Have liver problems or cirrhosis.

You should avoid coming into contact with anyone who has measles or the chicken pox while taking an ICS. If you or your child are exposed, tell your doctor right away.

Drugs like ADVAIR DISKUS can cause eye disorders:

- Cataracts: Clouding of the lens in the eye, blurry vision, eye pain;
- Glaucoma: An increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss;

- Central serous chorioretinopathy (CSCR): blurry vision or other changes in vision.

Contact your healthcare professional if you experience blurry vision or other vision problems. You should have regular eye exams.

**Other warnings you should know about:****Asthma specific warnings:**

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.

You should have your asthma assessed at regular intervals as agreed upon with your doctor. Once control of your asthma is achieved and maintained, your doctor may further adjust your dose of ADVAIR DISKUS. Do not stop or change the dose of your ADVAIR DISKUS unless your doctor has advised you to do so.

When LABA medicines are used alone without an ICS, they increase the risk of hospitalization and death from asthma problems. ADVAIR DISKUS contains both an ICS and LABA. Studies showed that when an ICS and LABA are used together, there is not a significant increased risk in hospitalizations and death from asthma problems.

Tell your doctor immediately if:

- There is a change in your symptoms such as more coughing, attacks of wheezing, chest tightness, or an unusual increase in the severity of the breathlessness.
- You wake up at night with chest tightness, wheezing or shortness of breath.
- You use increasing amounts of your fast acting ‘reliever’ medicine.

These could be warning signs that your condition may be worsening. Do not stop taking ADVAIR DISKUS without talking to your doctor.

**COPD specific warnings:**

- Tell your doctor immediately if you notice symptoms of a ‘flare up’.
- Patients with COPD have a higher chance of getting pneumonia (a lung infection). Drugs like ADVAIR DISKUS may also increase your chance of getting pneumonia. However, symptoms of pneumonia and COPD ‘flare ups’ frequently overlap. It is therefore important you tell your doctor immediately if you suspect an infection, as even mild chest infections should be treated immediately.

Your doctor may also recommend that you receive a flu shot each year.

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

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

- An unusual increase or decrease in the amount of phlegm.
- An unusual increase in the consistency and stickiness of the phlegm.
- The presence of blood in phlegm.
- A change in the colour of the phlegm to either brown, yellow or green.
- An unusual increase in the severity of the breathlessness, 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.

## INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Drugs that may interact with ADVAIR DISKUS include:

- medicines similar to ADVAIR DISKUS used for your lung disease, as it may increase the risk of experiencing possible side effects. This includes other medicines containing a LABA or a corticosteroid.
- medicines used to treat HIV infection or AIDS (e.g. ritonavir, atazanavir, indinavir, nelfinavir, saquinavir and cobicistat containing products).
- ketoconazole (used to treat fungal infections).
- beta-blockers used in the treatment of high blood pressure or other heart problems (e.g. propranolol) or in the treatment of glaucoma.
- medicines used to treat depression (i.e., tricyclic antidepressants, monoamine oxidase inhibitors).
- medicines used to decrease the level of potassium in your blood (i.e., diuretics). These are also known as “water pills” and are used to treat high blood pressure.
- methylxanthines (such as theophylline) used to treat asthma and COPD.

## PROPER USE OF THIS MEDICATION

It is very important that you use your ADVAIR DISKUS every day, twice a day, even if you have no symptoms. 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.

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.

### Usual Asthma Dose:

For patients 12 years of age and older, the usual dose is:

- One inhalation ADVAIR DISKUS 100 twice daily
- or One inhalation ADVAIR DISKUS 250 twice daily
- or One inhalation ADVAIR DISKUS 500 twice daily.

For children 4 to 11 years of age the usual dose is:

- One inhalation ADVAIR DISKUS 100 twice daily.

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

### Usual COPD Dose:

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

- One inhalation ADVAIR DISKUS 250 twice daily
- or One inhalation ADVAIR DISKUS 500 twice daily

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 DISKUS to pass more deeply into your lungs.

**Overdose:**

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

If you accidentally take a **larger dose than recommended**, you may notice that your heart is beating faster than usual and that you feel shaky. Other symptoms you may experience include headache, muscle weakness and aching joints.

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

**Missed Dose:**

It is **very important that you use 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 ADVAIR DISKUS:**

The ADVAIR DISKUS inhaler is packaged in a plastic-coated, moisture-protective foil pouch. **Do not open the foil pouch until you are ready to use the inhaler.** When you take your DISKUS out of its foil pouch, it will be in the **closed position**. Safely throw away the pouch. Write the “Discard by” date in the first blank line on the label. This date is 1 month from the date you have opened the foil pouch.

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

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 to use your ADVAIR DISKUS properly:**

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.

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

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

**1. Open**

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



**2. Slide**

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



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

**3. Exhale**

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



**4. Inhale**

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



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

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

**5. Close**

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



**6. Rinse**

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

**To get the most from your treatment, remember to take one inhalation of ADVAIR DISKUS twice a day, everyday or as prescribed by your doctor.**



Special attention should be paid if you:

- were previously taking another form of corticosteroids (like an injection or an oral tablet) and have switched to an ICS, to look out for tiredness, weakness, nausea and vomiting, low blood pressure.
- are being treated for diabetes as you may need more frequent blood sugar monitoring or a dosage adjustment of your diabetes medication.
- develop a mild yeast infection of the mouth or throat (thrush, Candidiasis) or, rarely, in the esophagus. Common signs are white, slightly raised, sore patches on your tongue and inner cheeks. Remember to rinse and gargle your mouth with water and spit after using ADVAIR DISKUS. Cleaning dentures may also help.
- are a child or adolescent with asthma, as your growth should be monitored regularly by a physician when being treated with corticosteroids. Studies have also shown that children whose asthma is not controlled do not grow as quickly as other children.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Medicines affect different people in different ways. Just because side effects have occurred in other patients does not mean you will get them. If you experience any side effects that bother you, please contact your doctor. This includes the following side effects, which usually wear off with continued treatment:

### Effects on heart

- faster heart beat than usual

### Effects on muscles and joints

- pain in joints
- muscle cramps

### Effects on nervous system

- feeling a little shaky
- headache
- behavioural changes (including agitation, anxiety, and irritability)
- disturbed sleep
- fainting
- spinning sensation (vertigo)
- dizziness

### Other Effects

- hoarseness and voice changes
- increased bruising

It is very important that you use your medicine regularly to control your asthma and to ask your doctor whether you need to be monitored in any special way.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
<b>Common</b>	Thrush: yeast infection of the mouth or throat; thick white patches in the mouth, tongue or on the throat, sore throat		√	
	Pneumonia (in COPD patients), symptoms such as increased cough with increase in mucus (sputum) production, fever accompanied by shaking chills, shortness of breath, sharp or stabbing chest pain during deep breaths, and increased rapid breathing.*		√	
<b>Uncommon</b>	Allergic reactions: lumpy skin rash or hives anywhere on the body.			√
	Fast or irregular heartbeat that does not go away on its own		√	
	Increase amount of sugar in blood (excessive thirst, frequent urination, dry skin, blurred vision and fatigue)		√	
	Blurry vision or eye pain (cataracts)		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Rare	Eosinophilic granulomatosis with polyangiitis: a flu-like illness, rash, pins and needles or numbness of arms or legs, severe sinusitis and worsening lung or breathing problems		√	
	Low blood potassium: muscle weakness and muscle spasms		√	
	Rounded face, loss of bone density, blurry vision or eye pain (glaucoma), slowing of growth in children and adolescents		√	
	Decreased adrenal function: symptoms may include tiredness, weakness, nausea and vomiting, low blood pressure		√	
	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.			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Rare	Mouth, throat becomes unusually irritated causing high pitched wheezing and choking		√	
	Esophageal candidiasis: Yeast infection of the esophagus (food tube); difficulty swallowing		√	
Very rare	Persistent pain and/or limited range of motion of a joint or a limb.		√	
Unknown	Decreased ability to fight infections. Symptoms of infection may include fever, pain, chills, feeling tired and sore throat	√		
	Worsening of lung symptoms such as increased shortness of breath, wheezing, cough and chest tightness accompanied by fever and more phlegm		√	

\*Symptoms of pneumonia and COPD exacerbations frequently overlap.

*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 out of reach and sight of children. Your medicine may harm them.**

Do not store ADVAIR DISKUS above 25°C. Keep in a dry place, away from direct heat or sunlight. Store ADVAIR DISKUS in the unopened foil pouch and only open when ready for use. Discard ADVAIR DISKUS 1 month after you open the foil pouch or when the counter reads 0, whichever comes first.

**Remember**

Keep your DISKUS dry and away from direct heat or sunlight. Keep it closed when not in use.

**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:  
100 Milverton Drive, Suite 800  
Mississauga, Ontario L5R 4H1  
1-800-387-7374

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**REPORTING SUSPECTED SIDE EFFECTS**

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

- **Report online at <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 1908C  
Ottawa, Ontario  
K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>.

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

**PART III: CONSUMER INFORMATION**

**PrADVAIR  
fluticasone propionate and salmeterol pressurised  
inhalation, suspension BP**

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

**ABOUT THIS MEDICATION**

**What the medication is used for:**

**Asthma (patients 12 years of age or older):**

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

ADVAIR should be used in patients:

- who have asthma that is not adequately controlled with a long-term asthma medication such as an inhaled corticosteroid (ICS) alone; or
- whose asthma severity requires treatment with both an ICS and long-acting beta<sub>2</sub> agonist (LABA).

ADVAIR should not be the first asthma medication you use unless advised by your doctor. It is only used when a regular ICS medicine along with a fast acting 'reliever' medicine, such as salbutamol are not adequately helping you with your breathing problems. ADVAIR helps to prevent breathlessness and wheezing from happening due to asthma.

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.

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

**What it does:**

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

Fluticasone propionate is an inhaled corticosteroid. 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.

Salmeterol xinafoate is a LABA. 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 with an inhaled corticosteroid it helps the small air passages to remain open.

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

Do not use ADVAIR if you:

- Are allergic or have had an allergic reaction to fluticasone propionate, salmeterol xinafoate.
- Have a medical history of cardiac tachyarrhythmias (problems of your heart beating fast and/or irregularly).
- Have an untreated fungal, bacterial or tuberculosis infection.

**What the medicinal ingredients are:**

fluticasone propionate and salmeterol xinafoate.

**What the nonmedicinal ingredients are:**

CFC-free propellant, HFA.

**What dosage forms it comes in:**

ADVAIR pressurised inhalation, suspension is a pressurized metered dose inhaler containing 125 or 250 mcg of fluticasone propionate, and 25 mcg of salmeterol per inhalation.

**WARNINGS AND PRECAUTIONS**

**ADVAIR is not for the treatment of acute asthma attacks.**

If you get a sudden attack of wheezing and breathlessness between your doses of ADVAIR, you should use your fast acting 'reliever' medicine, such as salbutamol which your doctor has prescribed to you. Use the medication as directed by your doctor.

You may need to also take steroid tablets or syrup during a severe asthma attack, during other illnesses or during times of stress. Your doctor may give you some steroid tablets or syrup to carry with you as well as a steroid warning card, which will give you advice on when and how to use them.

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

- Have eye problems such as glaucoma, cataracts, blurry vision or other changes in vision.
- Are suffering from any chest infection (cold, bronchitis).
- Have ever had to stop taking another medication for your breathing problems because you were allergic to it or it caused problems.
- Ever had a yeast infection (thrush) in your mouth.
- Are having treatment for a thyroid condition.
- Have diabetes.
- Have high blood pressure.
- Have heart problems.
- Have had tuberculosis (TB) infections.
- Are taking other “steroids” by mouth or by inhalation.
- Are pregnant, planning to become pregnant or breastfeeding.
- Are taking a medicine called ketoconazole, used to treat fungal infection.
- Are taking medicines used to treat HIV infection (e.g. ritonavir, atazanavir, indinavir, nelfinavir, saquinavir and cobicistat containing products).
- Have liver problems or cirrhosis.

You should avoid coming into contact with anyone who has measles or the chicken pox while taking an ICS. If you or your child are exposed, tell your doctor right away.

Drugs like ADVAIR can cause eye disorders:

- Cataracts: Clouding of the lens in the eye, blurry vision, eye pain;
- Glaucoma: An increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss;
- Central serous chorioretinopathy (CSCR): blurry vision or other changes in vision.

Contact your healthcare professional if you experience blurry vision or other vision problems. You should have regular eye exams.

**Asthma:**

After you start taking ADVAIR, 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.

You should have your asthma assessed at regular intervals as agreed upon with your doctor. Once control of your asthma is achieved and maintained, your doctor may further adjust your

dose of ADVAIR. Do not stop or change the dose of your ADVAIR unless your doctor has advised you to do so.

When LABA medicines are used alone without an ICS, they increase the risk of hospitalization and death from asthma problems. ADVAIR contains both an ICS and LABA. Studies showed that when an ICS and LABA are used together, there is not a significant increased risk in hospitalizations and death from asthma problems.

Tell your doctor immediately if:

- There is a change in your symptoms such as more coughing, attacks of wheezing, chest tightness, or an unusual increase in the severity of the breathlessness.
- You wake up at night with chest tightness, wheezing or shortness of breath.
- You use increasing amounts of your fast acting ‘reliever’ medicine.

These could be warning signs that your condition may be worsening. Do not stop taking ADVAIR without talking to your doctor.

**INTERACTIONS WITH THIS MEDICATION**

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Drugs that may interact with ADVAIR include:

- medicines similar to ADVAIR used for your lung disease, as it may increase the risk of experiencing possible side

effects. This includes other medicines containing a LABA or a corticosteroid.

- medicines used to treat HIV infection or AIDS (e.g. ritonavir, atazanavir, indinavir, nelfinavir, saquinavir and cobicistat containing products).
- ketoconazole (used to treat fungal infections).
- beta-blockers used in the treatment of high blood pressure or other heart problems (e.g. propranolol) or in the treatment of glaucoma.
- medicines used to treat depression (i.e., tricyclic antidepressants, monoamine oxidase inhibitors).
- medicines used to decrease the level of potassium in your blood (i.e., diuretics). These are also known as “water pills” and are used to treat high blood pressure.
- methylxanthines (such as theophylline) used to treat asthma.

### PROPER USE OF THIS MEDICATION

It is very important that you use 2 puffs of ADVAIR every day, twice a day, even if you have no symptoms. 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.

It is very important that you use ADVAIR regularly every day. Do not stop taking ADVAIR 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 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 with a spacer device because your dose may need to be changed. If using a spacer device, follow the manufacturer’s instructions.

#### **Usual Asthma Dose:**

For patients 12 years of age and older, the usual dose is:  
Two inhalations ADVAIR 125 pressurized inhalation, suspension twice daily  
or  
Two inhalations ADVAIR 250 pressurized inhalation, suspension twice daily.

At present, there are insufficient clinical data to recommend the use of ADVAIR in children younger than 12 years of age.

#### **Overdose:**

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

If you accidentally take a **larger dose than recommended**, you may notice that your heart is beating faster than usual and that you feel shaky. Other symptoms you may experience include headache, muscle weakness and aching joints.

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

#### **Missed Dose:**

It is **very important that you use ADVAIR 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 Prime ADVAIR:**

Before you use your ADVAIR 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.

#### **How to use your ADVAIR 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 you should use.

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. Open**

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. Your inhaler is now ready to use.



**2. Shake**

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



**3. Exhale**

Hold the inhaler upright between your fingers and thumb with your thumb on the base, below the mouthpiece. Breathe out as far as is comfortable. Once you have fully exhaled, place the mouthpiece between your teeth without biting, and close your lips around it.



**4. Inhale**

Just after starting to breathe in through your mouth, press down firmly on the top of the inhaler while still breathing in steadily and deeply.



Remove the inhaler from your mouth and hold your breath for 10 seconds or as long as is comfortable. **Breathe out slowly.**

Each time the inhaler is activated, the number on the counter will count down by one.

Each prescribed dose is usually given by a minimum of 2 puffs. Before taking your next puff, hold the inhaler upright and wait 30 seconds before repeating steps 2 through 4.



To keep out dust and lint, replace the mouthpiece cover by firmly pushing and snapping the cover into position in the correct orientation. If it does not click into place, turn the cover the other way round and try again. Do not use excessive force.

**5. Rinse**

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



**To get the most from your treatment, remember to take 2 puffs of ADVAIR twice a day, every day or as prescribed by your doctor.**

**Important**

Do not rush stage 4. 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 your 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

Medicines affect different people in different ways. Just because side effects have occurred in other patients does not mean you will get them. If you experience any side effects that bother you, please contact your doctor. This includes the following side effects, which usually wear off with continued treatment:

### Effects on heart

- faster heart beat than usual

### Effects on muscles and joints

- pain in joints
- muscle cramps

### Effects on nervous system

- feeling a little shaky
- headache
- behavioural changes (including agitation, anxiety, and irritability)
- disturbed sleep
- fainting
- spinning sensation (vertigo)
- dizziness

### Other Effects

- hoarseness and voice changes
- increased bruising

It is very important that you use your medicine regularly to control your asthma and to ask your doctor whether you need to be monitored in any special way.

Special attention should be paid if you:

- were previously taking another form of corticosteroids (like an injection or an oral tablet) and have switched to an ICS, to look out for tiredness, weakness, nausea and vomiting, low blood pressure.
- are being treated for diabetes as you may need more frequent blood sugar monitoring or a dosage adjustment of your diabetes medication.
- develop a mild yeast infection of the mouth or throat (thrush, Candidiasis) or, rarely, in the esophagus. Common signs are white, slightly raised, sore patches on your tongue and inner cheeks. Remember to rinse and gargle your mouth with water and spit after using ADVAIR. Cleaning dentures may also help.
- are a child or adolescent with asthma, as your growth should be monitored regularly by a physician when being treated with corticosteroids. Studies have also shown that children whose asthma is not controlled do not grow as quickly as other children.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
<b>Common</b>	Thrush: yeast infection of the mouth or throat; thick white patches in the mouth, tongue or on the throat, sore throat		√	
	Pneumonia (in COPD patients), symptoms such as increased cough with increase in mucus (sputum) production, fever accompanied by shaking chills, shortness of breath, sharp or stabbing chest pain during deep breaths, and increased rapid breathing.*		√	
<b>Uncommon</b>	Allergic reactions: lumpy skin rash or hives anywhere on the body.			√
	Fast or irregular heartbeat that does not go away on its own		√	
	Increase amount of sugar in blood (excessive thirst, frequent urination, dry skin, blurred vision and fatigue)		√	
	Blurry vision or eye pain (cataracts)		√	

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Rare	Eosinophilic granulomatosis with polyangiitis: a flu-like illness, rash, pins and needles or numbness of arms or legs, severe sinusitis and worsening lung or breathing problems		√	
	Low blood potassium: muscle weakness and muscle spasms		√	
	Rounded face, loss of bone density, blurry vision or eye pain (glaucoma), slowing of growth in children and adolescents		√	
	Decreased adrenal function: symptoms may include tiredness, weakness, nausea and vomiting, low blood pressure		√	
	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.			√

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Rare	Mouth, throat becomes unusually irritated causing high pitched wheezing and choking		√	
	Esophageal candidiasis: Yeast infection of the esophagus (food tube); difficulty swallowing		√	
Very rare	Persistent pain and/or limited range of motion of a joint or a limb.		√	
Unknown	Decreased ability to fight infections. Symptoms of infection may include fever, pain, chills, feeling tired and sore throat	√		
	Worsening of lung symptoms such as wheezing, shortness of breath, cough and chest tightness		√	

\*Symptoms of pneumonia and COPD exacerbations frequently overlap.

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

**HOW TO STORE IT**

**Keep out of reach and sight of children. Your medicine may harm them.**

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

Store ADVAIR 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**

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

- Report online at <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: **Canada Vigilance Program  
Health Canada  
Postal Locator 1908C  
Ottawa, Ontario  
K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>.

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

**MORE INFORMATION**

You may need to read this package insert again. **Please do not throw it away** until you have finished your medicine. This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.gsk.ca> or by contacting the sponsor, GlaxoSmithKline Inc., at:  
100 Milverton Drive, Suite 800  
Mississauga, Ontario  
L5R 4H1  
1-800-387-7374

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