**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use Fluticasone propionate and Salmeterol inhalation powder safely and effectively. See full prescribing information for Fluticasone propionate and Salmeterol inhalation powder.

**Fluticasone Propionate and Salmeterol inhalation powder 55 mcg/113 mcg**

**Fluticasone Propionate and Salmeterol inhalation powder 113 mcg/232 mcg**

**Fluticasone Propionate and Salmeterol inhalation powder 232 mcg/464 mcg**

FOR ORAL INHALATION USE

Initial U.S. Approval: 2000

**RECENT MAJOR CHANGES**

Boxed Warning – Asthma-Related Deaths - Removed 12/2017

Indications and Usage (1) 12/2017

Warnings and Precautions (5.1) 12/2017

**INDICATIONS AND USAGE**

Fluticasone propionate/salmeterol inhalation powder is a fixed dose combination product containing a corticosteroid and a LABA indicated for:

- Treatment of asthma in patients aged 12 years and older. (1)
- Important Limitation of Use:
  - Not indicated for the relief of acute bronchospasm. (1)

**DOSE AND ADMINISTRATION**

For oral inhalation only. (2.1)

- Starting dosage is based on prior asthma therapy and disease severity. (2.2)
- Treatment of asthma in patients 12 years and older: 1 inhalation of fluticasone propionate/salmeterol 55/14 mcg, 113/14 mcg, or 232/14 mcg twice daily. (2.2)
- Do not use with a spacer or volume holding chamber. (2.2)

**DOSE FORMS AND STRENGTHS**

Inhalation Powder containing fluticasone propionate 55 mcg, 113 mcg, or 232 mcg and salmeterol (14 mcg) per actuation. (3)

**CONTRAINDICATIONS**

- Primary treatment of status asthmaticus or acute episodes of asthma requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins or any ingredients of fluticasone propionate/salmeterol. (4)

**WARNINGS AND PRECAUTIONS**

- LABA monotherapy increases the risk of serious asthma-related events. (5.1)
- Deterioration of asthma and acute episodes: Do not use for relief of acute symptoms. Patients require immediate re-evaluation during rapidly deteriorating asthma. (5.2)
- Do not use in combination with another medication containing LABA because of risk of overdose. (5.3)
- Localized infections: *Candida albicans* infection of the mouth and pharynx may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation to help reduce the risk. (5.4)

**ADVERSE REACTIONS**

Most common adverse reactions (reported in greater than or equal to 3% of patients) include nasopharyngitis, oral candidiasis, back pain, headache and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Respiratory, LLC at 1-888-482-9522 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole): Use not recommended. May increase risk of systemic corticosteroid and cardiovascular effects. (7.1)
- Monamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of salmeterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

**USE IN SPECIFIC POPULATIONS**

- Hepatic impairment: Monitor for systemic corticosteroid effects. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 03/2018

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**Full Prescribing Information**

1. **Indications and Usage**

Fluticasone propionate/salmeterol multidose dry powder inhaler (FS MDPI) is indicated for the treatment of asthma in patients aged 12 years and older. Fluticasone propionate/salmeterol MDPI should be used for patients not adequately controlled on a long-term asthma control medication such as an inhaled corticosteroid or whose disease warrants initiation of treatment with both an inhaled corticosteroid and long-acting β2-adrenergic agonist (LABA).

2. **Dosing and Administration**

2.1 General

Fluticasone propionate/salmeterol MDPI should be administered as one inhalation twice daily by the orally inhaled route only. Advise the patient to rinse his/her mouth with water without swallowing after each dose.

2.2 Dosing

Fluticasone propionate/salmeterol MDPI should be administered as one inhalation twice daily at the same time each day. Do not use fluticasone propionate/salmeterol MDPI more than 2 times every 24 hours.

The starting dosage for fluticasone propionate/salmeterol MDPI is based upon patients’ asthma severity. The usual recommended starting dose for patients not on inhaled corticosteroids is 55/14 mcg twice daily. For other patients, the starting dose should be based on previous asthma drug therapy and disease severity. For patients switching to fluticasone propionate/salmeterol MDPI from another inhaled corticosteroid or combination product, select the low (55/14 mcg), medium (113/14 mcg), or high (232/14 mcg) dose strength of fluticasone propionate/salmeterol MDPI based on the strength of the previous inhaled corticosteroid product or the strength of the inhaled corticosteroid from a combination product and disease severity. For patients who do not respond to fluticasone propionate/salmeterol MDPI 55/14 mcg after 2 weeks of therapy, increasing the dose may provide additional asthma control. If a dose of fluticasone propionate/salmeterol MDPI fails to provide adequate control of asthma, the therapeutic regimen should be re-evaluated and additional therapeutic options (e.g., replacing the current strength of fluticasone propionate/salmeterol MDPI with a higher strength, or adding additional controller therapies) should be considered.

The highest recommended dose of fluticasone propionate/salmeterol MDPI is 232/14 mcg twice daily. More frequent administration or a greater number of inhalations (more than one inhalation twice daily) of the prescribed strength of fluticasone propionate/salmeterol MDPI is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. Patients using fluticasone propionate/salmeterol MDPI should not use additional LABA for any reason [see Warnings and Precautions (5.3, 5.11)].

If asthma symptoms arise in the period between doses, an inhaled, short-acting β2-agonist should be taken for immediate relief.

Improvement from symptomatology of asthma is often delayed after administration of fluticasone propionate/salmeterol MDPI can occur within 15 minutes of beginning treatment, although maximum benefit may not be achieved for 1 week or longer after starting treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

After asthma stability has been achieved, it is desirable to titrate to the lowest effective dosage to reduce the possibility of side effects.

For patients who do not respond adequately to the starting dose after 2 weeks of therapy, replacing the current strength of fluticasone propionate/salmeterol MDPI with a higher strength may provide additional improvement in asthma control. If a previously ineffective dosage regimen fails to provide adequate improvement in asthma control, the therapeutic regimen should be re-evaluated and additional therapeutic options (e.g., replacing the current strength of fluticasone propionate/salmeterol MDPI with a higher strength, or adding additional controller therapies) should be considered.

Fluticasone propionate/salmeterol MDPI does not require priming. Do not use fluticasone propionate/salmeterol MDPI with a spacer or volume holding chamber.

**Cleaning**

- Keep the inhaler in a cool dry place. Never wash or put any part of the inhaler in water.
- Routine maintenance is not required. If the mouthpiece needs cleaning, gently wipe the mouthpiece with a dry cloth or tissue as needed.

**Dose Counter**

The fluticasone propionate/salmeterol MDPI inhaler has a dose counter. When the patient receives the inhaler, the number 60 will be displayed. The dose counter will count down each time the mouthpiece is opened and closed. The dose counter window displays the number of actuations (inhalations) left in the inhaler in 10.00, 5.00, 0.50, 0.00, etc.). When the dose counter reaches 60, the number 60 will change to red to remind the patient to contact their pharmacist for a refill of medication or consult their physician for a prescription refill.

When the dose counter reaches 0, the background will change to solid red and the color of the numbers will change to black.

3. **Dosage Forms and Strengths**

Inhalation Powder. Fluticasone propionate/salmeterol MDPI is a multidose, inhalation-driven, dry powder inhaler for oral inhalation that meters 55 mcg, 113 mcg, or 232 mcg of fluticasone propionate with 14 mcg of salmeterol from the device reservoir and delivers 49 mcg, 100 mcg, or 202 mcg of fluticasone propionate with 12.75 mcg of salmeterol, respectively, from the mouthpiece per actuation. Fluticasone propionate/salmeterol MDPI is supplied as a white dry powder inhaler with a yellow cap in a sealed foil pouch with desiccant.

4. **Contraindications**

4.1 Status Asthmaticus

Fluticasone propionate/salmeterol MDPI is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required [see Warnings and Precautions (5.2)].

4.2 Hypersensitivity

Fluticasone propionate/salmeterol MDPI is contraindicated in patients with known severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to fluticasone propionate or any of the excipients [see Warnings and Precautions (5.10), Description (11)].

**Warnings and Precautions**

5.1 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 adult 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,-adrenergic Agonists].

5.2 Ongoing Asthma and Baseline Disease

Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta,-adrenergic Agonists

Four large, 26-week, randomized, blinded, 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 to budesonide, 1 trial compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder, and 1 trial compared mometasone furoate/formoterol to mometasone furoate. The fourth trial included pediatric subjects aged 4 to 11 years and compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder. The primary safety endpoint for all 4 trials was serious asthma-related events (hospitalizations, intubations, death). A blinded adjudication committee determined whether events were asthma-related.

The 5 adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk margin of 2.7. 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**

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma-related event</td>
<td>1.10 (0.85, 1.44)</td>
<td></td>
</tr>
<tr>
<td>Asthma-related death</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Asthma-related intubation (endotracheal)</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Asthma-related hospitalization</td>
<td>1.15 (0.91, 1.45)</td>
<td></td>
</tr>
</tbody>
</table>

ICS = Inhaled Corticosteroid; LABA = Long-acting Beta,-adrenergic Agonist.

*Randomized subjects who had taken at least 1 dose of study drug. Planned treatment used for analysis.

*Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials.

*Number of subjects with events 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 can have one or more events, but only the first event was counted for analysis. A single, blinded, independent adjudication committee determined whether events were asthma-related.

The pediatric safety trial included 6,208 pediatric patients aged 4 to 11 years who received ICS/LABA (fluticasone propionate/salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial 23/13,107 (0.9%) of patients treated with ICS/LABA and 21/3,101 (0.7%) of patients treated with ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significantly increased risk of a serious asthma-related event 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.

**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 events in subjects receiving salmeterol (13/13,179 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.
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5.2 Deterioration of Disease and Acute Episodes
Fluticasone propionate/salmeterol MDPI should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. Fluticasone propionate/salmeterol MDPI has not been studied in subjects with acutely deteriorating asthma. The initiation of fluticasone propionate/salmeterol MDPI in this setting is not appropriate.

Serious acute respiratory events, including fatalities, have been reported when salmeterol, a component of this product, has been initiated in patients with significantly worsening or acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, previous episodes of acute asthma, or a severe asthma attack). However, adverse events have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol contributed to these events.

Increasing use of inhaled, short-acting beta2-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, including consideration of the need for replacement of the current treatment regimen with salmeterol MDPI with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids.

Patients should not use more than 1 inhalation twice daily of fluticasone propionate/salmeterol MDPI.

Fluticasone propionate/salmeterol MDPI should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta2-agonist, not fluticasone propionate/salmeterol MDPI, should be used to relieve acute symptoms such as shortness of breath. When prescribing fluticasone propionate/salmeterol MDPI, the healthcare provider should also instruct the patient on the use of a short-acting beta2-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily use of fluticasone propionate/salmeterol MDPI.

When beginning treatment with fluticasone propionate/salmeterol MDPI, patients who have been taking oral or inhaled, short-acting beta2-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs. However, these patients may be able to use them as needed for severe asthma exacerbation (e.g., beta-agonist use, asthma symptoms should be carefully monitored during withdrawal of systemic corticosteroids to monitor asthma signs and symptoms). Patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to fluticasone propionate/salmeterol MDPI may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

During withdrawal from oral corticosteroids, patients may experience symptoms of systemic corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement in respiratory function.

5.7 Hypercorticism and Adrenal Suppression
Fluticasone propionate, a component of fluticasone propionate/salmeterol MDPI, will result in systemic suppression of HPA function that is primarily dose-related. A therapeutically equivalent doses of prednisone may result in systemic suppression of HPA function that is primarily dose-related. A

5.3 Excessive Use of Fluticasone Propionate/Salmeterol and Use with Other Long-Acting Beta2-Agonists
Fluticasone propionate/salmeterol MDPI should not be used more than recommended, at higher doses than recommended, or in combination with other medicines containing sympathomimetic amines. These medicines should not be used.

5.4 Local Effects of Inhaled Corticosteroids
In clinical trials, the development of localized infections of the mouth and pharynx with Candida albicans has occurred in subjects treated with fluticasone propionate/salmeterol MDPI. When such an infection develops, it should be treated with appropriate topical antifungal agents such as nystatin. Fluticasone propionate/salmeterol MDPI continues, but at times therapy with fluticasone propionate/salmeterol MDPI may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.5 Immunosuppression
Persons who are using 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 adults or children treated with corticosteroids. In such cases, more severe, potentially life-threatening complications may result. Corticosteroids may also mask the early symptoms of disseminated fungal infections (e.g., blastomycosis, histoplasmosis, coccidioidomycosis) or reactivation tuberculosis in previously infected individuals. Instruct patients to report any signs or symptoms of infection early. In cases of systemic fungal infections, antifungal therapy may be warranted.

5.6 Transferring Patients from Systemic Corticosteroid Therapy
Particular care is needed for patients who are transferred from systemically active corticosteroids to fluticasone propionate/salmeterol MDPI. Inadequate adrenal suppression may occur if patients are withdrawn from systemic corticosteroids too rapidly. Inadequate systemic effects may occur with fluticasone propionate/salmeterol MDPI, adding additional inhaled corticosteroids, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation twice daily of fluticasone propionate/salmeterol MDPI.

5.8 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors
The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, simeprevir) within 5 days of starting fluticasone propionate/salmeterol MDPI may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

5.9 Paradoxical Bronchospasm and Upper Airway Symptoms
As with other inhaled medicines, fluticasone propionate/salmeterol MDPI can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs following dosing with inhaled fluticasone propionate/salmeterol MDPI, it should be treated immediately with an inhaled, short-acting bronchodilator; inhaled fluticasone propionate/salmeterol MDPI should be discontinued immediately; and alternative therapy should be instituted. Upper airway symptoms of laryngeal spasm, laryngitis, irritation, or swelling, which can be induced by systemic corticosteroid withdrawal, have been reported in patients receiving inhaled fluticasone propionate/salmeterol MDPI.

5.10 Hypersensitivity Reactions, Including Anaphylaxis
Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of fluticasone propionate/salmeterol MDPI. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use fluticasone propionate/salmeterol MDPI [see Contraindications (4)].

5.11 Cardiovascular and Central Nervous System Effects
Excess corticosteroid stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [see Overdosage (10.2)]. Therefore, fluticasone propionate/salmeterol MDPI, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiogenic arrhythmias, and hypertension.
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Fluticasone Propionate and Salmeterol inhalation powder

Salmeterol, a component of fluticasone propionate/salmeterol MDPI, can produce a clinically significant cardiac arrhythmia in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTC interval, and ST-T wave changes. These findings are unknown. 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 in association with excessive use of inhaled sympathomimetic drugs.

5.12 Reduction in Bone Mineral Density
Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as a family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.

5.13 Effect on Growth
Orally inhaled corticosteroids, including fluticasone propionate/salmeterol MDPI, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving fluticasone propionate/salmeterol MDPI routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including fluticasone propionate/salmeterol MDPI, titrate each patient’s dosage to lowest dose that effectively controls his/her symptoms [see Dosage and Administration (2), Use in Specific Populations (8.4)].

5.14 Glaucoma and Cataracts
Glaucoma, increased intraocular pressure, and cataracts have been reported in patients following the long-term administration of inhaled corticosteroids, including fluticasone propionate/salmeterol MDPI. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with other Fluticasone Propionate and Salmeterol Inhalation Powder 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on development of cataracts or glaucoma was evaluated in a subset of 858 subjects who were enrolled in COPD in the 3-year survival trial. Ophthalmologic examinations were conducted at baseline and at 48, 108, and 158 weeks. Conclusions about cataracts cannot be drawn from this trial because the high incidence of cataracts at baseline (61% to 71%) resulted in an inadequate number of subjects treated with other Fluticasone Propionate and Salmeterol Inhalation Powder 500/50 who were eligible for evaluation of cataracts at the end of the trial (n = 53). The incidence of newly diagnosed glaucoma was 2% with other Fluticasone Propionate and Salmeterol Inhalation Powder 500/50, 5% with fluticasone propionate, 0% with salmeterol, and 2% with placebo.

5.15 Eosinophilic Conditions and Churg-Strauss Syndrome
In rare cases, patients on inhaled fluticasone propionate, a component of fluticasone propionate/salmeterol MDPI, may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert 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.

5.16 Coexisting Conditions
Fluticasone propionate/salmeterol MDPI, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders and during the administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as a family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.

5.17 Hypokalemia and Hyperglycemia
Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see Clinical Pharmacology (12.2)]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical trials with fluticasone propionate/salmeterol MDPI at recommended doses.

6. ADVERSE REACTIONS
Use of LABA may result in the following:
- Serious asthma-related events – hospitalizations, intubations, death [see Warnings and Precautions (5.11)]
- Cardiovascular and central nervous system effects [see Warnings and Precautions (5.11)]
- Systemic and local corticosteroid use may result in the following:
- Candida albicans infection [see Warnings and Precautions (5.5)]
- Immunosuppression [see Warnings and Precautions (5.5)]

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- Hypercorticism and adrenal suppression [see Warnings and Precautions (5.7)]
- Reduction in bone mineral density [see Warnings and Precautions (5.12)]
- Growth effects in pediatrics [see Warnings and Precautions (5.13)]
- Glaucome and cataracts [see Warnings and Precautions (5.14)]

6.1 Clinical Trials Experience in Asthma
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The incidence of adverse reactions associated with fluticasone propionate/salmeterol MDPI in Table 2 is based upon two placebo-controlled, 12-week, clinical studies (Study 1 and 2). A total of 1,384 adolescent and adult patients previously treated with inhaled corticosteroids were treated twice daily fluticasone propionate MDPI 55 mcg, 113 mcg, 232 mcg or fluticasone propionate/salmeterol MDPI 55/14 mcg, 113/14 mcg, 232/14 mcg, or placebo. Sixty percent of patients were female and 80% of patients were white. The average duration of exposure was 82 to 84 days in the active treatment groups compared with 75 days in the placebo group.

Table 2: Adverse Reactions with ≥3% Incidence with Fluticasone Propionate/Salmeterol MDPI, and More Common than Placebo in Subjects with Asthma

| Adverse Reaction | Fluticasone Propionate MDPI 55 mcg | Fluticasone Propionate MDPI 113 mcg | Fluticasone Propionate MDPI 232 mcg | Fluticasone Propionate/salmeterol MDPI 55/14 mcg | Fluticasone Propionate/salmeterol MDPI 113/14 mcg | Fluticasone Propionate/salmeterol MDPI 232/14 mcg | Placebo | n=129 | n=274 | n=145 | n=228 | n=269 | n=145 | n=273 |
|------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|--------|-------|-------|-------|-------|-------|-------|
| Infections and infestations | Nasopharyngitis | 5.4 | 5.8 | 4.8 | 8.6 | 4.8 | 6.9 | 4.4 |
| Oral candidiasis* | 3.1 | 2.9 | 4.8 | 1.6 | 2.2 | 3.4 | 0.7 | 0.8 |
| Musculoskeletal and connective tissue disorders | Back pain | 0 | 1.5 | 1.4 | 3.1 | 0.7 | 0.0 | 1.8 |
| Nervous system disorders | Headache | 1.6 | 7.3 | 4.8 | 5.5 | 4.8 | 2.8 | 4.4 |
| Respiratory disorders | Cough | 1.6 | 1.8 | 3.4 | 2.3 | 3.7 | 0.7 | 2.6 |

* Oral candidiasis includes oropharyngeal candidiasis, oral fungal infection, and oropharyngitis fungalis

Other adverse reactions not previously listed (and occurring in <3% of patients in Study 1 or more than three patients on fluticasone propionate/salmeterol MDPI), whether considered drug-related or not by the investigators, that were reported more frequently by patients with asthma treated with fluticasone propionate/salmeterol MDPI compared with patients treated with placebo include the following:

Sinusitis, oropharyngeal pain, pharyngitis, dizziness, influenza, rhinitis allergic, respiratory tract infection, rhinitis, nasal congestion, abdominal pain upper, myalgia, pain in extremity, dyspepsia, laceration, dermatitis contact, and palpitations.

6.2 Postmarketing Experience
In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post approval use of fluticasone propionate and/or salmeterol regardless of indication. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate and/or salmeterol or a combination of these factors.

Cardiac Disorders: Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular tachycardia), ventricular tachycardia

Endocrine Disorders: Cushing's syndrome

Eye Disorders: Glaucoma, blurred vision and central serous chorioretinopathy

Gastrointestinal Disorders: Abdominal pain, dyspepsia, xerostomia

Immune System Disorders: Immediate and delayed hypersensitivity reaction (including very rare anaphylactic reaction). Very rare anaphylactic reaction in patients with severe milk protein allergy.

Infections and infestations: Esophageal candidiasis

Metabolic and Nutrition Disorders: Hyperglycemia, weight gain

Musculoskeletal, Connective Tissue, and Bone Disorders: Arthralgia, cramps, myalgia, osteoporosis

Nervous System Disorders: Paresthesia, restlessness

Psychiatric Disorders: Agitation, aggression, depression. Behavioral changes, including hyperactivity and irritability. have been reported very rarely and primarily in children.

Reproductive System and Breast Disorders: Dysmenorrhea.
Fluticasone Propionate and Salmeterol inhalation powder

Respiratory, Thoracic, and Mediastinal Disorders: Chest congestion; chest tightness, dyspnea; facial and oropharyngeal edema, immediate bronchospasm, moderate bronchospasm; tracheitis; wheezing; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

Skin and Subcutaneous Tissue Disorders: Ecchymoses, photodermatitis.

Vascular Disorders: Pallor.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate and salmeterol, the individual components of this product, are substrates of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, lopinavir, ritonavir, saquinavir; ketoconazole; telithromycin) with fluticasone propionate/salmeterol MDPI is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

Ritonavir: Fluticasone Propionate: A drug interaction trial with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP3A4 inhibitor) alone produced no significant effect on plasma and urinary cortisol concentrations [see Clinical Pharmacology (12.2)]. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushings syndrome and adrenal suppression. Ketoconazole: Combining fluticasone propionate/salmeterol MDPI with ritonavir (1000 mcg/kg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol area under the curve (AUC) but had no effect on urinary cortisol extraction of cortisol.

Salmeterol: In a drug interaction trial in 20 healthy subjects, coadministration of inhaled salmeterol (50 mcg twice daily) and ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and Cmax increased 1.4-fold). Three (3) subjects were withdrawn due to beta₂-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration [see Clinical Pharmacology (12.3)].

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Fluticasone propionate/salmeterol MDPI 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, because the action of salmeterol, a component of this product, on the vascular system may be potentiated by these agents.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-receptor blockers with intrinsic sympathomimetic activity (e.g., betaxolol, carteolol, labetalol) should be used with caution. Although there is no evidence that these agents block the pulmonary effect of the propionate component, exposure, resulting in significantly reduced serum cortisol concentrations [see Clinical Pharmacology (12.3)]. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushings syndrome and adrenal suppression. Although there is no evidence that these agents block the pulmonary effect of the propionate component, exposure, resulting in significantly reduced serum cortisol concentrations [see Clinical Pharmacology (12.3)].

7.4 Non-Potassium-Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as salmeterol, a component of this product, but may also produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although their effectiveness should be monitored with caution.

7.5 beta-Blockers

7.6 Non-Depolarizing Neuromuscular Blocking Agents

7.7 Beta-Adrenergic Receptor Blocking Agents

Beta-receptor blockers with intrinsic sympathomimetic activity (e.g., betaxolol, carteolol, labetalol) should be used with caution. Although there is no evidence that these agents block the pulmonary effect of the propionate component, exposure, resulting in significantly reduced serum cortisol concentrations [see Clinical Pharmacology (12.3)]. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushings syndrome and adrenal suppression. Although there is no evidence that these agents block the pulmonary effect of the propionate component, exposure, resulting in significantly reduced serum cortisol concentrations [see Clinical Pharmacology (12.3)].

7.8 Oral Anticoagulants

7.9 Calcium Channel Blockers

7.10 Beta-Adrenergic Receptor Blocking Agents

Beta-receptor blockers with intrinsic sympathomimetic activity (e.g., betaxolol, carteolol, labetalol) should be used with caution. Although there is no evidence that these agents block the pulmonary effect of the propionate component, exposure, resulting in significantly reduced serum cortisol concentrations [see Clinical Pharmacology (12.3)]. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushings syndrome and adrenal suppression. Although there is no evidence that these agents block the pulmonary effect of the propionate component, exposure, resulting in significantly reduced serum cortisol concentrations [see Clinical Pharmacology (12.3)].

7.11 Calcium Channel Blockers

7.12 Antihypertensive Agents

7.13 Other Antihypertensive Agents

7.14 Antihypertensive Agents

7.15 Antihypertensive Agents

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of fluticasone propionate/salmeterol MDPI or individual monoproduc湍s, fluticasone propionate and salmeterol xinafoate, in pregnant women. There are clinical considerations with the use of fluticasone propionate/salmeterol MDPI in pregnant women [see Clinical Considerations]. Animal reproduction studies are available with the combination of fluticasone propionate and salmeterol xinafoate as well as individual monoproduc湍s. In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight and/or skeletal variations, in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a mcg/m² basis [see Data]. However, subcutaneous administration of fluticasone propionate alone diluted 1:1 to maternal subcutaneous dose also decreased fetal body weight, but did not induce teratogenicity at a maternal toxic dose less than the MRHDID on a mcg/m² basis [see Data]. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. Oral administration of salmeterol to pregnant rabbits caused teratogenicity characterized by intrauterine fetal death and fetal malformations at maternal oral doses approximately 70 times the MRHDID on a mcg/m² basis. These adverse effects generally occurred at large multiples of the MRHDID when salmeterol was administered by the oral route to achieve high systemic exposures. No such effects occurred at an oral salmeterol dose approximately 420 times the MRHDID [see Data].
approximately 700 times the MRHDID (on a mcg/m² basis at maternal oral doses of 1000 mcg/kg/day and higher), fetal toxic effects were observed characteristically resulting from beta-adrenergic receptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at a salmeterol dose approximately 420 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 600 mcg/kg/day). New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at a salmeterol dose approximately 7,000 times the MRHDID (on a mcg²/m² basis at a maternal oral dose of 10,000 mcg/kg/day).

In two embryo/fetal development studies, pregnant rats received salmeterol by oral administration at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. Salmeterol produced no maternal toxicity or embryo/fetal effects at dosages up to 10,000 times the MRHDID (on a mcg/m² basis at maternal oral doses up to 10,000 mcg/kg/day).

In a peri- and postnatal development study in pregnant rats dosed by the oral route from late gestation through delivery and lactation, salmeterol at a dose 3500 times the MRHDID (on mcg/m² basis with a maternal oral dose of 10,000 mcg/kg/day) was fetotoxic and decreased the fertility of survivors. Salmeterol xinafoate crossed the placenta following oral administration to mice and rats.

8.2 Lactation

Risk Summary

There are no available data on the presence of fluticasone propionate or salmeterol in human milk, the effects on the breastfed child, or the effects on milk production. Other corticosteroids have been detected in human milk. However, fluticasone propionate and salmeterol concentrations in plasma after inhaled therapeutic doses are low and therefore concentrations in human breast milk are likely to be correspondingly low [see Clinical Pharmacology (12.3)]. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for fluticasone propionate/salmeterol MDPI and any potential adverse effects on the breastfed child from fluticasone propionate/salmeterol MDPI or from the underlying maternal condition.

Data

Animal Data

Subcutaneous administration of tritiated fluticasone propionate at a dose in lactating rats approximately 0.2 times the MRHDID for adults (on a mcg/m² basis) resulted in measurable levels in milk. Oral administration of salmeterol at a dose in lactating rats approximately 2900 times the MRHDID for adults (on a mcg/m² basis) resulted in measurable levels in milk.

8.4 Pediatric Use

The safety and effectiveness of fluticasone propionate/salmeterol MDPI in pediatric patients below the age of 12 years have not been established.

Inhaled corticosteroids, including fluticasone propionate, a component of this product, may cause a reduction in growth velocity in adolescents [see Warning and Precautions (5.13)]. The growth of pediatric patients receiving orally inhaled corticosteroids, including fluticasone propionate/salmeterol MDPI and any potential adverse effects on the breastfed child from fluticasone propionate/salmeterol MDPI or from the underlying maternal condition.

8.5 Geriatric Use

No overall differences in safety or efficacy were observed in data collected in 54 subjects aged 65 years and older versus younger subjects who were treated with fluticasone propionate/salmeterol MDPI in placebo-controlled Phase 2 and 3 studies.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using fluticasone propionate/salmeterol MDPI have not been conducted in patients with hepatic impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic studies using fluticasone propionate/salmeterol MDPI have not been conducted in patients with renal impairment.

10 OVERDOSAGE

This product contains both fluticasone propionate and salmeterol; therefore, the risks associated with overdose for the individual components described below apply to fluticasone propionate/salmeterol MDPI. Treatment of overdosage consists of discontinuation of fluticasone propionate/salmeterol MDPI together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. Cardiac monitoring is recommended in cases of overdose.

10.1 Fluticasone propionate

Chronic overdosage of fluticasone propionate may result in signs/symptoms of hypercorticism [see Warnings and Precautions (5.7)]. Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,796 or 3,520 mcg of fluticasone propionate CFC inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at dosages of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was well tolerated. Repeat oral dosages up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in subjects were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups.

10.2 Salmeterol

The expected signs and symptoms of overdosage of salmeterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). Overdosage with salmeterol can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias.

As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of salmeterol.

11 DESCRIPTION

Fluticasone propionate/salmeterol MDPI 55/14 mcg, 113/14 mcg and 232/14 mcg are combinations of fluticasone propionate and salmeterol xinafoate.

One active component of this product is fluticasone propionate, a corticosteroid having the chemical name 3-(fluoromethyl) 6x,3-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate, and the following chemical structure:

Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is C₇₇H₉₅F₃O₇S. It is practically insoluble in water, freely soluble in ethanol, sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

The other active component of this product is salmeterol xinafoate, a beta₂-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. It has the chemical name 4-hydroxy-α-[[6-(4-phenylbutoxy) hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalencarboxylic acid and the following chemical structure:

Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is C₇₇H₉₅NO₄. C₇₇H₉₅NO₄. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

Fluticasone propionate/salmeterol MDPI is a white multidose dry powder inhaler (MDPI) for oral inhalation only. It contains a formulation blend of fluticasone propionate, salmeterol xinafoate, and lactose monohydrate (which may contain milk proteins). The opening of the mouthpiece cover meters 5.5 mg of the formulation from the device reservoir, which contains 55 mcg, 113 mcg, or 232 mcg of fluticasone propionate, and 14 mcg of salmeterol base, equivalent to 20.3 mcg of salmeterol xinafoate. Patient inhalation through the mouthpiece causes the deagglomeration and aerosolization of the drug particles as the formulation moves through the cyclone component of the device. This is followed by dispersion into the airstream.

Under standardized in vitro test conditions, the fluticasone propionate/salmeterol MDPI inhaler delivers 49 mcg, 100 mcg, or 202 mcg of fluticasone propionate and 12.75 mcg of salmeterol base, equivalent to 18.5 mcg of salmeterol xinafoate, with lactose from the mouthpiece when tested at a flow rate of 85 L/min for 1.4 seconds. The amount of drug delivered to the lung will depend on patient factors such as inspiratory flow profiles. In adult subjects (N=50, aged 18 to 45 years) with asthma, mean peak inspiratory flow (PIF) through the fluticasone propionate/salmeterol MDPI inhaler was 108.28 L/min (range: 70.37 to 129.24 L/min). In adolescent subjects (N=50, aged 12 to 17 years) with asthma, mean peak inspiratory flow (PIF) through the fluticasone propionate/salmeterol MDPI inhaler was 106.72 L/min (range: 73.64 to 125.51 L/min).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

This product contains both fluticasone propionate and salmeterol. The mechanisms of action described below for the individual components apply to this combination product. These drugs represent 2 different classes of medications (a synthetic corticosteroid and a LABA) that have different effects on clinical, physiologic, and inflammatory indices.
Fluticasone Propionate: Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone propionate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is 18 times that of dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasconstrictor assay in man are consistent with these results. When the anti-inflammatory activity of corticosteroids is measured in vivo, however, the relative anti-inflammatory activity of these drugs is unknown. Inhalation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) involved in inflammation. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Salmeterol: Salmeterol is a selective LABA. In vitro studies show salmeterol to be at least 50 times more selective for beta2-adrenoceptors than albuterol. Although beta2-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle, beta1- and beta-adrenoceptors are present. Receptors in the heart are also beta-adrenoceptors, with the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective beta2-adreno agonists may have cardiac effects. The pharmacologic effects of beta2-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3’5’-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are at least in part attributable to stimulation of intracellular adenyl cyclase, and inhibit platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs treated by the inhaled route. In humans, single doses of salmeterol administered via inhalation attenuate allergen-induced bronchial hyperresponsiveness.

12.2 Pharmacodynamics

Fluticasone propionate/salmeterol MDPI: Healthy Subjects: Cardiovascular Effects:

There were no clinical trials conducted with this product in healthy subjects. Other Fluticasone Propionate and Salmeterol Inhalation Powder Products: Healthy Subjects: Cardiovascular Effects:

Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four (4) trials (2 inhalations/day and 2 inhalations/day) were conducted in healthy adults (subjects aged 18 to 45 years) to determine the systemic pharmacodynamic effects of salmeterol. In these trials, salmeterol was given as fluticasone propionate/salmeterol MDPI (fluticasone propionate 500 mcg and salmeterol 50 mcg powder product, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg given alone, (2) 1 repeat-dose trial using 50 to 400 mcg of salmeterol powder given alone or as a fluticasone propionate 500 mcg and salmeterol 50 mcg powder product, (3) a repeat-dose trial for 11 days using 2 inhalations twice daily of fluticasone propionate 250 mcg and salmeterol 50 mcg powder product, fluticasone propionate powder 250 mcg, or salmeterol powder 50 mcg, and (4) a single-dose trial using 5 inhalations of fluticasone propionate 100 mcg over 20 minutes, fluticasone propionate powder 100 mcg powder product or placebo.

In these trials, no significant differences were observed in the pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given as fluticasone propionate and salmeterol powder product, concurrently with fluticasone propionate from separate inhalers, or as fluticasone propionate from a single inhaler. The systemic pharmacodynamic effects of salmeterol were not altered by the presence of fluticasone propionate in the fluticasone propionate and salmeterol powder product.


There are no data from controlled trials using this product in healthy subjects or subjects with asthma in serum cortisol. Other Fluticasone Xinafoate Products: Subjects with Asthma: Cardiovascular Effects: Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium (see Warnings and Precautions (5.11, 5.17)). The beta-adrenoceptor (beta2) agonist effects (heart rate, blood pressure) associated with salmeterol inhalation aerosol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol have been reported in volunteers and in subjects with asthma. Salmeterol doses up to 84 mcg administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol doses at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adult and adolescent subjects receiving 50 mcg doses of salmeterol inhalation powder (N=60) underwent continuous electrocardiographic monitoring four periods after the first dose and after 1 month of therapy, and no clinically significant dysrhythmias were noted.

Concomitant Use of Fluticasone Propionate/Salmeterol MDPI With Other Respiratory Medications:

Other Fluticasone Propionate and Salmeterol Inhalation Powder Products: Short-Acting Beta2-Agonists: In clinical trials in subjects with asthma, the mean daily need for albuterol by 166 adult and adolescent subjects aged 12 years and older using a fluticasone propionate and salmeterol powder product was approximately 1.3 inhalations/day and ranged from 0 to 8 inhalations/day. Five percent (5%) of subjects using a fluticasone propionate and salmeterol powder product in these trials averaged 6 or more inhalations per day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse events was observed among subjects who averaged 6 or more inhalations per day.

Methylxanthines: In clinical trials in subjects with asthma, 39 subjects receiving fluticasone propionate and salmeterol powder product showed no significant difference in heart rate, blood pressure, or serum electrolytes when compared to those receiving placebo.

12.3 Pharmacokinetics

Absorption

Fluticasone Propionate/salmeterol MDPI acts locally in the lung; therefore, plasma levels may not predict therapeutic effect. Trials using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate was negligible (<1%), primarily due to incomplete absorption and systemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung was systemically absorbed.

After administration of 232/14 mcg fluticasone propionate/salmeterol MDPI to patients aged 12 years and older with persistent asthma in a clinical trial, the mean Cmax value of fluticasone propionate was 66 pg/mL with a median tmax value of approximately 2 hours.

Salmeterol:

After administration of 232/14 mcg fluticasone propionate/salmeterol MDPI to patients aged 12 years and older with persistent asthma, the mean Cmax values of salmeterol was 60 pg/mL. The median tmax was 5 minutes.

Distribution

Fluticasone Propionate:

Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 99%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Salmeterol:

Volume of distribution data are not available for salmeterol. The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Elimination

Fluticasone Propionate:

Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Terminal half-life estimates of fluticasone propionate following oral inhalation administration of fluticasone propionate/salmeterol MDPI were approximately 10.8 hours.

Salmeterol:

The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β carboxylic acid derivative of fluticasone propionate, which is formed through the CYP3A4 pathway. This metabolite has less than 10% of the in vitro glucocorticoid receptor potency of fluticasone propionate.

Excretion

Less than 5% of a radiolabeled oral dose of salmeterol was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Salmeterol:

Terminal half-life estimates for salmeterol for fluticasone propionate/salmeterol MDPI were approximately 12.6 hours.

In healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days.

Special Populations:

A population pharmacokinetic analysis was performed for fluticasone propionate and salmeterol utilizing data from 9 controlled clinical trials that included 350 subjects with asthma aged 4 to 77 years who received treatment with a combination dry powder inhaler of fluticasone propionate and salmeterol, the combination of HFA-propelled fluticasone propionate and salmeterol inhalation aerosol, fluticasone propionate inhalation powder, HFA-propelled fluticasone propionate inhalation powder 50 mcg twice daily concurrently with a theophylline product had adverse event rates similar to those in 304 subjects receiving fluticasone propionate and salmeterol powder product without theophylline. Similar results were observed in subjects receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily concurrently with a theophylline product (n = 39) or without theophylline (n = 132).
Fertility and reproductive performance were unaffected in male and female rats at subcutaneous fluticasone propionate dosages up to 50 mcg/m²/day (approximately equivalent to the MRHDID for adults on a mcg/m² basis).

Salmeterol: In an 18-month carcinogenicity study in CD-1 mice, salmeterol at oral doses of 1400 mcg/kg and above (approximately 240 times the MRHDID on a mcg/m² basis) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cysts, and ovarian cysts at doses of 580 mcg/kg and above (approximately 240 times the MRHDID on a mcg/m² basis). No tumors were seen at 200 mcg/kg (approximately 35 times the MRHDID on a mcg/m² basis).

In a 24 month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 580 mcg/kg and above (approximately 240 times the MRHDID on a mcg/m² basis). These findings in rodents are similar to those reported previously for other beta adrenergic agonists drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test.

Fertility and reproductive performance were unaffected in male and female rats at oral doses up to 2000 mcg/kg (approximately 690 times the MRHDID for adults on a mcg/m² basis).

13.2 Animal Toxicology and/or Pharmacology

Preclinical: Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with beta-agonists or methylxanthines) when beta-agonists and methylxanthines are administered concurrently. The clinical relevance of these findings is unknown.

14 CLINICAL STUDIES

The safety and efficacy of Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler (FS MDPI) were evaluated in 3004 patients with asthma. The development program included 2 confirmatory trials of 12 weeks duration, a 26 week safety trial and three dose-ranging trials. The efficacy of fluticasone propionate/salmeterol MDPI is based primarily on the dose-ranging trials and the confirmatory trials described below.

14.1 Dose-Ranging Studies

Six doses of fluticasone propionate ranging from 16 mcg to 434 mcg (expressed as metered doses) administered twice daily via multidose dry powder inhaler were evaluated in 2 randomized, double-blind, placebo-controlled 12 week trials. Trial 201 was conducted in patients who were uncontrolled at baseline and who had been treated by short-acting beta-agonist alone or in combination with non-corticosteroid asthma medication. Low dose ICS patients may have been included after a minimum of 2 weeks washout. This trial contained an open-label active comparator fluticasone propionate inhalation powder 100 mcg administered twice daily. Trial 202 was conducted in patients who were uncontrolled at baseline and who had been treated with high dose ICS with or without a LABA. This study contained an open-label active comparator fluticasone propionate inhalation powder 250 mcg twice daily. The trials were dose-ranging trials of Fluticasone Propionate Multidose Dry Powder Inhaler (Fluticasone Propionate MDPI) not designed to provide comparative effectiveness data and should not be interpreted as evidence of superiority/inferiority to fluticasone propionate inhalation powder. The metered doses for fluticasone multidose dry powder inhaler (16, 28, 59, 118, 225, 434 mcg) used in Trial 201 and Trial 202 (Figure 1) were different from the metered doses for the comparator products (fluticasone inhalation powder) and the Phase 3 investigational products which are the basis of the proposed commercial labeled claim (55, 113, 232 mcg for fluticasone). The changes in doses between Phase 2 and 3 resulted from optimization of the manufacturing process.
The efficacy and safety of four doses of salmeterol xinafoate were evaluated in a double-blind, placebo-controlled study compared with single doses of fluticasone propionate MDPI and open label fluticasone propionate/salmeterol 100/50 mcg dry powder inhaler as comparator in patients with persistent asthma. The trials were dose-ranging trials of the salmeterol component of fluticasone propionate/salmeterol MDPI and not designed to provide comparative effectiveness data and should not be interpreted as evidence of superiority/inferiority of fluticasone propionate/salmeterol inhalation powder. The salmeterol doses studied were 6.8 mcg, 13.2 mcg, 26.8 mcg and 57.4 mcg in combination with fluticasone propionate 118 mcg delivered by MDPI (expressed as metered dose). The metered doses for salmeterol (6.8, 13.2, 26.8, 57.4 mcg) used in this study are slightly different from the metered doses for the comparator products (fluticasone/salmeterol inhalation powder) and the Phase 3 investigational products which are the basis of the proposed commercial labeled claim (55, 113, 232 mcg for fluticasone and 14 mcg for salmeterol). The phase 3 and commercial products were optimized to better match the strengths to the comparators. Plasma for pharmacokinetic characterization was obtained at each dosing period. Fluticasone propionate/salmeterol xinafoate MDPI 118/13.2 mcg had similar clinical efficacy with lower systemic exposure when compared to the 50 mcg of salmeterol in fluticasone propionate/salmeterol 100/50 mcg dry powder inhaler (Figure 2).

**Figure 2: Mean Baseline Adjusted FEV1 (mL) over 12 Hours (FAS)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change in FEV1 (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.053</td>
</tr>
<tr>
<td>FP MDPI 55 mcg</td>
<td>0.315</td>
</tr>
<tr>
<td>FP MDPI 113 mcg</td>
<td>0.319</td>
</tr>
<tr>
<td>FS MDPI 55/14 mcg</td>
<td>0.319</td>
</tr>
</tbody>
</table>

Estimated mean differences between fluticasone propionate/salmeterol MDPI 55/14 mcg and fluticasone propionate/salmeterol MDPI 113/14 mcg compared to placebo are 0.268 L (95% CI: 0.172, 0.360) and 0.262 L (95% CI: 0.168, 0.356), respectively. The estimated mean difference between fluticasone propionate MDPI 55 mcg and fluticasone propionate MDPI 113 mcg compared to placebo are 0.119 L (95% CI: 0.025, 0.212) and 0.151 L (95% CI: 0.057, 0.244), respectively. The estimated mean difference between fluticasone propionate/salmeterol MDPI 113/14 mcg and fluticasone propionate MDPI 113 mcg is 0.111 L (95% CI: 0.017, 0.206). The estimated mean difference between fluticasone propionate/salmeterol MDPI 55/14 mcg and fluticasone propionate MDPI 55 mcg is 0.147 L (95% CI: 0.083, 0.242). In addition, the mean FEV1 results at each visit are displayed in Figure 3.
There was supportive evidence of efficacy for fluticasone propionate/salmeterol MDPI compared with placebo for secondary endpoints such as the weekly average of daily trough morning peak expiratory flow and total daily use of rescue medication. There were fewer withdrawals due to worsening asthma in patients treated with fluticasone propionate/salmeterol MDPI than with placebo. The Asthma Quality of Life Questionnaire (AQLQ) for patients aged 12-17 years had a responder rate of 85% (95% CI: 1.56, 0.43) and 1.94 (95% CI: 1.16, 3.25), respectively. Improvements in lung function occurred within 15 minutes of the first dose (15 minutes postdose), the difference in LS mean change from baseline in FEV1, was 0.160 L and 0.187 L compared with placebo for fluticasone propionate/salmeterol MDPI 113/14 mcg and 232/14 mcg, respectively; unadjusted $p$-value <0.0001 for both doses compared with placebo. Maximum improvement in FEV1 generally occurred within 3 hours for both fluticasone propionate/salmeterol MDPI dose groups, and improvements were sustained over the 12 hours of testing at weeks 1 and 12 (Figure 7 and Figure 8). Following the initial dose, predose FEV1 relative to day 1 baseline improved markedly over the first week of treatment and the improvement was sustained over the 12 weeks of treatment in the trial. No diminution in the 12 hour bronchodilator effect was observed with either fluticasone propionate/salmeterol MDPI dose as assessed by FEV1 following 12 weeks of therapy.

Figure 7: Serial Spirometry: Mean Change from Baseline in FEV1 (L) at Day 1 by Time Point and Treatment Group Trial 2 (FAS; Serial Spirometry Subset)

Figure 8: Serial Spirometry: Mean Change from Baseline in FEV1 (L) at Week 12 by Time Point and Treatment Group Trial 2 (FAS; Serial Spirometry Subset)

FAS = full analysis set; FEV1 = forced expiratory volume in 1 second

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Fluticasone propionate/salmeterol inhalation powder is supplied in the following three strengths as a white dry-powder inhaler. Each inhaler has a yellow cap and is packaged individually in a foil pouch in a carton. Each inhaler contains 0.45g of the formulation and provides 60 actuations:
Inform patients that fluticasone propionate/salmeterol is not meant to relieve acute related hospitalization and asthma-related death. Available data show that when ICS

Serious Asthma Events

Inform patients with asthma that LABA when used alone increases the risk of asthma-

Not for Acute Symptoms

Inform patients that fluticasone propionate/salmeterol is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose. Advise patients to treat acute asthma symptoms with an inhaled, short-acting beta,-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

Instruct patients to seek medical attention if they experience any of the following:
• Decreasing effectiveness of inhaled, short-acting beta,-agonists
• Need for more inhalations than usual of inhaled, short-acting beta,-agonists

Tell patients they should not stop therapy with fluticasone propionate/salmeterol without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting Beta,-Agonists

Inform patients not to use other LABA for asthma.

Local Effects

Inform patients that localized infections with Candida albicans occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, treat it with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with fluticasone propionate/salmeterol, but at times therapy with fluticasone propionate/salmeterol may need to be temporarily interrupted under close medical supervision. Rinsing the mouth with water without swallowing after inhalation is advised to help reduce the risk of thrush.

Immunosuppression

Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections; or ocular herpetic simplex.

Hypercorticism and Adrenal Suppression

Advise patients that fluticasone propionate/salmeterol may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to fluticasone propionate/salmeterol.

Immediate Hypersensitivity Reactions

Advise patients that immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of fluticasone propionate/salmeterol. Patients should discontinue fluticasone propionate/salmeterol if such reactions occur and contact their healthcare provider or get emergency medical help. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of powder products containing lactose; therefore, patients with severe milk protein allergy should not take fluticasone propionate/salmeterol.

Reduction in Bone Mineral Density

Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Reduced Growth Velocity

Inform patients that orally inhaled corticosteroids, including fluticasone propionate, may cause a reduction in growth velocity when administered to adolescent patients. Physicians should closely follow the growth of adolescents taking corticosteroids by any route.
What is fluticasone propionate/salmeterol inhalation powder?

- Fluticasone propionate/salmeterol inhalation powder combines the inhaled corticosteroid (ICS) medicine fluticasone propionate and the LABA medicine salmeterol.
- ICS medicines such as fluticasone propionate help to decrease inflammation in the lungs. Inflammation in the lungs can lead to breathing problems.
- LABA medicines such as salmeterol help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing, cough, chest tightness, and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe.
- Fluticasone propionate/salmeterol inhalation powder is a prescription medicine used to control symptoms of asthma and to prevent symptoms such as wheezing in people 12 years of age and older.
- This product contains salmeterol. LABA medicines such as salmeterol when used alone increase the risk of hospitalizations and death from asthma problems. Fluticasone propionate/salmeterol inhalation powder contains an ICS and a LABA. When an ICS and LABA are used together, there is not a significant increased risk in hospitalizations and death from asthma problems.
- Fluticasone propionate/salmeterol inhalation powder is not for people 12 years of age and older with asthma who are well controlled with an asthma control medicine, such as a low or medium dose of an inhaled corticosteroid medicine. Fluticasone propionate/salmeterol inhalation powder is for people 12 years of age and older with asthma who need both an ICS and LABA medicine.
- Fluticasone propionate/salmeterol inhalation powder is not used to relieve sudden breathing problems and will not replace a rescue inhaler.
- It is not known if fluticasone propionate/salmeterol inhalation powder is safe and effective in children younger than 12 years of age.

How should I use fluticasone propionate/salmeterol inhalation powder?

- Read the step-by-step instructions for using fluticasone propionate/salmeterol inhalation powder at the end of this Patient Information leaflet.
- Fluticasone propionate/salmeterol inhalation powder comes in 3 different strengths. Your healthcare provider prescribed the strength that is best for you.
- Use fluticasone propionate/salmeterol inhalation powder exactly as your healthcare provider tells you to use it. Do not use fluticasone propionate/salmeterol inhalation powder more often than prescribed.
- Use 1 inhalation of fluticasone propionate/salmeterol inhalation powder 2 times each day. Use fluticasone propionate/salmeterol at the same time each day, about 12 hours apart. If you miss a dose of fluticasone propionate/salmeterol inhalation powder, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.
- If you take too much fluticasone propionate/salmeterol, call your healthcare provider or go to the nearest hospital emergency room right away if you have any unusual symptoms, such as worsening shortness of breath, chest pain, increased heart rate, or shakiness.
- Do not use other medicines that contain a LABA for any reason.
- Examples of other medicines that contain a LABA include salmeterol, formoterol fumarate, arformoterol tartrate, and indacaterol. Ask your healthcare provider or pharmacist if any of your other medicines are LABA medicines.
- Do not stop using fluticasone propionate/salmeterol inhalation powder unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- Fluticasone propionate/salmeterol inhalation powder does not relieve sudden asthma symptoms. You should not take extra doses of fluticasone propionate/salmeterol inhalation powder to relieve sudden asthma symptoms. Always have a rescue inhaler with you to treat sudden asthma symptoms. If you do not have a rescue inhaler, call your healthcare provider to have one prescribed for you.
- Call your healthcare provider or get medical care right away if:
  - your breathing problems get worse.
  - you need to use your rescue inhaler more often than usual.
  - your rescue inhaler does not work as well to relieve your symptoms.
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
  - you have asthma and your symptoms do not improve after using fluticasone propionate/salmeterol inhalation powder regularly for one week.

Do not use fluticasone propionate/salmeterol inhalation powder:

- to treat sudden, severe symptoms of asthma.
- if you have a severe allergy to milk proteins. Ask your healthcare provider if you are not sure.
- if you are allergic to fluticasone propionate or any of the inactive ingredients in fluticasone propionate/salmeterol inhalation powder. See the end of this leaflet for a complete list of ingredients in this product.

Tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems.
- have high blood pressure.
- have seizures.
- have thyroid problems.
- have diabetes.
- have liver problems.
- have weak bones (osteoporosis).
- have an immune system problem.
- have eye problems, such as glaucoma or cataracts.
- are allergic to milk proteins.

continued
Fluticasone Propionate and Salmeterol inhalation powder

What are the possible side effects with fluticasone propionate/salmeterol inhalation powder?
Fluticasone propionate/salmeterol inhalation powder can cause serious side effects, including:
• fungal infection in your mouth and throat (thrush). Rinse your mouth with water without swallowing after using fluticasone propionate/salmeterol inhalation powder to help reduce your chance of getting thrush.
• weakened immune system and increased chance of getting infections (immunosuppression).
• reduced adrenal function (adrenal insufficiency). Adrenal insufficiency is a condition where the adrenal glands do not make enough steroid hormones. This can happen when you stop taking oral corticosteroid medicines (such as prednisone) and start taking a medicine containing an inhaled steroid (such as fluticasone propionate/salmeterol inhalation powder). When your body is under stress such as from fever, trauma (such as a car accident), infection, or surgery, adrenal insufficiency can get worse and may cause death.

Symptoms of adrenal insufficiency include:
  ◦ feeling tired
  ◦ lack of energy
  ◦ weakness
  ◦ nausea and vomiting
  ◦ low blood pressure
• sudden breathing problems immediately after inhaling your medicine. If you have sudden breathing problems immediately after inhaling your medicine, stop using fluticasone propionate/salmeterol inhalation powder and call your healthcare provider right away.
• serious allergic reactions. Stop using fluticasone propionate/salmeterol inhalation powder and call your healthcare provider or get emergency medical help if you get any of the following symptoms of a serious allergic reaction:
  ◦ rash
  ◦ hives
  ◦ swelling of your face, mouth, and tongue
  ◦ breathing problems
• effects on heart.
  ◦ increased blood pressure
  ◦ a fast or irregular heartbeat
  ◦ chest pain
• effects on nervous system.
  ◦ tremor
  ◦ nervousness
• bone thinning or weakness (osteoporosis).
• slowed growth in children. The growth of a child should be checked often.
• eye problems including glaucoma and cataracts. You should have regular eye exams while using fluticasone propionate/salmeterol inhalation powder.
• changes in laboratory blood values (sugar, potassium, certain types of white blood cells).

Common side effects of fluticasone propionate/salmeterol inhalation powder include:
• infection of nose and throat (nasopharyngitis)
• thrush in your mouth or throat. Rinse your mouth with water without swallowing after use to help prevent this.
• back pain
• headache
• cough

These are not all the possible side effects of fluticasone propionate/salmeterol inhalation powder.
Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store fluticasone propionate/salmeterol inhalation powder?
• Store fluticasone propionate/salmeterol inhalation powder at room temperature between 59°F and 77°F (15°C and 25°C).
• Avoid exposure to extreme heat, cold, or humidity.
• Store fluticasone propionate/salmeterol inhalation powder in the unopened foil pouch and only open when ready for use.
• Keep the yellow cap on the inhaler closed during storage.
• Keep your fluticasone propionate/salmeterol inhalation powder inhaler dry and clean at all times.
• Throw away fluticasone propionate/salmeterol 30 days after opening the foil pouch, when the dose counter displays ‘0’, or after the expiration date on the product, whichever comes first.

Keep fluticasone propionate/salmeterol inhalation powder and all medicines out of the reach of children.

General information about the safe and effective use of fluticasone propionate/salmeterol inhalation powder.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use fluticasone propionate/salmeterol inhalation powder for a condition for which it was not prescribed. Do not give fluticasone propionate/salmeterol inhalation powder to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your healthcare provider or pharmacist for information about fluticasone propionate/salmeterol inhalation powder that is written for health professionals.

What are the ingredients in fluticasone propionate/salmeterol inhalation powder?
Active ingredients: fluticasone propionate, salmeterol xinafoate
Inactive ingredient: lactose monohydrate (may contain milk proteins)

This Patient Information leaflet has been approved by the U.S. Food and Drug Administration.
Marketed by: Teva Respiratory, LLC, Frazer, PA 19355; Manufactured by: Teva Pharmaceutical Industries Ltd., Jerusalem, Israel; Copyright ©2018, Teva Respiratory, LLC; All rights reserved.

For more information about fluticasone propionate/salmeterol inhalation powder, call 1-888-482-9522 or visit the reference branded product website at www.MYAIRDUO.com.

FPSPL-002
Rev. March 2018
Your fluticasone propionate/salmeterol inhaler

When you are ready to use your inhaler for the first time, remove the inhaler from the foil pouch. There are 2 main parts of your inhaler including the:

- white inhaler with the mouthpiece. See Figure A.
- yellow cap that covers the mouthpiece of the inhaler. See Figure A.

There is a dose counter in the back of the inhaler with a viewing window that shows you how many doses of medicine you have left. See Figure A.

- Your inhaler contains 60 doses (inhalations). See Figure B.
- The dose counter shows the number of doses left in your inhaler.
- When there are 20 doses left, the color of the numbers on the dose counter will change to red and you should refill your prescription or ask your healthcare provider for another prescription.
- When the dose counter displays '0' your inhaler is empty and you should stop using the inhaler and throw it away. See Figure B.

Important:
- Always close the cap after each inhalation so your inhaler will be ready for you to take your next dose. Do not open the cap unless you are ready for your next dose.
- You will hear a “click” sound when the cap is opened all the way. If you do not hear the “click” sound the inhaler may not be activated to give you a dose of medicine.
- This inhaler does not have an activation button or medicine canister. When you open the cap, a dose of fluticasone propionate/salmeterol will be activated for delivery of the medicine.
- Do not use a spacer or volume holding chamber with the inhaler. This inhaler does not need priming.

Using your fluticasone propionate/salmeterol inhaler:

Important: Make sure the cap is closed before you start using your inhaler.

Step 1. Open
- Hold the inhaler upright and open the yellow cap all the way until it “clicks”. See Figure C
- Each time you open the yellow cap and it “clicks”, 1 dose of fluticasone propionate/salmeterol is ready to be inhaled.

Remember:
- For the correct use of your inhaler, hold it upright as you open the yellow cap. See Figure D.
- Do not hold the inhaler in any other way as you open the yellow cap.
- Do not open the yellow cap until you are ready to take a dose of fluticasone propionate/salmeterol.

Step 2. Inhale
- Before you inhale, breathe out (exhale) through your mouth and push as much air from your lungs as you can. See Figure E.
- Do not exhale into the inhaler mouthpiece.

Important:
- Put the mouthpiece in your mouth and close your lips tightly around it. See Figure F.
- Do not block the vent above the mouthpiece with your lips or fingers. See Figure G.
Figure G
• Breathe in quickly and deeply through your mouth to deliver the dose of medicine to your lungs.
• Remove the inhaler from your mouth.
• Hold your breath for about 10 seconds or for as long as you comfortably can.
• Your inhaler delivers your dose of medicine as a very fine powder that you may or may not taste or feel. Do not take an extra dose from the inhaler even if you do not taste or feel the medicine.

Step 3. Close

Figure H
• Close the yellow cap firmly over the mouthpiece. See Figure H.
• Make sure you close the yellow cap after each inhalation so that the inhaler will be ready for your next dose.
• Rinse your mouth with water without swallowing after each inhalation.

How should I store the fluticasone propionate/salmeterol inhaler?
• Store your inhaler at room temperature between 59°F and 77°F (15°C and 25°C).
• Avoid exposure to extreme heat, cold, or humidity.
• Store your inhaler in the unopened foil pouch and only open when ready for use.
• Keep the yellow cap on the inhaler closed during storage.
• Keep your inhaler dry and clean at all times.
• Keep your inhaler and all medicines out of the reach of children.

Cleaning your fluticasone propionate/salmeterol inhaler
• Do not wash or put any part of your inhaler in water. Replace your inhaler if washed or placed in water.
• Your inhaler contains a powder and must be kept clean and dry at all times.
• You can clean the mouthpiece if needed using a dry cloth or tissue. Routine cleaning is not required.

Replacing your fluticasone propionate/salmeterol inhaler
• Immediately replace your inhaler if the mouthpiece cover is damaged or broken. Never take the inhaler apart.
• The dose counter on the back of your inhaler shows how many doses you have left.
• When there are 20 doses left, the color of the numbers on the dose counter will change to red and you should refill your prescription or ask your healthcare provider for another prescription.