Fluticasone Propionate and Salmeterol inhalation powder

• Limitations of Use:
  - Not indicated for the relief of acute bronchospasm. (1)
  - Do not use with a spacer or volume holding chamber. (2.2)

DOSE FORMS AND STRENGTHS
- Inhalation powder: 55 mcg/14 mcg, 113 mcg/14 mcg, or 232 mcg/14 mcg of fluticasone propionate/salmeterol in each 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 MDPI. (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 an additional medicine 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)
- Immunosuppression: Potential worsening of existing tuberculosis, fungal, bacterial, viral, parasitic infection, or ocular herpes simplex. Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.5)

DOSE AND ADMINISTRATION
- For oral inhalation only. (2.1)
  - Starting dosage is based on prior asthma therapy and disease severity. (2.2)
  - 1 inhalation of Fluticasone Propionate/Salmeterol 55 mcg/14 mcg, 113 mcg/14 mcg, or 232 mcg/14 mcg twice daily. (2.2)
  - Do not use with a spacer or volume holding chamber. (2.2)

ADVERSE REACTIONS
Most common adverse reactions (greater than or equal to 3%): nasopharyngitis, oral candidiasis, headache, cough and back pain. (6.1)

DRUG INTERACTIONS
- Avoid strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole): May increase risk of systemic corticosteroid and cardiovascular effects. (7.1)
- Monoamine 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 bronchodiatory 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: 07/2021
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)).
- 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 (5.3) and Description (7)).

5 WARNINGS AND PRECAUTIONS

5.1 Serious Asthma-Related Events — Hospitalizations, Intubations, Death

Use of LABA as monotherapy (without inhaled corticosteroids (ICS)) for asthma is associated with an increased risk of asthma-related death (see Salmeterol Multicenter Asthma Research Trial (SMART)).

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 Beta2-adrenergic Agonists (LABAs)).

Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta2-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 analysis set for all 4 trials was serious asthma-related events (hospitalizations, intubations, death). A blinded adjudication committee determined whether events were asthma-related.

The 3 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 2.2 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/Outcome</th>
<th>ICS/LABA</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma-related death</td>
<td>115/105</td>
<td>1.00 (0.70, 1.44)</td>
</tr>
<tr>
<td>Asthma-related intubation (endotracheal)</td>
<td>1/2</td>
<td>1.00 (0.60, 1.50)</td>
</tr>
<tr>
<td>Asthma-related hospitalization</td>
<td>115/105</td>
<td>1.00 (0.70, 1.50)</td>
</tr>
</tbody>
</table>

ICS = Inhaled Corticosteroid; LABA = Long-acting Beta2-adrenergic Agonist.

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

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

c 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 27/3,107 (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 to 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 (13/13,716) in subjects treated with salmeterol versus 3/13,719 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.

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 life-threatening acute asthma exacerbations) and in some patients with acutely deteriorating asthma (e.g., patients with significantly increasing symptoms; increasing need for inhaled, short-acting beta-agonists;
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Unmasking of Allergic Conditions Previously Suppressed by Systemic Corticosteroids

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).

Corticosteroid Withdrawal Symptoms

Patients requiring systemic corticosteroids should be weaned slowly from systemic corticosteroids using a withdrawal schedule that employs an initial reduction in the dose by about 25% of the daily dose. This can be followed by a similar reduction every 2 weeks. When the dose is reduced below 5 mg/day of prednisone or its equivalent, patients should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are being withdrawn from systemic corticosteroids. If such effects occur, Fluticasone Propionate/Salmeterol MDPI should be reduced slowly, consistently with accepted procedures for reducing systemic corticosteroids, and for management of asthma symptoms.

5.7 Hypercorticism and Adrenal Suppression

Fluticasone propionate, a component of Fluticasone Propionate/Salmeterol MDPI, may often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of Fluticasone Propionate/Salmeterol MDPI in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between use of fluticasone propionate and features of pituitary suppression has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing Fluticasone Propionate/Salmeterol MDPI. Because of the possibility of significant systemic absorption of inhaled corticosteroids, patients and caregivers should be informed and be ready to follow up with the physician if symptoms of adrenal insufficiency develop. Prompt recognition and appropriate intervention are required to ensure maintenance of adrenal function and, if necessary, replacement therapy.

5.8 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

The use of strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with Fluticasone Propionate/Salmeterol MDPI is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur (see Drug Interactions (7) and Clinical Pharmacology (12.3)).

5.9 Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medications, Fluticasone Propionate/Salmeterol MDPI can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs following dosing with inhaled fluticasone propionate/salmeterol medicines, it should be treated immediately with an inhaled, short-acting bronchodilator; inhaled fluticasone propionate/salmeterol medicines should be discontinued immediately; and alternative therapy should be instituted. Upper airway symptoms of laryngeal edema and stridor and choking have been reported in patients receiving inhaled fluticasone propionate/salmeterol medicines.

5.10 Hypersensitivity Reactions, Including Anaphylaxis

Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, after administration of Fluticasone Propionate/Salmeterol MDPI have been reported from 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

Strong beta-adrenergic stimulation has been associated with seizures, anagia, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia (see Overdosage). Therefore, Fluticasone Propionate/Salmeterol MDPI, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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. 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 prolonged immobilization, 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, tilor each patient’s dosage to the lowest dosage that effectively controls his/her symptoms (see Dosage and Administration (2) Use in Specific Population (8.4)).
Glucocorticoids, as well as other respiratory inhaled medications, 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 and were considered events that would not exclude a patient from future treatment with the drug. In a 2-year open-label extension study of moderate to severe asthmatics treated with Fluticasone Propionate/Salmeterol MDPI (n = 6,095) for up to 155 months, adverse events related to glucose and/or serum potassium were reported during 2.4% (146/6,095) of the patient-years of exposure, of which 1.8% (113/6,095) were considered by the investigator to be possibly related to the study medication (see Warnings and Precautions (5.14) and Safety Summary for Clinical Trials (10.1))."
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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 they should be administered with caution.

24 Non-Potassium-Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (e.g., triamterene and amiloride) can be acutely worsened by beta-agonists such as salmeterol, a component of this product, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of Fluticasone Propionate/Salmeterol MDPI with non-potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of fluticasone propionate/salmeterol MDPI or individual monoproducts, fluticasone propionate and salmeterol, 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 as well as individual components. 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 of salmeterol on a mcg/m² basis (see Table). Medications with a dose approximately 0.5 times the MRHDID and higher (on a mcg/m² basis with maternal oral doses of 100 mcg/kg/day) 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 characteristic of beta-adrenoceptor stimulation of maternal doses approximately 700 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).

The estimated maternal birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

In women with poorly, moderately controlled asthma, there is an increased risk of several perinatal adverse outcomes such as preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control.

Animal Data

Fluticasone Propionate and Salmeterol: In an embryo/fetal development study with pregnant rats that received the combination of subcutaneous administration of fluticasone propionate and oral administration of salmeterol at doses of 0/100, 30/10, 100/30, 100/1000, and 100/10,000 mcg/kg (as fluticasone propionate or salmeterol) during the period of organogenesis, findings were generally consistent with the individual monoproducts and there was no exacerbation of expected fetal effects. Omphalocoele, increased fetal body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, when combining fluticasone propionate at a dose approximately 2 times the MRHDID (on a mcg/m² basis) and salmeterol at a maternal subcutaneous dose of 100 mcg/kg/day and a dose of salmeterol at approximately 3500 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 10,000 mcg/kg/day). The rat no observed adverse effect level (NOAEL) was observed when combining fluticasone propionate at a dose 0.6 times the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 30 mcg/kg/day) and a dose of salmeterol at approximately 3500 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 10,000 mcg/kg/day). In an embryo/fetal development study with pregnant mice that received the combination of subcutaneous administration of fluticasone propionate and oral administration of salmeterol at doses of 0/1400, 40/10, 200/40, 1400/40, or 150/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) during the period of organogenesis, findings were generally consistent with the individual monoproducts and there was no exacerbation of expected fetal effects. Omphalocoele, increased fetal body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, when combining fluticasone propionate at a dose approximately 1.4 times the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 150 mcg/kg/day) and salmeterol at a dose approximately 1470 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 10,000 mcg/kg/day). Teratogenicity characteristic of beta-adrenoceptor stimulation of fluticasone propionate up to approximately 0.8 times the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 40 mcg/kg/day) and of salmeterol up to approximately 420 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 10,000 mcg/kg). Fluticasone Propionate: In embryo/fetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.5 times the MRHDID (on a mcg/m² basis with a maternal inhalation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose approximately 0.1 times the MRHDID (on a mcg/m² basis with a maternal inhalation dose of 5.5 mcg/kg/day).

In an embryo/fetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced reductions of fetal body weights, in the presence of maternal toxicity at doses approximately 0.02 times the MRHDID and higher (on a mcg/m² basis with a maternal subcutaneous dose of 0.57 mcg/kg/day). Teratogenicity was evident based upon a finding of cleft palate for 1 fetus at a dose approximately 0.2 times the MRHDID (on a mcg/m² basis with a maternal subcutaneous dose of 4 mcg/kg/day). The NOAEL was observed in rabbit fetuses with a dose approximately 0.004 times the MRHDID (on a mcg/m² basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).

In a pre- and post-natal development study in pregnant rats dosed by the subcutaneous route throughout delivery and lactation (gestation Day 7 to Postpartum Day 22), fluticasone propionate was not associated with decreases in pup body weight, and had no effects on developmental landmarks, learning, memory, reflexes, or fertility at doses up to approximate equivalence to the MRHDID (on a mcg/m² basis with maternal subcutaneous doses up to 50 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 doses up to 3500 times the MRHDID (on a mcg/m² basis at maternal oral doses up to 10,000 mcg/kg/day). In a peri- and post-natal 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 a mcg/m² basis with a maternal oral dose of 10,000 mcg/kg/day) was fetotoxic and decreased the fertility of survivors.

Salmeterol xinafate crossed the placenta following subcutaneous 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 (2.6)). 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

Subcutaneous administration of triitated 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 have been established for the treatment of asthma in pediatric patients aged 12 years and older whose asthma is inadequately controlled on a long term asthma control medication or (2) warrants initiation of treatment with both an ICS and a LABA.

Fluticasone Propionate/Salmeterol MDPI in pediatric patients aged 12 to 17 years for this indication is supported by evidence from two adequate and well-controlled trials in pediatric patients 12 years old and older with persistent symptomatic asthma despite ICS or ICS/LABA therapy (Trials 1 and 2) (see Clinical Studies (14)). In these trials, 58 adolescents received Fluticasone Propionate/Salmeterol MDPI one inhalation twice daily. The safety and effectiveness of Fluticasone Propionate/Salmeterol MDPI have not been established in pediatric patients younger than 12 years of age for the treatment of asthma. Effectiveness was not demonstrated in one adequate and well-controlled study conducted in 211 patients aged 4 to 11 years with persistent asthma on a stable asthma regimen who were treated with Fluticasone Propionate/Salmeterol MDPI 55 mcg/14 mcg one inhalation twice daily.

Effect on Growth

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 ICS, including Fluticasone Propionate/Salmeterol MDPI, should be closely monitored.

If an adolescent on any corticosteroid appears to have growth suppression, the possibility that he/ she is particularly sensitive to this effect of corticosteroids should be considered. In such patients, the potential growth effects of prolonged ICS treatment should be weighed against the clinical
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benefits obtained. To minimize the systemic effects of ICS, including Fluticasone Propionate/ Salmeterol MDPI, each patient should be titrated to the lowest strength that effectively controls his/ her asthma [see Dosage and Administration (2)].

8.5 Geriatric Use
No overall differences in safety or effectiveness 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 asthma 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 [see Clinical Pharmacology (12.3)], impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic impairment 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 overdose 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 bronchodilation. Cardiac monitoring is recommended in cases of overdose.

Fluticasone propionate
Chronic overdose of fluticasone propionate may result in signs/symptoms of hypercorticism [see Warnings and Precautions (5.7)].

Salmeterol
The expected signs and symptoms with overdose 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). Overdose 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 mcg/14 mcg, 113 mcg/14 mcg and 232 mcg/14 mcg are combinations of fluticasone propionate and salmeterol.

Fluticasone Propionate
One active component of this product is fluticasone propionate, a corticosteroid having the chemical name 5-(fluormethyl) 6x,9-difluoro-11ß,17-dihydroxy-16ß,21-diene-17ß-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 C29H36F3O5S. It is practically insoluble in water; freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

Salmeterol Xinafoate
The other active component of this product is salmeterol xinafoate, a beta-2-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-(100 mcg/50 mcg) (five times the maximum approved salmeterol dosage for that DPI per dosing interval), fluticasone propionate DPI 500 mcg and salmeterol DPI 50 mcg given concurrently, or fluticasone propionate DPI 500 mcg given alone.

Cumulative dose trial using 50 to 400 mcg of salmeterol DPI (1 time to 8 times the maximum approved salmeterol dosage for that DPI per dosing interval), fluticasone propionate DPI 500 mcg and salmeterol DPI 50 mcg given concurrently, or fluticasone propionate DPI 500 mcg given alone.

Repeat-dose trial for 11 days using 2 inhalations twice daily of fluticasone propionate and salmeterol DPI (250 mcg/50 mcg) (two times the maximum approved salmeterol dosage for that DPI per dosing interval), fluticasone propionate DPI 250 mcg, or salmeterol DPI 50 mcg, or fluticasone propionate DPI 250 mcg and salmeterol DPI 50 mcg given concurrently.

4. Single-dose trial using 5 inhalations of fluticasone propionate and salmeterol DPI (100 mcg/50 mcg) (five times the maximum approved salmeterol dosage for that DPI per dosing interval), fluticasone propionate DPI 100 mcg alone, 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 DPI, concurrently with fluticasone propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic effects of salmeterol were not altered by the presence of fluticasone propionate in the fluticasone propionate and salmeterol DPI product.
Other Salmeterol Products in Subjects with Asthma:

Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related CV effects and effects on blood glucose and/or serum potassium [see Warnings and Precautions (5.11, 5.17)]. The CV effects (heart rate, blood pressure) associated with salmeterol inhalation aerosol occurred with similar frequency, and are of similar type and severity, as those noted following albuterol inhalation.

The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in subjects with asthma. Salmeterol doses up to 48 mcg administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/minute, about the same as albuterol dosed at 160 mcg by inhalation aerosol (4 to 10 beats/minute). Adult and adolescent subjects receiving 50 mcg doses of salmeterol MDPI (N=60) underwent continuous electrocardiographic monitoring during two 12-hour 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:

Short-Acting Beta 2-Agonists:

Comparative studies in stable asthma not taking any short-acting beta-2-agonists demonstrated that, in short-term studies, the addition of Fluticasone Propionate/Salmeterol MDPI to salmeterol aerosol (50 mcg) did not affect the effect of salmeterol in reducing asthma symptoms, and in the long-term studies, the addition of Fluticasone Propionate/Salmeterol MDPI did not affect the effect of salmeterol in reducing symptoms requiring rescue medication. These studies also showed that the addition of Fluticasone Propionate/Salmeterol MDPI to salmeterol aerosol (50 mcg) did not affect the effect of salmeterol on nighttime symptoms.

Concomitant Use of Other Respiratory Medications:

The effect of Fluticasone Propionate/Salmeterol MDPI coadministration on theophylline levels was studied in a dose-escalation study in 12 healthy male volunteers. Subjects were administered Fluticasone Propionate/Salmeterol MDPI (100 mcg/5 mcg) or Fluticasone Propionate/Salmeterol MDPI (200 mcg/10 mcg) once daily concurrently with theophylline. The mean theophylline concentration increased at the Fluticasone Propionate/Salmeterol MDPI 100 mcg/5 mcg dose, but not at the Fluticasone Propionate/Salmeterol MDPI 200 mcg/10 mcg dose. The effect of Fluticasone Propionate/Salmeterol MDPI on theophylline levels was considered to be clinically insignificant.

Patients who were receiving theophylline therapy were withdrawn before the study and were not permitted to restart theophylline therapy during the study. The effect of Fluticasone Propionate/Salmeterol MDPI on theophylline levels was evaluated in 12 healthy adult volunteers in a multiple-dose, single-blind, crossover drug interaction trial in 11 healthy subjects. None of the Fluticasone Propionate/Salmeterol MDPI doses had a clinically meaningful effect on theophylline AUC or Cmax.

Following administration of Fluticasone Propionate/Salmeterol MDPI, salmeterol remained available in the body because it was not cleared via the kidneys, but was cleared primarily via the liver. In a study of healthy male volunteers, the mean elimination half-life (τ) of salmeterol was 10.8 hours for salmeterol administered as Fluticasone Propionate/Salmeterol MDPI. In a study of stable asthmatic patients, the mean elimination half-life of salmeterol was 12.6 hours for Fluticasone Propionate/Salmeterol MDPI. The elimination of salmeterol was not affected by concomitant administration of Fluticasone Propionate/Salmeterol MDPI and albuterol, which is eliminated by both renal and hepatic clearance.

The elimination of salmeterol was not significantly affected by the administration of Fluticasone Propionate/Salmeterol MDPI in patients with renal impairment. In a single-center, open-label, 5-day study in 12 subjects with normal renal function, the elimination half-life of salmeterol was 12.6 hours for Fluticasone Propionate/Salmeterol MDPI. In a double-blind, placebo-controlled crossover study in 18 healthy subjects, the elimination half-life of salmeterol was 12.6 hours for Fluticasone Propionate/Salmeterol MDPI.

The elimination halflife of salmeterol was not affected by concomitant administration of Fluticasone Propionate/Salmeterol MDPI and ketoconazole. In a single-center, open-label, 7-day study in 12 healthy subjects with normal renal function, the elimination half-life of salmeterol was 12.6 hours for Fluticasone Propionate/Salmeterol MDPI. In a double-blind, placebo-controlled crossover study in 18 healthy subjects, the elimination half-life of salmeterol was 12.6 hours for Fluticasone Propionate/Salmeterol MDPI.

Fluticasone Propionate and Salmeterol interaction studies:

The effect of Fluticasone Propionate/Salmeterol MDPI on theophylline levels was evaluated in 12 healthy adult volunteers in a multiple-dose, single-blind, crossover drug interaction trial in 11 healthy subjects. None of the Fluticasone Propionate/Salmeterol MDPI doses had a clinically meaningful effect on theophylline AUC or Cmax.

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Fluticasone Propionate and Salmeterol inhalation powder

In a repeat-dose trial in 12 healthy subjects, concomitant administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol C۵۰, at steady state (ratio with and without erythromycin 1.4 [90% CI: 0.96, 2.03], P = 0.12), a 3.6-beat/min increase in heart rate ([95% CI: 0.19, 7.03], P < 0.04), a 5.8-msec increase in QT interval ([95% CI: -6.14, 17.77], P = 0.34), and no change in plasma potassium.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone propionate:
Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1000 mcg/kg (approximately 10 times the MRHDID for adults on a mcg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately equivalent to the MRHDID for adults on a mcg/m² basis) for 104 weeks.

Fluticasone propionate did not cause induction of micronucleus in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the in vivo mouse micronucleus test.

Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (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, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. 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 leiomomas and ovarian cysts at doses of 680 mcg/kg and above (approximately 240 times the MRHDID on a mcg/m² basis). No tumors were seen at 210 mcg/kg (approximately 75 times the MRHDID on a mcg/m² basis). These findings in rodents are similar to those reported previously for other beta adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increase in microalbumin and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronuclear test.

Fertility and reproductive performance were unaffected in male and female rats at oral doses up to 2000 mcg/kg (approximately 680 times the MRHDID for adults on a mcg/m² basis).

13.2 Animal Toxicology and/or Pharmacology

Studies in laboratory animals (minkpigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) 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 304 patients with asthma. The development program included 2 confirmatory trials of 12 weeks duration, a 6-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 in Patients with Asthma

Six doses of fluticasone propionate ranging from 16 mcg to 434 mcg (expressed as metered dose) administered twice daily via MDPI were evaluated in 200 patients with asthma. The development program included 2 randomized, double-blind, placebo-controlled 12 week trials in patients with asthma.

- **Trial 201**: was conducted in patients whose asthma was uncontrolled at baseline and had been treated with short-acting beta-agonist alone or in combination with non-corticosteroid asthma medication. Low dose inhaled corticosteroids (ICS)-treated 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 whose asthma was uncontrolled at baseline and 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 MDPI not designed to provide comparative effectiveness data and should not be interpreted as superiority/inferiority to fluticasone propionate 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 inhaled MDPI 118 mcg/13.2 mcg had similar clinical efficacy with lower systemic exposure when compared to the 50 mcg of salmeterol in fluticasone propionate/salmeterol 100 mcg/50 mcg dry powder inhaler (Figure 2).

Figure 1: Baseline Adjusted Least Square Mean Change in Trough Morning FEV1 (L) over 12 weeks (FAS)

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

FAS = full analysis set; *Trials were not designed to provide comparative effectiveness data and should not be interpreted as superiority/inferiority to fluticasone propionate inhalation powder.

The efficacy and safety of four doses of salmeterol xinafate were evaluated in a double-blind, 6-period crossover study compared with single dose fluticasone propionate MDPI and open label fluticasone propionate/salmeterol 100 mcg/50 mcg dry powder inhaler (DPI) 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 to fluticasone propionate/salmeterol inhalation powder. The salmeterol doses studied were 6.8 mcg, 13.2 mcg, 26.8 mcg and 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 inhaled MDPI 118 mcg/13.2 mcg had similar clinical efficacy with lower systemic exposure when compared to the 50 mcg of salmeterol in fluticasone propionate/salmeterol 100 mcg/50 mcg dry powder inhaler (Figure 2).

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

FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler; FS DPI = fluticasone propionate dry powder inhaler comparator

Metered dose was calculated based on phase 2b formulation compositions.

14.2 Trials in the Treatment of Asthma

**Adult and Adolescent Patients Aged 12 Years and Older:**

Two 12-week randomized, double-blind, placebo-controlled, parallel-group, global clinical trials (Trials 1 and 2) were conducted in 1375 adult and adolescent patients (aged 12 years and older, with baseline FEV1 40% to 85% of predicted normal) with asthma that was not optimally controlled on their current therapy. Patients were randomized to receive 1 inhalation twice a day of Fluticasone Propionate/Salmeterol MDPI, fluticasone propionate MDPI alone, or placebo.

Maintenance asthma therapies were discontinued at randomization.

**Figure 1:** Baseline Adjusted Least Square Mean Change in Trough Morning FEV1 (L) over 12 weeks (FAS)
In this trial, adolescents and adult patients with persistent symptomatic asthma despite low-dose or mid-dose inhaled corticosteroids (ICS) or ICS/LABA therapy were included. After completing a run-in period where patients were treated with beclomethasone dipropionate inhalation aerosol 40 mcg twice daily and a single blind placebo MDPI, the patients who met the randomization criteria were randomized to 1 inhalation twice a day of the following treatments:

- Placebo MDPI (n=130)
- Fluticasone propionate MDPI 55 mcg (n=129)
- Fluticasone propionate MDPI 113 mcg (n=130)
- Fluticasone Propionate/Salmeterol MDPI 55 mcg/14 mcg (n=129), or
- Fluticasone Propionate/Salmeterol MDPI 113 mcg/14 mcg (n=129)

Baseline FEV1 measurements were similar across treatments: Fluticasone propionate MDPI 55 mcg was 2.132 L, Fluticasone propionate MDPI 113 mcg was 2.162 L, Fluticasone Propionate/Salmeterol MDPI 55 mcg/14 mcg was 2.302 L, Fluticasone Propionate/Salmeterol MDPI 113 mcg/14 mcg was 2.166 L, and placebo 2.188 L.

The primary endpoints for this trial were the change from baseline in trough FEV1, at week 12 for all patients and standardized baseline-adjusted FEV1, at week 12 analyzed for a subset of 312 patients who performed postdose serial spirometry. Patients in both Fluticasone Propionate/Salmeterol MDPI treatment groups had significantly greater improvements in trough FEV1 compared with both Fluticasone Propionate MDPI treatment groups and the placebo group.

- Fluticasone Propionate/Salmeterol MDPI 113 mcg/14 mcg: LS mean change of 0.319 L at 12 weeks
- Fluticasone Propionate/Salmeterol MDPI 55 mcg/14 mcg: LS mean change of 0.204 L at 12 weeks
- Fluticasone propionate MDPI 113 mcg: LS mean change of 0.204 L at 12 weeks
- Fluticasone propionate MDPI 55 mcg: LS mean change of 0.172 L at 12 weeks
- Placebo: LS mean change of 0.053 L at 12 weeks

The estimated mean differences between:

- Fluticasone Propionate/Salmeterol MDPI 55 mcg/14 mcg and Fluticasone Propionate/Salmeterol MDPI 113 mcg/14 mcg compared to placebo were 0.266 L (95% CI: 0.172, 0.360) and 0.262 L (95% CI: 0.168, 0.356), respectively.
- Fluticasone Propionate MDPI 55 mcg and Fluticasone propionate MDPI 113 mcg compared to placebo were 0.119 L (95% CI: 0.025, 0.212) and 0.051 L (95% CI: 0.057, 0.244), respectively.
- Fluticasone Propionate/Salmeterol MDPI 113 mcg/14 mcg and Fluticasone Propionate/Salmeterol MDPI 113 mcg was 0.101 L (95% CI: 0.077, 0.236).
- Fluticasone Propionate/Salmeterol MDPI 55 mcg/14 mcg and Fluticasone Propionate MDPI 55 mcg was 0.147 L (95% CI: 0.053, 0.242).

In addition, the mean FEV1 results at each visit are displayed in Figure 3.

Figure 3: Mean Change from Baseline in Trough FEV1, at Each Visit by Treatment Group Trial 1 (FAS)

Fluticasone Propionate and Salmeterol inhalation powder

Trial 1: In this trial, adolescents and adult patients with persistent symptomatic asthma despite low-dose or mid-dose inhaled corticosteroids (ICS) or ICS/LABA therapy were included. After completing a run-in period where patients were treated with beclomethasone dipropionate inhalation aerosol 40 mcg twice daily and a single blind placebo MDPI, the patients who met the randomization criteria were randomized to 1 inhalation twice a day of the following treatments:

- Placebo MDPI (n=130)
- Fluticasone propionate MDPI 55 mcg (n=129)
- Fluticasone propionate MDPI 113 mcg (n=130)
- Fluticasone Propionate/Salmeterol MDPI 55 mcg/14 mcg (n=129), or
- Fluticasone Propionate/Salmeterol MDPI 113 mcg/14 mcg (n=129)

Baseline FEV1 measurements were similar across treatments: Fluticasone propionate MDPI 55 mcg was 2.132 L, Fluticasone propionate MDPI 113 mcg was 2.162 L, Fluticasone Propionate/Salmeterol MDPI 55 mcg/14 mcg was 2.302 L, Fluticasone Propionate/Salmeterol MDPI 113 mcg/14 mcg was 2.166 L, and placebo 2.188 L.

The primary endpoints for this trial were the change from baseline in trough FEV1, at week 12 for all patients and standardized baseline-adjusted FEV1, at week 12 analyzed for a subset of 312 patients who performed postdose serial spirometry. Patients in both Fluticasone Propionate/Salmeterol MDPI treatment groups had significantly greater improvements in trough FEV1 compared with both Fluticasone Propionate MDPI treatment groups and the placebo group.

- Fluticasone Propionate/Salmeterol MDPI 113 mcg/14 mcg: LS mean change of 0.319 L at 12 weeks
- Fluticasone Propionate/Salmeterol MDPI 55 mcg/14 mcg: LS mean change of 0.204 L at 12 weeks
- Fluticasone propionate MDPI 113 mcg: LS mean change of 0.204 L at 12 weeks
- Fluticasone propionate MDPI 55 mcg: LS mean change of 0.172 L at 12 weeks
- Placebo: LS mean change of 0.053 L at 12 weeks

The estimated mean differences between:

- Fluticasone Propionate/Salmeterol MDPI 55 mcg/14 mcg and Fluticasone Propionate/Salmeterol MDPI 113 mcg/14 mcg compared to placebo were 0.266 L (95% CI: 0.172, 0.360) and 0.262 L (95% CI: 0.168, 0.356), respectively.
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- Fluticasone Propionate/Salmeterol MDPI 55 mcg/14 mcg and Fluticasone Propionate MDPI 55 mcg was 0.147 L (95% CI: 0.053, 0.242).

In addition, the mean FEV1 results at each visit are displayed in Figure 3.

Figure 3: Mean Change from Baseline in Trough FEV1, at Each Visit by Treatment Group Trial 1 (FAS)
Fluticasone Propionate Salmeterol MDPI dose as assessed by FEV1 following 12 weeks of therapy.

- 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.

Supportive evidence of efficacy for Fluticasone Propionate Salmeterol MDPI compared with placebo was derived from secondary endpoints such as the weekly average of daily trough morning peak expiratory flow and 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 AQOL for patients age ≥ 18 years or the PAQLQ for patients aged 12-17 were assessed in Trial 2. The responder rate for both measures was defined as an improvement in score of 0.5 or more as threshold. In Trial 2, the responder rate for patients receiving Fluticasone Propionate Salmeterol MDPI 113 mcg/14 mcg and Fluticasone Proportionate Salmeterol MDPI 232 mcg/14 mcg was 48% and 41%, respectively, compared to 27% for patients receiving placebo, with an odds ratio of 2.59 (95% CI: 1.56, 4.31) and 1.94 (95% CI: 1.16, 3.23), respectively.

Improvements in lung function occurred within 3 hours for both Fluticasone Propionate and Salmeterol MDPI doses, 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.

Fluticasone Propionate and Salmeterol inhalation powder

- Fluticasone Propionate Salmeterol MDPI 232 mcg/14 mcg and Fluticasone propionate MDPI 232 mcg was 0.093 L (95% CI: 0.009, 0.178).
- Fluticasone Propionate Salmeterol MDPI 113 mcg/14 mcg and Fluticasone propionate MDPI 113 mcg was 0.152 L (95% CI: 0.066, 0.237).

In addition, the mean FEV1 results at each visit are displayed in Figure 6.

Figure 6: Mean Change from Baseline in trough FEV1 at each visit by treatment group trial 2 (FAS)

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

Mean Change in FEV1 (L)

Week
0 1 2 3 4 5 6 7 8 9 10 11 12

FP MDPI 232 mcg/14 mcg

FS MDPI 232 mcg/14 mcg

FP MDPI 113 mcg

FS MDPI 113 mcg/14 mcg

Placebo

Mean Change in FEV1 (L)

-0.1 0.0 0.1 0.2 0.3 0.4 0.5

Day 1 Baseline Hour

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

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)

How Supplied

Fluticasone Propionate Salmeterol MDPI inhalation powder:

- a multidose, dry-powder inhaler (MDPI)
- each inhaler contains 0.45 grams of the formulation and provides 60 actuations
- available in 3 strengths

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Fluticasone Propionate Salmeterol MDPI inhalation powder:

- Available in 3 strengths
- how supplied and storage and handling

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

17 PATIENT COUNSELING INFORMATION

Advising patients to the FDA-approval patient labeling (Patient Information and Instructions for Use). Patients should be given the following information:

- Serious Asthma Events
- Not for Acute Symptoms
- Oropharyngeal Candidiasis

Inform patients with asthma that LABA when used alone increases the risk of asthma-related hospitalization and asthma-related death. Available data show that when ICS and LABA are used together, such as with Fluticasone Propionate/Salmeterol MDPI, there is not a significant increase in the risk of these events [see Warnings and Precautions (5.1)].

Inform patients that Fluticasone Propionate Salmeterol MDPI 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 [see Patient Counseling Information (17.7)].

Inform patients to seek medical attention if they experience any of the following:
- Decreasing effectiveness of inhaled, short-acting beta agonists
- Need for more inhaled medications than usual of inhaled, short-acting beta-agonists
- Significant decrease in lung function as outlined by the physician

Inform patients they should not stop therapy with Fluticasone Propionate Salmeterol without physician/provider guidance since symptoms may recur after discontinuation. Avoid use of additional long-acting beta-agonists.

Inform patients not to use other LABA for asthma [see Warnings and Precautions (5.3)].
Inform patients of adverse effects associated with beta 2-agonists, such as palpitations, chest prezaes (5.13). Physicians should inform patients that orally inhaled corticosteroids, including fluticasone propionate, may cause. Warnings and Precautions (5.10). Patients with severe milk protein allergy should not take Fluticasone Propionate/Salmeterol MDPI [see Warnings and Precautions (5.14)]. Reduced Growth Velocity. Inform patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk [see Warnings and Precautions (5.12)]. Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations [see Warnings and Precautions (5.14)]. Risks Associated with Beta-Agonist Therapy. Inform patients of adverse effects associated with beta,-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness [see Warnings and Precautions (5.10)]. Pregnancy. Inform patients who are pregnant or nursing that they should contact their physician about the use of Fluticasone Propionate/Salmeterol MDPI [see Use in Specific Populations (8.1)]. Use Daily for Best Effect. Patients should use Fluticasone Propionate/Salmeterol MDPI at regular intervals as directed. The daily dosage of Fluticasone Propionate/Salmeterol MDPI should not exceed 1 inhalation twice a day. Advise patients, if they miss a dose, to take their next dose at the same time they normally do and to not take 2 doses at one time. Individual patients will experience a variable time to onset and degree of symptom relief and full benefit may not be achieved until treatment has been administered for 1 to 2 weeks or longer. Patients should not increase the prescribed dosage but should contact their physicians if symptoms do not improve or if the condition worsens. Instruct patients not to stop use of Fluticasone Propionate/Salmeterol MDPI abruptly. Patients should contact their physicians immediately if they discontinue use of Fluticasone Propionate/Salmeterol MDPI. Dose Counter. Instruct patients that Fluticasone Propionate/Salmeterol MDPI has a dose counter that displays the number of actuations (inhalations) left in the inhaler. When the patient receives a new inhaler, the number 60 will be displayed. The dose counter will count down each time the mouthpiece is opened and closed. When the dose counter reaches 20, the color of the numbers will change to red to remind the patient to contact their pharmacist or healthcare provider for a refill of their medication. When the dose counter reaches 0, the patient should stop using the inhaler, and dispose of it in accordance with state and local regulations. Caring for and Storing the Inhaler. Instruct patients to not open their inhaler unless they are taking a dose. Repeated opening and closing the cover without taking medication will waste medication and may damage the inhaler. Advise patients to keep their inhaler dry and clean at all times. Never wash or put any part of the inhaler in water. Patient should replace inhaler if washed or placed in water. Advise patients to immediately replace inhaler if mouthpiece cover is damaged or broken. Gently wipe the mouthpiece with a dry cloth or tissue as needed. Instruct patients to store the inhaler at room temperature and to avoid exposure to extreme heat, cold, or humidity. Instruct patients not to take the inhaler apart. Instruct patients to discard this product when the dose counter displays 0, 30 days after opening the foil pouch or after the expiration date on the product, whichever comes first. Distributed by: Teva Pharmaceuticals USA, Inc. Parsippany, NJ 07054 ©2021 Teva Respiratory, LLC. All rights reserved. United States Patent Nos. 6709197, 6789872, 6789497, 6874646, 7150282, 8006690, 8651033, 8714149, 8978966, 9066957, 9216620, 9415008, 9463288, 9616024, 9731087, 9987229, 10022510, 10124131, 10195375, 10561808, 10765820.
Fluticasone Propionate/Salmeterol inhalation powder

- are pregnant or plan to become pregnant. It is not known if Fluticasone Propionate/Salmeterol inhalation powder may harm your unborn baby.
- are breastfeeding. It is not known if the medicines in Fluticasone Propionate/Salmeterol inhalation powder pass into your breast milk and if they can harm your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Fluticasone Propionate/Salmeterol inhalation powder and certain other medicines may interact with each other. This may cause serious side effects. Especially, tell your healthcare provider if you take antifungal or anti-HIV medicines.

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 is for oral inhalation only.
- Rinse your mouth with water without swallowing after each dose of Fluticasone Propionate/Salmeterol inhalation powder.
- 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 inhalation powder 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.
- Fluticasone Propionate/Salmeterol inhalation powder does not need priming. Do not use a spacer or volume holding chamber with Fluticasone Propionate/Salmeterol inhalation powder.
- Do not open the cap on your Fluticasone Propionate/Salmeterol inhalation powder inhaler until you are ready for your dose because this will waste your medicine or may damage your inhaler.
- If you take too much Fluticasone Propionate/Salmeterol inhalation powder, 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.

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 in patients ages 12 years and older include:

- infection of nose and throat
- 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).
• Store Fluticasone Propionate/Salmeterol inhalation powder in a dry place. 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.
• Do not take your Fluticasone Propionate/Salmeterol inhalation powder apart.
• 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 inhalation powder inhaler 30 days after opening the foil pouch, when the dose counter displays '0', or after the expiration date on the product, whichever comes first.

What are the ingredients in Fluticasone Propionate/Salmeterol inhalation powder?

Active ingredients: fluticasone propionate, salmeterol xinafoate
Inactive ingredient: lactose monohydrate (may contain milk proteins)

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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.

This Patient Information leaflet has been approved by the U.S. Food and Drug Administration.

FPSP-005
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Instructions for Use

Fluticasone Propionate and Salmeterol inhalation powder 55 mcg/14 mcg
Fluticasone Propionate and Salmeterol inhalation powder 113 mcg/14 mcg
Fluticasone Propionate and Salmeterol inhalation powder 232 mcg/14 mcg
for oral inhalation use

Your Fluticasone Propionate/Salmeterol inhalation powder 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. 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.

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.

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 inhalation powder 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 inhalation powder 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 inhalation powder is ready to be inhaled.

Figure C
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 inhalation powder.

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.

Figure E
- 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.
- 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
- 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 inhalation powder inhaler?
- Store your inhaler at room temperature between 59ºF and 77ºF (15ºC and 25ºC).
- 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 inhalation powder 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 inhalation powder 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.
- When the counter displays '0' your inhaler is empty and you should stop using the inhaler and throw it away.
- Throw away your inhaler 30 days after opening the foil pouch, when the dose counter displays '0', or after the expiration date on the product, whichever comes first.

Important information
- Do not open the yellow cap unless you are taking a dose. Repeatedly opening and closing the cap without inhaling a dose will waste the medicine and may damage your inhaler.
- Your inhaler contains dry powder so it is important that you do not blow or breathe into it.

Support
- If you have any questions about your Fluticasone Propionate/Salmeterol inhalation powder inhaler or how to use your inhaler, go to the reference branded product website at www.MYAIRDUO.com, or call 1-888-482-9522.

These Instructions for Use have been approved by the U.S. Food and Drug Administration.
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