AIRDUO RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder

- **Indications and Usage**: Treatment of asthma in patients aged 12 years and older. (1)

  - **Dosage 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 AIRDUO RESPICLICK 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)

- **Dosage Forms and Strengths**:
  - Inhalation Powder containing fluticasone propionate 55 mcg, 113 mcg, or 232 mcg and salmeterol (14 mcg) per actuation. (3)

- **Contraindications**:
  - 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. (4)

- **Warnings and Precautions**:
  - Paradoxical bronchospasm: Discontinue AIRDUO RESPICLICK and institute alternative therapy if paradoxical bronchospasm occurs. (5.9)
  - Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.16)

- **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)

- **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)
  - 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 bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)

- **Use in Specific Populations**:
  - Hepatic impairment: Monitor for systemic corticosteroid effects. (8.6)

- **Full Prescribing Information**: See the full prescribing information for AIRDUO RESPICLICK for a complete list of adverse reactions, drug interactions, and precautions. Revised: 03/2018

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**ADVERSE REACTIONS**

- **Common 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)

- **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)
  - Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of salmeterol on vascular system. (7.2)

- **Use in Specific Populations**:
  - Hepatic impairment: Monitor for systemic corticosteroid effects. (8.6)

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**17 Patient Counseling Information**

- **Full Prescribing Information**: See the full prescribing information for AIRDUO RESPICLICK for a complete list of adverse reactions, drug interactions, and precautions. Revised: 03/2018

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use AIRDUO RESPICLICK® safely and effectively. See full prescribing information for AIRDUO RESPICLICK.

AIRDUO RESPICLICK (fluticasone propionate and salmeterol) inhalation powder

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  - **Dosage and Administration**: For oral inhalation only. (2.1)
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    - Treatment of asthma in patients 12 years and older: 1 inhalation of AIRDUO RESPICLICK 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)

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

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- **Warnings and Precautions**:
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  - Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.16)

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  - Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole): Use not recommended. 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)

- **Use in Specific Populations**:
  - Hepatic impairment: Monitor for systemic corticosteroid effects. (8.6)

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**Full Prescribing Information**: See the full prescribing information for AIRDUO RESPICLICK for a complete list of adverse reactions, drug interactions, and precautions. Revised: 03/2018

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**17 Patient Counseling Information**

- **Full Prescribing Information**: See the full prescribing information for AIRDUO RESPICLICK for a complete list of adverse reactions, drug interactions, and precautions. Revised: 03/2018
AIRDUO RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AIRDUO RESPICLICK® is indicated for the treatment of asthma in patients aged 12 years and older. AIRDUO RESPICLICK® 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 beta, adrenergic agonist (LABA).

Important Limitations of Use: AIRDUO RESPICLICK is NOT indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

2.1 General

AIRDUO RESPICLICK 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

AIRDUO RESPICLICK should be administered at 1 inhalation twice daily (approximately 12 hours apart) by the orally inhaled route. AIRDUO RESPICLICK should be used at approximately the same time every day. Do not use AIRDUO RESPICLICK more than 2 times every 24 hours.

The starting dosage for AIRDUO RESPICLICK 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 AIRDUO RESPICLICK from another inhaled corticosteroid product, initial therapeutic dosage should be the equivalent from 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 AIRDUO RESPICLICK 55/14 mcg after 2 weeks of therapy, increasing the dose may provide additional asthma control. If a dosage regimen of AIRDUO RESPICLICK 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 AIRDUO RESPICLICK with a higher strength, or adding additional controller therapies) should be considered.

The recommended dosage of AIRDUO RESPICLICK is 232/14 mcg twice daily. More frequent administration or a greater number of inhalations (more than 2 inhalations daily) should be considered. The highest recommended dose of AIRDUO RESPICLICK 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 AIRDUO RESPICLICK is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. Patients using AIRDUO RESPICLICK 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 beta2-agonist should be taken for immediate relief.

Improvement in asthma control following inhaled administration of AIRDUO RESPICLICK 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 AIRDUO RESPICLICK with a higher strength may provide additional improvement in asthma control.

If a previously effective 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 AIRDUO RESPICLICK with a higher strength, adding additional controller therapies) should be considered.

AIRDUO RESPICLICK does not require priming. Do not use AIRDUO RESPICLICK 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 AIRDUO RESPICLICK inhaler has a dose counter. When the patient receives the inhaler, the number 60 will be displayed. The dose counter will count down from 60 to 0. When the mouthpiece is opened or closed, the dose counter window displays the number of actuations (inhalations) left in the inhaler in units of two (e.g., 60, 58, 56, etc.). When the dose counter reaches 20, the color of the numbers will change to red to remind the patient to contact their pharmacist for a refill of medication or contact 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. AIRDUO RESPICLICK 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 24 hr. therapy of fluticasone propionate with 12.1 mcg of salmeterol, respectively, from the mouthpiece per actuation. AIRDUO RESPICLICK is supplied as a dry white powder inhaler with a yellow cap in a sealed foil pouch with desiccant.

4 CONTRAINDICATIONS

4.1 Status Asthmaticus

AIRDUO RESPICLICK 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

AIRDUO RESPICLICK 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)].

5 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 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-agonist Agonists]. Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta2-agonist Agonists

Four large, 28-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/24-hr 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. All 4 trials showed a statistically significant increase in the risk of 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 2.7. Each individual trial met its pre-specified objective and demonstrated an adequate margin of safety. A meta-analysis of the 3 adult and adolescents trials did not show a significant increase in risk of a serious asthma-related event with LABA/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out risk for serious asthma-related events with ICS/LABA compared with ICS alone.

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>ICS/LABA (n = 17,537)*</th>
<th>ICS (n = 17,552)*</th>
<th>ICS/LABA vs. ICS Hazard Ratio (95% CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma-related event†</td>
<td>116</td>
<td>105</td>
<td>1.10 (0.85, 1.44)</td>
</tr>
<tr>
<td>Asthma-related death</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Asthma-related intubation (endotracheal)</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Asthma-related hospitalization (≥24-hour stay)</td>
<td>115</td>
<td>105</td>
<td></td>
</tr>
</tbody>
</table>

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

* Randomized subjects who had taken at least 1 dose of study drug. Planned treatment used for analysis.
† Estimated relative risk with a binomial 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 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 prespecified risk margin (2.5), 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 20-week, placebo-controlled, U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol versus 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

5.2 Deterioration of Disease and Acute Episodes

AIRDUO RESPICLICK should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. AIRDUO RESPICLICK has not been studied in subjects with acutely deteriorating asthma. The initiation of AIRDUO RESPICLICK in this setting is not appropriate.

Serious acute respiratory events, including fatalities, have been reported when salmeterol, a component of AIRDUO RESPICLICK, has been initiated in patients with...
AIRDUO RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder

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; decreasing response to inhaled, short-acting beta-agonists; increased frequency of emergency room visits; deteriorating lung function). However, these 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 beta-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of AIRDUO RESPICLICK with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalers of AIRDUO RESPICLICK per day.

AIRDUO RESPICLICK 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 beta-agonist, not AIRDUO RESPICLICK, should be used to relieve acute symptoms such as shortness of breath. When prescribing AIRDUO RESPICLICK, the healthcare provider should also prescribe an inhaled, short-acting beta-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily use of AIRDUO RESPICLICK.

When beginning treatment with AIRDUO RESPICLICK, patients who have been taking oral or inhaled, short-acting beta-agonists on a regular basis (e.g., 4 times a day) should be instructed to continue the regular use of these drugs at the same dosage for the first few days of therapy. After this initial period, patients should use AIRDUO RESPICLICK as directed. Patients should be instructed to discontinue the regular use of these drugs if they experience unacceptable side effects with treatment with AIRDUO RESPICLICK.

5.3 Excessive Use of AIRDUO RESPICLICK and Use with Other Long-Acting Beta-Agonists

AIRDUO RESPICLICK should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overuse of LABA may result in an increased risk of adverse reactions and may have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using AIRDUO RESPICLICK should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

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 AIRDUO RESPICLICK. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with AIRDUO RESPICLICK continues, but at a lower dose than previously used. Local irritation of the mouth and pharynx has been reported in subjects treated with AIRDUO RESPICLICK. If an oropharyngeal infection develops, 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 adolescents or adults using corticosteroids. In such patients who have not had these diseases or who have not been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophyaxis with varicella-zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG) may be indicated. If a patient is exposed to measles, prophyaxis with pooled intravenous immunoglobulin (IVIG) may be indicated. (See the respective package inserts for complete VZIG and IVIG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.6 Transferring Patients from Systemic Corticosteroid Therapy

Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in association with asthma exacerbations. After transferring from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent in other medications), particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although AIRDUO RESPICLICK may improve control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does not provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a medical identification warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthmatic attack.

Patients requiring systemic corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to AIRDUO RESPICLICK. Lung function (mean forced expiratory volume in 1 second [FEV1] or morning peak expiratory flow [AM PEF]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal from systemic corticosteroids. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of AIRDUO RESPICLICK with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalers of AIRDUO RESPICLICK per day. During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.7 Hypercorticism and Adrenal Suppression

Fluticasone propionate, a component of AIRDUO RESPICLICK, will often help control symptoms of patients with less severe asthma (e.g., rhinitis, conjunctivitis, eczema, athletes foot, eosinophilic conditions). During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Because of the possibility of significant systemic absorption of inhaled corticosteroids, patients treated with AIRDUO RESPICLICK 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 suppression.

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 sensitive to these effects. If such effects occur, AIRDUO RESPICLICK should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and for management of asthma symptoms.

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, neflurain, saquinavir, ketoconazole, telithromycin) with AIRDUO RESPICLICK is not recommended because increased systemic corticosteroid and inhaled corticosteroid adverse effects may occur. [See Drug Interactions (7.1), Clinical Pharmacology (12.3)].

5.9 Paradoxical Bronchospasm and Upper Airway Asymptoms

As with other inhaled medicines, AIRDUO RESPICLICK can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs with inhalation of inhaled corticosteroids, and for management of asthma symptoms.

5.10 Hypersensitivity Reactions, Including Anaphylaxis

Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, broncho- spasm, hypotension), including anaphylaxis, may occur after administration of AIRDUO RESPICLICK. There have been reports of anaphylactic reactions in patients with previous bronchospasm and/or inhaled corticosteroid allergy. An inhaled pharmacologic challenge should be performed in these patients. Therefore, patients with severe milk protein allergy should not use AIRDUO RESPICLICK (see Contraindications (4)).

5.11 Cardiovascular and Central Nervous System Effects

Excessive beta-2 agonist stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitiation, nausia, dizziness, fatigue, malaise, and insomnia [see Overdose (10.2)]. Therefore, AIRDUO RESPICLICK, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Salmeterol, a component of AIRDUO RESPICLICK, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salmeterol as a single dose, if these effects occur, the dose should 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 segment depression. The clinical significance of these findings is 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 uncertain.
AIRDUO RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder

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 AIRDUO RESPICLICK, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving AIRDUO RESPICLICK routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including AIRDUO RESPICLICK, titrate each patient’s dosage to the lowest dosage 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, a component of AIRDUO RESPICLICK. 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 658 subjects with COPD in the 3-year survival trial. Ophthalmic 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 for 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 AIRDUO RESPICLICK, 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 initiation 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 eosinophilic conditions has not been established.

5.16 Coexisting Conditions

AIRDUO RESPICLICK, like many medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in patients with neuropathy presenting in their patients. A causal relationship between fluticasone propionate and convulsive disorders or thyrotoxicosis has been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to 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, Cushingoid features, growth velocity reduction in children/adolescents, hypercorticism.

Eve Disorders: Glaucoma, blurred vision and central serous chorioretinopathy.

Metabolic Disorders: Adrenal insufficiency

Immun 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

Musculoskeletal Disorders: Hyperglycemia, weight gain.

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.

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

Skin and Subcutaneous Tissue Disorders: Eczematos, photodermatitis.

Vascular Disorders: Pallor.

6 DRUG INTERACTIONS

AIRDUO RESPICLICK has been concomitantly with other drugs, including short-acting beta-agonists, and intranasal corticosteroids, commonly used in patients with asthma without adverse drug reactions [see Clinical Pharmacology (12.2)]. No formal drug interaction trials have been performed with AIRDUO RESPICLICK.

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate and salmeterol, the individual components of AIRDUO RESPICLICK are substrates of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nelfinavir, saquinavir, ketoconazole, telithromycin) with AIRDUO RESPICLICK is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.
**AIRDUO RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder**

**Ritonavir: Fluticasone Propionate:** A drug interaction trial with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP3A4 inhibitor) can significantly increase plasma fluticasone propionate 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 hyperglycemia and edema. The concomitant use of fluticasone propionate and ritonavir is not recommended.

**Ketoconazole: Fluticasone Propionate:** Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mcg 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 excretion of cortisol. [12.3]

In a drug interaction trial in 20 healthy subjects, coadministration of cortisol area under the curve (AUC) but had no effect on urinary excretion of cortisol. [12.3]

**IN VITRO AND IN VIVO STUDIES**

**Animal Reproduction Studies**

In an embryo/fetal development study with pregnant rats dosed by the inhalation route at approximately 2 times the MRHDID (on a mcg/m2 basis with a maternal subcutaneous dose of 15 mcg/kg/day). Cleft palate and fetal skeletal variations were observed in mouse fetuses at a dose approximately 0.5 times the MRHDID (on a mcg/m2 basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.16 times the MRHDID (on a mcg/m2 basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryo/fetal development study in pregnant rabbits that were dosed with 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 2 times the MRHDID (on a mcg/m2 basis with a maternal subcutaneous dose of 3500 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 from late gestation through delivery and lactation (Gestation Day 17 to PND 21, salmeterol at a maternal oral dose of 10,000 mcg/kg/day). The NOAEL was observed 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).

**Clinical Considerations**

**7.3 Beta-Adrenergic Receptor Blocking Agents**

Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of AIRDUO RESPICLICK, but may also produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with these agents while being treated with salmeterol. However, uncontrolled hypoglycemia can be prevented by the use of a beta-adrenergic blocking agent and a long-acting oral corticosteroid suggests that rodents are more prone to teratogenic effects from oral corticosteroids than humans. Oral administration of salmeterol to pregnant rabbits did not cause teratogenicity characteristic of beta-adrenoceptor stimulation at maternal oral doses up to 100 mcg/kg/day. In an embryo/fetal development study with pregnant rabbits dosed by the inhalation route at approximately 2 times the MRHDID (on a mcg/m2 basis with a maternal subcutaneous dose of 15 mcg/kg/day). The rat NOAEL was observed with a dose approximately 0.16 times the MRHDID (on a mcg/m2 basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryo/fetal development study in pregnant rabbits that were dosed with the subcutaneous route throughout organogenesis, salmeterol propionate produced teratogenicity. The NOAEL was observed with a dose approximately 0.1 times the MRHDID (on a mcg/m2 basis with a maternal subcutaneous dose of 5.5 mcg/kg/day). In an embryo/fetal development study in pregnant rabbits that were dosed with the subcutaneous route throughout organogenesis, salmeterol 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 2 times the MRHDID (on a mcg/m2 basis with a maternal subcutaneous dose of 3500 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 from late gestation through delivery and lactation (Gestation Day 17 to PND 21, salmeterol at a maternal oral dose of 10,000 mcg/kg/day). The NOAEL was observed 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).

**Fluticasone Propionate:** In embryo/fetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone propionate was teratogenic in both species. Omphalocele, decreased 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 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 at approximately 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 350 times the MRHDID (on a mcg/m2 basis at a maternal oral dose of 1000 mcg/kg/day).

In an embryo/fetal development study with pregnant mice that received the combination of fluticasone propionate and salmeterol at doses of 0/1000, 30/0, 10/100, 30/100, and 100/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) during the period of organogenesis, findings were generally consistent with the individual monoproduts and there was no exacerbation of expected fetal effects.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

**Risk Summary**

There are no randomized clinical studies of AIRDUO RESPICLICK or individual monoproduts, fluticasone propionate and salmeterol xinafoate, in pregnant women. There are clinical considerations with the use of AIRDUO RESPICLICK in pregnant women [see Clinical Considerations]. Animal reproduction studies are available with the combination of fluticasone propionate and salmeterol xinafoate as well as individual monoproduts. In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight and/or skeletal variations, in rats, mice, and rabbits were observed with substantially 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, fluticasone propionate administered via inhalation to rats decreased fetal body weight, but did not induce teratogenicity at a maternalxic dose less than the MRHDID on a mcg/m2 basis [see Data]. Experience with oral corticosteroids in human patients that road their more prone to teratogenic effects from corticosteroids than humans. Oral administration of salmeterol to pregnant rabbits caused teratogenicity characteristic of beta-adrenoceptor stimulation at maternal oral 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 risk of major birth defects and miscarriage for the indicated population during the period of organogenesis, findings were generally consistent with the individual monoproduts and there was no exacerbation of expected fetal effects. In women with poorly or moderately controlled asthma, there is an increased risk of severe corticosteroid effects including Cushings syndrome and adrenal suppression. The concomitant use of fluticasone propionate and oral administration of salmeterol at doses of 0/1000, 30/0, 10/100, 30/100, and 100/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) during the period of organogenesis, findings were generally consistent with the individual monoproduts and there was no exacerbation of expected fetal effects.

**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 0/1000, 30/0, 10/100, 30/100, and 100/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) during the period of organogenesis, findings were generally consistent with the individual monoproduts and there was no exacerbation of expected fetal effects.
AIRDUO RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder

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 AIRDUO RESPICLICK and any potential adverse effects on the breastfed child from AIRDUO RESPICLICK 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 AIRDUO RESPICLICK in pediatric patients below the age of 12 years have not been established. Inhaled corticosteroids, including fluticasone propionate, a component of AIRDUO RESPICLICK, may cause a reduction in growth velocity in adolescents [see Warnings and Precautions (6.13)]. The growth of pediatric patients receiving orally inhaled corticosteroids, including AIRDUO RESPICLICK, should be 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. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including AIRDUO RESPICLICK, 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 efficacy were observed in data collected in 54 subjects aged 65 years and older versus younger subjects who were treated with AIRDUO RESPICLICK in placebo-controlled Phase 2 and 3 studies.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using AIRDUO RESPICLICK 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 AIRDUO RESPICLICK have not been conducted in patients with renal impairment.

10 OVERDOSAGE

AIRDUO RESPICLICK contains both fluticasone propionate and salmeterol; therefore, the risks associated with overdosage for the individual components described below apply to AIRDUO RESPICLICK. Treatment of overdosage consists of discontinuation of AIRDUO RESPICLICK 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 overdosage.

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 1,760 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 also well tolerated. Repeat oral doses 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 with overdosage of salmeterol are those of excessive beta2-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta2-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 sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of salmeterol.

11 DESCRIPTION

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

One active component of AIRDUO RESPICLICK is fluticasone propionate, a corticosteroid having the chemical formula C21H26F4O4·H2O, and the following chemical structure:

Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is C21H26F4O4·H2O. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

The other active component of AIRDUO RESPICLICK 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][aminomethyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalene-carboxylate and the following chemical structure:

Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is C30H28NO8·C3H8O3. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

AIRDUO RESPICLICK 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 mcg 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 AIRDUO RESPICLICK 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 AIRDUO RESPICLICK 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 AIRDUO RESPICLICK inhaler was 106.72 L/min (range: 73.64 to 125.51 L/min).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

AIRDUO RESPICLICK contains both fluticasone propionate and salmeterol. The mechanisms of action described below for the individual components apply to AIRDUO RESPICLICK. 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 budesonide, 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 vasoconstrictor assay in man are consistent with these results. The clinical significance of these findings is unknown. Inflammation 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) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Salmeterol Xinafoate: Salmeterol is a selective LABA. In vitro studies show salmeterol to be at least 50 times more selective for beta-adrenoceptors than albuterol. Although beta2-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta2-adrenoceptors are the predominant receptors in the heart, there are also beta2-adrenoceptors in 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-agonists may have cardiac effects.
AIRDUO RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder

The pharmacologic effects of beta-2-adrenergic agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells. In vitro testing of salmeterol is a potent and selective inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D$_2$, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyperresponsiveness.

12.2 Pharmacodynamics

AIRDUO RESPICLICK: Healthy Subjects: Cardiovascular Effects:

There were no clinical trials conducted with AIRDUO RESPICLICK 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 were performed with healthy adult and adolescent subjects (n=77, 51, 17, and 12-17) in 3-mg increments. Subjects with Asthma: Adults and Adolescents: Hypothalamic-Pituitary-Adrenal Axis Effects:

There are no data from controlled trials using the AIRDUO RESPICLICK in healthy subjects to document the effects with AIRDUO RESPICLICK in serum cortisol.

Other Salmeterol 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). The effects of salmeterol were assessed in two (2) studies (1) a single effect (5 mg) and (2) multiple effects (50 mcg daily for 11 days). Using 2 inhalations twice daily of a fluticasone propionate 250 mcg and salmeterol powder product, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg given alone, (2) a cumulative dose trial using 50 to 400 mcg of salmeterol powder given alone or as a fluticasone propionate 500 mcg and salmeterol powder 50 mcg, and (3) a repeated dose trial using 2 inhalations twice daily of fluticasone propionate 250 mcg and salmeterol powder 50 mcg 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 and salmeterol powder 50 mcg product, fluticasone propionate powder 100 mcg, or salmeterol powder 50 mcg over 24-hour period. In these studies, changes in cardiovascular parameters 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, 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 powder product.

AIRDUO RESPICLICK: Subjects with Asthma: Cardiovascular Effects:

There are no data from controlled trials using the AIRDUO RESPICLICK in healthy subjects to document the effects with AIRDUO RESPICLICK in serum cortisol.

Other Fluticasone Propionate and Salmeterol Inhalation Powder Products: Short-Acting Beta$_{2}$-Agonists:

In clinical trials in subjects with asthma, the mean daily dose for albuterol by 166 adult and adolescent subjects aged 12 years and older using a fluticasone propionate and salmeterol (1:2) powder product was approximately 1.3 inhalations/day and ranged from 0 to 9 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 using salmeterol powder alone (n=86) or in the 2:1 fluticasone propionate: salmeterol treatment arm (n=90). Methylxanthines:

In clinical trials in subjects with asthma, 39 subjects receiving fluticasone propionate and salmeterol powder product, fluticasone propionate 100 mcg and salmeterol 50 mcg, fluticasone propionate 250 mcg and salmeterol 50 mcg, or fluticasone propionate 500 mcg and salmeterol 50 mcg twice daily concurrently with a theophylline product had adverse events 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).

12.3 Pharmacokinetics

Absorption

Fluticasone Propionate:

AIRDUO RESPICLICK 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 presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung was systemically absorbed.

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After administration of 232/14 mcg AIRDUO RESPICLICK 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 AIRDUO RESPICLICK 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 phosphorylkinetics and had a terminal elimination half-life of approximately 7.8 hours. Terminal half-life estimates of fluticasone propionate following oral inhalation administration of AIRDUO RESPICLICK were approximately 10.8 hours.

Metabolism

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 affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Excretion

Less than 5% of a radiolabeled oral dose 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 AIRDUO RESPICLICK were approximately 12.6 hours.

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (greater than 99%) and has a long elimination half-life of 20-24 hours.

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 aerosol, or CFC-propelled fluticasone propionate inhalation aerosol. The population pharmacokinetic analyses for fluticasone propionate and salmeterol showed no clinically relevant differences in clearance, volume, or other parameters by age, gender, race, body weight, body mass index, or percent of predicted FEV1, on apparent clearance and apparent volume of distribution.

Age:

No pharmacokinetic studies have been performed with AIRDUO RESPICLICK in children or geriatric patients. A subgroup analysis was conducted to compare patients aged 4 to 17 (n=15) and 18 (n=23) years following administration of 232/14 mcg AIRDUO RESPICLICK. No overall differences in fluticasone propionate and salmeterol pharmacokinetics were observed.

Sex:

A subgroup analysis was conducted to compare male (n=21) and female (n=16) patients following administration of 232/14 mcg AIRDUO RESPICLICK. No overall differences in fluticasone propionate and salmeterol pharmacokinetics were observed.

Renal Impairment: The effect of renal impairment of the pharmacokinetics of AIRDUO RESPICLICK has not been evaluated.

Hepatic Impairment: Formal pharmacokinetic studies using AIRDUO RESPICLICK 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.
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Fertility and reproductive performance were unaffected in male and female rats at inhalation 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 (mimipods, 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 AIRDUO RESPICLICK 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 AIRDUO RESPICLICK 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 had been treated by short-acting beta-agonist alone or in combination with non-steroidal 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 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 ARMONAIR RESPICLICK 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 (see Figure 1) are slightly 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.

Figure 1: Baseline Adjusted Least Square Mean Change in Trough Morning FEV1, (L) over 12 weeks (FAS)
There was supportive evidence of efficacy for AIRDUO RESPICLICK 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. The Asthma Quality of Life Questionnaire (AQLQ) for patients aged 18 years or the pediatric AQLQ (PAQLQ) for patients aged 12-17 were assessed in Trial 1. The responder rate for both measures was defined as an improvement in score of 0.5 or more as threshold.

In Trial 1, the responder rate for patients receiving AIRDUO RESPICLICK 55/14 mcg and AIRDUO RESPICLICK 113/14 mcg was 51% and 57%, respectively, compared to 40% for patients receiving placebo, with an odds ratio of 1.53 (95% Cl: 0.93, 2.55) and 2.04 (95% Cl: 1.23, 3.41), 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 0.216 and 0.164 L compared with placebo for AIRDUO RESPICLICK 55/14 mcg and 113/14 mcg, respectively; unadjusted p-value <0.0001 for both doses compared with placebo. Refer to Figure 4 below. Maximum improvement in FEV1, generally occurred within 3 hours for AIRDUO RESPICLICK 55/14 mcg and within 6 hours for AIRDUO RESPICLICK 113/14 mcg and improvements were sustained over the 12 hours of testing at weeks 1 and 12 (Figure 4 and Figure 5). 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 AIRDUO RESPICLICK dose as assessed by FEV1, relative to day 1 baseline improved markedly over the first week of treatment and showed some diminution over the 12 weeks of treatment.

Two Phase 3 clinical trials were conducted; 2 trials comparing AIRDUO RESPICLICK with ARMONAIR RESPICLICK alone or placebo (Trial 1 and Trial 2).

Trials Comparing AIRDUO RESPICLICK with Fluticasone Salmeterol Multidose Dry Powder Inhaler (AIRDUO RESPICLICK) 55 mcg and 113 mcg (1 inhalation twice a day) with Fluticasone/Salmeterol Multidose Dry Powder Inhaler (ARMONAIR RESPICLICK) 55/14 mcg and 113/14 mcg (1 inhalation twice a day) and placebo in adolescents and adult patients with persistent symptomatic asthma despite low-dose or mid-dose inhaled corticosteroid or inhaled long-acting beta-2 agonist/LABA therapy. Patients received single-blinded placebo MDPI and were switched from their baseline ICS therapy to QVAR 40 mcg twice daily during the run-in period. Patients who met all randomization criteria were randomly assigned to receive treatment as follows: 130 received placebo, 129 received ARMONAIR RESPICLICK 55 mcg, 130 received ARMONAIR RESPICLICK 113 mcg, 129 received AIRDUO RESPICLICK 55/14 mcg, and 129 received AIRDUO RESPICLICK 113/14 mcg. Baseline FEV1 measurements were similar across treatments: ARMONAIR RESPICLICK 55 mcg 2.132 L, ARMONAIR RESPICLICK 113 mcg 2.166 L, AIRDUO RESPICLICK 55/14 mcg 2.302 L, AIRDUO RESPICLICK 113/14 mcg 2.162 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 AUEC0-12h at week 12 analyzed for a subset of 312 patients who performed postdose serial spirometry.

Patients receiving AIRDUO RESPICLICK 55/14 mcg and AIRDUO RESPICLICK 113/14 mcg had significantly greater improvements in trough FEV1 (AIRDUO RESPICLICK 55/14 mcg, LS mean change of 0.172 L at 12 weeks). ARMONAIR RESPICLICK 113 mcg (LS mean change of 0.204 L at 12 weeks), and placebo (LS mean change of 0.053 L at 12 weeks). Estimated mean differences between AIRDUO RESPICLICK 55/14 mcg and AIRDUO RESPICLICK 113/14 mcg compared to placebo are 0.266 L (95% CI: 0.172, 0.360) and 0.262 L (95% CI: 0.168, 0.356), respectively. The estimated mean differences between AIRDUO RESPICLICK 55 mcg and ARMONAIR RESPICLICK 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 AIRDUO RESPICLICK 113/14 mcg and ARMONAIR RESPICLICK 113 mcg is 0.111 L (95% CI: 0.017, 0.206). The estimated mean difference between AIRDUO RESPICLICK 55/14 mcg and ARMONAIR RESPICLICK 55 mcg is 0.147 L (95% CI: 0.053, 0.242). In addition, the mean FEV1 results at each visit are displayed in Figure 3.
AIRDUO RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder

Figure 5: Serial Spirometry: Mean Change from Baseline in FEV₁ at Week 12 by Time Point and Treatment Group Trial 1 (FAS; Serial Spirometry Subset)

Figure 6: Mean Change from Baseline in Trough FEV₁ at Each Visit by Treatment Group Trial 1 (FAS; Serial Spirometry Subset)

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

AIRDUO RESPICLICK is supplied in the following 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.
AIRDUO RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder

<table>
<thead>
<tr>
<th>STRENGTH</th>
<th>NDC CODE</th>
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<tbody>
<tr>
<td>AIRDUO RESPICLICK 55/14 mcg</td>
<td>NDC 59310-805-06</td>
</tr>
<tr>
<td>AIRDUO RESPICLICK 113/14 mcg</td>
<td>NDC 59310-812-06</td>
</tr>
<tr>
<td>AIRDUO RESPICLICK 232/14 mcg</td>
<td>NDC 59310-822-06</td>
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</tbody>
</table>

Each AIRDUO RESPICLICK inhaler has a dose counter attached to the actuator. Patients should never try to alter the numbers for the dose counter. Discard the inhaler when the counter displays 0, 30 days after opening the foil pouch or after the expiration date on the product, whichever comes first. The labeled amount of medication in each actuation cannot be assured after the counter displays 0, even though the inhaler is not completely empty and will continue to operate (see Patient Counseling Information (17)).

16.2 Storage and Handling
Store at room temperature (between 15° and 25°C; 59° and 77°F) in a dry place; excursions permitted from 39° F to 86° F (15°C to 30°C). Avoid exposure to extreme heat, cold, or humidity. Keep out of reach of children. AIRDUO RESPICLICK should be stored inside the unopened moisture-protective foil pouch and only removed from the pouch immediately before initial use. Discard AIRDUO RESPICLICK 30 days after opening the foil pouch or when the counter reads 0, whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler apart.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use). Patients should be given the following information:

- **Severe Asthma Events**
- 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 AIRDUO RESPICLICK, there is not a significant increase in the risk of these events.

- **Not for Acute Symptoms**
- Inform patients that AIRDUO RESPICLICK 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
  - Significant decrease in lung function as outlined by the physician

- **Not Use Additional Long-Acting Beta-Adrenergics**
- Instruct 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 AIRDUO RESPICLICK, but at times therapy with AIRDUO RESPICLICK may need to be temporarily interrupted under close medical supervision. Rinse 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 herpes simplex.

- **Hypercorticism and Adrenal Suppression**
- Advise patients that AIRDUO RESPICLICK 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 AIRDUO RESPICLICK.

- **Immediate Hypersensitivity Reactions**
- Advise patients that immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of AIRDUO RESPICLICK. Patients should discontinue AIRDUO RESPICLICK 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 AIRDUO RESPICLICK.

- **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.

- **Caring for and Storing the Inhaler**
- 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 to never open the 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.

- **Rx only**
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- Frazer, PA 19355
- Manufactured by: Teva Pharmaceutical Industries Ltd.
- Jerusalem, Israel
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- AIRDPI-003
- Rev. March 2018

AIRDUO RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder

**Ocular Effects**
Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.

**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.

**Pregnancy**
Inform patients who are pregnant or nursing that they should contact their physician about the use of AIRDUO RESPICLICK.

**Use Daily for Best Effect**
Patients should use AIRDUO RESPICLICK at regular intervals as directed. The daily dosage of AIRDUO RESPICLICK 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 AIRDUO RESPICLICK abruptly. Patients should contact their physicians immediately if they discontinue use of AIRDUO RESPICLICK.

**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.

**Inform patients that AIRDUO RESPICLICK 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 cap is opened and closed. The dose-counter window displays the number of actuations left in the inhaler in units of two (e.g., 60, 58, 56, etc.). When the counter displays 20, the color of the numbers 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. Inform patients to discard AIRDUO RESPICLICK when the dose counter displays 0, 30 days after opening the foil pouch or after the expiration date on the product, whichever comes first.

**Rx only**
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Frazer, PA 19355
Manufactured by: Teva Pharmaceutical Industries Ltd.
Jerusalem, Israel
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AIRDPI-003
Rev. March 2018
**AIRDUO RESPICLICK** (fluticasone propionate and salmeterol) inhalation powder

**PATIENT INFORMATION**

**AIRDUO® RESPICLICK®** (ayr´ due oh res-pē-klik)
(fluticasone propionate and salmeterol) inhalation powder

55 mcg/14 mcg

**AIRDUO RESPICLICK** (ayr´ due oh res-pē-klik)
(fluticasone propionate and salmeterol) inhalation powder

113 mcg/14 mcg

**AIRDUO RESPICLICK** (ayr´ due oh res-pē-klik)
(fluticasone propionate and salmeterol) inhalation powder

232 mcg/14 mcg

for oral inhalation use

**What is AIRDUO RESPICLICK?**

- AIRDUO RESPICLICK 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.
- AIRDUO RESPICLICK 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.
- AIRDUO RESPICLICK contains salmeterol. LABA medicines such as salmeterol when used alone increase the risk of hospitalizations and death from asthma problems. AIRDUO RESPICLICK 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.
- AIRDUO RESPICLICK 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. AIRDUO RESPICLICK is for people 12 years of age and older with asthma who need both an ICS and LABA medicine.
- AIRDUO RESPICLICK is not used to relieve sudden breathing problems and will not replace a rescue inhaler.
- It is not known if AIRDUO RESPICLICK is safe and effective in children younger than 12 years of age.

**Do not use AIRDUO RESPICLICK:**

- 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 AIRDUO RESPICLICK. See the end of this leaflet for a complete list of ingredients in AIRDUO RESPICLICK.

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.

**How should I use AIRDUO RESPICLICK?**

- Read the step-by-step instructions for using AIRDUO RESPICLICK at the end of this Patient Information leaflet.
- AIRDUO RESPICLICK comes in 3 different strengths. Your healthcare provider prescribed the strength that is best for you.
- Use AIRDUO RESPICLICK exactly as your healthcare provider tells you to use it. Do not use AIRDUO RESPICLICK more often than prescribed.
- Use 1 inhalation of AIRDUO RESPICLICK 2 times each day. Use AIRDUO RESPICLICK at the same time each day, about 12 hours apart. If you miss a dose of AIRDUO RESPICLICK, 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 AIRDUO RESPICLICK, 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 AIRDUO RESPICLICK unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- AIRDUO RESPICLICK does not relieve sudden asthma symptoms. You should not take extra doses of AIRDUO RESPICLICK 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 AIRDUO RESPICLICK regularly for one week.

**What are the possible side effects with AIRDUO RESPICLICK?**

AIRDUO RESPICLICK can cause serious side effects, including:

- fungal infection in your mouth and throat (thrush). Rinse your mouth with water without swallowing after using AIRDUO RESPICLICK to help reduce your chance of getting thrush.
- weakened immune system and increased chance of getting infections (immunosuppression).

continued
• 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 AIRDUO RESPICLICK). 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 AIRDUO RESPICLICK and call your healthcare provider right away.
• serious allergic reactions. Stop using AIRDUO RESPICLICK 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 AIRDUO RESPICLICK.
• changes in laboratory blood values (sugar, potassium, certain types of white blood cells).
Common side effects of AIRDUO RESPICLICK 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 AIRDUO RESPICLICK. 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 AIRDUO RESPICLICK?
• Store AIRDUO RESPICLICK at room temperature between 59°F and 77°F (15°C and 25°C).
• Avoid exposure to extreme heat, cold, or humidity.
• Store AIRDUO RESPICLICK in the unopened foil pouch and only open when ready for use.
• Keep the yellow cap on the inhaler closed during storage.
• Keep your AIRDUO RESPICLICK inhaler dry and clean at all times.
• Throw away AIRDUO RESPICLICK 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 AIRDUO RESPICLICK and all medicines out of the reach of children.

Instructions for Use
AIRDUO RESPICLICK® (ayr´ due oh res-pé-klik)
(fluticasone propionate and salmeterol) inhalation powder
55 mcg/14 mcg
AIRDUO RESPICLICK (ayr´ due oh res-pé-klik)
(fluticasone propionate and salmeterol) inhalation powder
113 mcg/14 mcg
AIRDUO RESPICLICK (ayr´ due oh res-pé-klik)
(fluticasone propionate and salmeterol) inhalation powder
232 mcg/14 mcg
for oral inhalation use

Your AIRDUO RESPICLICK Inhaler
When you are ready to use AIRDUO RESPICLICK for the first time, remove the AIRDUO RESPICLICK inhaler from the foil pouch. There are 2 main parts of your AIRDUO RESPICLICK 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.
AIRDUO RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder

- 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.
- AIRDUO RESPICLICK does not have an activation button or medicine canister. When you open the cap, a dose of AIRDUO will be activated for delivery of the medicine.
- Do not use a spacer or volume holding chamber with AIRDUO RESPICLICK. AIRDUO RESPICLICK does not need priming.

Using your AIRDUO RESPICLICK 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 AIRDUO RESPICLICK is ready to be inhaled.

**Figure C**

**Remember:**
- For the correct use of AIRDUO RESPICLICK, hold the inhaler 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 AIRDUO RESPICLICK.

**Figure D**

**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.

**Figure F**

**Figure G**

**Step 3. Close**
- 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 AIRDUO RESPICLICK 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.
AIRDUO RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder

• 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 AIRDUO RESPICLICK?

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

Cleaning your AIRDUO RESPICLICK inhaler

• Do not wash or put any part of your AIRDUO RESPICLICK inhaler in water. Replace your inhaler if washed or placed in water.
• AIRDUO RESPICLICK 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 AIRDUO RESPICLICK 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 AIRDUO RESPICLICK inhaler is empty and you should stop using the inhaler and throw it away.
• Throw away AIRDUO RESPICLICK 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 AIRDUO RESPICLICK inhaler contains dry powder so it is important that you do not blow or breathe into it.

Support

• If you have any questions about AIRDUO RESPICLICK or how to use your inhaler, go to www.AIRDUORESPICLICK.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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