HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ARMONAIR RESPICLICK (fluticasone propionate) inhalation powder 55 mcg

ARMONAIR RESPICLICK (fluticasone propionate) inhalation powder 113 mcg

ARMONAIR RESPICLICK (fluticasone propionate) inhalation powder 232 mcg

FOR ORAL INHALATION USE

Initial U.S. Approval: 1994

INDICATIONS AND USAGE

ARMONAIR RESPICLICK is a corticosteroid indicated for:

- Maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. (1)

Important Limitation of Use:

- Not indicated for the relief of acute bronchospasm. (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 ARMONAIR RESPICLICK 55 mcg, 113 mcg, or 232 mcg twice daily.
- Do not use with a spacer or volume holding chamber. (2.2)

DOSAGE FORMS AND STRENGTHS

- Inhalation powder containing 55 mcg, 113 mcg, or 232 mcg of fluticasone propionate per actuation. (3)

CONTRAINDICATIONS

- Primary treatment of status asthmaticus or other acute episodes of asthma requiring intensive measures. (4.1)
- Severe hypersensitivity to milk proteins or any ingredients of ARMONAIR RESPICLICK. (4.2)

WARNINGS AND PRECAUTIONS

- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation. (5.1)
- Deterioration of asthma and acute episodes: Do not use for relief of acute symptoms. Patients require immediate re-evaluation during rapidly deteriorating asthma. (5.2)
- Immunosuppression: Potential worsening of existing tuberculosis, fungal, bacterial, viral, parasitic infections or ocular herpes simplex. Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.3)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from systemic corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to ARMONAIR RESPICLICK. (5.4)
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue ARMONAIR RESPICLICK slowly. (5.5)
- Decreases in bone mineral density: Monitor patients with major risk factors for decreased bone mineral content. (5.7)
- Monitor growth of pediatric patients. (5.8)
- Close monitoring for glaucoma and cataracts is warranted. (5.9)
- Paradoxical bronchospasm: Discontinue ARMONAIR RESPICLICK and institute alternative therapy if paradoxical bronchospasm occurs. (5.10)

ADVERSE REACTIONS

Most common adverse reactions (reported in greater than or equal to 3% of subjects) are: nasopharyngitis, upper respiratory tract infection, oral candidiasis, headache, and cough. (6.1)

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

DRUG INTERACTIONS

Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole): Use not recommended. May increase risk of systemic corticosteroid effects. (7.1)

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ARMONAIR™ RESPICLICK® is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older.

Important Limitation of Use: ARMONAIR RESPICLICK is NOT indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

2.1 General

ARMONAIR RESPICLICK should be administered only by the orally inhaled route *[see Instructions for Use in the Patient Information leaflet]*. Advise the patient to rinse his/her mouth with water without swallowing after each dose.

2.2 Dosing

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

The starting dosage for ARMONAIR RESPICLICK is based upon patients' asthma severity. The usual recommended starting dose for patients not on inhaled corticosteroids is 55 mcg twice daily. For other patients, the starting dose should be based on previous asthma drug therapy and disease severity. For patients switching to ARMONAIR RESPICLICK from another inhaled corticosteroid product, select the low (55 mcg), medium (113 mcg) or high (232 mcg) dose strength of ARMONAIR RESPICLICK based on the strength of the previous inhaled corticosteroid product and disease severity. For patients who do not respond to ARMONAIR RESPICLICK 55 mcg after 2 weeks of therapy, increasing the dose may provide additional asthma control.

If a dosage regimen of ARMONAIR 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 ARMONAIR RESPICLICK with a higher strength, or adding additional controller therapies) should be considered.

The highest recommended dose is 232 mcg twice daily. If symptoms arise between doses, an inhaled short-acting beta$_2$-agonist should be used for immediate relief.

The maximum benefit may not be achieved for up to 2 weeks 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. The safety and efficacy of ARMONAIR RESPICLICK when administered in excess of recommended dosages have not been established.

ARMONAIR RESPICLICK does not require priming. Do not use ARMONAIR 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 ARMONAIR RESPICLICK inhaler has a dose counter. When the patient receives the inhaler, the number 60 will be displayed. The dose counter will count down each time the mouthpiece is opened and closed. The dose counter window displays the number of actuations (inhalations) left in the inhaler in 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 consult their physician for a prescription refill. When the dose counter reaches 0, the background will change to solid red and the color of the numbers will change to black.

3 DOSAGE FORMS AND STRENGTHS

Inhalation Powder. ARMONAIR RESPICLICK is a multidose, inhalation-driven, dry powder inhaler for oral inhalation that meters 55 mcg, 113 mcg, or 232 mcg of fluticasone propionate from the device reservoir and delivers 51 mcg, 103 mcg, or 210 mcg of fluticasone propionate, respectively, from the mouthpiece per actuation. ARMONAIR RESPICLICK is supplied as a white dry powder inhaler with a green cap in a sealed foil pouch with desiccant.

4 CONTRAINDICATIONS

4.1 Status Asthmaticus

ARMONAIR 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

ARMONAIR 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 (5.6), Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 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 ARMONAIR RESPICLICK. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal

therapy while treatment with ARMONAIR RESPICLICK continues, but at times therapy with ARMONAIR RESPICLICK may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.2 Acute Asthma Episodes

ARMONAIR RESPICLICK is not indicated for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta$_2$-agonist, not ARMONAIR RESPICLICK, should be used to relieve acute symptoms such as shortness of breath. When prescribing ARMONAIR RESPICLICK, the physician must provide the patient with an inhaled, short-acting beta$_2$-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily use of ARMONAIR RESPICLICK. Instruct patients to contact their physicians immediately if episodes of asthma not responsive to bronchodilators occur during the course of treatment with ARMONAIR RESPICLICK. During such episodes, patients may require therapy with oral corticosteroids.

5.3 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 children 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 developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella-zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG 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; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.4 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 patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal 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) may be most susceptible, 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 ARMONAIR 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 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 asthma attack.

Patients requiring systemic corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to ARMONAIR RESPICLICK. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with ARMONAIR RESPICLICK. Lung function (mean forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [AM PEF]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of systemic corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to ARMONAIR RESPICLICK may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, 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.

5.5 Hypercorticism and Adrenal Suppression

ARMONAIR RESPICLICK will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since ARMONAIR RESPICLICK is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of ARMONAIR RESPICLICK in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing ARMONAIR RESPICLICK.

Because of the possibility of significant systemic absorption of inhaled corticosteroids, patients treated with ARMONAIR 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 response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these

effects. If such effects occur, the dosage of ARMONAIR RESPICLICK should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and for management of asthma symptoms.

5.6 Hypersensitivity Reactions, Including Anaphylaxis

Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of ARMONAIR RESPICLICK. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ARMONAIR RESPICLICK *[see Contraindications (4.2)]*.

5.7 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences, such as fracture, is unknown. Patients with major risk factors for decreased bone mineral content, such as 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.

5.8 Effect on Growth

Orally inhaled corticosteroids, including ARMONAIR RESPICLICK, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving ARMONAIR RESPICLICK routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including ARMONAIR 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)]*.

5.9 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. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

5.10 Paradoxical Bronchospasm

As with other inhaled medicines, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with ARMONAIR RESPICLICK, it should be treated immediately with an inhaled, short-acting bronchodilator; ARMONAIR RESPICLICK should be discontinued immediately; and alternative therapy should be instituted.

5.11 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with ARMONAIR RESPICLICK is not recommended because increased systemic corticosteroid adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

5.12 Eosinophilic Conditions and Churg-Strauss Syndrome

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

6 ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (*5.1*)]*
- Immunosuppression *[see Warnings and Precautions (5.3)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.5)]*
- Reduction in bone mineral density *[see Warnings and Precautions (5.7)]*
- Growth effects in pediatrics *[see Warnings and Precautions (5.8)]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

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

The incidence of adverse reactions associated with ARMONAIR RESPICLICK in Table 1 is based upon two placebo-controlled, 12-week, clinical studies (Study 1 and 2). A total of 822 adolescent and adult patients previously treated with inhaled corticosteroids were treated with twice daily ARMONAIR RESPICLICK 55 mcg, 113 mcg, 232 mcg or placebo. Sixty percent of patients were female and 80% of patients were white. The average duration of exposure was 82 days in ARMONAIR RESPICLICK groups compared with 75 days in the placebo group.

Table 1: Adverse Reactions with ≥ 3% Incidence with ARMONAIR RESPICLICK, and More Common than Placebo in Subjects with Asthma

Adverse Reaction	ARMONAIR RESPICLICK 55 mcg (n=129) %	ARMONAIR RESPICLICK 113 mcg (n=274) %	ARMONAIR RESPICLICK 232 mcg (n=146) %	Placebo (n=273) %
Infections and infestations				
Nasopharyngitis	5.4	5.8	4.8	4.4
URTI	5.4	4.7	5.5	4.8
Oral candidiasis*	3.1	2.9	4.8	0.7
Nervous system disorders				
Headache	1.6	7.3	4.8	4.4
Respiratory disorders				
Cough	1.6	1.8	3.4	2.6

* Oral candidiasis includes oropharyngeal candidiasis, oral fungal infection, oropharyngitis fungal
URTI = upper respiratory tract infection

Other adverse reactions not previously listed (and occurring in <3% of patients and in three or more patients on ARMONAIR RESPICLICK), whether considered drug-related or not by the investigators, that were reported more frequently by patients with asthma treated with ARMONAIR RESPICLICK compared with patients treated with placebo include the following: Oropharyngeal pain, hypertension, rhinitis allergic, influenza, pyrexia, dizziness, respiratory tract infection, muscle spasms, rhinitis, epistaxis, ligament sprain, musculoskeletal pain, pain in extremity, throat irritation, and vomiting.

Long Term Safety Study: This was a 26-week, open label study of 674 patients previously treated with inhaled corticosteroids who were treated twice daily with ARMONAIR RESPICLICK 113 mcg, 232 mcg, AIRDUO RESPICLICK 113/14 mcg, 232/14 mcg, fluticasone propionate aerosol 110 mcg, 220 mcg, fluticasone propionate and salmeterol inhalation powder 250/50 mcg, 500/50 mcg. The types of adverse reactions among ARMONAIR RESPICLICK treatments were similar to those reported above in placebo controlled studies.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post-approval use of fluticasone propionate. 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 or a combination of these factors.

Ear, Nose, and Throat: Aphonia, facial and oropharyngeal edema, and throat soreness.

Endocrine and Metabolic: Cushingoid features, growth velocity reduction in children/adolescents, hyperglycemia, and osteoporosis.

Eye: Cataracts, blurred vision, and central serous chorioretinopathy.

Immune System Disorders: Immediate and delayed hypersensitivity reactions, including anaphylaxis, rash, angioedema, and bronchospasm, have been reported. Anaphylactic reactions in patients with severe milk protein allergy have been reported.

Infections and Infestations: Esophageal candidiasis.

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

Respiratory: Asthma exacerbation, bronchospasm, chest tightness, dyspnea, immediate bronchospasm, pneumonia, and wheeze.

Skin: Contusions and ecchymoses.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate is a substrate of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with ARMONAIR RESPICLICK is not recommended because increased systemic corticosteroid adverse effects may occur.

Ritonavir: 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 Cushing's syndrome and adrenal suppression.

Ketoconazole: Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol area under the curve (AUC), but had no effect on urinary excretion of cortisol.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of ARMONAIR RESPICLICK in pregnant women. There are clinical considerations with the use of ARMONAIR RESPICLICK in pregnant women *[see Clinical Considerations]*. In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight, and/or skeletal variations in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a mcg/m^2 basis *[see Data]*. However, fluticasone propionate administered via inhalation to rats decreased fetal body weight, but did not induce teratogenicity at a maternal toxic dose approximately 2 times the MRHDID on a mcg/m^2 basis *[see Data]*. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. The estimated risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

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

Data

Animal Data

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, at a dose approximately 2 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 100 mcg/kg/day). The rat no observed adverse effect level (NOAEL) was observed at approximately 0.6 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 30 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/m^2 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/m^2 basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryo/fetal development study with pregnant rats dosed by the inhalation route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.5 times the MRHDID (on a mcg/m^2 basis with a maternal inhalation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose

approximately 0.1 times the MRHDID (on a mcg/m^2 basis with a maternal inhalation dose of 5.5 mcg/kg/day).

In an embryofetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced reductions of fetal body weights, in the presence of maternal toxicity at doses approximately 0.02 times the MRHDID and higher (on a mcg/m^2 basis with a maternal subcutaneous dose of 0.57 mcg/kg/day). Teratogenicity was evident based upon a finding of cleft palate for 1 fetus at a dose approximately 0.2 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 4 mcg/kg/day). The NOAEL was observed in rabbit fetuses with a dose approximately 0.004 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).

Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

In a pre- and post-natal development study in pregnant rats dosed from late gestation through delivery and lactation (Gestation Day 17 to Postpartum Day 22), fluticasone propionate was not associated with decreases in pup body weight, and had no effects on developmental landmarks, learning, memory, reflexes, or fertility at doses up to approximate equivalence to the MRHDID (on a mcg/m^2 basis with maternal subcutaneous doses up to 50 mcg/kg/day).

8.2 Lactation

Risk Summary

There are no available data on the presence of fluticasone propionate 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 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 ARMONAIR RESPICLICK and any potential adverse effects on the breastfed child from ARMONAIR 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/m^2 basis) resulted in measurable levels in milk.

8.4 Pediatric Use

The safety and effectiveness of ARMONAIR RESPICLICK in pediatric patients below the age of 12 years have not been established.

Effects on Growth: Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. A reduction of growth velocity in children or teenagers may occur as a result of poorly controlled asthma or from use of corticosteroids, including inhaled

corticosteroids. The effects of long-term treatment of children and adolescents with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known.

8.5 Geriatric Use

No overall differences in safety or efficacy were observed in data collected in 135 subjects aged 65 years and older versus younger subjects who were treated with ARMONAIR RESPICLICK in placebo-controlled Phase 2 and 3 studies.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using ARMONAIR RESPICLICK have not been conducted in patients with hepatic impairment. Since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

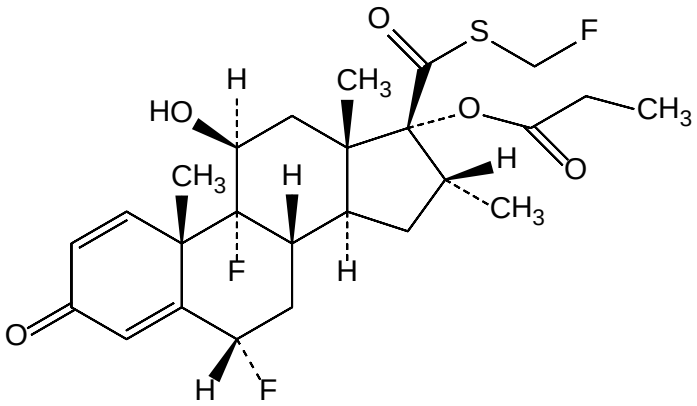
Formal pharmacokinetic studies using ARMONAIR RESPICLICK have not been conducted in patients with renal impairment.

10 OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism *[see Warnings and Precautions (5.5)]*. 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.

11 DESCRIPTION

The active component of ARMONAIR RESPICLICK 55 mcg, ARMONAIR RESPICLICK 113 mcg, and ARMONAIR RESPICLICK 232 mcg is fluticasone propionate, a corticosteroid having the chemical name S-(fluoromethyl) 6α,9-difluoro-11ß,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17ß-carbothioate, 17-propionate, and the following chemical structure:



Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

ARMONAIR RESPICLICK is a multidose dry powder inhaler for oral inhalation only. It contains a formulation blend of fluticasone propionate and alpha lactose monohydrate (which may contain milk proteins). The opening of the mouthpiece cover meters 11.5 mg of the formulation from the device reservoir, which contains 55 mcg, 113 mcg, or 232 mcg of fluticasone propionate. 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 ARMONAIR RESPICLICK inhaler delivers 51 mcg, 103 mcg, or 210 mcg of fluticasone propionate with lactose from the mouthpiece when tested at a flow rate of 88 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 ARMONAIR 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 ARMONAIR RESPICLICK inhaler was 106.72 L/min (range: 73.64 to 125.51 L/min).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone propionate has been shown in vitro to exhibit a binding affinity for the human

glucocorticoid receptor that is 18 times that of dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie 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.

Though effective for the treatment of asthma, corticosteroids do not affect asthma symptoms immediately. Individual patients will experience a variable time of onset and degree of symptom relief. Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. When corticosteroids are discontinued, asthma stability may persist for several days or longer.

Trials in subjects with asthma have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects with recommended doses of orally inhaled fluticasone propionate. This is explained by a combination of a relatively high local anti-inflammatory effect, negligible oral systemic availability (<1%), and the minimal pharmacological activity of the only metabolite detected in man.

12.2 Pharmacodynamics

ARMONAIR RESPICLICK: *Hypothalamic Pituitary Adrenal Axis Effects.*

The potential systemic effects of ARMONAIR RESPICLICK on the HPA axis were not fully studied, but other clinical trials evaluated the systemic effects of fluticasone propionate inhalation powder on the HPA axis in healthy subjects and in subjects with asthma.

ARMONAIR RESPICLICK: *Subjects with Asthma: Adults and Adolescents: Hypothalamic Pituitary Adrenal Axis Effects.*

There are no data regarding serum cortisol from controlled trials using ARMONAIR RESPICLICK in healthy subjects or subjects with asthma.

12.3 Pharmacokinetics

Absorption

Fluticasone propionate acts locally in the lung; therefore, plasma levels do 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.

Following ARMONAIR RESPICLICK administration, the peak plasma concentration of fluticasone propionate occurs at approximately 1 hour after inhalation.

The mean peak concentration following a 232 mcg single oral inhalation of ARMONAIR RESPICLICK to patients 12 years and older with persistent asthma was 73 pg/mL.

Distribution

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.

Elimination

Terminal half-life estimate of fluticasone propionate following oral inhalation administration of ARMONAIR RESPICLICK was approximately 11.2 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 of fluticasone propionate was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations

Age: No pharmacokinetic studies have been performed with ARMONAIR RESPICLICK in children or geriatric patients. A subgroup analysis was conducted to compare patients aged 12-17 (n=16) and ≥18 (n=23) years following administration of 232 mcg ARMONAIR RESPICLICK. No overall differences in fluticasone propionate pharmacokinetics were observed.

Sex: A subgroup analysis was conducted to compare male (n=22) and female (n=17) patients following administration of 232 mcg ARMONAIR RESPICLICK. No overall differences in fluticasone propionate pharmacokinetics were observed.

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

Hepatic Impairment: Formal pharmacokinetic studies using ARMONAIR RESPICLICK have not been conducted in patients with hepatic impairment. However, since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma.

Drug Interaction Studies: In vitro and in vivo drug interaction studies have not been conducted with ARMONAIR RESPICLICK. Known clinically significant drug interactions are outlined in *Drug Interactions (7).*

Inhibitors of Cytochrome P450 3A4: *Ritonavir*: Fluticasone propionate is a substrate of CYP3A4. Coadministration of fluticasone propionate and the strong CYP3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction trial in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable, peak levels (C_{max}) averaged 11.9 pg/mL (range: 10.8 to 14.1 pg/mL) and $AUC_{0-\tau}$ averaged 8.43 pg•h/mL (range: 4.2 to 18.8 pg•h/mL). Fluticasone propionate C_{max} and $AUC_{0-\tau}$ increased to 318 pg/mL (range: 110 to 648 pg/mL) and 3,102.6 pg•h/mL (range: 1,207.1 to 5,662.0 pg•h/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Ketoconazole: In a placebo-controlled crossover trial in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Following orally inhaled fluticasone propionate alone, $AUC_{2\text{-last}}$ averaged 1.559 ng•h/mL (range: 0.555 to 2.906 ng•h/mL) and $AUC_{2-\infty}$ averaged 2.269 ng•h/mL (range: 0.836 to 3.707 ng•h/mL). Fluticasone propionate $AUC_{2\text{-last}}$ and $AUC_{2-\infty}$ increased to 2.781 ng•h/mL (range: 2.489 to 8.486 ng•h/mL) and 4.317 ng•h/mL (range: 3.256 to 9.408 ng•h/mL), respectively, after coadministration of ketoconazole with orally inhaled fluticasone propionate. This increase in plasma fluticasone propionate concentration resulted in a decrease (45%) in serum cortisol AUC.

Erythromycin: In a multiple-dose drug interaction trial, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 10 times the MRHDID for adults on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately equivalent to the MRHDID for adults on a mcg/m^2 basis) for 104 weeks.

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

Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately equivalent to the MRHDID for adults on a mcg/m^2 basis).

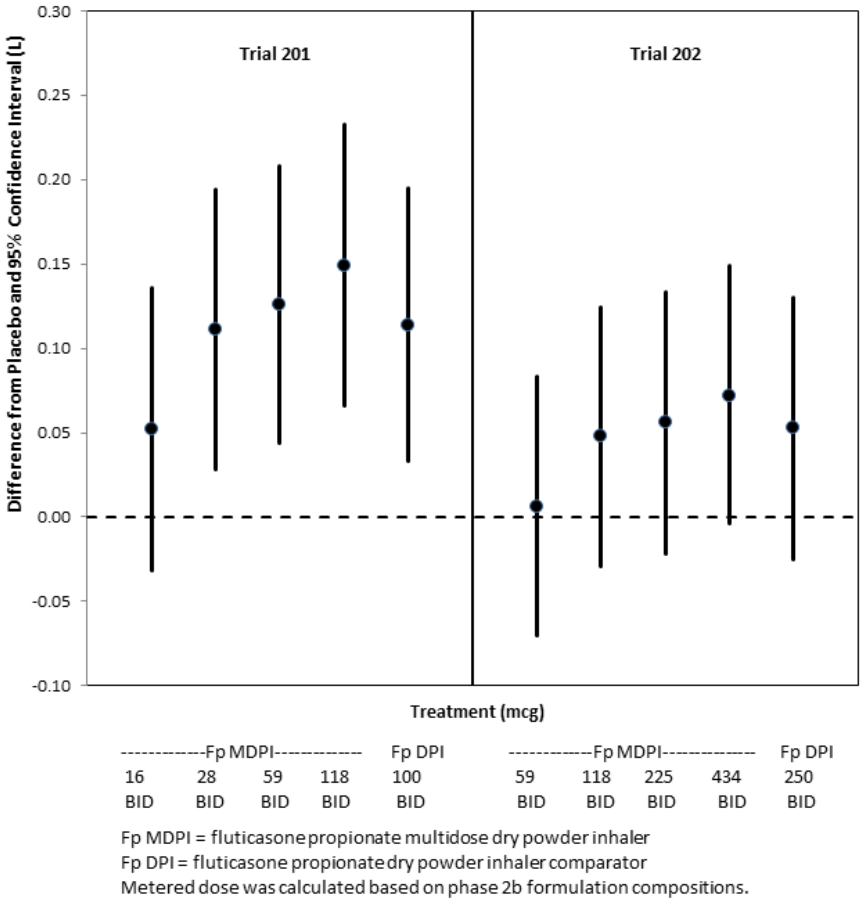
14 CLINICAL STUDIES

The safety and efficacy of ARMONAIR RESPICLICK were evaluated in 2130 patients with asthma. The development program included 2 confirmatory trials of 12 weeks duration, a 26 week safety trial and two dose-ranging trials of 12 weeks duration. The efficacy of ARMONAIR RESPICLICK is based primarily on the dose-ranging trials and the confirmatory trials described below.

14.1 Dose-Ranging Trials

Six doses of fluticasone propionate ranging from 16 mcg to 434 mcg (expressed as metered doses) administered twice daily via a 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 SABA alone or in combination with non-corticosteroid asthma medication. Low dose ICS patients may have been included after a minimum of 2 weeks washout. This trial contained an open-label active comparator fluticasone propionate inhalation powder 100 mcg administered twice daily. Trial 202 was conducted in patients who were uncontrolled at baseline and 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 and 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 FEV_1 (L) over 12 weeks (FAS)[a]



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

14.2 Trials in the Maintenance Treatment of Asthma

Adult and Adolescent Patients Aged 12 Years and Older:

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

Trials Comparing ARMONAIR RESPICLICK with Placebo

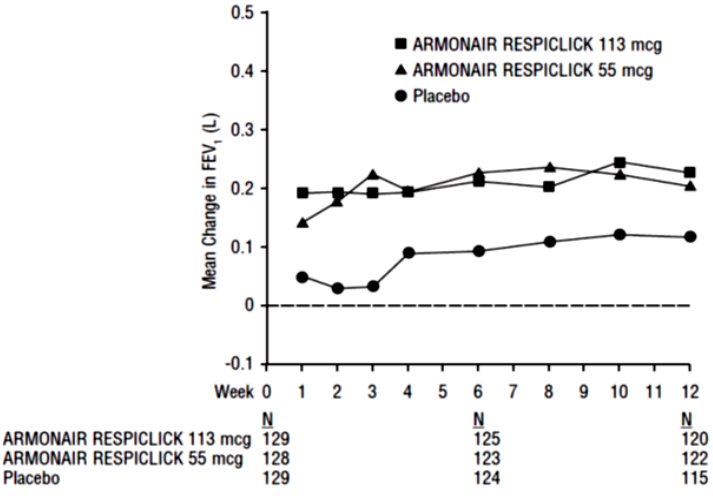
Two double-blind, parallel-group clinical trials, Trial 1 and Trial 2, were conducted with ARMONAIR RESPICLICK in 1375 adult and adolescent patients (aged 12 years and older, with baseline FEV_1 40% to 85% of predicted normal) with asthma that was not optimally controlled on their current therapy. All treatments were given as 1 inhalation twice a day from the RESPICLICK inhaler, and other maintenance therapies were discontinued.

Trial 1: This randomized, double-blind, placebo-controlled, 12-week, global efficacy and safety trial compared Fluticasone Propionate Multidose Dry Powder Inhaler (ARMONAIR

RESPICLICK) 55 mcg and 113 mcg (1 inhalation twice a day), Fluticasone/Salmeterol Multidose Dry Powder Inhaler (AIRDUO 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 corticosteroid/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 FEV_1 measurements were similar across treatments: ARMONAIR RESPICLICK 55 mcg 2.134 L, ARMONAIR RESPICLICK 113 mcg 2.166 L, and placebo 2.188 L. The primary endpoints for this trial were the change from baseline in trough FEV_1 at week 12 for all patients and standardized baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12 analyzed for a subset of 312 patients who performed postdose serial spirometry.

Patients receiving ARMONAIR RESPICLICK 55 mcg and ARMONAIR RESPICLICK 113 mcg had significantly greater improvements in trough FEV_1 (ARMONAIR RESPICLICK 55 mcg, LS mean change of 0.172 L at 12 weeks and ARMONAIR RESPICLICK 113 mcg, LS mean change of 0.204 L at 12 weeks) compared with placebo (LS mean change of 0.053 L at 12 weeks). Estimated mean differences between ARMONAIR 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. In addition, the mean FEV_1 results at each visit are displayed in Figure 2.

Figure 2: Mean Change from Baseline in Trough FEV_1 at Each Visit by Treatment Group Trial 1 (FAS)



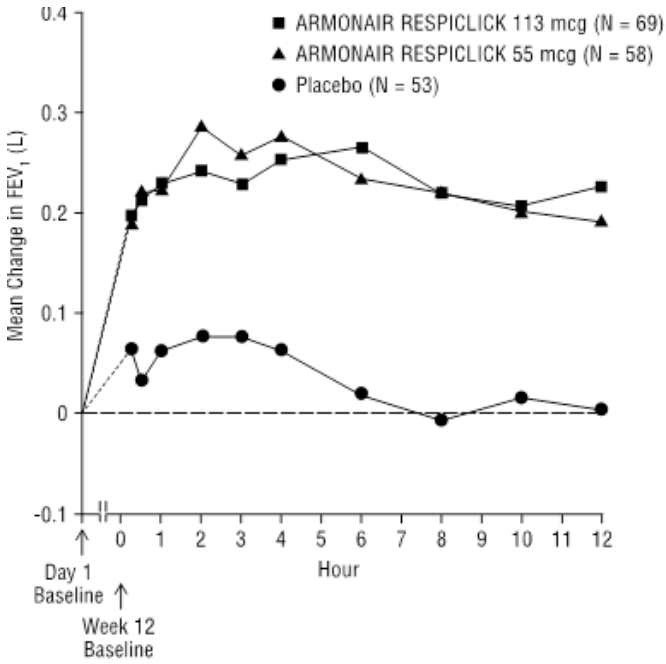
FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second

There was supportive evidence of efficacy for ARMONAIR RESPICLICK compared with placebo for secondary endpoints such as the weekly average of daily trough morning peak expiratory flow and the total daily use of rescue medication. The Asthma Quality of Life Questionnaire (AQLQ) for patients' age ≥ 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 ARMONAIR RESPICLICK 55 mcg and ARMONAIR RESPICLICK 113 mcg was 46% and 45%, respectively, compared to 40% for patients receiving placebo with odds ratios of 1.23 (95% CI: 0.74, 2.06) and 1.25 (95% CI: 0.75, 2.08), respectively.

Improvements in FEV_1 for both ARMONAIR RESPICLICK dose groups were sustained over the 12 hours of testing at week 12 (Figure 3). No diminution in the 12 hour bronchodilator effect was observed with ARMONAIR RESPICLICK as assessed by FEV_1 following 12 weeks of therapy.

Figure 3: Serial Spirometry: Mean Change from Baseline in FEV_1 (L) at Week 12 by Time Point and Treatment Group Trial 1 (FAS; Serial Spirometry Subset)



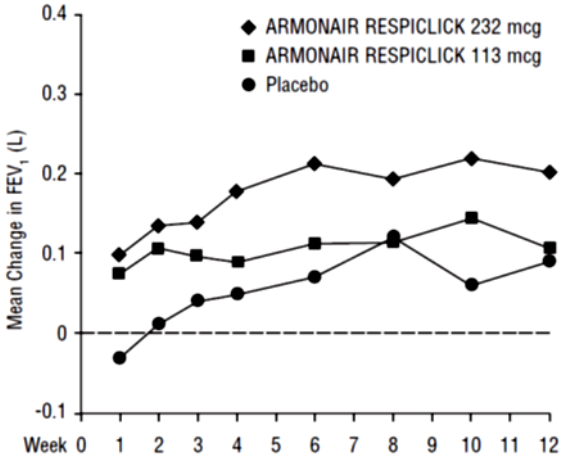
FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second

Trial 2: This randomized, double-blind, placebo-controlled, 12-week, global efficacy and safety trial compared Fluticasone Propionate Multidose Dry Powder Inhaler (ARMONAIR RESPICLICK) 113 mcg and 232 mcg (1 inhalation twice a day), Fluticasone/Salmeterol Multidose Dry Powder Inhaler (AIRDUO RESPICLICK) 113/14 mcg and 232/14 mcg (1 inhalation twice a day), and placebo in adolescents and adult patients with persistent symptomatic asthma despite inhaled corticosteroid or inhaled corticosteroid/LABA therapy. Patients received single-blinded placebo MDPI and were switched from their baseline ICS therapy to ARMONAIR RESPICLICK 55 mcg twice daily during the run-in period. Patients who met all randomization criteria were randomly assigned to receive treatment as follows: 145 patients received placebo, 146 patients received ARMONAIR RESPICLICK 113 mcg, 146 patients received ARMONAIR RESPICLICK 232 mcg, 145 patients received AIRDUO RESPICLICK 113/14 mcg, and 146 patients received AIRDUO RESPICLICK 232/14 mcg. Baseline FEV_1 measurements were similar across treatments, as follows: ARMONAIR

RESPICLICK 113 mcg 2.069 L, ARMONAIR RESPICLICK 232 mcg 2.075 L, and placebo 2.141 L. The primary endpoints for this trial were the change from baseline in trough FEV_1 at week 12 for all patients and standardized baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12 analyzed for a subset of 312 patients who performed postdose serial spirometry.

Efficacy results in this trial were similar to those observed in Trial 1. Patients receiving ARMONAIR RESPICLICK 113 mcg and ARMONAIR RESPICLICK 232 mcg had significantly greater improvements in trough FEV_1 (ARMONAIR RESPICLICK 113 mcg, LS mean change of 0.119 L at 12 weeks and ARMONAIR RESPICLICK 232 mcg, LS mean change of 0.179 L at 12 weeks) compared with placebo (LS mean change of -0.004 L at 12 weeks). Estimated mean differences between ARMONAIR RESPICLICK 113 mcg and ARMONAIR RESPICLICK 232 mcg compared to placebo are 0.123 L (95% CI: 0.038, 0.208) and 0.183 L (95% CI: 0.098, 0.268), respectively. In addition, the mean FEV_1 results at each visit are displayed in Figure 4.

Figure 4: Mean (Change from Baseline in Trough FEV_1 at Each Visit by Treatment Group Trial 2 (FAS)



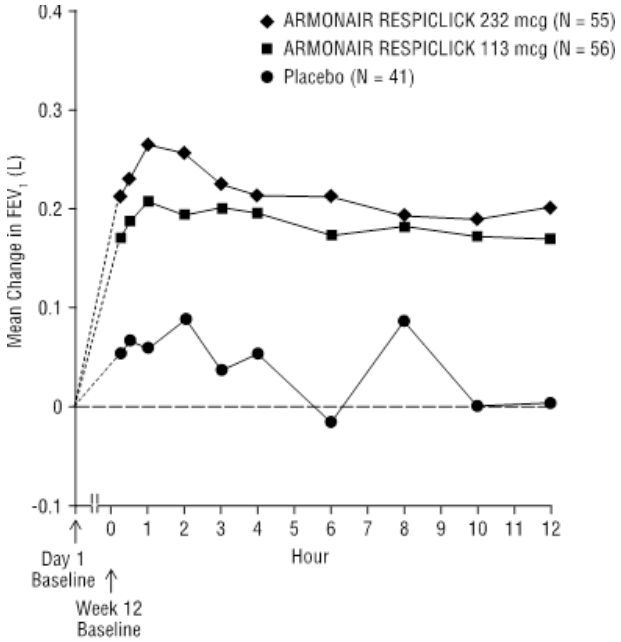
	N		N		N
ARMONAIR RESPICLICK 232 mcg	146		142		136
ARMONAIR RESPICLICK 113 mcg	145		138		135
Placebo	143		121		107

FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second

There was supportive evidence of efficacy for ARMONAIR 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. There were fewer withdrawals due to worsening asthma in patients treated with ARMONAIR RESPICLICK than with placebo. The AQLQ (patients age ≥ 18 years) or the PAQLQ (patients aged 12-17) were assessed in Trial 2. The responder rate for patients receiving ARMONAIR RESPICLICK 113 mcg and ARMONAIR RESPICLICK 232 mcg was 38% and 44%, respectively, compared to 27% for patients receiving placebo, with an odds ratio of 1.75 (95% CI:1.05, 2.93) and 2.12 (95% CI: 1.27, 3.53), respectively.

Improvements in FEV_1 for both ARMONAIR RESPICLICK dose groups were sustained over the 12 hours of testing at week 12 (Figure 5). No diminution in the 12 hour bronchodilator effect was observed with ARMONAIR RESPICLICK as assessed by FEV_1 following 12 weeks of therapy.

Figure 5: Serial Spirometry: Mean Change from Baseline in FEV_1 (L) at Week 12 by Time Point and Treatment Group Trial 2 (FAS; Serial Spirometry Subset)



FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ARMONAIR RESPICLICK is supplied in the following three strengths as a white dry-powder inhaler. Each inhaler has a green cap and is packaged individually in a foil pouch in a carton. Each inhaler contains 0.9g of the formulation and provides 60 actuations:

STRENGTH	**NDC CODE**
ARMONAIR RESPICLICK 55 mcg	NDC 59310-705-06
ARMONAIR RESPICLICK 113 mcg	NDC 59310-711-06
ARMONAIR RESPICLICK 232 mcg	NDC 59310-722-06

Each ARMONAIR 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 15º and 25ºC; 59º and 77ºF) in a dry place; excursions permitted from 59ºF to 86ºF (15ºC to 30ºC). Avoid exposure to extreme heat, cold, or humidity.

Keep out of reach of children.

ARMONAIR RESPICLICK should be stored inside the unopened moisture-protective foil pouch and only removed from the pouch immediately before initial use. Discard ARMONAIR 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:

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 ARMONAIR RESPICLICK, but at times therapy with ARMONAIR RESPICLICK may need to be temporarily interrupted under close medical supervision. Rinsing the mouth with water without swallowing after inhalation is advised to help reduce the risk of thrush.

Status Asthmaticus and Acute Asthma Symptoms

Inform patients that ARMONAIR RESPICLICK is not a bronchodilator and is not intended for use as rescue medicine for acute asthma exacerbations. Advise patients to treat acute asthma symptoms with an inhaled, short-acting $beta_2$-agonist such as albuterol. Instruct the patient to contact their physicians immediately if there is deterioration of their asthma.

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 ARMONAIR RESPICLICK may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, instruct 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 ARMONAIR RESPICLICK.

Immediate Hypersensitivity Reactions

Advise patients that immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, and hypotension), including anaphylaxis, may occur after administration of

ARMONAIR RESPICLICK. Patients should discontinue ARMONAIR 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 ARMONAIR 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 ARMONAIR RESPICLICK, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of adolescents taking corticosteroids by any route.

Ocular Effects

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

Pregnancy

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

Use Daily for Best Effect

Patients should use ARMONAIR RESPICLICK at regular intervals as directed. The daily dosage of ARMONAIR 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 the 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 to not stop use of ARMONAIR RESPICLICK abruptly. Patients should contact their physicians immediately if they discontinue use of ARMONAIR RESPICLICK.

Caring for and Storing the Inhaler

Instruct patients to not open their inhaler unless they are taking a dose. Repeated opening and closing the cover without taking medication will waste medication and may damage the inhaler.

Advise patients to keep their inhaler dry and clean at all times. **Never wash or put any part of the inhaler in water.** Patient should replace inhaler if washed or placed in water.

Advise patients to immediately replace inhaler if mouthpiece cover is damaged or broken.

Gently wipe the mouthpiece with a dry cloth or tissue as needed.

Instruct patients to store the inhaler at room temperature and to avoid exposure to extreme heat, cold, or humidity.

Instruct patients to never take the inhaler apart.

Inform patients that ARMONAIR RESPICLICK has a dose counter attached to the actuator. 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 ARMONAIR 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

Marketed by: Teva Respiratory, LLC
Frazer, PA 19355

Manufactured by: IVAX Pharmaceuticals Ireland
Waterford, Ireland

United States Patent Nos. 6701917, 6718972, 6748947, 6871646, 7540282, 8006690, 8651103, 8714149, 8978966, 9216260, 9463288, 9616024, 9731087.

ARMON-003

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