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

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 $beta_2$ adrenergic agonist (LABA).

Important Limitation 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 as 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 or combination product, select the low (55/14 mcg), medium (113/14 mcg) or high (232/14 mcg) dose strength of AIRDUO RESPICLICK based on the strength of the previous inhaled corticosteroid product or the strength of the inhaled corticosteroid from a combination product and disease severity. For patients who do not respond to 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 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 beta$_2$-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 reevaluated 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 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. 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 49 mcg, 100 mcg, or 202 mcg of fluticasone propionate with 12.75 mcg of salmeterol, respectively, from the mouthpiece per actuation. AIRDUO RESPICLICK is supplied as a white dry powder inhaler with a yellow cap in a sealed foil pouch with desiccant.

4 CONTRAINDICATIONS

4.1 Status Asthmaticus

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 Beta$_2$-adrenergic Agonists]*.

Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta$_2$-adrenergic Agonists

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

The 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 non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the 3 adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

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

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

ICS = Inhaled Corticosteroid; LABA = Long-acting $Beta_2$-adrenergic Agonist.

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

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

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

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

Salmeterol Multicenter Asthma Research Trial (SMART)

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

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 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 $beta_2$-agonists; decreasing response to usual medications; increasing need for systemic corticosteroids; recent 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 $beta_2$-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 1 inhalation twice daily of AIRDUO RESPICLICK.

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 $beta_2$-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 $beta_2$-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 $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

5.3 Excessive Use of AIRDUO RESPICLICK and Use with Other Long-Acting $Beta_2$-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 overdose may result. Clinically significant cardiovascular effects and fatalities 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

Salmeterol: In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1400 mcg/kg and above (approximately 240 times the MRHDID on a mcg/m^2 basis) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at 200 mcg/kg (approximately 35 times the MRHDID on a mcg/m^2 basis).

In a 24 month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 680 mcg/kg and above (approximately 240 times the MRHDID on a mcg/m^2 basis). No tumors were seen at 210 mcg/kg (approximately 75 times the MRHDID on a mcg/m^2 basis). These findings in rodents are similar to those reported previously for other beta adrenergic agonist drugs. The relevance of these findings to human use is unknown.

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

Fertility and reproductive performance were unaffected in male and female rats at oral doses up to 2000 mcg/kg (approximately 690 times the MRHDID for adults on a mcg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

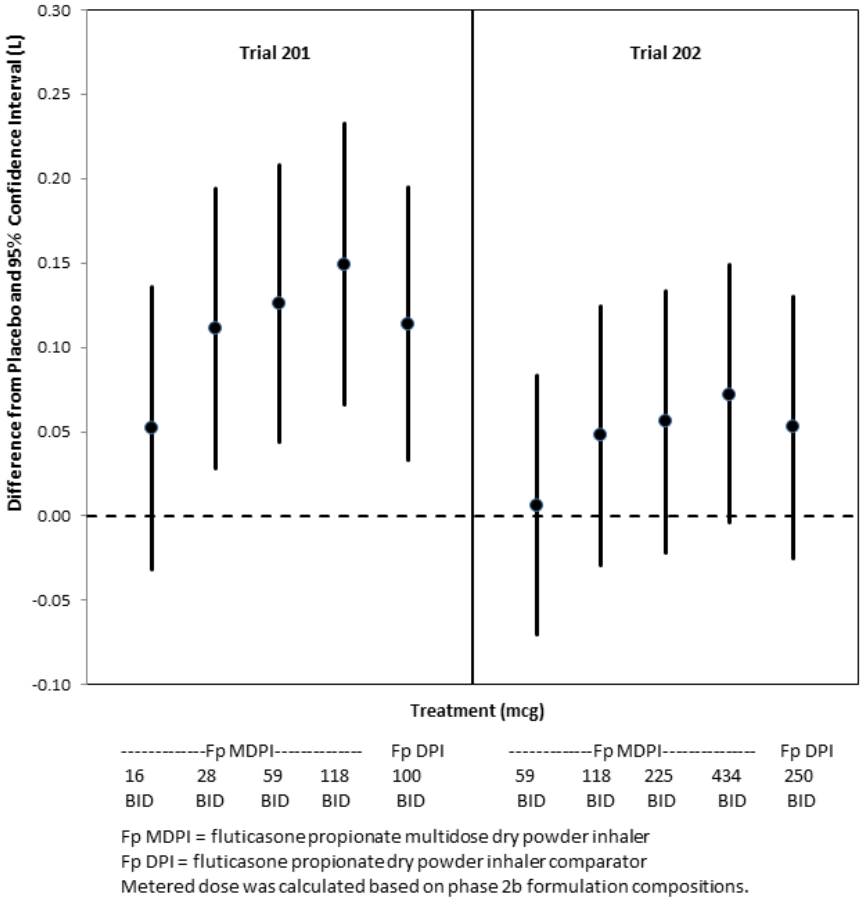
The safety and efficacy of AIRDUO RESPICLICK were evaluated in 3004 patients with asthma. The development program included 2 confirmatory trials of 12 weeks duration, a 26 week safety trial and three dose-ranging trials. The efficacy of AIRDUO RESPICLICK is based primarily on the dose-ranging trials 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 $beta_2$-agonist alone or in combination with non-corticosteroid asthma medication. Low dose ICS patients may have been included after a minimum of 2 weeks washout. This trial contained an open-label active comparator fluticasone propionate inhalation powder 100 mcg administered twice daily. Trial 202 was conducted in patients who were uncontrolled at baseline and 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 2) 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]

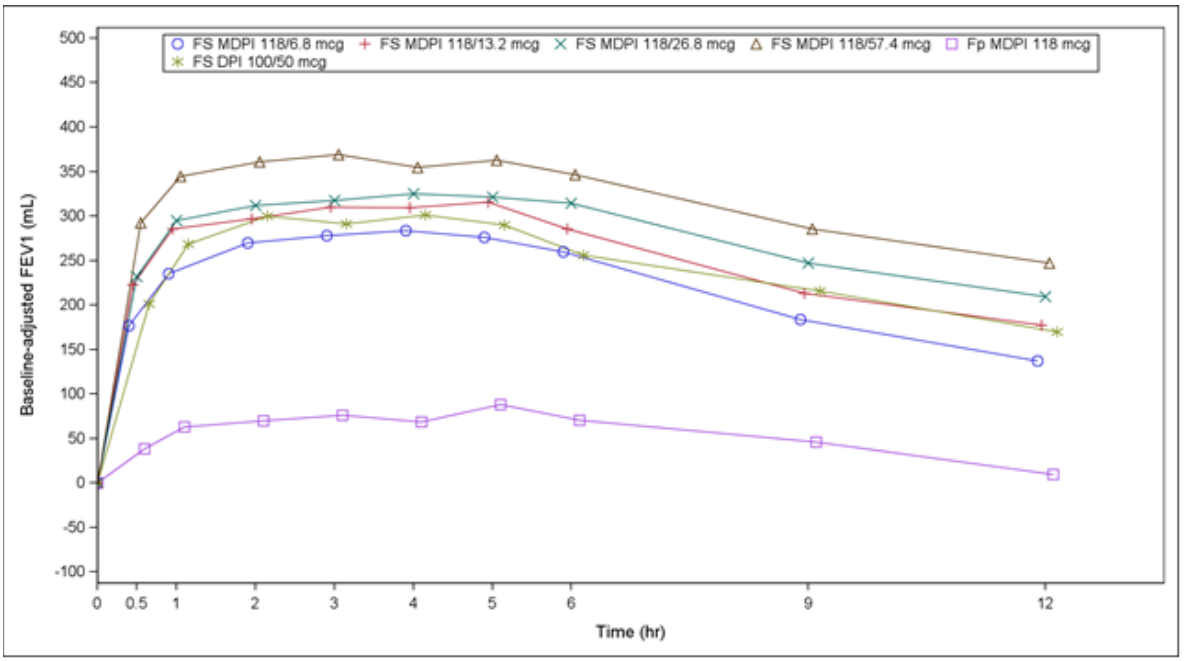


FAS = full analysis set; [a]Trials were not designed to provide comparative effectiveness data and should not be interpreted as superiority/inferiority to fluticasone propionate inhalation powder

The efficacy and safety of four doses of salmeterol xinafoate were evaluated in a double blind, 6-period crossover study compared with single dose fluticasone propionate MDPI and open label fluticasone propionate/salmeterol 100/50 mcg dry powder inhaler as comparator in patients with persistent asthma. The trials were dose-ranging trials of the salmeterol component of AIRDUO RESPICLICK and not designed to provide comparative effectiveness data and should not be interpreted as evidence of superiority/inferiority to fluticasone propionate/salmeterol inhalation powder. The salmeterol doses studied were 6.8 mcg, 13.2 mcg, 26.8 mcg and 57.4 mcg in combination with fluticasone propionate 118 mcg delivered by MDPI (expressed as metered dose). The metered doses for salmeterol (6.8, 13.2, 26.8, 57.4 mcg) used in this study are slightly different from the metered doses for the comparator products (fluticasone/salmeterol inhalation

powder) and the Phase 3 investigational products which are the basis of the proposed commercial labeled claim (55, 113, 232 mcg for fluticasone and 14 mcg for salmeterol). The phase 3 and commercial products were optimized to better match the strengths to the comparators. Plasma for pharmacokinetic characterization was obtained at each dosing period. Fluticasone propionate/salmeterol xinafoate MDPI 118/13.2 mcg had similar clinical efficacy with lower systemic exposure when compared to the 50 mcg of salmeterol in fluticasone propionate/salmeterol 100/50 mcg dry powder inhaler (Figure 3).

Figure 3: Mean Baseline Adjusted FEV_1 (mL) over 12 Hours (FAS)[a]



FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler: Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS DPI = fluticasone propionate/salmeterol dry powder inhaler; FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second; [a]Trial was not designed to provide comparative effectiveness data and should not be interpreted as superiority/inferiority to fluticasone propionate/salmeterol 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; 2 trials comparing AIRDUO RESPICLICK with ARMONAIR RESPICLICK alone or placebo (Trial 1 and Trial 2).

Trials Comparing AIRDUO RESPICLICK with Fluticasone Propionate Alone or Placebo

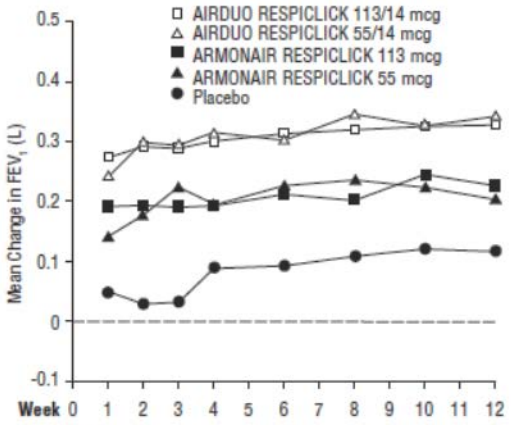
Two double-blind, parallel-group clinical trials, Trial 1 and Trial 2, were conducted with AIRDUO RESPICLICK in 1375 adult and adolescent patients (aged 12 years and older, with baseline FEV_1 40% to 85% of predicted normal) with asthma that was not optimally controlled on their current therapy. All 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) with 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 2.132 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 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 AIRDUO RESPICLICK 55/14 mcg and AIRDUO RESPICLICK 113/14 mcg had significantly greater improvements in trough FEV_1 (AIRDUO RESPICLICK 55/14 mcg, LS mean change of 0.319 L at 12 weeks and AIRDUO RESPICLICK 113/14 mcg, LS mean change of 0.315 L at 12 weeks) compared with ARMONAIR RESPICLICK 55 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 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. 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 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 1(FAS)



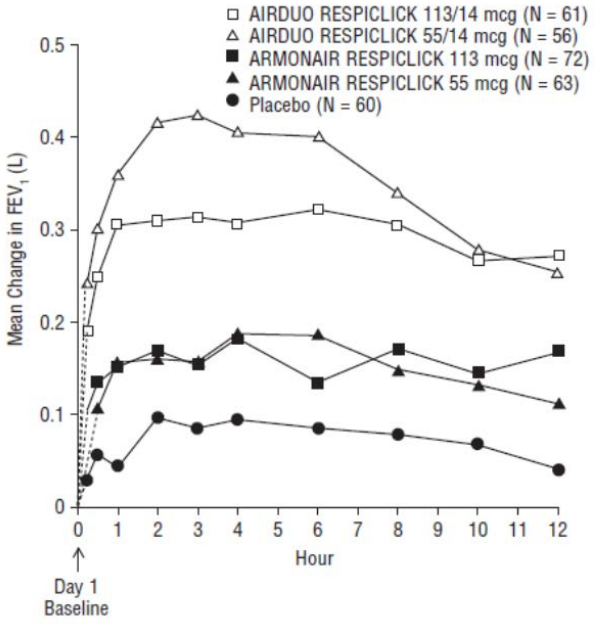
	N	N	N
AIRDUO RESPICLICK 113/14 mcg	126	126	126
AIRDUO RESPICLICK 55/14 mcg	128	123	123
ARMONAIR RESPICLICK 113 mcg	129	125	120
ARMONAIR RESPICLICK 55 mcg	128	123	122
Placebo	129	124	115

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

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 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 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% CI: 0.93, 2.55) and 2.04 (95% CI: 1.23, 3.41), respectively.

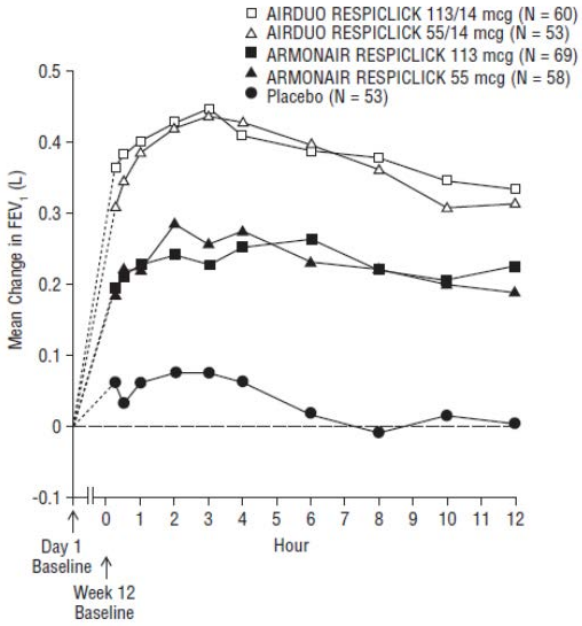
Improvements in lung function occurred within 15 minutes of the first dose (15 minutes postdose, the difference in LS mean change from baseline in FEV_1 was 0.216 and 0.164 L compared with placebo for AIRDUO RESPICLICK 55/14 mcg and 113/14 mcg, respectively; unadjusted p-value <0.0001 for both doses compared with placebo. Refer to Figure 5 below. Maximum improvement in FEV_1 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 5 and Figure 6). Following the initial dose, predose FEV_1 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 FEV_1 following 12 weeks of therapy.

Figure 5: Serial Spirometry: Mean Change from Baseline in FEV_1 (L) at Day 1 by Time Point and Treatment Group Trial 1 (FAS; Serial Spirometry Subset)



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

Figure 6: 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)

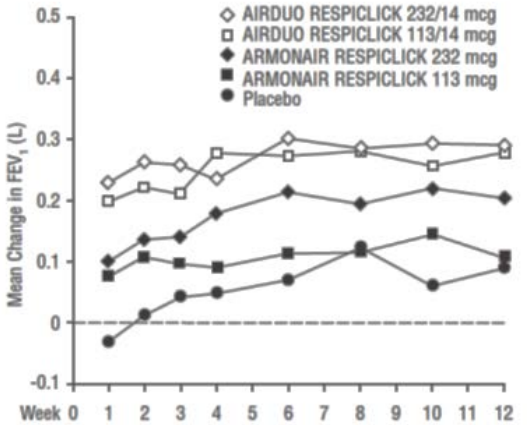


FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second

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) with 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: ARMONAIR RESPICLICK 113 mcg 2.069 L, ARMONAIR RESPICLICK 232 mcg 2.075 L, AIRDUO RESPICLICK 113/14 mcg 2.157 L, AIRDUO RESPICLICK 232/14 mcg 2.083 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 AIRDUO RESPICLICK 113/14 mcg and AIRDUO RESPICLICK 232/14 mcg had significantly greater improvements in trough FEV_1 (AIRDUO RESPICLICK 113/14 mcg, LS mean change of 0.271 L at 12 weeks and AIRDUO RESPICLICK 232/14 mcg, LS mean change of 0.272 L at 12 weeks) compared with ARMONAIR RESPICLICK 113 mcg (LS mean change of 0.119 L at 12 weeks), ARMONAIR RESPICLICK 232 mcg (LS mean change of 0.179 L at 12 weeks), and placebo (LS mean change of -0.004 L at 12 weeks). Estimated mean differences between AIRDUO RESPICLICK 113/14 mcg and AIRDUO RESPICLICK 232/14 mcg compared to placebo are 0.274 L (95% CI: 0.189, 0.360) and 0.276 L (95% CI: 0.191, 0.361), respectively. The 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. The estimated mean difference between AIRDUO RESPICLICK 232/14 mcg and ARMONAIR RESPICLICK 232 mcg is 0.093 L (95% CI: 0.009, 0.178). The estimated mean difference between AIRDUO RESPICLICK 113/14 mcg and ARMONAIR RESPICLICK 113 mcg is 0.152 L (95% CI: 0.066, 0.237). In addition, the mean FEV_1 results at each visit are displayed in Figure 7.

Figure 7: Mean Change from Baseline in Trough FEV_1 at Each Visit by Treatment Group Trial 2 (FAS)



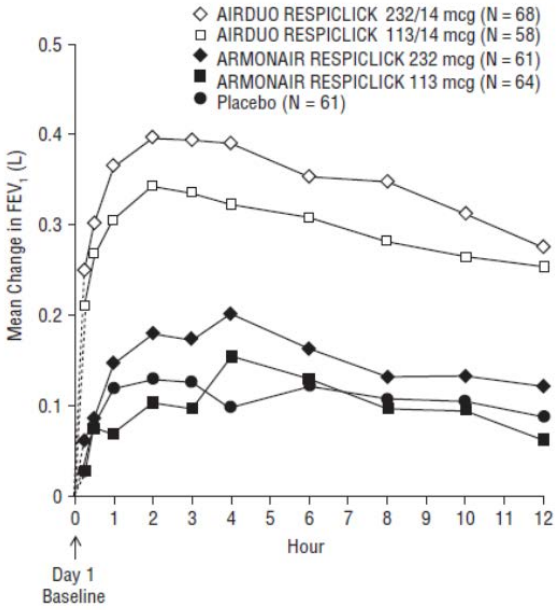
	N	N	N
AIRDUO RESPICLICK 232/14 mcg	145	142	136
AIRDUO RESPICLICK 113/14 mcg	140	137	136
ARMONAIR RESPICLICK 232 mcg	146	142	136
ARMONAIR RESPICLICK 113 mcg	145	138	135
Placebo	143	121	107

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

There was supportive evidence of efficacy for 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. There were fewer withdrawals due to worsening asthma in patients treated with AIRDUO RESPICLICK than with placebo. 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 2. The responder rate for both measures was defined as an improvement in score of 0.5 or more as threshold. In Trial 2, the responder rate for patients receiving AIRDUO RESPICLICK 113/14 mcg and AIRDUO RESPICLICK 232/14 mcg was 48% and 41%, respectively, compared to 27% for patients receiving placebo, with an odds ratio of 2.59 (95% CI: 1.56, 4.31) and 1.94 (95% CI: 1.16, 3.23), respectively.

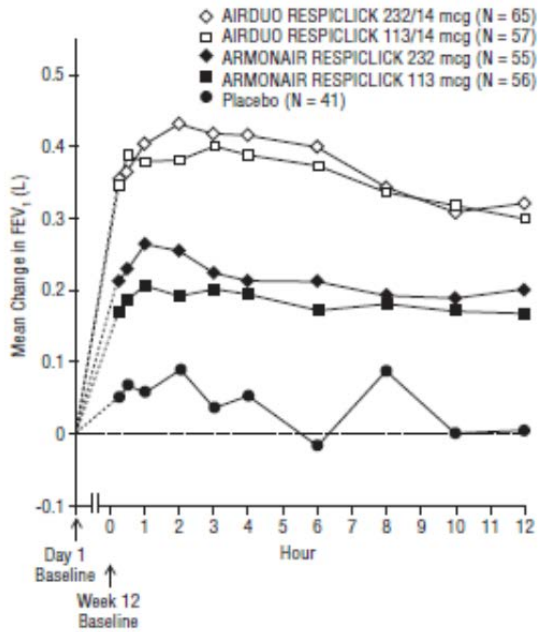
Improvements in lung function occurred within 15 minutes of the first dose (15 minutes postdose, the difference in LS mean change from baseline in FEV_1 was 0.160 L and 0.187 L compared with placebo for AIRDUO RESPICLICK 113/14 mcg and 232/14 mcg, respectively; unadjusted p-value <0.0001 for both doses compared with placebo. Maximum improvement in FEV_1 generally occurred within 3 hours for both AIRDUO RESPICLICK dose groups, and improvements were sustained over the 12 hours of testing at weeks 1 and 12 (Figure 8 and Figure 9). Following the initial dose, predose FEV_1 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 FEV_1 following 12 weeks of therapy.

Figure 8: Serial Spirometry: Mean Change from Baseline in FEV_1 (L) at Day 1 by Time Point and Treatment Group Trial 2 (FAS; Serial Spirometry Subset)



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

Figure 9: 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

AIRDUO RESPICLICK is supplied in the following three strengths as a white dry-powder inhaler. Each inhaler has a yellow cap and is packaged individually in a foil pouch in a carton. Each inhaler contains 0.45g of the formulation and provides 60 actuations:

STRENGTH	NDC CODE
AIRDUO RESPICLICK 55/14 mcg	NDC 59310-805-06
AIRDUO RESPICLICK 113/14 mcg	NDC 59310-812-06
AIRDUO RESPICLICK 232/14 mcg	NDC 59310-822-06

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 15º and 25ºC; 59º and 77ºF) in a dry place; excursions permitted from 59º F to 86º F (15ºC to 30ºC). 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:

Serious 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, 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$_2$-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$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

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

Do Not Use Additional Long-Acting Beta$_2$-Agonists

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. Rinsing the mouth with water without swallowing after inhalation is advised to help reduce the risk of thrush.

Immunosuppression

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

Instructions for Use
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

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.**

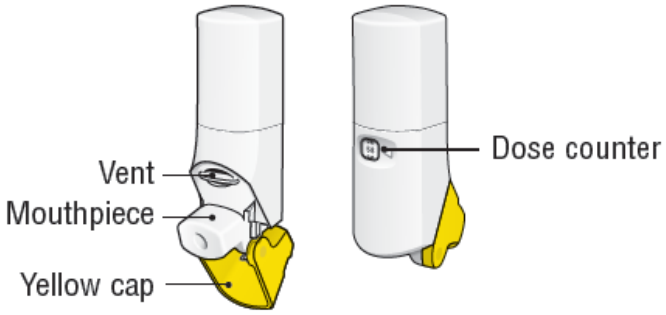


Figure A

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

Figure B

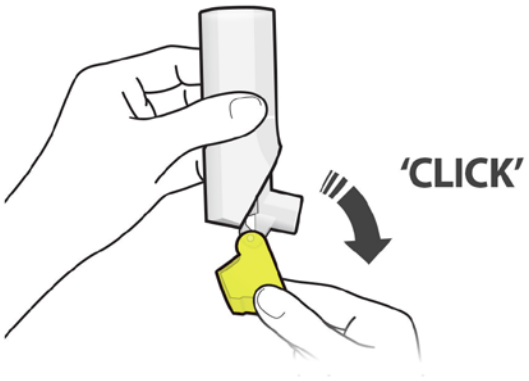
Important:

- **Always close the cap after each inhalation so your inhaler will be ready for you to take your next dose**. Do not open the cap unless you are ready for your next dose.
- You will hear a “click” sound when the cap is opened all the way. If you do not hear the “click” sound the inhaler may not be activated to give you a dose of medicine.
- **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.

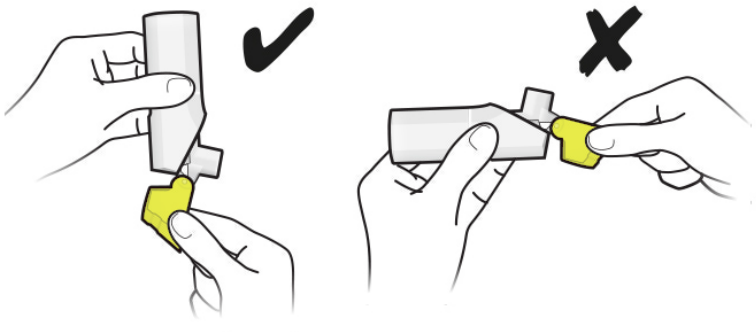
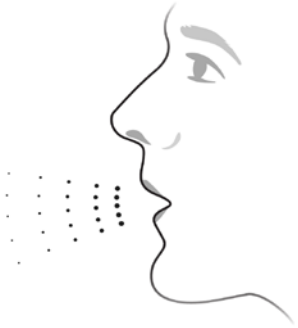


Figure D

Step 2. Inhale

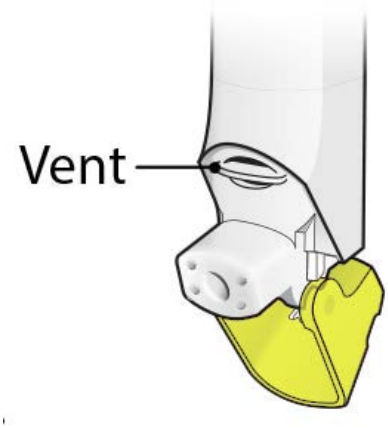


- Before you inhale, breathe out (exhale) through your mouth and push as much air from your lungs as you can. **See Figure E.**
- **Do not** exhale into the inhaler mouthpiece.

Figure E

- Put the mouthpiece in your mouth and close your lips tightly around it. **See Figure F.**

Figure F



- **Do not** block the vent above the mouthpiece with your lips or fingers. **See Figure G.**

Figure G

- **Breathe in quickly and deeply through your mouth** to deliver the dose of medicine to your lungs.
- Remove the inhaler from your mouth.
- **Hold your breath for about 10 seconds** or for as long as you comfortably can.

- Your 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.

Step 3. Close

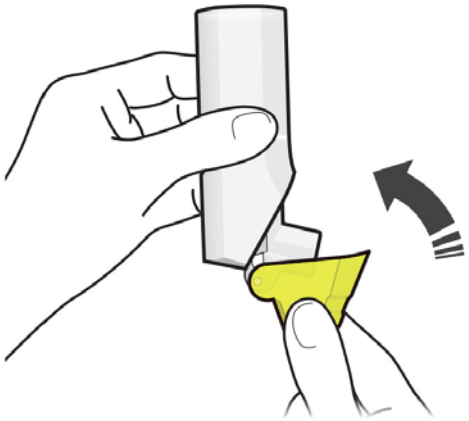


Figure H

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

How should I store AIRDUO RESPICLICK?

- Store AIRDUO RESPICLICK at room temperature between 59ºF and 77ºF (15ºC and 25ºC).
- 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.

AIRDIFU-002

Rev. December 2017