HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROAIR RESPICLICK safely and effectively. See full prescribing information for PROAIR RESPICLICK.

PROAIR® RESPICLICK® (albuterol sulfate) inhalation powder, for oral inhalation use
Initial U.S. Approval: 1981

---------- INDICATIONS AND USAGE ----------
PROAIR RESPICLICK is a beta$_2$-adrenergic agonist indicated for:
- Treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease. (1.1)
- Prevention of exercise-induced bronchospasm in patients 4 years of age and older. (1.2)

---------- DOSAGE AND ADMINISTRATION ----------
For oral inhalation only
- Treatment or prevention of bronchospasm in adults and children 4 years of age and older: 2 inhalations every 4 to 6 hours by oral inhalation. In some patients, 1 inhalation every 4 hours may be sufficient. (2.1)
- Prevention of exercise-induced bronchospasm in adults and children 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise by oral inhalation. (2.2)
- PROAIR RESPICLICK does not require priming. (2.3)
- Do not use with a spacer or volume holding chamber. (2.3)
- Keep the inhaler clean and dry at all times. Routine maintenance is not required. If the mouthpiece needs cleaning, gently wipe the mouthpiece with a dry cloth or tissue as needed. Never wash or put any part of the inhaler in water. (2.3)
- Discard 13 months after opening the foil pouch, when the dose counter displays 0, or after the expiration date on the product, whichever comes first. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
Inhalation powder: dry powder inhaler that delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouthpiece per actuation. The inhaler is supplied for 200 inhalation doses. (3)

---------- CONTRAINDICATIONS ----------
- Patients with hypersensitivity to albuterol. (4)
- Patients with severe hypersensitivity to milk proteins. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Life-threatening paradoxical bronchospasm may occur. Discontinue PROAIR RESPICLICK immediately and treat with alternative therapy. (5.1)
- Need for more doses of PROAIR RESPICLICK than usual may be a sign of deterioration of asthma and requires reevaluation of treatment. (5.2)
- PROAIR RESPICLICK is not a substitute for corticosteroids. (5.3)
- Cardiovascular effects may occur. Use with caution in patients sensitive to sympathomimetic drugs and patients with cardiovascular or convulsive disorders. (5.4, 5.7)
- Excessive use may be fatal. Do not exceed recommended dose. (5.5)
- Immediate hypersensitivity reactions may occur. Discontinue PROAIR RESPICLICK immediately. (5.6)
- Hypokalemia and changes in blood glucose may occur. (5.7, 5.8)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (≥1% and >placebo) are back pain, pain, gastroenteritis viral, sinus headache, urinary tract infection, nasopharyngitis, oropharyngeal pain and vomiting. (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 ----------
- Other short-acting sympathomimetic aerosol bronchodilators and adrenergic drugs: May potentiate effect. (7)
- Beta-blockers: May decrease effectiveness of PROAIR RESPICLICK and produce severe bronchospasm. Patients with asthma should not normally be treated with beta-blockers. (7.1)
- Diuretics, or non-potassium sparing diuretics: May potentiate hypokalemia or ECG changes. Consider monitoring potassium levels. (7.2)
- Digoxin: May decrease serum digoxin levels. Consider monitoring digoxin levels. (7.3)
- Monoamine oxidase (MAO) inhibitors and tricyclic antidepressants: May potentiate effect of albuterol on the cardiovascular system. Consider alternative therapy in patients taking MAOs or tricyclic antidepressants. (7.4)

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

Revised: 09/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Bronchospasm

PROAIR RESPICLICK is indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.

1.2 Exercise-Induced Bronchospasm

PROAIR RESPICLICK is indicated for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Bronchospasm

The recommended dosage is 2 inhalations every 4 to 6 hours by oral inhalation. More frequent administration or a larger number of inhalations is not recommended. In some patients, 1 inhalation every 4 hours may be sufficient.

2.2 Recommended Dosage for Exercise-Induced Bronchospasm

The recommended dosage is 2 inhalations 15 to 30 minutes before exercise by oral inhalation.

2.3 Administration and Maintenance Information

Administer PROAIR RESPICLICK by oral inhalation only. PROAIR RESPICLICK inhaler does not require priming. Do not use PROAIR RESPICLICK with a spacer or volume holding chamber.

Keep the inhaler clean and dry at all times. Never wash or put any part of your 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.

2.4 Dose Counter

The PROAIR RESPICLICK inhaler has a dose counter attached to the actuator. When the patient receives the inhaler, the number 200 will be displayed. The dose counter will count down each time the inhaler is actuated. 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. Discard PROAIR RESPICLICK 13 months after opening the foil pouch, when the dose counter displays 0 or after the expiration date on the product, whichever comes first *[see Patient Counseling Information (17)]*.

3 DOSAGE FORMS AND STRENGTHS

Inhalation powder: a multi-dose breath-actuated dry powder inhaler that delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouth piece per actuation. Each inhaler is supplied for 200 inhalations.

4 CONTRAINDICATIONS

PROAIR RESPICLICK is contraindicated in patients with a history of hypersensitivity to albuterol and/or severe hypersensitivity to milk proteins. Rare cases of hypersensitivity reactions, including urticaria, angioedema, and rash have been reported after the use of albuterol sulfate. There have been reports of anaphylactic reactions in patients using inhalation therapies containing lactose *[see Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Paradoxical Bronchospasm

PROAIR RESPICLICK can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, PROAIR RESPICLICK should be discontinued immediately and alternative therapy instituted.

5.2 Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of PROAIR RESPICLICK, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, eg, corticosteroids.

5.3 Use of Anti-Inflammatory Agents

The use of beta-adrenergic-agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

5.4 Cardiovascular Effects

PROAIR RESPICLICK, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of PROAIR RESPICLICK at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T-wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PROAIR RESPICLICK, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.5 Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

5.6 Hypersensitivity Reactions including Anaphylaxis

Immediate hypersensitivity reactions may occur after administration of albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. PROAIR RESPICLICK contains small amounts of lactose, which may contain trace levels of milk proteins. Hypersensitivity reactions including anaphylaxis, angioedema, pruritus, and rash have been reported with the use of therapies containing lactose (lactose is an inactive ingredient in PROAIR RESPICLICK). The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving PROAIR RESPICLICK.

5.7 Coexisting Conditions

PROAIR RESPICLICK, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator. Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.8 Hypokalemia

As with other beta-agonists, PROAIR RESPICLICK may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

6 ADVERSE REACTIONS

Use of PROAIR RESPICLICK may be associated with the following:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.1)]*
- Cardiovascular Effects *[see Warnings and Precautions (5.4)]*
- Immediate hypersensitivity reactions *[see Warnings and Precautions (5.6)]*
- Hypokalemia *[see Warnings and Precautions (5.8)*

6.1 Clinical Trials Experience

A total of 1289 subjects were treated with PROAIR RESPICLICK during the clinical development program. The most common adverse reactions (≥1% and > placebo) were back pain, pain, gastroenteritis viral, sinus headache, and urinary tract infection. 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.

Adults and Adolescents 12 years of Age and Older: The adverse reaction information presented in Table 1 below concerning PROAIR RESPICLICK is derived from the 12-week blinded treatment period of three studies which compared PROAIR RESPICLICK 180 mcg four times daily with a double-blinded matched placebo in 653 asthmatic patients 12 to 76 years of age.

Table 1: Adverse Reactions Experienced by Greater Than or Equal to 1.0% of Adult and Adolescent Patients in the PROAIR RESPICLICK Group and Greater Than Placebo in three 12-Week Clinical Trials[1]

Preferred Term	Number (%) of patients	
	PROAIR RESPICLICK 180 mcg QID N=321	Placebo N=333
Back pain	6 (2%)	4 (1%)
Pain	5 (2%)	2 (<1%)
Gastroenteritis viral	4 (1%)	3 (<1%)
Sinus headache	4 (1%)	3 (<1%)
Urinary tract infection	4 (1%)	3 (<1%)

1. This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of greater than or equal to 1.0% in the PROAIR RESPICLICK group and greater than placebo.

In a long-term study of 168 patients treated with PROAIR RESPICLICK for up to 52 weeks (including a 12-week double-blind period), the most commonly reported adverse events greater than or equal to 5% were upper respiratory infection, nasopharyngitis, sinusitis, bronchitis, cough, oropharyngeal pain, headache, and pyrexia.

In a small cumulative dose study, tremor, palpitations, and headache were the most frequently occurring (≥5%) adverse events.

Pediatric Patients 4 to 11 Years of Age: The adverse reaction information presented in Table 2 below concerning PROAIR RESPICLICK is derived from a 3-week pediatric clinical trial which compared PROAIR RESPICLICK 180 mcg albuterol 4 times daily with a double-blinded matched placebo in 185 asthmatic patients 4 to 11 years of age.

Table 2: Adverse Reactions Experienced by Greater Than or Equal to 2.0% of Patients 4 to 11 Years of Age in the PROAIR RESPICLICK Group and Greater Than Placebo in the 3 Week Trial

Preferred Term	Number (%) of patients	
	PROAIR RESPICLICK 180 mcg QID N=93	Placebo N=92
Nasopharyngitis	2 (2%)	1 (1%)
Oropharyngeal pain	2 (2%)	1 (1%)
Vomiting	3 (3%)	1 (1%)

6.2 Postmarketing Experience

In addition to the adverse reactions reported from clinical trials with PROAIR RESPICLICK, the following adverse events have been reported during use of other inhaled albuterol sulfate products: Urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), rare cases of aggravated bronchospasm, lack of efficacy, asthma exacerbation (potentially fatal), muscle cramps, and various oropharyngeal side-effects such as throat irritation, altered taste, glossitis, tongue ulceration, and gagging. 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.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as: angina, hypertension or hypotension, palpitations, central nervous system stimulation, insomnia, headache, nervousness, tremor, muscle cramps, drying or irritation of the oropharynx, hypokalemia, hyperglycemia, and metabolic acidosis.

7 DRUG INTERACTIONS

Other short-acting sympathomimetic bronchodilators should not be used concomitantly with PROAIR RESPICLICK. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

7.1 Beta-Blockers

Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as PROAIR RESPICLICK, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, eg, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic-blocking agents in patients with asthma. In this setting, consider cardioselective beta-blockers, although they should be administered with caution.

7.2 Diuretics

The ECG changes and/or hypokalemia which may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics. Consider monitoring potassium levels.

7.3 Digoxin

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and PROAIR RESPICLICK.

7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

PROAIR RESPICLICK should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of use of albuterol during pregnancy. Available data from published epidemiological studies and postmarketing case reports of pregnancy outcomes following inhaled albuterol use do not consistently demonstrate a risk of major birth defects or miscarriage. There are clinical considerations with use of albuterol in pregnant women *[see Clinical Considerations]*. In animal reproduction studies, when albuterol sulfate was administered subcutaneously to pregnant mice there was evidence of cleft palate at less than and up to 9 times the maximum recommended human daily inhalation dose (MRHDID) *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are 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 preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women should be closely monitored and medication adjusted as necessary to maintain optimal control.

Labor or Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of PROAIR RESPICLICK for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk. PROAIR RESPICLICK has not been approved for the management of pre-term labor. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with $beta_2$-agonists, including albuterol.

Data

Animal Data

In a mouse reproduction study, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure nine-tenths the maximum recommended human dose (MRHDID) for adults (on a mg/m^2 basis at a maternal dose of 0.25 mg/kg) and in 10 of 108 (9.3%) fetuses at approximately 9 times the MRHDID (on a mg/m^2 basis at a maternal dose of 2.5 mg/kg). Similar effects were not observed at approximately one-eleventh the MRHDID for adults (on a mg/m^2 basis at a maternal dose of 0.025 mg/kg). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol (positive control).

In a rabbit reproduction study, orally administered albuterol sulfate induced cranioschisis in 7 of 19 fetuses (37%) at approximately 750 times the MRHDID (on a mg/m^2 basis at a maternal dose of 50 mg/kg).

In a rat reproduction study, an albuterol sulfate/HFA-134a formulation administered by inhalation did not produce any teratogenic effects at exposures approximately 80 times the MRHDID (on a mg/m^2 basis at a maternal dose of 10.5 mg/kg).

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

8.2 Lactation

Risk Summary

There are no available data on the presence of albuterol in human milk, the effects on the breastfed child, or the effects on milk production. However, plasma levels of albuterol after inhaled therapeutic doses are low in humans, and if present in breast milk, albuterol has a low oral bioavailability *[see Clinical Pharmacology (12.3)]*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for albuterol and any potential adverse effects on the breastfed child from albuterol or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of PROAIR RESPICLICK for the treatment or prevention of bronchospasm with reversible obstructive airway disease have been established in pediatric patients 12 to 17 years of age. Use of PROAIR RESPICLICK for this indication is supported by evidence from two 12-week clinical trials in 318 patients 12 years of age and older with asthma comparing doses of 180 mcg four times daily with placebo, one long-term safety study in children 12 years of age and older, and one single-dose crossover study comparing doses of 90 and 180 mcg with albuterol sulfate inhalation aerosol (ProAir® HFA) in 71 patients *[see Clinical Studies (14.1)]*.

The safety and effectiveness of PROAIR RESPICLICK for treatment of exercise-induced bronchospasm have been established in children 12 years of age and older. Use of PROAIR RESPICLICK for this indication is supported by evidence from one single-dose crossover study in 38 patients age 16 and older with exercise-induced bronchospasm comparing doses of 180 mcg with placebo *[see Clinical Studies (14.2)]*. The safety profile for patients ages 12 to 17 was consistent with the overall safety profile seen in these studies.

The safety of PROAIR RESPICLICK in children 4 to 11 years of age is based on two single-dose, controlled, crossover studies: one with 61 patients comparing doses of 90 and 180 mcg with matched placebo and albuterol HFA MDI and one with 15 patients comparing a dose of 180 mcg with matched albuterol HFA MDI; and one 3-week clinical trial in 185 patients 4 to 11 years of age with asthma comparing a dose of 180 mcg four times daily with matched albuterol HFA MDI. The effectiveness of PROAIR RESPICLICK in children 4 to 11 years with exercise-induced bronchospasm is extrapolated from clinical trials in patients 12 years of age and older with asthma and exercise-induced bronchospasm, based on data from a single-dose study comparing the bronchodilatory effect of PROAIR RESPICLICK 90 mcg and 180 mcg with placebo in 61 patients with asthma, and data from a 3-week clinical trial in 185 asthmatic children 4 to 11 years of age comparing a dose of 180 mcg albuterol 4 times daily with placebo *[see Clinical Studies (14.1)]*.

The safety and effectiveness of PROAIR RESPICLICK in pediatric patients below the age of 4 years have not been established.

8.5 Geriatric Use

Clinical studies of PROAIR RESPICLICK did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Warnings and Precautions (5.4, 5.7)]*.

All beta$_2$-adrenergic agonists, including albuterol, are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

10 OVERDOSAGE

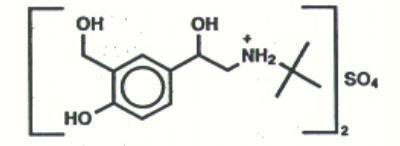
The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, eg, seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of PROAIR RESPICLICK.

Treatment consists of discontinuation of PROAIR RESPICLICK together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of PROAIR RESPICLICK.

11 DESCRIPTION

The active ingredient of PROAIR RESPICLICK inhalation powder is albuterol sulfate, a racemic salt of albuterol. Albuterol sulfate is a beta$_2$-adrenergic agonist. It has the chemical name α^1-[(*tert*-butylamino) methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1) (salt), and the following chemical structure:



The molecular weight of albuterol sulfate is 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$. Albuterol sulfate is a white to off-white crystalline powder. It is soluble in water and slightly soluble in ethanol. Albuterol sulfate is the official U.S. Adopted Name in the United States, and salbutamol sulfate is the recommended World Health Organization international nonproprietary name.

PROAIR RESPICLICK is an inhalation-driven, multi-dose inhalation powder (dry powder inhaler) for oral inhalation only. It contains a formulation blend of albuterol sulfate with alpha-lactose monohydrate. Each actuation provides a metered dose of 2.6 mg of the formulation containing 117 mcg of albuterol sulfate (equivalent to 97 mcg of albuterol base) and lactose from the device reservoir. Under standardized *in vitro* test conditions with fixed flow rates ranging from 58 to 71 L/min, and with a total air volume of 2 L, the PROAIR RESPICLICK inhaler delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) with lactose from the mouthpiece. The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile. In a study that investigated the peak inspiratory flow rate (PIFR) in asthma (n=27, ages 12 to 17 years old and n=50, ages 18 to 45 years old) and COPD (n=50, over 50 years old) patients, the mean PIFR achieved by subjects was >60 L/min (range = 31 to 110 L/min.), indicating that patients would be able to achieve the required inspiratory flow to operate the MDPI device correctly. The inhaler is provided for 200 actuations (inhalations).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Albuterol sulfate is a beta$_2$-adrenergic agonist. The pharmacologic effects of albuterol sulfate are attributable to activation of beta$_2$-adrenergic receptors on airway smooth muscle. Activation of beta$_2$-adrenergic receptors leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3',5'-adenosine monophosphate (cyclic AMP).

This increase of cyclic AMP is associated with the activation of protein kinase A, which in turn inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Albuterol relaxes the smooth muscle of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta-receptors in the human heart, 10% to 50% of which are cardiac beta$_2$-adrenergic receptors. The precise function of these receptors has not been established *[see Warnings and Precautions (5.4)]*.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. However, inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes [*see Warnings and Precautions (5.4)]*.

12.2 Pharmacodynamics

In a pharmacodynamic (PD) trial conducted in 47 patients, the PD and safety profiles were similar for PROAIR RESPICLICK and ProAir HFA. Comparable changes from baseline in the PD measures (serum glucose and potassium concentrations, QTcB, QTcF, heart rate, systolic blood pressure, and diastolic blood pressure) were observed following cumulative dose administration up to 1440 mcg of both PROAIR RESPICLICK and ProAir HFA. The overall safety, efficacy and PD profile of PROAIR RESPICLICK and ProAir HFA were comparable.

Following 90 or 180 mcg single-dose inhalation, the bronchodilatory effect of PROAIR RESPICLICK was significantly greater than placebo and comparable to that of ProAir HFA in patients 12 years of age and older (N=71) and pediatric patients 4 to 11 years of age (N=61) with persistent asthma.

Cardiac Electrophysiology

As with other beta$_2$-adrenergic agonists, PROAIR RESPICLICK prolonged QT intervals following a 1440 mcg cumulative dose. The prolongation was comparable to that of ProAir HFA.

12.3 Pharmacokinetics

Absorption

Albuterol was rapidly absorbed into the systemic circulation with peak plasma concentrations occurring at half an hour following single- or multiple-dose oral inhalation(s) of PROAIR RESPICLICK. In a cumulative dose study, the AUC_{0-t} was comparable between PROAIR RESPICLICK group and ProAir HFA group; C_{max} value was approximately one-third higher in PROAIR RESPICLICK group than ProAir HFA group.

Distribution

The volume of distribution has not been determined for PROAIR RESPICLICK. Published literature suggests that albuterol exhibits low *in vitro* plasma protein binding (10%).

Elimination

The accumulation ratio (~1.6 fold) was observed following one week QID dosing. The corresponding effective half-life was approximately 5 hours, which was consistent with the elimination half-life following both single- or multiple-dose administration.

Metabolism

Information available in the published literature suggests that the primary enzyme responsible for the metabolism of albuterol in humans is SULTIA3 (sulfotransferase). When racemic albuterol was administered either intravenously or via

inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration-time curves between the (R)- and (S)-albuterol enantiomers, with (S)-albuterol concentrations being consistently higher. However, without charcoal pretreatment, after either oral or inhalation administration the differences were 8- to 24-fold, suggesting that the (R)-albuterol is preferentially metabolized in the gastrointestinal tract, presumably by SULTIA3.

Excretion
The primary route of elimination of albuterol is through renal excretion (80% to 100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the feces. Following intravenous administration of racemic albuterol, between 25% and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the urine.

Specific Populations

No pharmacokinetic studies for PROAIR RESPICLICK have been conducted in neonates or elderly subjects. The systemic exposure in children 6 to 11 years of age is similar to that of adults following 180 mcg single dose inhalation of PROAIR RESPICLICK. The influence of gender or race on the pharmacokinetics of PROAIR RESPICLICK has not been studied.

Patients with Renal Impairment: The effect of renal impairment on the pharmacokinetics of albuterol was evaluated in 5 subjects with creatinine clearance of 7 to 53 mL/min, and the results were compared with those from healthy volunteers. Renal disease had no effect on the half-life, but there was a 67% decline in albuterol clearance. Caution should be used when administering high doses of PROAIR RESPICLICK to patients with renal impairment *[see Use in Specific Populations (8.5)]*.

Patients with Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of PROAIR RESPICLICK has not been evaluated.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 15 times and 6 times the maximum recommended daily inhalation dose (MRHDID) for adults and children, respectively, on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1,900 times and 740 times the MRHDID for adults and children, respectively, on a mg/m^2 basis). In a 22-month study in Golden Hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 250 times and 100 times the MRHDID for adults and children, respectively, on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 380 times the MRHDID for adults on a mg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

Preclinical: Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of the plasma concentrations. In structures

outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

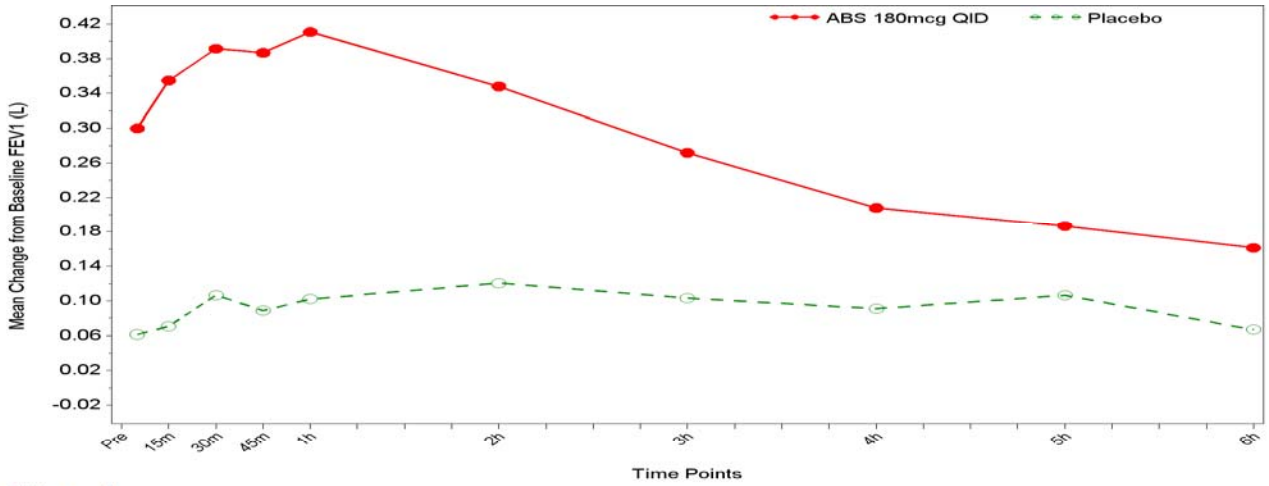
Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when β-agonists and methylxanthines were administered concurrently. The clinical significance of these findings is unknown.

14 CLINICAL STUDIES

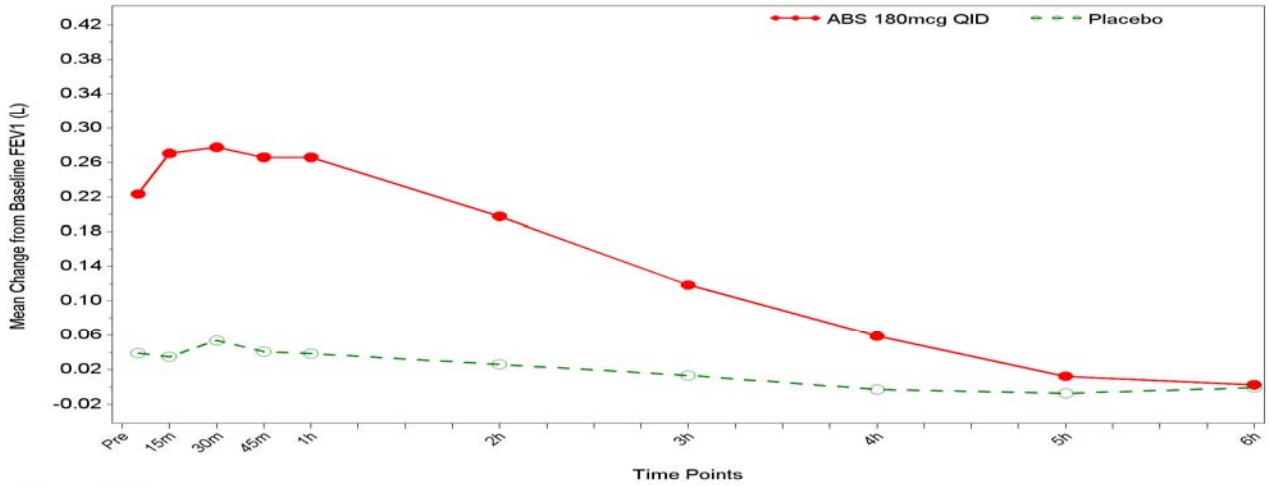
14.1 Bronchospasm Associated with Asthma

Adult and Adolescent Patients 12 Years of Age and Older

In two 12-week, randomized, double-blind, placebo-controlled studies of identical design (Study 1 and Study 2), PROAIR RESPICLICK (153 patients) was compared to a matched placebo dry powder inhaler (163 patients) in asthmatic patients 12 to 76 years of age at a dose of 180 mcg albuterol four times daily. Patients were maintained on inhaled corticosteroid treatment. Serial FEV_1 measurements, shown below in Figure 1 as average of the mean changes from test-day baseline at Day 1 and Day 85, demonstrated that two inhalations of PROAIR RESPICLICK produced significantly greater improvement in FEV_1 $AUC_{0\text{-}6hr}$ over the pre-treatment value than placebo in Study 1. Consistent results were observed in Study 2.



Day 1



Day 85

Figure 1: FEV_1 as Mean Change from Test-Day, Pre-Dose Baseline in a 12-Week Clinical Trial (Study 1)

In Study 1, 44 of 78 patients treated with PROAIR RESPICLICK achieved a 15% increase in FEV_1 within 30 minutes post-dose on Day 1. The median time to onset was 5.7 minutes, and median duration of effect as measured by a 15% increase was approximately 2 hours. Consistent results were observed in Study 2. In a double-blind, randomized, placebo–controlled, single-dose crossover study evaluating PROAIR RESPICLICK and ProAir HFA in 71 adult and adolescent subjects ages 12 and older with persistent asthma, PROAIR RESPICLICK had bronchodilator efficacy that was significantly greater than placebo at administered doses of 90 and 180 mcg.

Pediatric Patients 4 to 11 Years of Age

In a 3-week, randomized, double-blind, placebo-controlled trial, PROAIR RESPICLICK (92 patients) was compared to a matched placebo (92 patients) in asthmatic children 4 to 11 years of age at a dose of 180 mcg albuterol four times daily. Serial FEV_1 measurements, expressed as the baseline-adjusted percent-predicted FEV_1 $AUC_{0\text{-}6h}$ over the 3-week treatment period, demonstrated that 2 inhalations of PROAIR RESPICLICK produced significantly greater improvement in FEV_1 over the pre-treatment value than the matched placebo.

In this study, 48 of 92 patients treated with PROAIR RESPICLICK achieved a 15% increase in FEV_1 within 30 minutes post-dose on Day 1. The median time to onset was 5.9 minutes, and the median duration of effect as measured by a 15% increase was approximately 1 hour.

In a placebo-controlled, single-dose, crossover study in 61 patients 4 to 11 years of age, PROAIR RESPICLICK, administered at albuterol doses of 90 and 180 mcg, was compared with a matched placebo and with albuterol HFA MDI. PROAIR RESPICLICK provided similar bronchodilation when administered as one or two inhalations (baseline-adjusted percent-predicted serial FEV_1 observed over 6 hours post-dose), whereas two inhalations from albuterol HFA MDI provided significantly greater bronchodilation compared to a single inhalation.

14.2 Exercise-Induced Bronchospasm

In a randomized, single-dose, crossover study in 38 adult and adolescent patients with exercise-induced bronchospasm (EIB), two inhalations of PROAIR RESPICLICK taken 30 minutes before exercise prevented EIB for the hour following exercise (defined as the maintenance of FEV_1 within 80% of post-dose, pre-exercise baseline values) in 97% (37 of 38) of patients as compared to 42% (16 of 38) of patients when they received placebo.

Patients who participated in these clinical trials were allowed to use concomitant steroid therapy.

16 HOW SUPPLIED/STORAGE AND HANDLING

PROAIR RESPICLICK inhalation powder is supplied as a white inhaler with a red cap, in a sealed foil pouch, one pouch per carton.

Actuations	**Net Contents**	**NDC**
200	0.65 g	59310-580-20

Store at room temperature (between 15°C and 25°C; 59°F and 77°F). Avoid exposure to extreme heat, cold, or humidity.

Keep out of reach of children.

PROAIR RESPICLICK inhaler has a dose counter. Patients should never try to alter the numbers for the dose counter. Discard the inhaler 13 months after opening the foil pouch, when the counter displays 0, 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 Dosage and Administration (2.4), Patient Counseling Information (17)]*.

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:

Frequency of Use

The action of PROAIR RESPICLICK should last for 4 to 6 hours. Instruct patients to not use PROAIR RESPICLICK more frequently than recommended. Instruct patients to not increase the dose or frequency of doses of PROAIR RESPICLICK without consulting the physician. If patients find that treatment with PROAIR RESPICLICK becomes less effective for symptomatic relief, symptoms become worse, and/or they need to use the product more frequently than usual, they should seek medical attention immediately *[see Warnings and Precautions (5.2)]*.

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.

Routine maintenance is not required. If the mouthpiece needs cleaning, instruct patients to 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 PROAIR RESPICLICK has a dose counter. When the patient receives the inhaler, the number 200 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 (eg, 200, 198, 196, 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 PROAIR RESPICLICK when the dose counter displays 0 or after the expiration date on the product, whichever comes first *[see Dosage and Administration (2.3), (2.4)]*.

Paradoxical Bronchospasm

Inform patients that PROAIR RESPICLICK can produce paradoxical bronchospasm. Instruct patients to discontinue PROAIR RESPICLICK if paradoxical bronchospasm occurs *[see Warnings and Precautions (5.1)]*.

Concomitant Drug Use

Inform patients that, while they are taking PROAIR RESPICLICK, they should take other inhaled drugs and asthma medications only as directed by a physician *[see Drug Interactions (7)]*.

Common Adverse Events

Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, and nervousness.

Pregnancy

Inform patients who are pregnant or nursing that they should contact their physician about the use of PROAIR RESPICLICK *[see Use in Specific Populations (8.1)]*.

General Information on Use

Effective and safe use of PROAIR RESPICLICK includes an understanding of the way that it should be administered. Do not use a spacer or volume holding chamber with PROAIR RESPICLICK. Patients should be instructed on the proper use of the inhaler. See the FDA-approved Patient Information and Patient Instructions for Use. Discard PROAIR RESPICLICK 13 months after opening the foil pouch, when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

In general, the technique for administering PROAIR RESPICLICK to children is similar to that for adults. Children should use PROAIR RESPICLICK under adult supervision, as instructed by the patient's physician.

Distributed by:

Teva Pharmaceuticals USA, Inc.

Parsippany, NJ 07054

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

PROR-006

Rev. 09/2020

PATIENT INFORMATION
PROAIR® RESPICLICK® (prō´ār res-pē-klik)
(albuterol sulfate)
inhalation powder

What is PROAIR RESPICLICK?

PROAIR RESPICLICK is a prescription medicine used in people 4 years of age and older to:

- treat or prevent bronchospasm in people who have reversible obstructive airway disease
- prevent exercise-induced bronchospasm

It is not known if PROAIR RESPICLICK is safe and effective in children under 4 years of age.

Do not use PROAIR RESPICLICK if you are allergic to albuterol sulfate, lactose, milk proteins, or any of the ingredients in PROAIR RESPICLICK. See the end of this leaflet for a complete list of ingredients in PROAIR RESPICLICK.

Before using PROAIR RESPICLICK, tell your doctor about all of your medical conditions, including if you:

- have heart problems
- have high blood pressure (hypertension)
- have convulsions (seizures)
- have thyroid problems
- have diabetes
- have low potassium levels in your blood
- are pregnant or plan to become pregnant. It is not known if PROAIR RESPICLICK will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if PROAIR RESPICLICK passes into your breast milk. Talk to your doctor about the best way to feed your baby if you are using PROAIR RESPICLICK.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

PROAIR RESPICLICK and other medicines may affect each other and cause side effects. PROAIR RESPICLICK may affect the way other medicines work, and other medicines may affect the way PROAIR RESPICLICK works.

Especially tell your doctor if you take:

- other inhaled medicines or asthma medicines
- beta blocker medicines
- diuretics
- digoxin
- monoamine oxidase inhibitors
- tricyclic antidepressants

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use PROAIR RESPICLICK?

- For detailed instructions on how to use the inhaler, see **"Instructions for Use"** at the end of this Patient Information.
- Use PROAIR RESPICLICK exactly as your doctor tells you to use it.
- If your child needs to use PROAIR RESPICLICK, watch your child closely to make sure your child uses the inhaler correctly. Your doctor will show you how your child should use PROAIR RESPICLICK.
- Each dose of PROAIR RESPICLICK should last up to 4 hours to 6 hours.
- **Do not** increase your dose or take extra doses of PROAIR RESPICLICK without first talking to your doctor.
- Do not use a spacer or volume holding chamber with PROAIR RESPICLICK.
- PROAIR RESPICLICK does not need priming.
- Get medical help right away if PROAIR RESPICLICK no longer helps your symptoms.
- Get medical help right away if your symptoms get worse or if you need to use your inhaler more often.
- While you are using PROAIR RESPICLICK, **do not** use other inhaled rescue medicines and asthma medicines unless your doctor tells you to do so.
- Call your doctor if your asthma symptoms like wheezing and trouble breathing become worse over a few hours or days. Your doctor may need to give you another medicine (for example, corticosteroids) to treat your symptoms.

What are the possible side effects of PROAIR RESPICLICK?

PROAIR RESPICLICK may cause serious side effects, including:

- **worsening trouble breathing, coughing and wheezing (paradoxical bronchospasm).** If this happens stop using PROAIR RESPICLICK and call your doctor or get emergency help right away.
- **heart problems, including faster heart rate and higher blood pressure**
- **possible death in people with asthma who use too much PROAIR RESPICLICK**
- **allergic reactions.** Call your doctor right away if you have the following symptoms of an allergic reaction:

- itchy skin
- swelling beneath your skin or in your throat
- rash
- worsening trouble breathing

- **worsening of other medical problems in people who also use PROAIR RESPICLICK including increases in blood sugar**
- **low potassium levels in your blood**

The most common side effects of PROAIR RESPICLICK include:

- back pain
- pain
- upset stomach
- sinus headache
- urinary tract infection
- your heart feels like it is pounding or racing (palpitations)
- chest pain
- fast heart rate
- shakiness
- nervousness
- headache
- dizziness
- sore throat
- runny nose
- vomiting

These are not all of the possible side effects of PROAIR RESPICLICK.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PROAIR RESPICLICK?

- Store PROAIR RESPICLICK at room temperature between 59ºF and 77ºF (15ºC and 25ºC).
- Avoid exposure to extreme heat, cold, or humidity.
- Keep the cap on the inhaler closed during storage.
- Keep your PROAIR RESPICLICK inhaler dry and clean at all times.
- **Do not wash or put any part of your PROAIR RESPICLICK inhaler in water.** Replace your inhaler if washed or placed in water.

Keep PROAIR RESPICLICK and all medicines out of the reach of children.

General information about the safe and effective use of PROAIR RESPICLICK.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use PROAIR RESPICLICK for a condition for which it was not prescribed. Do not give PROAIR RESPICLICK to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or doctor for information about PROAIR RESPICLICK that was written for health professionals.

For more information, go to www.MyProAir.com or call 1-888-482-9522.

What are the ingredients in PROAIR RESPICLICK?

Active ingredient: albuterol sulfate

Inactive ingredients: lactose (may contain milk proteins)

Distributed by:
Teva Pharmaceuticals USA, Inc.
Parsippany, NJ 07054

PRORPL-005

This Patient Information has been approved by the U.S. Food and Drug Administration.
Revised: 09/2020

Instructions for Use
PROAIR® RESPICLICK® *(prō´ār res-pē-klik)*
(albuterol sulfate)
inhalation powder

Your PROAIR RESPICLICK Inhaler

When you are ready to use PROAIR RESPICLICK for the first time, remove the PROAIR RESPICLICK inhaler from the foil pouch.

There are 2 main parts of your PROAIR RESPICLICK inhaler including:

- the white inhaler with the mouthpiece. **See Figure A**.
- the red 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**.

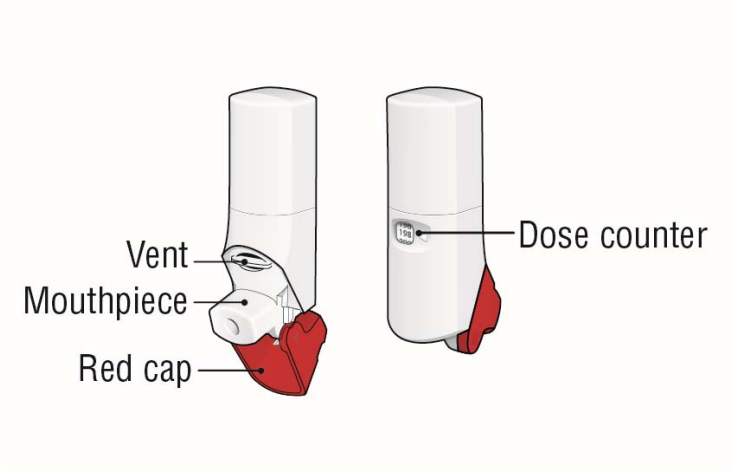


Figure A

- Your PROAIR RESPICLICK inhaler contains 200 doses (inhalations). **See Figure B**.
- The dose counter shows the number of doses left in your inhaler.
- When there are 20 doses left, the dose counter will change to red, and you should refill your prescription or ask your doctor 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**.

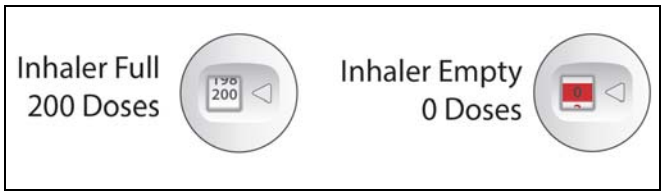


Figure B

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 fully. If you do not hear the “click” sound the inhaler may not be activated to give you a dose of medicine.
- **PROAIR RESPICLICK does not have an activation button or medicine canister**. When you open the cap, a dose of PROAIR will be activated for delivery of the medicine.
- In general, the technique for administering PROAIR RESPICLICK to children is similar to that for adults. Children should use PROAIR RESPICLICK under adult supervision, as instructed by the patient’s physician.
- Do not use a spacer or volume holding chamber with PROAIR RESPICLICK. PROAIR RESPICLICK does not need priming.

Using your PROAIR RESPICLICK inhaler:

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

Step 1. Open

- Hold the inhaler upright and open the red cap fully until you feel and hear a “click”. **See Figure C**.
- Each time you open the red cap and it “clicks”, a dose of PROAIR RESPICLICK is ready to be inhaled.

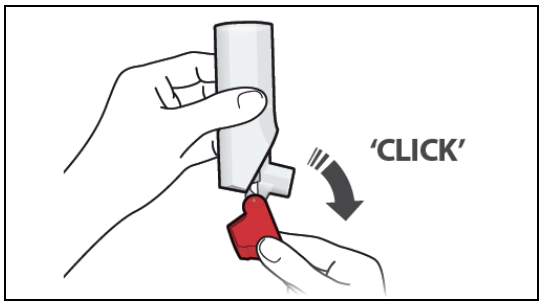


Figure C

Remember:

- For the correct use of PROAIR RESPICLICK, **hold the inhaler upright** as you open the red cap. **See Figure D**.
- **Do not** hold the inhaler in any other way as you open the red cap.
- **Do not** open the red cap until you are ready to take a dose of PROAIR RESPICLICK.

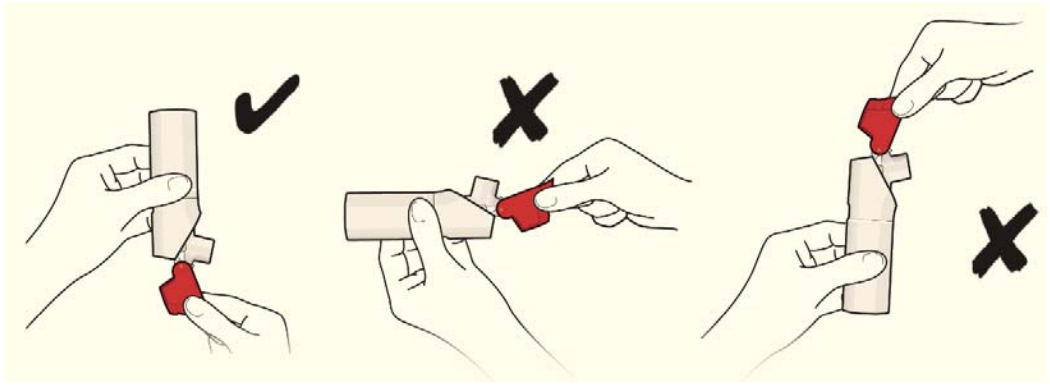
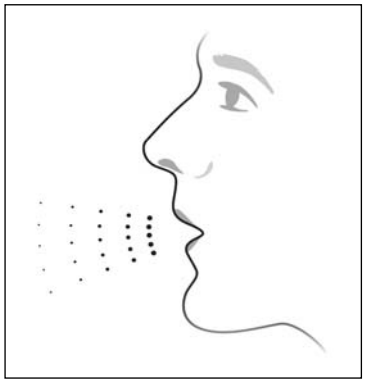


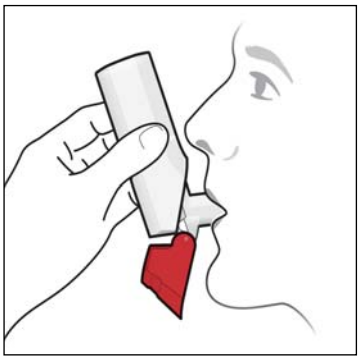
Figure D

Step 2. Inhale



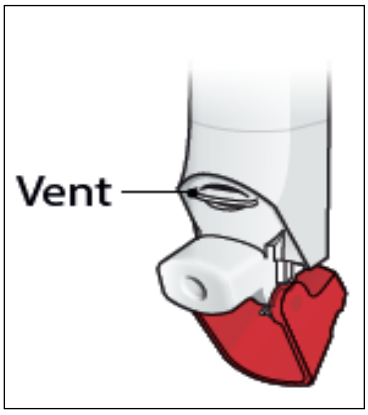
- Before you inhale, breathe out (exhale) through your mouth and push as much air from your lungs as you can. **See Figure E.**
- **Do not** exhale into the inhaler mouthpiece.

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 PROAIR 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

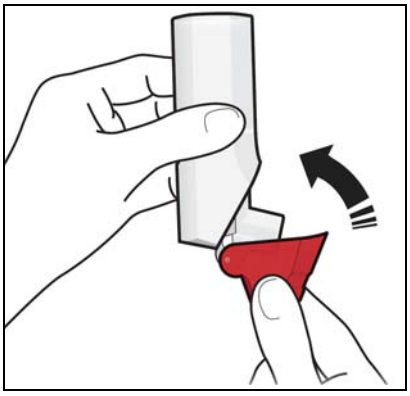


Figure H

- Close the red cap firmly over the mouthpiece. **See Figure H**.
- Make sure you close the red cap after each inhalation so that the inhaler will be ready for your next dose.
- **If you need another dose** close the red cap and then repeat steps 1-3.

Storing your PROAIR RESPICLICK inhaler

- Store PROAIR RESPICLICK at room temperature between 59ºF and 77ºF (15ºC and 25ºC).
- Avoid exposure to extreme heat, cold, or humidity.
- Keep the red cap on the inhaler closed during storage.
- Keep your PROAIR RESPICLICK inhaler dry and clean at all times.
- **Do not wash or put any part of your PROAIR RESPICLICK inhaler in water.** Replace your inhaler if washed or placed in water.
- **Keep your PROAIR RESPICLICK inhaler and all medicines out of the reach of children.**

Cleaning your PROAIR RESPICLICK inhaler

- **Do not wash or put any part of your PROAIR RESPICLICK inhaler in water.** Replace your inhaler if washed or placed in water.
- PROAIR RESPICLICK contains a powder and must be kept clean and dry at all times.
- If the mouthpiece needs cleaning, gently wipe it with a dry cloth or tissue.

Replacing your PROAIR RESPICLICK inhaler

- The dose counter on the back of your inhaler shows how many doses you have left. Do not try to change the numbers for the dose counter.
- When there are 20 doses left, the dose counter color will change to red, and you should refill your prescription or ask your doctor for another prescription.

- When the dose counter displays '0' your PROAIR RESPICLICK inhaler is empty, and you should stop using the inhaler and throw it away.
- Throw away your PROAIR RESPICLICK inhaler 13 months after removing it from the foil pouch for the first time, when the dose counter displays '0', or after the expiration date on the package, whichever comes first.

Important information

- Do not open the red 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 PROAIR RESPICLICK inhaler contains dry powder so it is important that you do not blow or breathe into it.
- **Do not** take the inhaler apart.

Support

- If you have any questions about PROAIR RESPICLICK or how to use your inhaler, go to www.ProAir.com or call 1-888-482-9522.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Distributed by:
Teva Pharmaceuticals USA, Inc.
Parsippany, NJ 07054

PRORIFU-005

Revised September 2020

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROAIR DIGIHALER safely and effectively. See full prescribing information for PROAIR DIGIHALER.

PROAIR® DIGIHALER® (albuterol sulfate) inhalation powder, for oral inhalation use
Initial U.S. Approval: 1981

---------- INDICATIONS AND USAGE ----------
ProAir Digihaler is a beta$_2$-adrenergic agonist indicated for:
- Treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease. (1.1)
- Prevention of exercise-induced bronchospasm in patients 4 years of age and older. (1.2)

---------- DOSAGE AND ADMINISTRATION ----------
For oral inhalation only
- Treatment or prevention of bronchospasm in adults and children 4 years of age and older: 2 inhalations every 4 to 6 hours by oral inhalation. In some patients, 1 inhalation every 4 hours may be sufficient. (2.1)
- Prevention of exercise-induced bronchospasm in adults and children 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise by oral inhalation. (2.2)
- ProAir Digihaler does not require priming. (2.3)
- Do not use with a spacer or volume holding chamber. (2.3)
- Keep the inhaler clean and dry at all times. Routine maintenance is not required. If the mouthpiece needs cleaning, gently wipe the mouthpiece with a dry cloth or tissue as needed. Never wash or put any part of the inhaler in water. (2.3)
- Discard 13 months after opening the foil pouch, when the dose counter displays 0, or after the expiration date on the product, whichever comes first. (2.3)
- ProAir Digihaler contains a built-in electronic module which detects, records, and stores data on inhaler events for transmission to the mobile App. Use of the App is not required for administration of medication to the patient. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
Inhalation powder: dry powder inhaler 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouthpiece per actuation. The inhaler is supplied for 200 inhalation doses. ProAir Digihaler includes a built-in electronic module. (3)

---------- CONTRAINDICATIONS ----------
- Patients with hypersensitivity to albuterol. (4)
- Patients with severe hypersensitivity to milk proteins. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Life-threatening paradoxical bronchospasm may occur. Discontinue ProAir Digihaler immediately and treat with alternative therapy. (5.1)
- Need for more doses of ProAir Digihaler than usual may be a sign of deterioration of asthma and requires reevaluation of treatment. (5.2)
- ProAir Digihaler is not a substitute for corticosteroids. (5.3)
- Cardiovascular effects may occur. Use with caution in patients sensitive to sympathomimetic drugs and patients with cardiovascular or convulsive disorders. (5.4, 5.7)
- Excessive use may be fatal. Do not exceed recommended dose. (5.5)
- Immediate hypersensitivity reactions may occur. Discontinue ProAir Digihaler immediately. (5.6)
- Hypokalemia and changes in blood glucose may occur. (5.7, 5.8)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (≥1% and >placebo) are back pain, pain, gastroenteritis viral, sinus headache, urinary tract infection, nasopharyngitis, oropharyngeal pain and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Respiratory, LLC at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------
- Other short-acting sympathomimetic aerosol bronchodilators and adrenergic drugs: May potentiate effect. (7)
- Beta-blockers: May decrease effectiveness of ProAir Digihaler and produce severe bronchospasm. Patients with asthma should not normally be treated with beta-blockers. (7.1)
- Diuretics, or non-potassium sparing diuretics: May potentiate hypokalemia or ECG changes. Consider monitoring potassium levels. (7.2)
- Digoxin: May decrease serum digoxin levels. Consider monitoring digoxin levels. (7.3)
- Monoamine oxidase (MAO) inhibitors and tricyclic antidepressants: May potentiate effect of albuterol on the cardiovascular system. Consider alternative therapy in patients taking MAOs or tricyclic antidepressants. (7.4)

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

Revised: 09/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Bronchospasm

ProAir® Digihaler® is indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.

1.2 Exercise-Induced Bronchospasm

ProAir Digihaler is indicated for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Bronchospasm

The recommended dosage is 2 inhalations every 4 to 6 hours by oral inhalation. More frequent administration or a larger number of inhalations is not recommended. In some patients, 1 inhalation every 4 hours may be sufficient.

2.2 Recommended Dosage for Exercise-Induced Bronchospasm

The recommended dosage is 2 inhalations 15 to 30 minutes before exercise by oral inhalation.

2.3 Administration and Maintenance Information

Administer ProAir Digihaler by oral inhalation only. ProAir Digihaler inhaler does not require priming. Do not use ProAir Digihaler with a spacer or volume holding chamber.

Keep the inhaler clean and dry at all times. Never wash or put any part of your 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.

2.4 Dose Counter

ProAir Digihaler inhaler has a dose counter attached to the actuator. When the patient receives the inhaler, the number 200 will be displayed. The dose counter will count down each time the inhaler is actuated. 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. Discard ProAir Digihaler 13 months after opening the foil pouch, when the dose counter displays 0 or after the expiration date on the product, whichever comes first *[see Patient Counseling Information (17)]*.

2.5 Storage of Data on Inhaler Events

ProAir Digihaler contains a built-in electronic module which detects, records, and stores data on inhaler events, including peak inspiratory flow rate (L/min), for transmission to the mobile App where inhaler events are categorized. Use of the App is not required for administration of albuterol sulfate to the patient. There is no evidence the use of the App leads to improved clinical outcomes, including safety and effectiveness *[see How Supplied/Storage and Handling (16)]*.

3 DOSAGE FORMS AND STRENGTHS

Inhalation Powder: multi-dose breath-actuated dry powder inhaler that delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouth piece per actuation. Each inhaler is supplied for 200 inhalations. *[see How Supplied/Storage and Handling (16)]*.

4 CONTRAINDICATIONS

ProAir Digihaler is contraindicated in patients with a history of hypersensitivity to albuterol and/or severe hypersensitivity to milk proteins. Rare cases of hypersensitivity reactions, including urticaria, angioedema, and rash have been reported after the use of albuterol sulfate. There have been reports of anaphylactic reactions in patients using inhalation therapies containing lactose *[see Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Paradoxical Bronchospasm

ProAir Digihaler can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, ProAir Digihaler should be discontinued immediately and alternative therapy instituted.

5.2 Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of ProAir Digihaler, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

5.3 Use of Anti-Inflammatory Agents

The use of beta-adrenergic-agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

5.4 Cardiovascular Effects

ProAir Digihaler, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of ProAir Digihaler at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T-wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, ProAir Digihaler, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.5 Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

5.6 Hypersensitivity Reactions including Anaphylaxis

Immediate hypersensitivity reactions may occur after administration of albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. ProAir Digihaler contains small amounts of lactose, which may contain trace levels of milk proteins. Hypersensitivity reactions including anaphylaxis, angioedema, pruritus, and rash have been reported with the use of therapies containing lactose (lactose is an inactive ingredient in ProAir Digihaler). The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving ProAir Digihaler.

5.7 Coexisting Conditions

ProAir Digihaler, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders,

hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator. Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.8 Hypokalemia

As with other beta-agonists, ProAir Digihaler may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

6 ADVERSE REACTIONS

Use of ProAir Digihaler may be associated with the following:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.1)]*
- Cardiovascular Effects *[see Warnings and Precautions (5.4)]*
- Immediate hypersensitivity reactions *[see Warnings and Precautions (5.6)]*
- Hypokalemia *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

A total of 1289 subjects were treated with albuterol sulfate inhalation powder (ProAir RespiClick hereafter referred to as albuterol sulfate MDPI) during the clinical development program. The most common adverse reactions (≥1% and > placebo) were back pain, pain, gastroenteritis viral, sinus headache, and urinary tract infection. 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.

Adults and Adolescents 12 years of Age and Older: The adverse reaction information presented in Table 1 below concerning albuterol sulfate MDPI is derived from the 12-week blinded treatment period of three studies which compared albuterol sulfate MDPI 180 mcg four times daily with a double-blinded matched placebo in 653 asthmatic patients 12 to 76 years of age.

Table 1: Adverse Reactions Experienced by Greater Than or Equal to 1.0% of Adult and Adolescent Patients in the Albuterol sulfate MDPI Group and Greater Than Placebo in three 12-Week Clinical Trials[1]

Preferred Term	Number (%) of patients	
	Albuterol sulfate MDPI 180 mcg QID N=321	Placebo N=333
Back pain	6 (2%)	4 (1%)
Pain	5 (2%)	2 (<1%)
Gastroenteritis viral	4 (1%)	3 (<1%)
Sinus headache	4 (1%)	3 (<1%)
Urinary tract infection	4 (1%)	3 (<1%)

1. This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of greater than or equal to 1.0% in the albuterol sulfate MDPI group and greater than placebo.

In a long-term study of 168 patients treated with albuterol sulfate MDPI for up to 52 weeks (including a 12-week double-blind period), the most commonly reported adverse events greater than or equal to 5% were upper respiratory infection, nasopharyngitis, sinusitis, bronchitis, cough, oropharyngeal pain, headache, and pyrexia.

In a small cumulative dose study, tremor, palpitations, and headache were the most frequently occurring (≥5%) adverse events.

Pediatric Patients 4 to 11 Years of Age: The adverse reaction information presented in Table 2 below concerning albuterol sulfate MDPI is derived from a 3-week pediatric clinical trial which compared albuterol sulfate MDPI 180 mcg four times daily with a double-blinded matched placebo in 185 asthmatic patients 4 to 11 years of age.

Table 2: Adverse Reactions Experienced by Greater Than or Equal to 2.0% of Patients 4 to 11 Years of Age in the Albuterol sulfate MDPI Group and Greater Than Placebo in the 3 Week Trial

Preferred Term	Number (%) of patients	
	Albuterol sulfate MDPI 180 mcg QID N=93	Placebo N=92
Nasopharyngitis	2 (2%)	1 (1%)
Oropharyngeal pain	2 (2%)	1 (1%)
Vomiting	3 (3%)	1 (1%)

6.2 Postmarketing Experience

In addition to the adverse reactions reported from clinical trials with albuterol sulfate MDPI, the following adverse events have been reported during use of other inhaled albuterol sulfate products: Urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), rare cases of aggravated bronchospasm, lack of efficacy, asthma exacerbation (potentially fatal), muscle cramps, and various oropharyngeal side-effects such as throat irritation, altered taste, glossitis, tongue ulceration, and gagging. 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.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as: angina, hypertension or hypotension, palpitations, central nervous system stimulation, insomnia, headache, nervousness, tremor, muscle cramps, drying or irritation of the oropharynx, hypokalemia, hyperglycemia, and metabolic acidosis.

7 DRUG INTERACTIONS

Other short-acting sympathomimetic bronchodilators should not be used concomitantly with ProAir Digihaler. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

7.1 Beta-Blockers

Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as ProAir Digihaler, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic-blocking agents in patients with asthma. In this setting, consider cardioselective beta-blockers, although they should be administered with caution.

7.2 Diuretics

The ECG changes and/or hypokalemia which may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics. Consider monitoring potassium levels.

7.3 Digoxin

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and ProAir Digihaler.

7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

ProAir Digihaler should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of use of albuterol during pregnancy. Available data from published epidemiological studies and postmarketing case reports of pregnancy outcomes following inhaled albuterol use do not consistently demonstrate a risk of major birth defects or miscarriage. There are clinical considerations with use of albuterol in pregnant women *[see Clinical Considerations]*. In animal reproduction studies, when albuterol sulfate was administered subcutaneously to pregnant mice there was evidence of cleft palate at less than and up to 9 times the maximum recommended human daily inhalation dose (MRHDID) *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are 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 preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women should be closely monitored and medication adjusted as necessary to maintain optimal control.

Labor or Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of ProAir Digihaler for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk. ProAir Digihaler has not been approved for the management of pre-term labor. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with $beta_2$-agonists, including albuterol.

Data

Animal Data

In a mouse reproduction study, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure nine-tenths the maximum recommended human dose (MRHDID) for adults (on a mg/m^2 basis at a maternal dose of 0.25 mg/kg) and in 10 of 108 (9.3%) fetuses at approximately 9 times the MRHDID (on

a mg/m^2 basis at a maternal dose of 2.5 mg/kg). Similar effects were not observed at approximately one-eleventh the MRHDID for adults (on a mg/m^2 basis at a maternal dose of 0.025 mg/kg). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol (positive control).

In a rabbit reproduction study, orally administered albuterol sulfate induced cranioschisis in 7 of 19 fetuses (37%) at approximately 750 times the MRHDID (on a mg/m^2 basis at a maternal dose of 50 mg/kg).

In a rat reproduction study, an albuterol sulfate/HFA-134a formulation administered by inhalation did not produce any teratogenic effects at exposures approximately 80 times the MRHDID (on a mg/m^2 basis at a maternal dose of 10.5 mg/kg).

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

8.2 Lactation

Risk Summary

There are no available data on the presence of albuterol in human milk, the effects on the breastfed child, or the effects on milk production. However, plasma levels of albuterol after inhaled therapeutic doses are low in humans, and if present in breast milk, albuterol has a low oral bioavailability *[see Clinical Pharmacology (12.3)]*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ProAir Digihaler and any potential adverse effects on the breastfed child from albuterol or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of ProAir Digihaler for the treatment or prevention of bronchospasm with reversible obstructive airway disease have been established in pediatric patients 12 to 17 years of age. Use of ProAir Digihaler for this indication is supported by evidence from two 12-week clinical trials in 318 patients 12 years of age and older with asthma comparing doses of 180 mcg four times daily with placebo, one long-term safety study in children 12 years of age and older, and one single-dose crossover study comparing doses of 90 and 180 mcg with albuterol sulfate inhalation aerosol (ProAir® HFA) in 71 patients *[see Clinical Studies (14.1)]*.

The safety and effectiveness of ProAir Digihaler for treatment of exercise-induced bronchospasm have been established in children 12 years of age and older. Use of ProAir Digihaler for this indication is supported from one single-dose crossover study in 38 patients age 16 and older with exercise-induced bronchospasm comparing doses of 180 mcg with placebo *[see Clinical Studies (14.2)]*. The safety profile for patients ages 12 to 17 was consistent with the overall safety profile seen in these studies.

The safety of ProAir Digihaler in children 4 to 11 years of age is based on two single-dose, controlled, crossover studies: one with 61 patients comparing doses of 90 and 180 mcg with matched placebo and albuterol HFA MDI and one with 15 patients comparing a dose of 180 mcg with matched albuterol HFA MDI; and one 3-week clinical trial in 185 patients 4 to 11 years of age with asthma comparing a dose of 180 mcg four times daily with matched albuterol HFA MDI. The effectiveness of albuterol sulfate MDPI in children 4 to 11 years with exercise-induced bronchospasm is extrapolated from clinical trials in patients 12 years of age and older with asthma and exercise-induced bronchospasm, based on data from a single-dose study comparing the bronchodilatory effect of albuterol sulfate MDPI 90 mcg and 180 mcg with placebo in 61 patients with asthma, and data from a 3-week clinical trial in 185 asthmatic children 4 to 11 years of age comparing a dose of 180 mcg albuterol 4 times daily with placebo *[see Clinical Studies (14.1)]*.

The safety and effectiveness of ProAir Digihaler in pediatric patients below the age of 4 years have not been established.

8.5 Geriatric Use

Clinical studies of albuterol sulfate MDPI did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences

in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Warnings and Precautions (5.4, 5.7)]*.

All beta$_2$-adrenergic agonists, including albuterol, are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

10 OVERDOSAGE

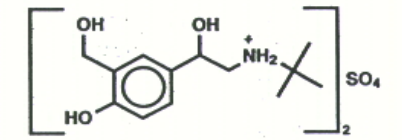
The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of ProAir Digihaler.

Treatment consists of discontinuation of ProAir Digihaler together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of ProAir Digihaler.

11 DESCRIPTION

The active ingredient of ProAir Digihaler inhalation powder is albuterol sulfate, a racemic salt of albuterol. Albuterol sulfate is a beta$_2$-adrenergic agonist. It has the chemical name α^1-[(*tert*-butylamino) methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1) (salt), and the following chemical structure:



The molecular weight of albuterol sulfate is 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$. Albuterol sulfate is a white to off-white crystalline powder. It is soluble in water and slightly soluble in ethanol. Albuterol sulfate is the official U.S. Adopted Name in the United States, and salbutamol sulfate is the recommended World Health Organization international nonproprietary name.

ProAir Digihaler is inhalation-driven, multi-dose inhalation powder (dry powder inhaler) for oral inhalation only. It contains a formulation blend of albuterol sulfate with alpha-lactose monohydrate. Each actuation provides a metered dose of 2.6 mg of the formulation containing 117 mcg of albuterol sulfate (equivalent to 97 mcg of albuterol base) and lactose from the device reservoir. Under standardized *in vitro* test conditions with fixed flow rates ranging from 58 to 71 L/min, and with a total air volume of 2 L, ProAir Digihaler inhaler delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) with lactose from the mouthpiece. The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile. In a study that investigated the peak inspiratory flow rate (PIFR) in asthma (n=27, ages 12 to 17 years old and n=50, ages 18 to 45 years old) and COPD (n=50, over 50 years old) patients, the mean PIFR achieved by subjects was >60 L/min (range = 31 to 110 L/min.), indicating that patients would be able to achieve the required inspiratory flow to operate the MDPI device correctly. The inhaler is provided for 200 actuations (inhalations).

ProAir Digihaler contains a QR code on the electronic module which is built-in to the top of the inhaler and automatically detects, records and stores data on inhaler events, including peak inspiratory flow rate (L/min). ProAir Digihaler may pair with and transmit data to the mobile App where inhaler events are categorized.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Albuterol sulfate is a beta$_2$-adrenergic agonist. The pharmacologic effects of albuterol sulfate are attributable to activation of beta$_2$-adrenergic receptors on airway smooth muscle. Activation of beta$_2$-adrenergic receptors leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3',5'-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP is associated with the activation of protein kinase A, which in turn inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Albuterol relaxes the smooth muscle of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta-receptors in the human heart, 10% to 50% of which are cardiac beta$_2$-adrenergic receptors. The precise function of these receptors has not been established *[see Warnings and Precautions (5.4)]*.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. However, inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes [*see Warnings and Precautions (5.4)]*.

12.2 Pharmacodynamics

In a pharmacodynamic (PD) trial conducted in 47 patients, the PD and safety profiles were similar for albuterol sulfate MDPI and ProAir HFA. Comparable changes from baseline in the PD measures (serum glucose and potassium concentrations, QTcB, QTcF, heart rate, systolic blood pressure, and diastolic blood pressure) were observed following cumulative dose administration up to 1440 mcg of both albuterol sulfate MDPI and ProAir HFA. The overall safety, efficacy and PD profile of albuterol sulfate MDPI and ProAir HFA were comparable.

Following 90 or 180 mcg single-dose inhalation, the bronchodilatory effect of albuterol sulfate MDPI was significantly greater than placebo and comparable to that of ProAir HFA in patients 12 years of age and older (N=71) and pediatric patients 4 to 11 years of age (N=61) with persistent asthma.

Cardiac Electrophysiology

As with other beta$_2$-adrenergic agonists, albuterol sulfate MDPI prolonged QT intervals following a 1440 mcg cumulative dose. The prolongation was comparable to that of ProAir HFA.

12.3 Pharmacokinetics

Absorption

Albuterol was rapidly absorbed into the systemic circulation with peak plasma concentrations occurring at half an hour following single- or multiple-dose oral inhalation(s) of albuterol sulfate MDPI. In a cumulative dose study, the AUC_{0-t} was comparable between albuterol sulfate MDPI group and ProAir HFA group; C_{max} value was approximately one-third higher in albuterol sulfate MDPI group than ProAir HFA group.

Distribution

The volume of distribution has not been determined for albuterol sulfate MDPI. Published literature suggests that albuterol exhibits low *in vitro* plasma protein binding (10%).

Elimination

The accumulation ratio (~1.6 fold) was observed following one week QID dosing. The corresponding effective half-life was approximately 5 hours, which was consistent with the elimination half-life following both single- or multiple-dose administration.

Metabolism
Information available in the published literature suggests that the primary enzyme responsible for the metabolism of albuterol in humans is SULTIA3 (sulfotransferase). When racemic albuterol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration-time curves between the (R)- and (S)-albuterol enantiomers, with (S)-albuterol concentrations being consistently higher. However, without charcoal pretreatment, after either oral or inhalation administration the differences were 8- to 24-fold, suggesting that the (R)-albuterol is preferentially metabolized in the gastrointestinal tract, presumably by SULTIA3.

Excretion
The primary route of elimination of albuterol is through renal excretion (80% to 100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the feces. Following intravenous administration of racemic albuterol, between 25% and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the urine.

Specific Populations

No pharmacokinetic studies for ProAir Digihaler have been conducted in neonates or elderly subjects. The systemic exposure in children 6 to 11 years of age is similar to that of adults following 180 mcg single dose inhalation of albuterol sulfate MDPI. The influence of gender or race on the pharmacokinetics of ProAir Digihaler has not been studied.

Patients with Renal Impairment: The effect of renal impairment on the pharmacokinetics of albuterol was evaluated in 5 subjects with creatinine clearance of 7 to 53 mL/min, and the results were compared with those from healthy volunteers. Renal disease had no effect on the half-life, but there was a 67% decline in albuterol clearance. Caution should be used when administering high doses of ProAir Digihaler to patients with renal impairment *[see Use in Specific Populations (8.5)]*.

Patients with Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of ProAir Digihaler has not been evaluated.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 15 times and 6 times the maximum recommended daily inhalation dose (MRHDID) for adults and children, respectively, on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1,900 times and 740 times the MRHDID for adults and children, respectively, on a mg/m^2 basis). In a 22-month study in Golden Hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 250 times and 100 times the MRHDID for adults and children, respectively, on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 380 times the MRHDID for adults on a mg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

Preclinical: Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

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 β-agonists and methylxanthines were administered concurrently. The clinical significance of these findings is unknown.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

The safety and effectiveness of ProAir Digihaler has been established in the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and in the prevention of exercise-induced bronchospasm in patients 4 years of age and older. The use of ProAir Digihaler for these indications is supported by adequate and well-controlled studies in adults and pediatric patients of albuterol sulfate inhalation powder (ProAir RespiClick hereafter referred to as albuterol sulfate MDPI) *[see Use in Specific Populations (8.4), Clinical Studies (14.2, 14.3)]*.

14.2 Bronchospasm Associated with Asthma

Adult and Adolescent Patients 12 Years of Age and Older

In two 12-week, randomized, double-blind, placebo-controlled studies of identical design (Study 1 and Study 2), albuterol sulfate MDPI (153 patients) was compared to a matched placebo dry powder inhaler (163 patients) in asthmatic patients 12 to 76 years of age at a dose of 180 mcg albuterol four times daily. Patients were maintained on inhaled corticosteroid treatment. Serial FEV_1 measurements, shown below in Figure 1 as average of the mean changes from test-day baseline at Day 1 and Day 85, demonstrated that two inhalations of albuterol sulfate MDPI produced significantly greater improvement in FEV_1 $AUC_{0\text{-}6hr}$ over the pre-treatment value than placebo in Study 1. Consistent results were observed in Study 2.

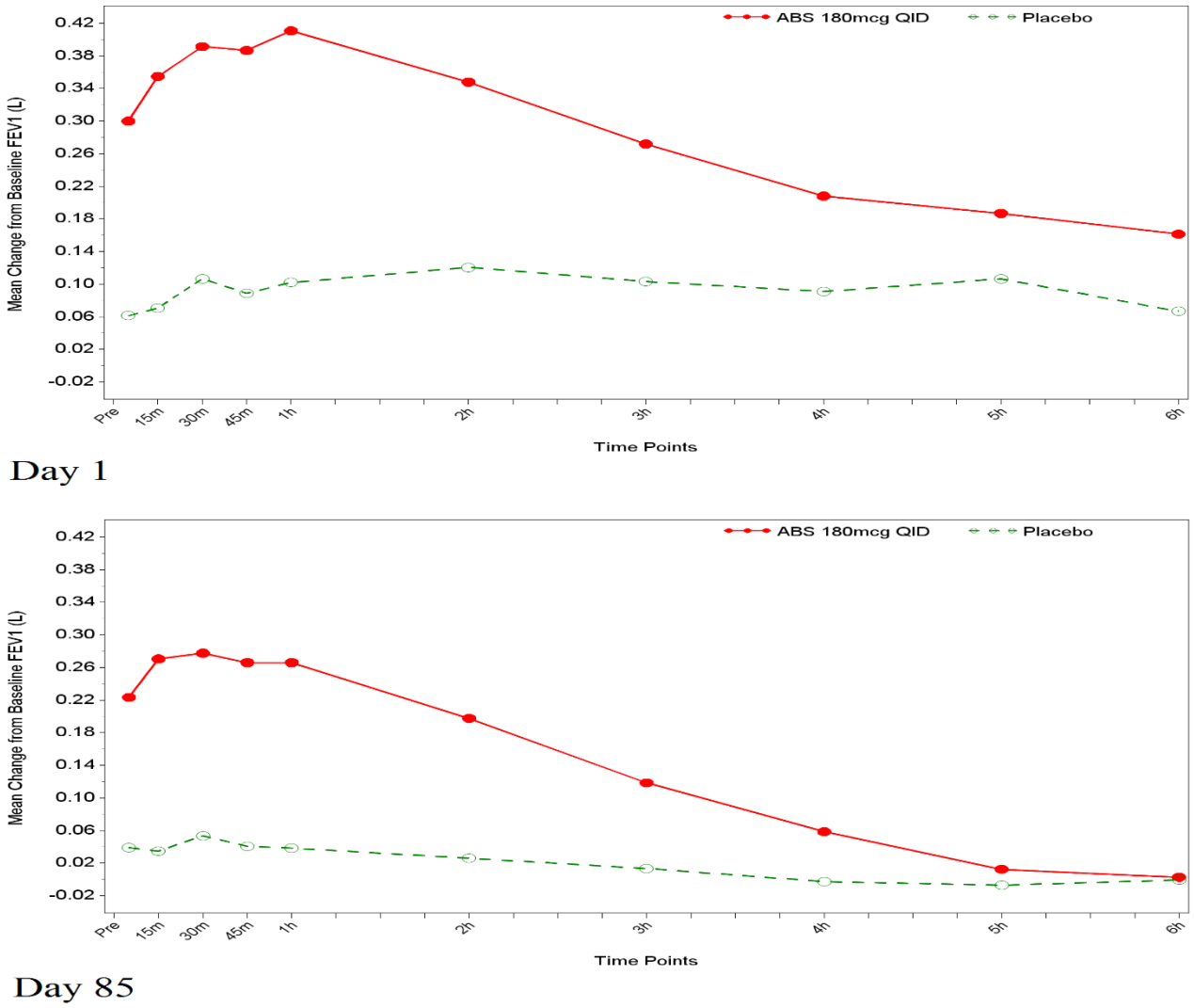


Figure 1: FEV_1 as Mean Change from Test-Day, Pre-Dose Baseline in a 12-Week Clinical Trial (Study 1)

In Study 1, 44 of 78 patients treated with albuterol sulfate MDPI achieved a 15% increase in FEV_1 within 30 minutes post-dose on Day 1. The median time to onset was 5.7 minutes, and median duration of effect as measured by a 15% increase was approximately 2 hours. Consistent results were observed in Study 2. In a double-blind, randomized, placebo–controlled, single-dose crossover study evaluating albuterol sulfate MDPI and ProAir HFA in 71 adult and adolescent subjects ages 12 and older with persistent asthma, ProAir RespiClick had bronchodilator efficacy that was significantly greater than placebo at administered doses of 90 and 180 mcg.

Pediatric Patients 4 to 11 Years of Age

In a 3-week, randomized, double-blind, placebo-controlled trial, albuterol sulfate MDPI (92 patients) was compared to a matched placebo (92 patients) in asthmatic children 4 to 11 years of age at a dose of 180 mcg albuterol four times daily. Serial FEV_1 measurements, expressed as the baseline-adjusted percent-predicted FEV_1 $AUC_{0\text{-}6h}$ over the 3-week treatment period, demonstrated that 2 inhalations of albuterol sulfate MDPI produced significantly greater improvement in FEV_1 over the pre-treatment value than the matched placebo.

In this study, 48 of 92 patients treated with albuterol sulfate MDPI achieved a 15% increase in FEV_1 within 30 minutes post-dose on Day 1. The median time to onset was 5.9 minutes, and the median duration of effect as measured by a 15% increase was approximately 1 hour.

In a placebo-controlled, single-dose, crossover study in 61 patients 4 to 11 years of age, albuterol sulfate MDPI, administered at albuterol doses of 90 and 180 mcg, was compared with a matched placebo and with albuterol HFA MDI. Albuterol sulfate MDPI provided similar bronchodilation when administered as one or two inhalations (baseline-adjusted

percent-predicted serial FEV_1 observed over 6 hours post-dose), whereas two inhalations from albuterol HFA MDI provided significantly greater bronchodilation compared to a single inhalation.

14.3 Exercise-Induced Bronchospasm

In a randomized, single-dose, crossover study in 38 adult and adolescent patients with exercise-induced bronchospasm (EIB), two inhalations of albuterol sulfate MDPI taken 30 minutes before exercise prevented EIB for the hour following exercise (defined as the maintenance of FEV_1 within 80% of post-dose, pre-exercise baseline values) in 97% (37 of 38) of patients as compared to 42% (16 of 38) of patients when they received placebo.

Patients who participated in these clinical trials were allowed to use concomitant steroid therapy.

16 HOW SUPPLIED/STORAGE AND HANDLING

ProAir Digihaler inhalation powder is supplied as a white inhaler with a red cap, in a sealed foil pouch, one pouch per carton.

Actuations	**Net Contents**	**NDC**
200	0.65 g	59310-117-20

Store at room temperature (between 15°C and 25°C; 59°F and 77°F). Avoid exposure to extreme heat, cold, or humidity.

Keep out of reach of children.

ProAir Digihaler inhaler has a dose counter. Patients should never try to alter the numbers for the dose counter. Discard the inhaler 13 months after opening the foil pouch, when the counter displays 0, 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 Dosage and Administration (2.4), Patient Counseling Information (17)]*.

ProAir Digihaler contains a QR code and a built-in electronic module which automatically detects, records, and stores data on inhaler events, including peak inspiratory flow rate (L/min). ProAir Digihaler may pair with and transmit data to the mobile App via Bluetooth® wireless technology where inhaler events are categorized.

ProAir Digihaler contains a lithium-manganese dioxide battery and should be disposed of in accordance with state and local regulations.

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:

Frequency of Use

The action of ProAir Digihaler should last for 4 to 6 hours. Instruct patients to not use ProAir Digihaler more frequently than recommended. Instruct patients to not increase the dose or frequency of doses of ProAir Digihaler without consulting the physician. If patients find that treatment with ProAir Digihaler becomes less effective for symptomatic relief, symptoms become worse, and/or they need to use the product more frequently than usual, they should seek medical attention immediately *[see Warnings and Precautions (5.2)]*.

Use of ProAir Digihaler Electronic Module and Mobile App

Direct the patient to the Instructions for Use (IFU) on how to download the App and use the inhaler. Advise the patient that pairing of the inhaler to the App, having Bluetooth turned on, or being near their smartphone is not required for delivery of the medication from the inhaler or for normal use of the product *[see Dosage and Administration (2.5)]*.

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.

Routine maintenance is not required. If the mouthpiece needs cleaning, instruct patients to 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 ProAir Digihaler has a dose counter. When the patient receives the inhaler, the number 200 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., 200, 198, 196, 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 ProAir Digihaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first *[see Dosage and Administration (2.3), (2.4)]*.

Paradoxical Bronchospasm

Inform patients that ProAir Digihaler can produce paradoxical bronchospasm. Instruct patients to discontinue ProAir Digihaler if paradoxical bronchospasm occurs *[see Warnings and Precautions (5.1)]*.

Concomitant Drug Use

Inform patients that, while they are taking ProAir Digihaler, they should take other inhaled drugs and asthma medications only as directed by a physician *[see Drug Interactions (7)]*.

Common Adverse Events

Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, and nervousness.

Pregnancy

Inform patients who are pregnant or nursing that they should contact their physician about the use of ProAir Digihaler *[see Use in Specific Populations (8.1)]*.

General Information on Use

Effective and safe use of ProAir Digihaler includes an understanding of the way that it should be administered. Do not use a spacer or volume holding chamber with ProAir Digihaler. Patients should be instructed on the proper use of the inhaler. See the FDA-approved Patient Information and Patient Instructions for Use. Discard ProAir Digihaler 13 months after opening the foil pouch, when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

In general, the technique for administering ProAir Digihaler to children is similar to that for adults. Children should use ProAir Digihaler under adult supervision, as instructed by the patient's physician.

Distributed by:

Teva Pharmaceuticals USA, Inc.

Parsippany, NJ 07054

United States Patent Nos. 6701917, 6718972, 6748947, 6871646, 7540282, 8006690, 8651103, 8978966, 9216260, 9463288, 9731087, 9782550, 9782551, 10022510, 10124131

PRORDH-002

Rev. 09/2020

PATIENT INFORMATION
ProAir® Digihaler® (prō´ār di´ji haye´´ ler)
(albuterol sulfate)
inhalation powder

What is ProAir Digihaler?
ProAir Digihaler is a prescription medicine used in people 4 years of age and older to:
- treat or prevent bronchospasm in people who have reversible obstructive airway disease
- prevent exercise-induced bronchospasm

ProAir Digihaler contains a built-in electronic module that records and stores information about inhaler events. The ProAir Digihaler may be used with, and transmits information to, an App through Bluetooth® wireless technology.
ProAir Digihaler does not need to be connected to the App in order for you to take your medicine. The electronic module does not control or interfere with delivery of the medicine through the inhaler.

It is not known if ProAir Digihaler is safe and effective in children under 4 years of age.

Do not use ProAir Digihaler if you are allergic to albuterol sulfate, lactose, milk proteins, or any of the ingredients in ProAir Digihaler. See the end of this leaflet for a complete list of ingredients in ProAir Digihaler.

Before using ProAir Digihaler, tell your doctor about all of your medical conditions, including if you:
- have heart problems
- have high blood pressure (hypertension)
- have convulsions (seizures)
- have thyroid problems
- have diabetes
- have low potassium levels in your blood
- are pregnant or plan to become pregnant. It is not known if ProAir Digihaler will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if ProAir Digihaler passes into your breast milk. Talk to your doctor about the best way to feed your baby if you are using ProAir Digihaler.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
ProAir Digihaler and other medicines may affect each other and cause side effects. ProAir Digihaler may affect the way other medicines work, and other medicines may affect the way ProAir Digihaler works.

Especially tell your doctor if you take:
- other inhaled medicines or asthma medicines
- beta blocker medicines
- diuretics
- digoxin
- monoamine oxidase inhibitors
- tricyclic antidepressants

Ask your doctor or pharmacist for a list of these medicines if you are not sure.
Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use ProAir Digihaler?
- For detailed instructions on how to use the inhaler, see **"Instructions for Use"** at the end of this Patient Information.
- For detailed instructions on how to set up the App, go to www.ProAirDigihaler.com or call Teva at 1-888-603-0788.
- Connection to the App, having your Bluetooth turned on, or being near your smartphone is not required for your ProAir Digihaler to work and for you to get your medicine.
- The electronic module does not control or interfere with delivery of the medicine through the inhaler.
- Use ProAir Digihaler exactly as your doctor tells you to use it.
- If your child needs to use ProAir Digihaler, watch your child closely to make sure your child uses the inhaler correctly. Your doctor will show you how your child should use ProAir Digihaler.
- Each dose of ProAir Digihaler should last up to 4 hours to 6 hours.
- **Do not** increase your dose or take extra doses of ProAir Digihaler without first talking to your doctor.
- Do not use a spacer or volume holding chamber with ProAir Digihaler.
- ProAir Digihaler does not need priming.
- Get medical help right away if ProAir Digihaler no longer helps your symptoms.
- Get medical help right away if your symptoms get worse or if you need to use your inhaler more often.
- While you are using ProAir Digihaler, **do not** use other inhaled rescue medicines and asthma medicines unless your doctor tells you to do so.

Call your doctor if your asthma symptoms, like wheezing and trouble breathing, become worse over a few hours or days. Your doctor may need to give you another medicine (for example, corticosteroids) to treat your symptoms.

What are the possible side effects of ProAir Digihaler?
ProAir Digihaler may cause serious side effects, including:

- **worsening trouble breathing, coughing and wheezing (paradoxical bronchospasm).** If this happens stop using ProAir Digihaler and call your doctor or get emergency help right away.
- **heart problems, including faster heart rate and higher blood pressure**
- **possible death in people with asthma who use too much ProAir Digihaler**
- **allergic reactions.** Call your doctor right away if you have the following symptoms of an allergic reaction:
  - itchy skin
  - swelling beneath your skin or in your throat
  - rash
  - worsening trouble breathing
- **worsening of other medical problems in people who also use ProAir Digihaler including increases in blood sugar**
- **low potassium levels in your blood**

The most common side effects of ProAir Digihaler include:

- back pain
- pain
- upset stomach
- sinus headache
- urinary tract infection
- your heart feels like it is pounding or racing (palpitations)
- chest pain
- fast heart rate
- shakiness
- nervousness
- headache
- dizziness
- sore throat
- runny nose
- vomiting

These are not all of the possible side effects of ProAir Digihaler.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ProAir Digihaler?

- Store ProAir Digihaler at room temperature between 59ºF and 77ºF (15ºC and 25ºC).
- Avoid exposure to extreme heat, cold, or humidity.
- Keep the cap on the inhaler closed during storage.
- Keep your ProAir Digihaler inhaler dry and clean at all times.
- **Do not wash or put any part of your ProAir Digihaler inhaler in water.** Replace your inhaler if washed or placed in water.

Keep ProAir Digihaler and all medicines out of the reach of children.

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

What are the ingredients in ProAir Digihaler?
Active ingredient: albuterol sulfate
Inactive ingredients: lactose (may contain milk proteins)
For more information about ProAir Digihaler, call 1-888-603-0788, or go to www.ProAirDigihaler.com
The Bluetooth® word mark and logos are registered trademarks owned by the Bluetooth SIG, Inc. and any use of such marks by Teva Respiratory, LLC is under license.

Distributed by:
Teva Pharmaceuticals USA, Inc.
Parsippany, NJ 07054

PRODHPL-002
This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 09/2020

Instructions for Use
ProAir® Digihaler® (prō´ār di´ji haye´´ler)
(albuterol sulfate)
inhalation powder

Your ProAir Digihaler Inhaler

When you are ready to use ProAir Digihaler for the first time, remove the ProAir Digihaler inhaler from the foil pouch.

There are 3 main parts of your ProAir Digihaler inhaler including:

- the white inhaler with the mouthpiece. **See Figure A.**
- the red cap that covers the mouthpiece and vent of the inhaler. **See Figure A.**
- the electronic module. **See Figure A.**

There is an electronic module built into the top of the inhaler that records and stores information about inhaler events. The electronic module sends information through Bluetooth® wireless technology to a mobile application (App). The electronic module does not control or interfere with delivery of the medicine through the inhaler.

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.**

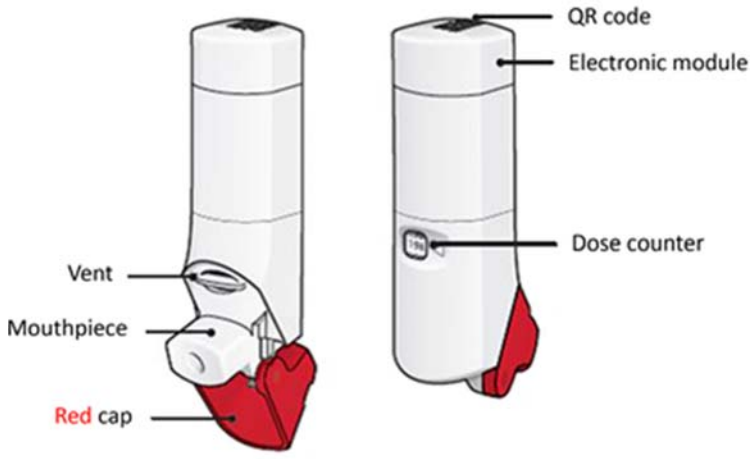


Figure A

- Your ProAir Digihaler inhaler contains 200 doses (inhalations). **See Figure B.**
- The dose counter shows the number of doses left in your inhaler.
- When there are 20 doses left, the dose counter will change to red and you should refill your prescription or ask your doctor 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 fully. If you do not hear the “click” sound the inhaler may not be activated to give you a dose of medicine.
- **ProAir Digihaler does not have an activation button or medicine canister.** When you open the cap, a dose of ProAir Digihaler will be activated for delivery of the medicine.
- **ProAir Digihaler does not need to be wirelessly connected to the mobile application (App) in order for it to work and for you to take your medicine.**
- In general, the technique for administering ProAir Digihaler to children is similar to that for adults. Children should use ProAir Digihaler under adult supervision, as instructed by the patient’s physician.
- Do not use a spacer or volume holding chamber with ProAir Digihaler. ProAir Digihaler does not need priming.

Using your ProAir Digihaler inhaler:

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

Step 1. Open

- Hold the inhaler upright and open the red cap fully until you feel and hear a “click”. **See Figure C**.
- Each time you open the red cap and it “clicks”, a dose of ProAir Digihaler is ready to be inhaled.

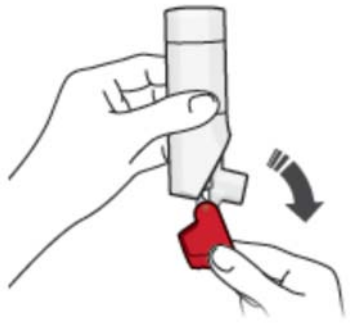


Figure C

Remember:

- For the correct use of ProAir Digihaler, **hold the inhaler upright** as you open the red cap. **See Figure D.**
- **Do not** hold the inhaler in any other way as you open the red cap.
- **Do not** open the red cap until you are ready to take a dose of ProAir Digihaler.

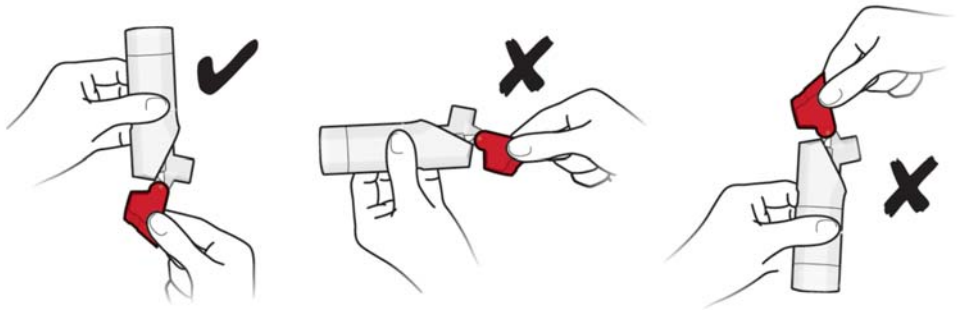


Figure D

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.**

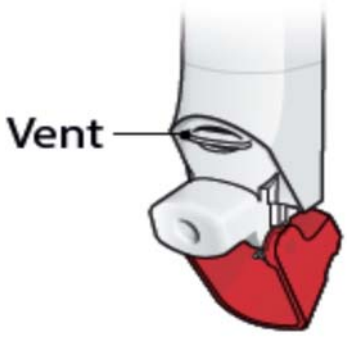


Figure G

- **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 ProAir Digihaler 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

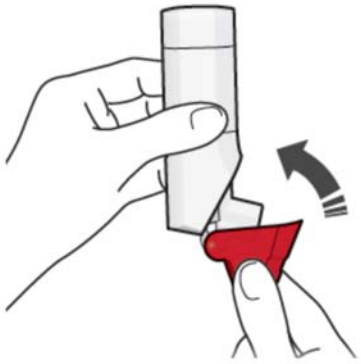


Figure H

- Close the red cap firmly over the mouthpiece. **See Figure H.**
- Make sure you close the red cap after each inhalation so that the inhaler will be ready for your next dose.
- **If you need another dose,** close the red cap and then repeat steps 1-3.

Storing your ProAir Digihaler inhaler

- Store ProAir Digihaler at room temperature between 59ºF and 77ºF (15ºC and 25ºC).
- Avoid exposure to extreme heat, cold, or humidity.
- Keep the red cap on the inhaler closed during storage.
- Keep your ProAir Digihaler inhaler dry and clean at all times.
- **Do not wash or put any part of your ProAir Digihaler inhaler in water.** Replace your inhaler if washed or placed in water.
- **Keep your ProAir Digihaler inhaler and all medicines out of the reach of children.**

Cleaning your ProAir Digihaler inhaler

- **Do not wash or put any part of your ProAir Digihaler inhaler in water.** Replace your inhaler if washed or placed in water.
- ProAir Digihaler contains a powder and must be kept clean and dry at all times.
- If the mouthpiece needs cleaning, gently wipe it with a dry cloth or tissue.

Replacing your ProAir Digihaler inhaler

- The dose counter on the back of your inhaler shows how many doses you have left. **Do not** try to change the numbers for the dose counter.
- When there are 20 doses left, the dose counter color will change to red and you should refill your prescription or ask your doctor for another prescription.
- When the dose counter displays ‘0’ your ProAir Digihaler inhaler is empty and you should stop using the inhaler and throw it away.
- Throw away your ProAir Digihaler inhaler 13 months after removing it from the foil pouch for the first time, when the dose counter displays ‘0’, or after the expiration date on the package, whichever comes first.
- ProAir Digihaler contains a lithium – manganese dioxide battery and should be thrown away (disposed of) in accordance with state and local regulations.

Important information

- Do not open the red 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 ProAir Digihaler inhaler contains dry powder so it is important that you do not blow or breathe into it.
- **Do not** take the inhaler apart.

Support

- For instructions on setting up the App, go to www.ProAirDigihaler.com or call Teva at 1-888-603-0788.
- If you have any questions about ProAir Digihaler, how to use your inhaler, go to www.ProAirDigihaler.com or call 1-888-603-0788.

This device complies with part 15 of the FCC Rules. Operation is subject to the following two conditions:
(1) This device may not cause harmful interference, and
(2) This device must accept any interference received, including interference that may cause undesired operation. Changes or modifications not expressly approved by Teva could void the user’s authority to operate the equipment.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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