PROAIR RESPICLICK (albuterol sulfate) inhalation powder is indicated for:

- Prevention of exercise-induced bronchospasm in patients 4 years of age and older.
- Treatment or prevention of bronchospasm in patients 4 years of age and older.

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. In some patients, 1 inhalation every 4 hours may be sufficient.
- Prevention of exercise-induced bronchospasm in patients 4 years of age and older: 2 inhalations every 4 to 6 hours. In some patients, 1 inhalation every 4 hours may be sufficient.

Dosage Forms and Strengths

Inhalation powder: PROAIR RESPICLICK is a dry powder inhaler that meters 117 mcg of albuterol sulfate from the device reservoir and 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.

### 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)

### 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 MAOIs or tricyclic antidepressants. (7.4)

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

Revised: 09/2016

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

For prevention of exercise-induced bronchospasm, the recommended dosage for adults and children 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise.

For treatment of acute episodes of bronchospasm or prevention of symptoms associated with bronchospasm, the recommended dosage for adults and children 4 years of age or older is 2 inhalations repeated every 4 to 6 hours. More frequent administration or a larger number of inhalations is not recommended. In some patients, 1 inhalation every 4 hours may be sufficient.

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.
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: PROAIR RESPICLICK is a multi-dose breath-actuated dry powder inhaler that meters 117 mcg of albuterol sulfate (equivalent to 97 mcg of albuterol base) from the device reservoir and delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouthpiece upon actuation. Each inhaler is supplied for 200 inhalation doses. PROAIR RESPICLICK inhalation powder is supplied as a white dry powder inhaler with a red cap in a sealed foil pouch.

4 CONTRAINDICATIONS
Use of 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 anaphylaxis, 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 responds 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, eg, 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 Immediate Hypersensitivity Reactions
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, 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. Severe clinical 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 shifting, 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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PROAIR RESPICLICK 180 mcg QID</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td></td>
<td>N=321</td>
</tr>
<tr>
<td>Back pain</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Pain</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Gastroenteritis viral</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Sinus headache</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 (1%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PROAIR RESPICLICK 180 mcg QID</td>
</tr>
<tr>
<td></td>
<td>N=93</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Vomitting</td>
<td>3 (3%)</td>
</tr>
</tbody>
</table>

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 agranulocytosis, 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 relation 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, and 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.
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 in children 12 years of age and older is based on 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 with matched placebo 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 in the elderly 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-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, such as 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 diazysos is beneficial for overdosage of PROAIR RESPICLICK.

DESCRIPTION

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

The molecular weight of albuterol sulfate is 576.7, and the empirical formula is \((C_{22}H_{26}N_2O_5\)\(\cdot\)H\(\cdot\)SO\(\cdot\)4\(\cdot\)H\(\cdot\)SO\)\(\cdot\)4\(\cdot\)H\(\cdot\)SO\). Albuterol sulfate is a white to off-white crystalline powder. It is soluble in water and slightly soluble in ethanol, practically insoluble in ether. 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 lactose as a diluent and bronchodilator. Each actuation provides a 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) as measured by 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 in children 12 to 17 years of age and older with reversible obstructive airway disease is based on two 12-week clinical trials in 318 patients 12 years old and 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)].
PROAIR RESPICLICK (albuterol sulfate) inhalation powder

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 adenyl cyclase 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 airways irrespective of the nature of the mediator 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 isopropenol at comparable doses while producing fewer cardiovascular effects. However, inhaled albuterol, like other beta-2-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 for both treatment groups. Comparable changes from baseline were also observed for serum glucose and potassium concentrations, QTcB, QTcF, heart rate, systolic blood pressure, and diastolic blood pressure.

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 area under the curve (AUC0-∞) was comparable between PROAIR RESPICLICK group and ProAir HFA group; Cmax 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 SULT1A3 (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 SULT1A3.

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

Age: 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.

Sex: The influence of sex on the pharmacokinetics of PROAIR RESPICLICK has not been studied.

Race: The influence of race on the pharmacokinetics of PROAIR RESPICLICK has not been studied.

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/m2 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/m2 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/m2 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/m2 basis).

13.2 Animal Toxicology and/or Pharmacology

Preclinical: In 3 laboratory animals (minipigs, rodents, and dogs) the influence of race on the pharmacokinetics of PROAIR RESPICLICK has not been studied. 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/m2 basis).

14 CLINICAL STUDIES

14.1 Bronchospasm Associated with Asthma

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 FEV1, 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 FEV1, AUCh(4) over the pre-treatment value than placebo in Study 1. Consistent results were observed in Study 2.
PROAIR RESPICLICK (albuterol sulfate) inhalation powder

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.

Paradoxical Bronchospasm

Inform patients that PROAIR RESPICLICK can produce paradoxical bronchospasm. Instruct patients to discontinue PROAIR RESPICLICK if paradoxical bronchospasm occurs.

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.

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.

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.

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Horsham, PA 19044
Manufactured by:
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United States Patent Nos. 6748947, 6871646, 6446627, 7540282, 8006690, 6701917, 6718972, 8651103, 8978966, 9216260

PATIENT INFORMATION

PROAIR RESPICLICK (prō’är 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.

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Who should not use PROAIR RESPICLICK?
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.

What should I tell my doctor before using PROAIR RESPICLICK?
Before you use PROAIR RESPICLICK, tell your doctor 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
• have any other medical conditions
• 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
  • digoxin
  • beta blocker medicines
  • diuretics
  • 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, 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. Paradoxical bronchospasm is more likely to happen with your first use of a new asthma inhalation medicine.

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

The most common side effects of PROAIR RESPICLICK include:
• back pain
• body aches and pain
• chest pain
• fast heart rate
• shakiness
• nervousness
• headache
• dizziness
• sore throat
• runny nose

Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all of the possible side effects of PROAIR RESPICLICK.
For more information, ask your doctor or pharmacist.
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 59°F and 77°F (15°C and 25°C).
• 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.

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.
This Patient Information leaflet summarizes the most important information about PROAIR RESPICLICK. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about PROAIR RESPICLICK that is 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)

Marketed by:
Teva Respiratory, LLC
Horsham, PA 19044
Manufactured by:
Teva Pharmaceutical Industries, Ltd.
Jerusalem, Israel

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PRORPL-003   Rev. 09/16
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.

- 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.

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.

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.

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.

Using your PROAIR RESPICLICK inhaler:

Important: Make sure the red cap is closed before you start using your inhaler.
Do not block the vent above the mouthpiece with your lips or fingers. See Figure G.

Breathe in quickly and deeply through your mouth, to deliver the dose of medicine to your lungs.

Remove the inhaler from your mouth.

Hold your breath for about 10 seconds or for as long as you comfortably can.

Your 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

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.

How should I store PROAIR RESPICLICK?

- Store PROAIR RESPICLICK at room temperature between 59°F and 77°F (15°C and 25°C).
- 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.
- 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.
- 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.