PROAIR RESPICLICK inhalation powder is a beta2-adrenergic agonist indicated for:

1.1 Bronchospasm
- Treatment or prevention of bronchospasm in adults and children 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)

1.2 Exercise-Induced Bronchospasm
- Treatment or prevention of exercise-induced bronchospasm in adults and children 4 years of age and older. (1.2)
- Prevention of exercise-induced bronchospasm in patients 4 years of age and older. (1.2)

**Dosage and Administration**

For oral inhalation only, treatment 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. (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. (2.2)

**DOSAGE AND ADMINISTRATION**

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: PROAIR RESPICLICK is a 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 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)

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PROAIR RESPICLICK (albuterol sulfate) inhalation powder

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 mouth piece per 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 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 Paroxysmal Bronchospasm

PROAIR RESPICLICK can produce paroxysmal bronchospasm that may be life threatening. If paroxysmal 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, to the therapeutic regimen.

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 or dose modified. 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, bronchoospasm, 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 concomitant disorders, hypothyroidism, 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:

- Paroxysmal 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.

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, bronchoconstriction, 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.

6.3 Drug Interactions

PROAIR RESPICLICK should be used cautiously in patients with hypertension. 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.

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 do not block the pulmonary effect of beta-agonists, such as PROAIR RESPICLICK, but may produce severe bronchoconstriction 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.

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>PROAIR RESPICLICK 180 mcg QID</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=321</td>
<td>N=333</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, sinuses, 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>PROAIR RESPICLICK 180 mcg QID</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=93</td>
<td>N=92</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Vomiting</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, bronchoconstriction, anaphylaxis, and oropharyngeal edema. 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.
PROAIR RESPICLICK (albuterol sulfate) inhalation powder

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 therapeutic benefits of maintaining 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 (MRHID) [see Data]. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryonic Risk
In women with poorly 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 preterm labor. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with beta-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-times the maximum recommended human dose (MRHID) for adults (on a mg/m² basis at a maternal dose of 0.25 mg/kg) and in 10 of 108 (9.3%) fetuses at approximately 9 times the MRHID (on a mg/m² basis at a maternal dose of 2.5 mg/kg). Similar effects were not observed at approximately one-eleventh the MRHID for adults (on a mg/m² 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 MRHID for adults (on a mg/m² 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 MRHID (on a mg/m² 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 breastfed infants. 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 in children 12 years of age and older with reversible obstructive airway disease is based on 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 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 bronchoconstriction 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 103 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)].

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 bronchoconstriction. 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 beta₂-adrenergic agonist. It has the chemical name \( \text{C}_{13}\text{H}_{21}\text{NO}_{3}\cdot\text{H}_2\text{SO}_4 \) and the empirical formula is \( \text{C}_{13}\text{H}_{21}\text{NO}_{3}\cdot\text{H}_2\text{SO}_4 \), Belbuterol 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 90 mcg of albuterol sulfate (equivalent to 70 mcg of albuterol) in one inhalation. The theoretical amount of drug inhaled per actuation is 25 mcg (90 mcg of albuterol sulfate per 300 mcg of metered dose).

The molecular weight of albuterol sulfate is 578.7. and the empirical formula is \( \text{C}_{13}\text{H}_{21}\text{NO}_{3}\cdot\text{H}_2\text{SO}_4 \). Belbuterol 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) in one inhalation. The theoretical amount of drug inhaled per actuation is 25 mcg (90 mcg of albuterol sulfate equivalent to 70 mcg of albuterol) in one inhalation. 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 MDI device correctly. The inhaler is provided for 200 actuations (inhalations).

12  CLINICAL PHARMACOLOGY

12.1  Mechanism of Action
Albuterol sulfate is a beta₂-adrenergic agonist. The pharmacologic effects of albuterol sulfate are attributable to activation of beta₂-adrenergic receptors on airway smooth muscle. Activation of beta₂-adrenergic receptors leads to the activation of adenylate- clase 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
PROAIR RESPICLICK (albuterol sulfate) inhalation powder

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,-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,-adrenergic receptors. The precise function of these receptors has not been established [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,-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 AUC0-t was comparable between PROAIR RESPICLICK 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 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 which 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.

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)].

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).
In Study 1, 44 of 78 patients treated with PROAIR RESPICLICK achieved a 15% increase in FEV1, 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 FEV1 measurements, expressed as the baseline-adjusted percent-predicted FEV1, AUC over the 3-week treatment period, demonstrated that 2 inhalations of PROAIR RESPICLICK produced significantly greater improvement in FEV1 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 FEV1, 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 FEV1, 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 FEV1 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 oral bronchodilator therapy. 16 HOW SUPPLIED/STORAGE AND HANDLING

PROAIR RESPICLICK inhalation powder is supplied as a white dry powder inhaler with a red cap sealed in a foil pouch in boxes of one. Each inhaler contains 0.65g of the formulation and provides 200 actuations (NDC 59310-580-20). Store at room temperature (between 15° and 25°C; 59° 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 dose counter displays 0 or after the expiration date on the product, whichever comes first. 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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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 PROAIR RESPICLICK in an air-containing 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.
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

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
Instructions for Use

PROAIR RESPICLICK (prô’ər 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.

Figure A

Inhaler Full
200 Doses

Inhaler Empty
0 Doses

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.

IMPORTANT:

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

Figure C

Figure D

Figure E

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.

Steps 1-3

- 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.