INDICATIONS AND USAGE

ProAir Digihaler is a drug product containing a beta-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. 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)
- ProAir Digihaler does not require priming. (2.3)
- Do not use with a spacer or volume holding chamber. (2.3)
- ProAir Digihaler does not require priming. (2.3)

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 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)

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)

CONTRAINdications

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

PATIENT COUNSELING INFORMATION

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

Revised: 12/2018
**PROAIR® DIGIHALER™ (albuterol sulfate) inhalation powder**

**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

**1.1 Bronchospasm**

ProAir® Digihaler™ inhalation powder 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 Bronchospasm**

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.

**2.2 Exercise-Induced Bronchospasm**

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

**2.3 Administration Information**

Administer ProAir Digihaler by oral inhalation only.

*Priming:* ProAir Digihaler inhaler does not require priming.

*Cleaning:* Do not use ProAir Digihaler with a spacer or volume holding chamber.

*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 every time the inhaler is actuated. When the dose counter reaches 0, the number 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)].

**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:** ProAir Digihaler 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 Digihaler inhalation powder is supplied as a white dry powder inhaler with a red cap in a sealed foil pouch. ProAir Digihaler includes a built-in electronic module [*see How Supplied/Storage and Handling (16)].

**4 CONTRAINDICATIONS**

Use of 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, 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 involving urticaria, 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 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 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, may 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 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 Digihaler contains small amounts of lactose, which may contain trace levels of milk proteins. Hypersensitivity reactions involving urticaria, 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 patients with ischemic heart disease 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 ketoadiposis.

**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 Respiscick 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**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Nebulized Albuterol MDPI 180 mcg QID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain</td>
<td>6 (2%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Pain</td>
<td>5 (2%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Gastroenteritis viral</td>
<td>4 (1%)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>Sinus headache</td>
<td>4 (1%)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 (1%)</td>
<td>3 (&lt;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 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, asthmas, 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 1.0% of Pediatric Patients in the Albuterol sulfate MDPI Group and Greater Than Placebo in a 3-Week Pediatric Clinical Trial**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Nebulized Albuterol MDPI 180 mcg QID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain</td>
<td>8 (4%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Sinus headache</td>
<td>4 (2%)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4 (2%)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (2%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (2%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (2%)</td>
<td>2 (&lt;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 albuterol sulfate MDPI group and greater than placebo.
7.1 with ProAir Digihaler. If additional adrenergic drugs are to be administered by any gestational age in the neonate. Pregnant women should be closely monitored and of preeclampsia in the mother and prematurity, low birth weight, and small for Clinical Considerations

indicated population(s) are unknown. In the U.S. general population, the estimated
there was evidence of cleft palate at less than and up to 9 times the maximum studies, when albuterol sulfate was administered subcutaneously to pregnant mice of albuterol in pregnant women
a risk of major birth defects or miscarriage. There are clinical considerations with use pregnancy outcomes following inhaled albuterol use do not consistently demonstrate
available
There are no randomized clinical studies of use of albuterol during pregnancy. Available data from published epidemiological studies and postmarketing case reports of
Risk Summary
There are no available data on the presence of albuterol in human milk, the effects on 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.

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.

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. However, elderly patients generally require a smaller dose selection for an elderly patient should be cautious, usually starting at the low end of the dosage 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 OVERDOSE
The expected symptoms with overdose 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, muscle, 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 if such therapy is deemed appropriate.

There is insufficient evidence to determine if dialysis is beneficial for overdosage of ProAir Digihaler.

11 DESCRIPTION

The active ingredient of ProAir inhalation powder is albuterol, a racemic salt of albuterol. Albuterol sulfate is a beta2-adrenergic agonist. It has the chemical name 1-[[(2S,3S)-3-(butylamino) methyl] -4-hydroxy-m-xylene-α,α-diol sulfate (2:1) (salt), and the following chemical structure:

```
\[
\begin{align*}
\text{CH}_3
\end{align*}
\]
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The molecular weight of albuterol sulfate is 576.7, and the empirical formula is (C\(_9\)H\(_{13}\)NO\(_3\))\(_2\)H\(_2\)SO\(_4\). Albuterol 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 mcg 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 asthmatic patients (n=27, ages 12 to 17 years old and n=50, ages 18 to 45 years old) and COPD patients (n=30, 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 is a beta2-adrenergic agonist. The pharmacologic effects of albuterol are attributable to activation of beta2-adrenergic receptors on airway smooth muscle. Activation of beta2-adrenergic receptors leads to the activation of adenlycyclase and to an increase in the intracellular concentration of cyclic-3',5'-adenosine monophosphate (cyclic AMP). This increase in 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 beta2-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 beta2-adrenergic receptors. The precise function of these receptors has not been established.

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 beta2-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 (4.4)].

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. Comparative 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.

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 MRHIDD 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 MRHIDD 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 MRHIDD 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 (pinal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.
whereas two inhalations from albuterol HFA MDI provided significantly greater improvement in FEV1 AUC0-6hr over the pre-treatment value than placebo in Study 1. Consistent results were observed in Study 2.

In a placebo-controlled, single-dose, crossover study evaluating albuterol sulfate MDPI and ProAir HFA in 71 adult and adolescent subjects ages 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 albuterol sulfate MDPI produced significantly greater improvement in FEV1, AUCDay, over the pre-treatment value than placebo in Study 1. Consistent results were observed in Study 2.

In Study 1, 44 of 78 patients treated with albuterol sulfate MDPI 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 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 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 albuterol sulfate MDPI produced significantly greater improvement in FEV1, AUCDay, over the pre-treatment value than placebo in Study 1. Consistent results were observed in Study 2.

In this study, 48 of 92 patients treated with albuterol sulfate MDPI 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, 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 produced 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.
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.

Marketed by: Teva Respiratory, LLC
Frazier, PA 19355

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PATIENT INFORMATION

ProAir® Digihaler™ (pro-ar 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 bronchospasms 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. 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 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
- body aches and 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
What are the ingredients in ProAir Digihaler?

Active ingredient: albuterol sulfate

Inactive ingredients: lactose (may contain milk proteins)

How should I store ProAir Digihaler?

- Store ProAir Digihaler 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 Digihaler inhaler dry and clean at all times.

How do I use ProAir Digihaler?

- Each time you open the red cap and it “clicks”, a dose of ProAir Digihaler is ready to be inhaled. See Figure C.
- 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.

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.

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.

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

Figure F

• 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
• 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.

Figure H