ProAir® Digihaler™ (albuterol sulfate) Inhalation Powder 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

IMPORTANT SAFETY INFORMATION

• Do not use ProAir Digihaler (albuterol sulfate) Inhalation Powder if you are allergic to albuterol sulfate, lactose, milk proteins, or any of the ingredients in ProAir Digihaler. Ask your healthcare provider if you have any questions or are not sure

• Before using ProAir Digihaler, tell your healthcare provider 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 planning to become pregnant
  • are breastfeeding or planning to breastfeed

Discover the first digital rescue inhaler

ProAir® Digihaler™ has built-in Bluetooth® wireless technology and sensors that can track when the inhaler is used.

The sensors also measure inspiratory flow rates, which may help you understand if your technique needs improvement.

The recorded information is then sent automatically to your smartphone.

Please read the accompanying full Prescribing Information including Patient Information and additional Important Safety Information throughout
IMPORTANT SAFETY INFORMATION (continued)

- Tell your healthcare provider about all the medicines you take, especially:
  - other inhaled medicines or asthma medicines
  - beta blocker medicines
  - diuretics
  - digoxin
  - monoamine oxidase inhibitors
  - tricyclic antidepressants

- Do not increase your dose or take extra doses of ProAir Digihaler without first talking to your healthcare provider.

- Get medical help right away if ProAir Digihaler no longer helps your symptoms, your symptoms get worse or 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 healthcare provider tells you to do so.

Please read the accompanying full Prescribing Information including Patient Information and additional Important Safety Information throughout.
**Understanding your inhaler use**

The app creates reports about daily and weekly inhaler use that you can share with your doctor during a visit or by email or text.

**ProAir® Digihaler™ also has features that can:**

- Let you know if you exceed the recommended daily use of your inhaler
- Notify you when your inhalation technique may need improvement
- Show local environmental conditions, including pollen count forecast
- Allow you to record how you feel each day

**IMPORTANT SAFETY INFORMATION (continued)**

**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 healthcare provider or get emergency help right away. This 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 healthcare provider 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
- **changes in laboratory blood values (sugar, potassium)**

Please read the accompanying full Prescribing Information including Patient Information and additional Important Safety Information throughout.
Why is it important to track your rescue inhaler use?

Find out by asking your doctor these questions:

1. Why should I be aware of how often I am using my rescue inhaler?
2. What can I learn by tracking my inhaler use?
3. Would using a digital inhaler be the right choice for me?

Get started with the ProAir® Digihaler™ app

Download the app  Scan QR code  Pair up to 5 inhalers

Find more information and support at ProAirDigihaler.com

IMPORTANT SAFETY INFORMATION (continued)

• 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
  • headache
  • dizziness
  • sore throat
  • runny nose

• These are not all of the possible side effects of ProAir Digihaler. For more information, ask your healthcare provider or pharmacist

• You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088

Please read the accompanying full Prescribing Information including Patient Information and additional Important Safety Information throughout

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

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

INDICATIONS AND USAGE
ProAir Digihaler is a drug product containing a beta-2-adrenergic agonist indicated for:
• Treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease. (1.1)
• Prevention of exercise-induced bronchospasm in patients 4 years of age and older. (1.2)

DOSEAGE 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)
• 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)
• ProAir Digihaler contains a built-in electronic module which detects, records, and stores data on inhaler events for transmission to the mobile App. Use of the App is not required for administration of medication to the patient. (2.3)

DOSEAGE FORMS AND STRENGTHS
Inhalation powder: ProAir Digihaler 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. ProAir Digihaler includes a built-in electronic module. (3)

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

FULL PRESCRIBING INFORMATION: CONTENTS*
1 INDICATIONS AND USAGE
1.1 Bronchospasm
1.2 Exercise-Induced Bronchospasm
2 DOSAGE AND ADMINISTRATION
2.1 Bronchospasm
2.2 Exercise-Induced Bronchospasm
2.3 Administration Information
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Paradoxical Bronchospasm
5.2 Deterioration of Asthma
5.3 Use of Anti-Inflammatory Agents
5.4 Cardiovascular Effects
5.5 Do Not Exceed Recommended Dose
5.6 Immediate Hypersensitivity Reactions
5.7 Coexisting Conditions
5.8 Hypokalemia
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Beta-Blockers
7.2 Diuretics
7.3 Digoxin
7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Overview of Clinical Studies
14.2 Bronchospasm Associated with Asthma
14.3 Exercise-Induced Bronchospasm
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
Control asthma in many patients. Early consideration should be given to adding anti-

The use of beta-adrenergic-agonist bronchodilators alone may not be adequate to

and/or symptoms. Although such effects are uncommon after administration of

days or longer. If the patient needs more doses of ProAir Digihaler, this may be

2. Exercise-Induced Bronchospasm

For prevention of exercise-induced bronchospasm, the recommended dosage for

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 of a single 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.

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

Cleaning:

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

inhaler in water.

• Routine maintenance is not required. If the mouthpiece needs cleaning, gently

wipe the mouthpiece with a dry cloth or tissue as needed.

Dose Counter: ProAir Digihaler inhaler has a dose counter attached to the actuator.

When the patient receives the inhaler, the number 200 will be displayed. The dose

counter will count down each time the inhaler is actuated. When the dose counter

reaches 20, the color of the numbers will change to red to remind the patient to

contact their pharmacist for a refill of medication or consult their physician for a

prescription refill. When the dose counter reaches 0, the background will change to

solid red. Discard ProAir Digihaler 13 months after opening the foil pouch, when the

dose counter displays 0 or after the expiration date on the product, whichever comes

first [see Patient Counseling Information (17)].

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 anaphylaxis, angioedema, pruritus, and rash have been reported with the use

of the inhaler. Use of ProAir Digihaler is contraindicated in patients with a history of hypersensitivity

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

5.8 Hypokalemia

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

6 ADVERSE REACTIONS

Use of ProAir Digihaler may be associated with the following:

• 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 albuterol sulfate inhalation powder

(ProAir® RespirClick 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 Trials3

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol sulfate MDPI 180 mcg QID</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=321</td>
<td>N=333</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 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% and >placebo) 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.

2
7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

Evaluate the serum digoxin levels in patients who are currently receiving digoxin and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully cardioselective beta-blockers, although they should be administered with caution.

6.2 Postmarketing Experience

In addition to the adverse reactions reported from clinical trials with albuterol sulfate MDPI, the following adverse events have been reported during use of other inhaled albuterol sulfate products: Urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), rare cases of aggravated bronchospasm, lack of efficacy, asthma exacerbation (potentially fatal), muscle cramps, and various oropharyngeal side-effects such as throat irritation, altered taste, glossitis, tongue ulceration, and gagging. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

7 DRUG INTERACTIONS

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

7.1 Beta-Blockers

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

7.2 Diuretics

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

7.3 Digoxin

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

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. While 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 moderately to severely 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.

8.2 Lactation

Risk Summary

There are no available data on the presence of albuterol in human milk, the effects on the breastfed child, or the effects on milk production. However, plasma levels of albuterol after inhaled therapeutic doses are low in humans, and if present in breast milk, albuterol has a low oral bioavailability (Clinical Pharmacology [12.3]). The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ProAir Digihaler and any potential adverse effects on the breastfed child from albuterol or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of ProAir Digihaler for the treatment or prevention of bronchospasm 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 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 inhalation aerosol (ProAir HFA) in 71 patients [see Clinical Studies (14.1)]. The safety and effectiveness of ProAir Digihaler for treatment of exercise-induced bronchospasm in children 12 years of age and older is based on one single-dose crossover study comparing doses of 180 mcg with placebo [see Clinical Studies (14.2)]. The safety profile for patients ages 12 to 17 was consistent with the overall safety profile seen in these studies.

The safety of ProAir Digihaler in children 4 to 11 years of age is based on two single-dose crossover, 3-week crossover studies: one with 61 patients comparing doses of 90 and 180 mcg with matched placebo and albuterol HFA MDI and one with 15 patients comparing a dose of 180 mcg with matched albuterol HFA MDI; and one 3-week clinical trial in 185 patients 4 to 11 years of age with asthma comparing a dose of 180 mcg four times daily with matched albuterol HFA MDI. The effectiveness of albuterol sulfate MDPI in children 4 to 11 years with exercise-induced bronchospasm is extrapolated from clinical trials in patients 12 years of age and older with asthma and exercise-induced bronchospasm, based on data from a single-dose study comparing the bronchodilatory effect of albuterol sulfate MDPI 90 mcg and 180 mcg with placebo in 61 patients with asthma, and data from a 3-week clinical trial in 185 asthmatic children 4 to 11 years of age comparing a dose of 180 mcg albuterol 4 times daily with placebo [see Clinical Studies (14.1)]. The safety and effectiveness of ProAir Digihaler in pediatric patients below the age of 4 years has not been established.

8.5 Geriatric Use

Clinical studies of albuterol sulfate MDPI did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, and cardiac function, and of concomitant disease or other drug therapy [see Warnings and Precautions (5.4, 5.7)]. All beta2-adrenergic agonists, including albuterol, are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

10 OVERDOSAGE

The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia.

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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Albuterol sulfate MDPI 180 mcg QID N=93</th>
<th>Placebo N=92</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (3%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>
The molecular weight of albuterol sulfate is 576.7, and the empirical formula is (C\text{\textsubscript{9}}H\text{\textsubscript{17}}NO\text{\textsubscript{4}})\text{\textsubscript{3}}\cdot H\text{\textsubscript{2}}SO\text{\textsubscript{4}}. Albuterol sulfate is a white to off-white crystalline powder. It is soluble in water and slightly soluble in ethanol. Albuterol sulfate is the official U.S. Adopted Name in the United States, and salbutamol sulfate is the recommended World Health Organization international nonproprietary name.

**11 DESCRIPTION**

**11.1 Mechanism of Action**

Albuterol sulfate is a beta\textsubscript{2}-adrenergic agonist. The pharmacologic effects of albuterol sulfate are attributable to activation of beta\textsubscript{2}-adrenergic receptors on airway smooth muscle. Activation of beta\textsubscript{2}-adrenergic receptors leads to the activation of adenylcyclase in the cell, resulting in the increased cellular cAMP levels. cAMP increases intracellular calcium concentrations, which results in bronchodilation.

The activation of beta\textsubscript{2}-adrenergic receptors on smooth muscle cells results in the release of intracellular calcium ions, which activate the contractile machinery of the smooth muscle cells. This leads to the relaxation of the smooth muscle cells, resulting in bronchodilation.

**11.2 Pharmacodynamics**

In a pharmacodynamic (PD) trial conducted in 47 patients, the PD and safety profiles were similar for albuterol sulfate MDPI and ProAir HFA. Comparable changes were observed in the PD measures (serum glucose and potassium concentrations, QTcB, QTcF, heart rate, systolic blood pressure, and diastolic blood pressure) were observed between the two groups. In a 28-day, double-blind, placebo-controlled study, patients were randomized to receive albuterol sulfate MDPI or placebo, and the PD measures were observed over a period of 28 days.

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

Albuterol sulfate is a beta\textsubscript{2}-adrenergic agonist. The pharmacologic effects of albuterol sulfate are attributable to activation of beta\textsubscript{2}-adrenergic receptors on airway smooth muscle. Activation of beta\textsubscript{2}-adrenergic receptors leads to the activation of adenylcyclase in the cell, resulting in the increased cellular cAMP levels. cAMP increases intracellular calcium concentrations, which results in bronchodilation.

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**12.2 Pharmacodynamics**

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**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 (MRHID) for adults and children, respectively, on a mg/m\textsuperscript{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 MRHID for adults and children, respectively, on a mg/m\textsuperscript{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 MRHID for adults and children, respectively, on a mg/m\textsuperscript{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 in vitro assay using cultured human lymphocytes.

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

**13.2 Animal Toxicology and/or Pharmacology**

**Pharmacology:** 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 (pinea and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.
Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when β-agonists and methylxanthines were administered concomitantly. The clinical significance of these findings is unknown.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

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

14.2 Bronchospasm Associated with Asthma

Pediatric Patients 4 to 11 Years of Age

In two 12-week, randomized, double-blind, placebo-controlled studies of identical design (Study 1 and Study 2), albuterol sulfate MDPI (153 patients) was compared to a matched placebo dry powder inhaler (163 patients) in asthmatic patients 12 to 76 years of age at a dose of 180 mcg albuterol four times daily. Patients were maintained on inhaled corticosteroid treatment. Serial 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 over the pre-treatment value than placebo in Study 1. Consistent results were observed in Study 2.

14.3 Exercise-Induced Bronchospasm

In a randomized, single-dose, crossover study in 38 adult and adolescent patients with exercise-induced bronchospasm (EIB), two inhalations of albuterol sulfate MDPI 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 steroid therapy.

16 HOW SUPPLIED/STORAGE AND HANDLING

ProAir Digihaler (NDC 59310-117-20) 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.

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 Digihaler inhaler has a dose counter. Patients should never try to alter the numbers for the dose counter. Discard the inhaler 13 months after opening the foil pouch, when the counter displays 0, or after the expiration date on the product, whichever comes first. The labeled amount of medication in each inhalation cannot be assured after the counter displays 0, even though the inhaler is not completely empty and will continue to operate [see Patient Counseling Information (17)].

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

17 PATIENT COUNSELING INFORMATION

Advising the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use), Patients should be given the following information:

Frequency of Use

Instruct patients to 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.

Instruct patients to keep their inhaler dry and clean at all times. Never wash or put any part of the inhaler in water. Patient should replace inhaler if washed or placed in water.

Routine maintenance is not required. If the mouthpiece needs cleaning, instruct patients to gently wipe the mouthpiece with a dry cloth or tissue as needed.

Instruct patients to store the inhaler at room temperature and to avoid exposure to extreme heat, cold, or humidity.

Instruct patients to never take the inhaler apart.

Inform patients that ProAir Digihaler has a dose counter. When the patient receives the inhaler, the number 200 will be displayed. The dose counter will count down each time the mouthpiece cap is opened and closed. The dose counter window displays the number of actuations left in the inhaler in units of two (e.g., 200, 198, 196, etc.). When the counter displays 20, the color of the numbers will change to red to remind the patient to contact their pharmacist for a refill of medication or consult their physician for a prescription refill. When the dose counter reaches 0, the background will change to solid red. Inform patients to discard ProAir Digihaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

Paradoxical Bronchospasm

Inform patients that ProAir Digihaler can produce paradoxical bronchospasm. Instruct patients to discontinue ProAir Digihaler if paradoxical bronchospasm occurs.

Concomitant Drug Use

Inform patients that, while they are taking ProAir Digihaler, they should take other inhaled drugs and asthma medications only as directed by a physician.

Common Adverse Events

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

Pregnancy

Inform patients who are pregnant or nursing that they should contact their physician about the use of ProAir Digihaler.

General Information on Use

Effective and safe use of ProAir Digihaler includes an understanding of the way that it works and how to use the inhaler properly.

Instruct patients to never try to alter the numbers for the dose counter. Discard the inhaler 13 months after opening the foil pouch, when the counter displays 0, or after the expiration date on the product, whichever comes first.
PROAIR® DIGIHALER™ (albuterol sulfate) inhalation powder

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.

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United States PatentNos. 6701917, 6718972, 6748947, 6871646, 7540282, 8006690, 8651103, 8978966, 9216260, 9463288, 9731087, 9782550, 9782551, 1002510, 10124131

PATIENT INFORMATION
ProAir® Digihaler™ (prō ār di’ ji hāy ē’ ler)
(albuterol sulfate)
Inhalation Powder

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

ProAir Digihaler contains a built-in electronic module that records and stores information about inhaler events. The ProAir Digihaler may be used with, and transmits information to, an App through Bluetooth® wireless technology.

ProAir Digihaler does not need to be connected to the app in order for you to take your medicine. The electronic module does not control or interfere with delivery of the medicine through the inhaler.

It is not known if ProAir Digihaler is safe and effective in children under 4 years of age. Do not use ProAir Digihaler if you are allergic to albuterol sulfate, lactose, milk proteins, or any of the ingredients in ProAir Digihaler. See the end of this leaflet for a complete list of ingredients in ProAir Digihaler.

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

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

ProAir Digihaler and other medicines may affect each other and cause side effects. ProAir Digihaler may affect the way other medicines work, and other medicines may affect the way ProAir Digihaler works. Especially tell your doctor if you take:
• other inhaled medicines or asthma medicines
• beta blocker medicines
• diuretics
• digoxin
• monoamine oxidase inhibitors
• tricyclic antidepressants

ProAir® DIGIHALER™ (albuterol sulfate) inhalation powder

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
• headache
• dizziness
• sore throat
• runny nose

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

**How should I store ProAir Digihaler?**
• Store ProAir Digihaler at room temperature between 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.

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

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

**What are the ingredients in ProAir Digihaler?**
Active ingredient: albuterol sulfate
Inactive ingredients: lactose (may contain milk proteins)

For more information about ProAir Digihaler, call 1-888-603-0788 or go to www.ProAirDigihaler.com

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**Instructions for Use**

**ProAir® Digihaler™ (prō’är di’ji hay´e̊ ler)**
(albuterol sulfate)
inhalation powder

**Your ProAir® Digihaler Inhaler**
When you are ready to use ProAir Digihaler for the first time, remove the ProAir Digihaler inhaler from the foil pouch.
There are 3 main parts of your ProAir Digihaler inhaler including:
• the white inhaler with the mouthpiece. **See Figure A.**
• the red cap that covers the mouthpiece and vent of the inhaler. **See Figure A.**
• the electronic module. **See Figure A.**

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

There is a dose counter in the back of the inhaler with a viewing window that shows you how many doses of medicine you have left. **See Figure A.**

**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.

- 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.
- 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.

Storing your ProAir Digihaler inhaler

- 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 red cap on the inhaler closed during storage.
- Keep your ProAir Digihaler inhaler dry and clean at all times.
- Keep your ProAir Digihaler inhaler and all medicines out of the reach of children.

Cleaning your ProAir Digihaler inhaler

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

Replacing your ProAir Digihaler inhaler

- The counter on the back of your inhaler shows how many doses you have left.
- When there are 20 doses left, the dose counter color will change to red and you should refill your prescription or ask your doctor for another prescription.
- When the counter displays ‘0’ your ProAir Digihaler inhaler is empty and you should stop using the inhaler and throw it away.
- Throw away your ProAir Digihaler inhaler 13 months after removing it from the foil pouch for the first time, when the dose counter displays ‘0’, or after the expiration date on the package, whichever comes first.
- ProAir Digihaler contains a lithium – manganese dioxide battery and should be thrown away (disposed of) in accordance with state and local regulations.

Important information

- Do not open the red cap unless you are taking a dose. Repeatedly opening and closing the cap without inhaling a dose will waste the medicine and may damage your inhaler.
- Your ProAir Digihaler inhaler contains dry powder so it is important that you do not blow or breathe into it.

Support

- For instructions on setting up the App, go to www.ProAirDigihaler.com or call Teva at 1-888-603-0788.
- If you have any questions about ProAir Digihaler, how to use your inhaler, go to www.ProAirDigihaler.com or call 1-888-603-0788.
- This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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