

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 beta₂-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)
- Keep the inhaler clean and dry at all times. Routine maintenance is not required. If the mouthpiece needs cleaning, gently wipe the mouthpiece with a dry cloth or tissue as needed. Never wash or put any part of the inhaler in water. (2.3)
Discard 13 months after opening the foil pouch, when the dose counter displays 0, or after the expiration date on the product, whichever comes first. (2.3)
- ProAir Digihaler contains a built-in electronic module which detects, records, and stores data on inhaler events for transmission to the mobile App. Use of the App is not required for administration of medication to the patient. (2.3)

DOSAGE FORMS AND STRENGTHS

Inhalation powder: 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)

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

Most common adverse reactions ($\geq 1\%$ and $>$ placebo) are back pain, pain, gastroenteritis viral, sinus headache, urinary tract infection, nasopharyngitis, oropharyngeal pain and vomiting. (6.1)

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

DRUG INTERACTIONS

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

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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.

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 urticaria, angioedema, and rash have been reported after the use of albuterol sulfate. There have been reports of anaphylactic reactions in patients using inhalation therapies containing lactose [see *Warnings and Precautions (5.6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Paradoxical Bronchospasm

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

5.2 Deterioration of Asthma

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

5.3 Use of Anti-Inflammatory Agents

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

5.4 Cardiovascular Effects

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

5.5 Do Not Exceed Recommended Dose

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

5.6 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 including anaphylaxis, angioedema, pruritus, and rash have been reported with the use of therapies containing lactose (lactose is an inactive ingredient in ProAir Digihaler). The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving ProAir Digihaler.

5.7 Coexisting Conditions

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

5.8 Hypokalemia

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

6 ADVERSE REACTIONS

Use of ProAir Digihaler may be associated with the following:

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

6.1 Clinical Trials Experience

A total of 1289 subjects were treated with albuterol sulfate inhalation powder (ProAir RespiClick hereafter referred to as albuterol sulfate MDPI) during the clinical development program. The most common adverse reactions ($\geq 1\%$ 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 Trials¹

Preferred Term	Number (%) of patients	
	Albuterol sulfate MDPI 180 mcg QID N=321	Placebo N=333
Back pain	6 (2%)	4 (1%)
Pain	5 (2%)	2 (<1%)

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

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

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

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

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

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

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

6.2 Postmarketing Experience

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

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

7 DRUG INTERACTIONS

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

7.1 Beta-Blockers

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

7.2 Diuretics

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

7.3 Digoxin

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

7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

In women with poorly or moderately controlled asthma, there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women should be closely monitored and medication adjusted as necessary to maintain optimal control.

Labor or Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of ProAir Digihaler for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk. ProAir Digihaler has not been approved for the management of pre-term labor. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with beta₂-agonists, including albuterol.

Data

Animal Data

In a mouse reproduction study, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure nine-tenths the maximum recommended human dose (MRHDID) for adults (on a mg/m² basis at a maternal dose of 0.25 mg/kg) and in 10 of 108 (9.3%) fetuses at approximately 9 times the MRHDID (on a mg/m² basis at a maternal dose of 2.5 mg/kg). Similar effects were not observed at approximately one-eleventh the MRHDID for adults (on a mg/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 MRHDID (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 MRHDID (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 the breastfed child, or the effects on milk production. However, plasma levels of albuterol after inhaled therapeutic doses are low in humans, and if present in breast milk, albuterol has a low oral bioavailability [*see Clinical Pharmacology (12.3)*].

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

8.4 Pediatric Use

The safety and effectiveness of ProAir Digihaler for the treatment or prevention of bronchospasm 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 sulfate inhalation aerosol (ProAir[®] HFA) in 71 patients [see *Clinical Studies (14.1)*].

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

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

The safety and effectiveness of ProAir Digihaler in pediatric patients below the age of 4 years 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, or 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

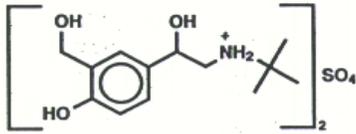
The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness,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

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

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

11 DESCRIPTION

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



The molecular weight of albuterol sulfate is 576.7, and the empirical formula is (C₁₃H₂₁NO₃)₂•H₂SO₄. Albuterol sulfate is a white to off-white crystalline powder. It is soluble in water and slightly soluble in ethanol. Albuterol sulfate is the official U.S. Adopted Name in the United States, and salbutamol sulfate is the recommended World Health Organization international nonproprietary name.

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Albuterol sulfate is a 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 adenylyl cyclase and to an increase in the intracellular concentration of cyclic-3',5'-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP is associated with the activation of protein kinase A, which in turn inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation.

Albuterol relaxes the smooth muscle of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the 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 [*see Warnings and Precautions (5.4)*].

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. However, inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in

some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes [see *Warnings and Precautions* (5.4)].

12.2 Pharmacodynamics

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

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

Cardiac Electrophysiology

As with other beta₂-adrenergic agonists, albuterol sulfate MDPI prolonged QT intervals following a 1440 mcg cumulative dose. The prolongation was comparable to that of ProAir HFA.

12.3 Pharmacokinetics

Absorption

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

Distribution

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

Elimination

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

Metabolism

Information available in the published literature suggests that the primary enzyme responsible for the metabolism of albuterol in humans is SULT1A3 (sulfotransferase). When racemic albuterol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration-time curves between the (R)- and (S)-albuterol enantiomers, with (S)-albuterol concentrations being consistently higher. However, without charcoal pretreatment, after either oral or inhalation administration the differences were 8- to 24-fold, suggesting that the (R)-albuterol is preferentially metabolized in the gastrointestinal tract, presumably by SULT1A3.

Excretion

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

Specific Populations

Age: No pharmacokinetic studies for ProAir Digihaler have been conducted in neonates or elderly subjects. The systemic exposure in children 6 to 11 years of age is similar to that of adults following 180 mcg single dose inhalation of albuterol sulfate MDPI.

Sex: The influence of sex on the pharmacokinetics of ProAir Digihaler has not been studied.

Race: The influence of race on the pharmacokinetics of ProAir Digihaler 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 Digihaler to patients with renal impairment [see *Use in Specific Populations (8.5)*].

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 15 times and 6 times the maximum recommended daily inhalation dose (MRHDID) for adults and children, respectively, on a mg/m² basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1,900 times and 740 times the MRHDID for adults and children, respectively, on a mg/m² basis). In a 22-month study in Golden Hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 250 times and 100 times the MRHDID for adults and children, respectively, on a mg/m² basis).

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

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 380 times the MRHDID for adults on a mg/m² basis).

13.2 Animal Toxicology and/or Pharmacology

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

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

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

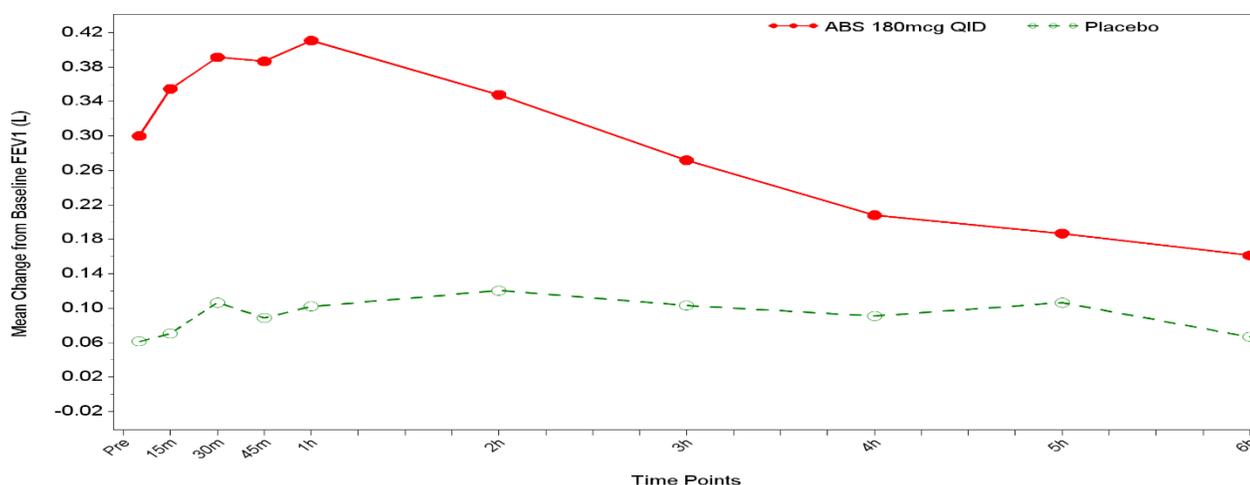
The safety and effectiveness of ProAir Digihaler has been established in the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and in the prevention of exercise-induced

bronchospasm in patients 4 years of age and older. The use of ProAir Digihaler for these indications is supported by adequate and well-controlled studies in adults and pediatric patients of albuterol sulfate inhalation powder (ProAir RespiClick hereafter referred to as albuterol sulfate MDPI) [see Use in Specific Populations (8.4), Clinical Studies (14.2, 14.3)].

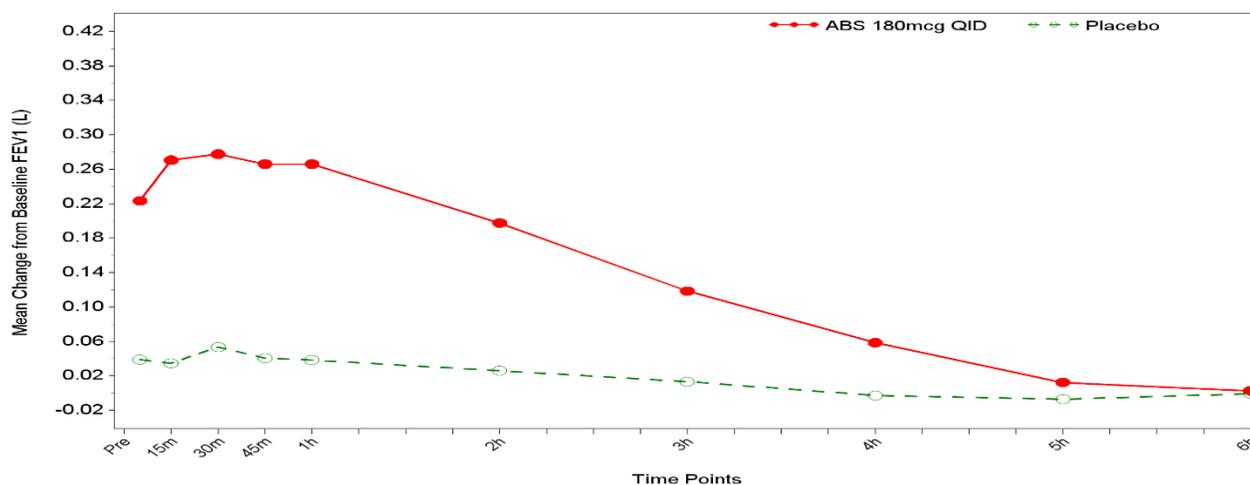
14.2 Bronchospasm Associated with Asthma

Adult and Adolescent Patients 12 Years of Age and Older

In two 12-week, randomized, double-blind, placebo-controlled studies of identical design (Study 1 and Study 2), albuterol sulfate MDPI (153 patients) was compared to a matched placebo dry powder inhaler (163 patients) in asthmatic patients 12 to 76 years of age at a dose of 180 mcg albuterol four times daily. Patients were maintained on inhaled corticosteroid treatment. Serial 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 AUC_{0-6hr} over the pre-treatment value than placebo in Study 1. Consistent results were observed in Study 2.



Day 1



Day 85

Figure 1: FEV₁ as Mean Change from Test-Day, Pre-Dose Baseline in a 12-Week Clinical Trial (Study 1)

In Study 1, 44 of 78 patients treated with albuterol sulfate MDPI achieved a 15% increase in 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 (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_{0-6h} over the 3-week treatment period, demonstrated that 2 inhalations of albuterol sulfate MDPI produced significantly greater improvement in FEV₁ over the pre-treatment value than the matched placebo.

In this study, 48 of 92 patients treated with albuterol sulfate MDPI achieved a 15% increase in 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 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.

14.3 Exercise-Induced Bronchospasm

In a randomized, single-dose, crossover study in 38 adult and adolescent patients with exercise-induced bronchospasm (EIB), two inhalations of albuterol sulfate MDPI taken 30 minutes before exercise prevented EIB for the hour following exercise (defined as the maintenance of 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 actuation 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 QR code and a built-in electronic module which automatically detects, records, and stores data on inhaler events, including peak inspiratory flow rate (L/min). ProAir Digihaler may pair with and transmit data to the mobile App via Bluetooth® wireless technology where inhaler events are categorized.

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

17 PATIENT COUNSELING INFORMATION

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

Frequency of Use

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

Use of ProAir Digihaler Electronic Module and Mobile App

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

Caring for and Storing the Inhaler

Instruct patients to not open their inhaler unless they are taking a dose. Repeated opening and closing the cover without taking medication will waste medication and may damage the inhaler.

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

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

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

Instruct patients to never take the inhaler apart.

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

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

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

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