PROAIR HFA Inhalation Aerosol is 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)

INDICATIONS AND USAGE
PROAIR HFA Inhalation Aerosol is a beta2-adrenergic agonist indicated for:
- 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, one 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)
- Priming information: Prime PROAIR HFA before using for the first time, or when the inhaler has not been used for more than 2 weeks. To prime PROAIR HFA, release 3 sprays into the air away from the face. Shake well before each spray. (2.3)
- Cleaning information: At least once a week, wash the actuator with warm water, shake off excess, and air dry thoroughly. (2.3)
- PROAIR HFA Inhaler should be discarded when the dose counter displays 0 or after the expiration date on the product, whichever comes first. (2.3)

Dosage and Administration
Inhalation Aerosol: Each actuation delivers 108 mcg of albuterol sulfate from the actuator mouthpiece (equivalent to 90 mcg of albuterol base). Supplied in 8.5-g canister containing 200 actuations. (3)

Contraindications
Hypersensitivity to albuterol and any other PROAIR HFA Inhalation Aerosol Components. (4)

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2. Dosage and Administration
3. Dosage Forms and Strengths
4. Contraindications
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6. Adverse Reactions
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- Bronchospasm
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5. Warnings and Precautions
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- Digoxin
- Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

8. Use in Specific Populations
- Pregnancy
- Lactation

WARNING AND PRECAUTIONS
- Life-threatening paradoxical bronchospasm may occur. Discontinue PROAIR HFA immediately and treat with alternative therapy. (5.1)
- Need for more doses of PROAIR HFA than usual may be a sign of deterioration of asthma and requires reevaluation of treatment. (5.2)
- PROAIR HFA 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 HFA immediately. (5.6)
- Hypokalemia and changes in blood glucose may occur. (5.7, 5.8)

DRUG INTERACTIONS
- Other short-acting sympathomimetic aerosol bronchodilators and adrenergic drugs: May potentiate effect. (7)
- Beta-blockers: May decrease effectiveness of PROAIR HFA 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)

See 17 for Patient Counseling Information and FDA-approved patient labeling.

Full Prescribing Information
Revised: 02/2019

SUGGESTED READING
- TO REPORT SUSPECTED ADVERSE REACTIONS, contact Teva Respiratory, LLC at 1-888-482-9522 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Bronchospasm

PROAIR HFA Inhalation Aerosol 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 HFA Inhalation Aerosol 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 usual dosage for adults and children 4 years and older is two inhalations repeated every 4 to 6 hours. More frequent administration or a larger number of inhalations is not recommended. In some patients, one inhalation every 4 hours may be sufficient.

2.2 Exercise-Induced Bronchospasm

The usual dosage for adults and children 4 years of age or older is two inhalations 15 to 30 minutes before exercise.

2.3 Administration Information

Administer PROAIR HFA by oral inhalation only. Shake well before each spray. To maintain proper use of this product and to prevent medication build-up and blockage, it is important to follow the cleaning directions carefully.

Priming: Prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing three sprays into the air, away from the face.

Cleaning: As with all HFA-containing albuterol inhalers, to maintain proper use of this product and to prevent medication build-up and blockage, it is important to clean the mouthpiece regularly. The inhaler may cease to deliver medication if the plastic actuator mouthpiece is not properly cleaned and dried. To clean: Wash the plastic mouthpiece with warm running water for 30 seconds, shake off excess water, and air dry thoroughly at least once a week. If the patient has more than one PROAIR HFA inhaler, the patient should wash each one separately to prevent contamination of the wrong actuator. In this way, the patient can be sure to always know the correct number of remaining doses. Never attach a canister of medication from any other inhaler to the PROAIR HFA actuator and never attach the PROAIR HFA canister to an actuator from any other inhaler. If the mouthpiece becomes blocked, washing the mouthpiece will remove the blockage. If it is necessary to use the inhaler before it is completely dry, shake off excess water, replace canister, spray twice into the air away from face, and take the prescribed dose. After such use, the mouthpiece should be rewatched and allowed to air dry thoroughly. [see FDA-Approved Patient Labeling (17.9)]

Dose Counter: PROAIR HFA has a dose counter attached to the actuator. When the patient receives the inhaler, a black dot will appear in the viewing window until it has been primed 3 times, at which point the number 200 will be displayed. The dose counter will count down each time a spray is released. 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. After the dose counter reaches 0, the background will change to solid red. PROAIR HFA inhaler should be discarded when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

3 DOSAGE FORMS & STRENGTHS

PROAIR HFA is an inhalation aerosol. PROAIR HFA is supplied as an 8.5 g/200 actuations pressurized aluminum canister with a red plastic actuator with a dose counter and white dust cap each in boxes of one. Each actuation delivers 120 mcg of albuterol sulfate from the canister valve and 108 mcg of albuterol sulfate from the counter and white dust cap.

4 CONTRAINDICATIONS

PROAIR HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol and any other PROAIR HFA Inhalation Aerosol components. Rare cases of hypersensitivity reactions, including urticaria, angioedema, and rash have been reported after the use of albuterol sulfate [see Warnings and Precautions (5.6)].

5 WARNINGS & PRECAUTIONS

5.1 Paradoxical Bronchospasm

PROAIR HFA Inhalation Aerosol can produce paradoxical bronchospasm that may be life threatening. Paradoxical bronchospasm occurs. PROAIR HFA Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

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 HFA Inhalation Aerosol than usual, 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-2-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 HFA Inhalation Aerosol, 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 HFA Inhalation Aerosol, in patients with a history of heart disease they may be an important consideration in selecting an appropriate dosage regimen, in adjusting the patient’s therapy, and in monitoring treatment with PROAIR HFA Inhalation Aerosol. If, in the opinion of the physician, the response of a patient treated with PROAIR HFA Inhalation Aerosol is insufficient, the possibility of using higher doses of PROAIR HFA Inhalation Aerosol or other treatment should be considered.

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 unanticipated 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 hypotension. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving PROAIR HFA Inhalation Aerosol.

5.7 Coexisting Conditions

PROAIR HFA Inhalation Aerosol, 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 inhaled albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.8 Hypokalemia

As with other beta-agonists, PROAIR HFA Inhalation Aerosol may produce significant increases in heart rate in some patients treated with cardioselective beta-receptor blockers, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

6 ADVERSE REACTIONS

Use of PROAIR HFA 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

In a total of 1090 subjects were treated with PROAIR HFA Inhalation Aerosol, or with the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol, during the worldwide clinical development program. 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.

Adult and Adolescents 12 Years of Age and Older: The adverse reaction information presented in the table below concerning PROAIR HFA Inhalation Aerosol is derived from a 6-week, blinded study which compared PROAIR HFA Inhalation Aerosol (180 mcg four times daily) with a double-blinded matched placebo HFA-Inhalation Aerosol and an evaluator-blinded marketed active comparator HFA-134a albuterol inhaler in 172 asthmatic patients 12 to 76 years of age. The table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the PROAIR HFA Inhalation Aerosol treatment group and more frequently in the PROAIR HFA Inhalation Aerosol treatment group than in the matched placebo group. Overall, the incidence and nature of the adverse events reported for PROAIR HFA Inhalation Aerosol and the marketed active comparator HFA-134a albuterol inhaler were comparable.

### Adverse Experience Incidences (% of Patients) in a Six-Week Clinical Trial*

<table>
<thead>
<tr>
<th>Body System/Adverse Event (as Preferred Term)</th>
<th>PROAIR HFA Inhalation Aerosol (N = 58)</th>
<th>Matched active comparator HFA-134a albuterol inhaler (N = 56)</th>
<th>Matched Placebo HFA-134a Inhalation Aerosol (N = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td>Headache</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Pain</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nervous System</td>
<td>Dizziness</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>Pharyngitis</td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>

* This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of at least 3.0% in the PROAIR HFA Inhalation Aerosol group and more frequently in the PROAIR HFA Inhalation Aerosol group than in the placebo HFA Inhalation Aerosol group.
Adverse events reported by less than 3% of the patients receiving PROAIR HFA Inhalation Aerosol but by a greater proportion of PROAIR HFA Inhalation Aerosol, patients than the matched placebo patients, which have the potential to be related to PROAIR HFA Inhalation Aerosol, included chest pain, infection, diarrhea, glossitis, accidental injury (nervous system), anxiety, dyspea, ear disorder, ear pain, and urinary tract infection.

Small cumulative dose studies, tremor, nervousness, and headache were the most frequently occurring adverse events.

Pediatric Patients 4 to 11 Years of Age: Adverse events reported in a 3-week pediatric clinical trial comparing the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol (180 mcg albuterol four times daily) to a matching placebo inhaled albuterol occurred at a low incidence rate (no greater than 2% in the active treatment group) and were similar to those seen in adult and adolescent trials.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of PROAIR HFA. 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. Reports have included rare cases of agranulocytosis, lack of efficacy, asthma exacerbation (reported fatal in one case), muscle cramps, and various ophthalmic side-effects such as throat irritation, altered taste, glossitis, tongue ulceration, and gagging. The following adverse events have been observed in postapproval use of inhaled albuterol: urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles). In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as: angina, hypotension, palpitations, tachycardia, 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 aerosol bronchodilators should not be used concomitantly with PROAIR HFA Inhalation Aerosol. 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 HFA Inhalation Aerosol, 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 administration of inhaled albuterol: urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles). In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as: angina, hypotension, palpitations, tachycardia, nervous system stimulation, insomnia, headache, nervousness, tremor, muscle cramps, drying or irritation of the oropharynx, hypokalemia, hyperglycemia, and metabolic acidosis.

7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

PROAIR HFA Inhalation Aerosol 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 MAOI inhibitors or tricyclic antidepressants.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to asthma medications during pregnancy. For more information, contact the Mothers To Baby Pregnancy Studies conducted by the Organization of Teratology Information Specialists at 1-877-311-8972 or visit http://mothertobaby.org/pregnancy-studies/.

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 preclampsia 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 HFA Inhalation Aerosol for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk. PROAIR HFA Inhalation Aerosol has not been approved for the management of pre-term labor.

In women experiencing pre-eclampsia, including preeclampsia superimposed on chronic hypertension, use of inhaled albuterol should be cautious, usually starting at the low end of the dosing range, reflecting the concern that any increase in the uterine contractility associated with beta-agonists may contribute to the risk of preterm delivery.

In a mouse reproduction study, orally administered albuterol sulfate induced cleft palate in 5 of 111 (4.5%) fetuses at an exposure nine-times the 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 0.004 mg/kg). 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 reproduction study, and when the dose was the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol comparing doses of 180 mcg four times daily with placebo, the fetuses of 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 reproduction study, albuterol four times daily with placebo in 55 patients with asthma and a 3-week clinical trial in 50 patients 4 to 11 years of age with asthma using the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol comparing doses of 180 mg/m² four times daily with placebo.

The safety and effectiveness of PROAIR HFA Inhalation Aerosol for treatment or prevention of bronchospasm in children 12 years of age and older with reversible obstructive airway disease is based on one 6-week clinical trial in 116 patients 12 years of age and older with asthma comparing doses of 180 mg/m² four times daily with placebo.

The safety and effectiveness of PROAIR HFA Inhalation Aerosol for treatment of exercise-induced bronchospasm in children 12 years of age and older is based on one single-dose study in 24 adults with asthma comparing doses of 90, 180, and 270 mcg with placebo in 58 patients [see Clinical Studies (14.1)].

The safety and effectiveness of PROAIR HFA Inhalation Aerosol in children 4 to 11 years of age is based on one 3-week clinical trial in 50 patients 4 to 11 years of age with asthma using the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol comparing doses of 180 mcg four times daily with placebo.

The safety of PROAIR HFA Inhalation Aerosol in children 4 to 11 years of age is extrapolated from clinical trials in patients 12 years of age and older with asthma and exercise-induced bronchospasm, based on data from a single-dose study comparing the bronchodilatory effect of PROAIR HFA 90 mcg and 180 mcg with placebo in 52 patients with asthma and a 3-week clinical trial using the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol in 95 asthmatic children 4 to 11 years of age comparing a dose of 180 mcg albuterol four times daily with placebo [see Clinical Studies (14.1)].

The safety and effectiveness of PROAIR HFA Inhalation Aerosol in pediatric patients below the age of 4 years have not been established.

8.5 Pediatric Use

Clinical studies of PROAIR HFA Inhalation Aerosol 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 beta-adrenergic agonists, including albuterol, are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.
10 OVERDOSAGE
The expected symptoms with overdose are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overt hyperkalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of PROAIR HFA Inhalation Aerosol. Treatment consists of discontinuation of PROAIR HFA Inhalation Aerosol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication may produce coronary vasoconstriction. There is insufficient evidence to determine if dialysis is beneficial for overdose of PROAIR HFA Inhalation Aerosol.

The oral median lethal dose of albuterol sulfate in mice is greater than 2,000 mg/kg (approximately 6,800 times the maximum recommended daily inhalation dose for adults on a mg/m² basis and approximately 1,400 times the maximum recommended daily inhalation dose for children on a mg/m² basis). In young rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 3,000 times the maximum recommended daily inhalation dose for adults on a mg/m² basis and approximately 1,400 times the maximum recommended daily inhalation dose for children on a mg/m² basis). The inhalation median lethal dose has not been determined in animals.

11 DESCRIPTION
The active ingredient of PROAIR HFA (albuterol sulfate) Inhalation Aerosol is albuterol sulfate, a racemic salt, of albuterol. Albuterol sulfate has the chemical name α-(tert-butylinino)-m-xyleno-α-diol sulfate (2:1) (salt), and has the following chemical structure:

![Chemical Structure]

The molecular weight of albuterol sulfate is 576.7, and the empirical formula is (C₁₃H₂₁NO₃)x•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 generic name. PROAIR HFA Inhalation Aerosol is a pressurized metered-dose inhaler (MDI) containing (R)-albuterol sulfate for oral inhalation only. It contains a microcrystalline suspension of albuterol sulfate in propellant HFA-134a (1, 1, 1, 2-tetrafluoroethane) and ethanol. 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.

Geriatric, Pediatric, Hepatic/Renal Impairment: No pharmacokinetic studies for PROAIR HFA Inhalation Aerosol have been conducted in neonates or elderly subjects. The effect of hepatic impairment on the pharmacokinetics of PROAIR HFA Inhalation Aerosol has not been evaluated. 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 consistent 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 HFA Inhalation Aerosol to patients with renal impairment [see Use in Specific Populations (8.5)].

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomysomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 15 times and 6 times the maximum recommended human 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 in vitro bone marrow 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
13.2.1 Inhalation: 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 from human tissues. Recent studies in laboratory animals (mice, rats, 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.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses (380 - 1,300 times the maximum human exposure based on comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or salivation. These effects are similar to those produced by the structurally related chlorofluorocarbons (CFCs), which have been used extensively in metered-dose inhalers.

In animals and humans, propellant HFA-134a was found to be rapidly absorbed and to reach maximum plasma concentration (Cmax) and mean residence time are both extremely short leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

14 CLINICAL STUDIES
14.1 Bronchospasm Associated with Asthma
14.1.1 Adult and Adolescent Patients 12 Years of Age and Older: In a 6-week, randomized, double-blind, placebo-controlled trial, PROAIR HFA Inhalation Aerosol (58 patients) was compared to a matched placebo HFA inhalation aerosol (58 patients) in asthmatic patients 12 to 76 years of age at a dose of 180 mcg albuterol four times daily. An evaluator-blinded active comparator HFA-134a albuterol inhaler arm (56 patients) was included.
PROAIR HFA (albuterol sulfate) INHALATION AEROSOL

Serial FEV1 measurements, shown below as percent change from test-day baseline at Day 1 and at Day 43, demonstrated that two inhalations of PROAIR HFA Inhalation Aerosol produced significantly greater improvement in FEV1 over the pre-treatment value than the matched placebo, as well as a comparable bronchodilator effect to the marketed active comparator HFA-134a albuterol inhaler.

FEV1, as Mean Percent Change from Test-Day Pre-Dose in a 6-Week Clinical Trial

14.2 Exercise-Induced Bronchospasm

In a randomized, single-dose, crossover study in 24 adults and adolescents with exercise-induced bronchospasm (EIB), two inhalations of PROAIR HFA taken 30 minutes before exercise prevented EIB for the hour following exercise (defined as maintenance of FEV1 within 80% of post-dose, pre-exercise baseline values) in 83% (20 of 24) of patients as compared to 25% (6 of 24) of patients when they received placebo. Some patients who participated in these clinical trials were using concomitant steroid therapy.

16 HOW SUPPLIED/STORAGE & HANDLING

PROAIR HFA (albuterol sulfate) Inhalation Aerosol is supplied as a pressurized aluminum canister with a red plastic actuator with a dose counter and white dust cap each in boxes of one. Each canister contains 8.5 g of the formulation and provides 200 actuations (NDC 59310-579-22). Each actuation delivers 120 mcg of albuterol sulfate from the canister valve and 108 mcg of albuterol sulfate from the actuator mouthpiece (equivalent to 90 mcg of albuterol base).

SHAKE WELL BEFORE USE: Store between 15° and 25°C (59° and 77°F). Contents under pressure. Do not puncture or incinerate. Protect from freezing temperatures and prolonged exposure to direct sunlight. Exposure to temperatures above 120°F may cause bursting. For best results, canister should be at room temperature before use. Avoid spraying in eyes. Keep out of reach of children.

PROAIR HFA Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.

17 PATIENT COUNSELING INFORMATION

17.1 Frequency of Use

The action of PROAIR HFA Inhalation Aerosol should last for 4 to 6 hours. Do not use PROAIR HFA Inhalation Aerosol more frequently than recommended. Instruct patients to not increase the dose or frequency of doses of PROAIR HFA Inhalation Aerosol without consulting the physician. If patients find that treatment with PROAIR HFA Inhalation Aerosol 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.

17.2 Priming and Cleaning

Primed: Priming is essential to ensure appropriate albuterol content in each actuation. Instruct patients to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing three sprays into the air, away from the face.

Cleaning: To ensure proper dosing and prevent actuator orifice blockage, instruct patients to wash the red plastic actuator mouthpiece and dry thoroughly at least once a week. Instruct patients that if they have more than one PROAIR HFA inhaler, they should wash each one at separate times to prevent attaching the wrong canister to the wrong plastic actuator. In this way, they can be sure they will always know the correct number of remaining doses. Patients should be instructed to never attach a canister of medicine from any other inhaler to the PROAIR HFA actuator and never attach the PROAIR HFA canister to an actuator from any other inhaler. Patients should not remove the canister from the actuator except during cleaning because reattachment may release a dose into the air and the dose counter will count down each time a spray is released. Detailed cleaning instructions are included in the illustrated information for the Patient leaflet.

17.3 Dose Counter

Patients should be informed that PROAIR HFA has a dose counter attached to the actuator. When the patient receives the inhaler, a black dot will appear in the viewing window until it has been primed 3 times, at which point the number 200 will be displayed. The dose counter will count down each time a spray is released. The dose-counter window displays the number of sprays 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. Patients should be informed to discard PROAIR HFA inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

17.4 Paradoxical Bronchospasm

Instruct patients that PROAIR HFA Inhalation Aerosol can produce paradoxical bronchospasm. Instruct patients to discontinue PROAIR HFA Inhalation Aerosol if paradoxical bronchospasm occurs.

17.5 Concomitant Drug Use

While patients are taking PROAIR HFA Inhalation Aerosol, other inhaled drugs and asthma medications should be taken only as directed by a physician.
17.6 Common Adverse Events
Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, or nervousness.

17.7 Pregnancy
Patients who are pregnant or nursing should contact their physician about the use of PROAIR HFA Inhalation Aerosol. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to asthma medications during pregnancy [see Use in Specific Populations (8.1)].

17.8 General Information on Use
Effective and safe use of PROAIR HFA Inhalation Aerosol includes an understanding of the way that it should be administered.
Shake well before each spray.
Use PROAIR HFA Inhalation Aerosol only with the actuator supplied with the product.
Discard the PROAIR HFA inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first. Never immerse the canister in water to determine how full the canister is (“float test”). In general, the technique for administering PROAIR HFA Inhalation Aerosol to children is similar to that for adults. Children should use PROAIR HFA Inhalation Aerosol under adult supervision, as instructed by the patient’s physician.

17.9 FDA-Approved Patient Labeling
See tear-off illustrated Information for the Patient leaflet.
Get medical help right away if PROAIR HFA no longer helps your symptoms. While you are using PROAIR HFA, 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 HFA?
PROAIR HFA may cause serious side effects, including:
- worsening trouble breathing, coughing and wheezing (paradoxical bronchospasm). If this happens stop using PROAIR HFA and call your doctor or get emergency help right away. Paradoxical bronchospasm is more likely to happen with your first use of a new canister of medicine.
- heart problems including faster heart rate and higher blood pressure
- possible death in people with asthma who use too much PROAIR HFA
- allergic reactions. Call your doctor right away if you have the following symptoms of an allergic reaction:
  - itchy skin
  - swelling beneath your skin or in your throat
  - rash
  - worsening trouble breathing
- low potassium levels in your blood
- worsening of other medical problems in people who also use corticosteroids to treat your symptoms.

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of PROAIR HFA. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PROAIR HFA?
- Store PROAIR HFA at room temperature between 59° F and 77° F (15° C and 25° C).
- Avoid exposure to extreme heat and cold.
- Shake the PROAIR HFA canister well before use.
- Do not puncture the PROAIR HFA canister.
- Do not store the PROAIR HFA canister near heat or a flame. Temperatures above 120° F may cause the canister to burst.
- Do not throw the PROAIR HFA canister into a fire or an incinerator.
- Avoid spraying PROAIR HFA in your eyes.

Keep PROAIR HFA and all medicines out of the reach of children.

General Information about the safe and effective use of PROAIR HFA
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PROAIR HFA for a condition for which it was not prescribed. Do not give PROAIR HFA to other people, even if they have the same symptoms that you have. It may harm them. This Patient Information summarizes the most important information about PROAIR HFA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about PROAIR HFA that is written for health professionals.
Instructions for Use
PROAIR® HFA (prə ər) (albuterol sulfate) Inhalation Aerosol

Read this Instructions for Use before you start using PROAIR HFA and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

The Parts of Your PROAIR HFA Inhaler Device:
There are 2 main parts of your PROAIR HFA inhaler device including a:
- red plastic actuator that sprays the medicine from the canister.
  See Figure A.
- protective dust cap that covers the mouthpiece of the actuator.
  See Figure A.
There is also a metal canister that holds the medicine. See Figure A. There is also a dose counter attached to the back of the actuator with a viewing window that shows you how many sprays of medicine you have left. See Figure B.
You will see a black dot in the viewing window on the actuator until the device has been primed 3 times. See Figure B and “Priming Your PROAIR HFA Device” below.

Each Time You Use Your PROAIR HFA Device:
- Make sure the canister fits firmly in the plastic actuator.
- Look into the mouthpiece to make sure there are no foreign objects there, especially if the cap has not been used to cover the mouthpiece.

Reading the Dose Counter on Your PROAIR HFA Actuator
- The dose counter will count down each time a spray is released. The dose counter window shows the number of sprays left in your inhaler in units of 2 sprays. For example, there are 190 sprays left if the arrow is exactly opposite the number 190, or 189 sprays left if the arrow points between 190 and 188. See Figure D.
- When the dose counter reaches 0, it will continue to show 0 and you should replace your PROAIR HFA device.
- The dose counter cannot be reset and is permanently attached to the actuator. Never change the numbers for the dose counter or touch the pin inside the actuator.
- Do not remove the canister from the plastic actuator except during cleaning. Reattaching the canister to the actuator may accidently release a dose of PROAIR HFA into the air. The dose counter will count down each time a spray is released.

Using Your PROAIR HFA Device:
Step 1. Shake the inhaler well before each spray. Take the cap off the mouthpiece of the actuator.
Step 2. Hold the inhaler with the mouthpiece down. See Figure E.
Step 3. Breathe out through your mouth and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it. See Figure F.
Step 4. Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth. See Figure F.
Step 5. Right after the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.

Step 6. **Hold your breath as long as you can**, up to 10 seconds, then breathe normally.

If your doctor has told you to use more sprays, wait 1 minute and shake the inhaler again. Repeat Steps 2 through Step 6.

Step 7. Put the cap back on the mouthpiece after every time you use the inhaler. Make sure the cap snaps firmly into place.

**Cleaning Your PROAIR HFA Device:**
It is very important to keep the plastic actuator clean so the medicine will not build-up and block the spray. See Figure G and Figure H.

- **Do not try to clean the metal canister or let it get wet.** The inhaler may stop spraying if it is not cleaned correctly.
- If you have more than 1 PROAIR HFA inhaler, wash each device at separate times to prevent putting the wrong canister together with the wrong plastic actuator. This way you can be sure you will always know the correct number of remaining doses of PROAIR HFA.
- **Wash the actuator** at least 1 time each week as follows:
  - Take the canister out of the actuator, and take the cap off the mouthpiece.
  - Hold the actuator under the faucet and run warm water through it for about 30 seconds. See Figure I.

  ◦ Turn the actuator upside down and run warm water through the mouthpiece for about 30 seconds. See Figure J.

  ◦ Shake off as much water from the actuator as you can. Look into the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat the washing instructions.
  ◦ Let the actuator air-dry completely, such as overnight. See Figure K.

If you need to use your inhaler before the actuator is completely dry:
- Shake as much water off the actuator as you can.
- Put the canister in the actuator and make sure it fits firmly.
- Shake the inhaler well and spray it twice into the air away from your face. Put the cap back on the mouthpiece.
- Take your PROAIR HFA dose as prescribed.
- Follow the Cleaning Instructions above.

**Replacing Your PROAIR HFA Device**
- **When the dose counter on the actuator says the number 20,** the color of the numbers will change to red. The red numbers are to remind you to refill your prescription or ask your doctor for another prescription for PROAIR HFA. When the dose counter reaches 0, the background color will change to solid red.
- **Throw the PROAIR HFA inhaler away** as soon as the dose counter says 0 or after the expiration date on the PROAIR HFA packaging, whichever comes first. You should not keep using the inhaler after 200 sprays even though the canister may not be completely empty. You cannot be sure you will receive any medicine after using 200 sprays.
- **Do not use the inhaler** after the expiration date on the PROAIR HFA packaging.

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.
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