

1 **PROVENTIL HFA - albuterol sulfate aerosol, with Dose Indicator**  
2 **Merck Sharp & Dohme Corp.**

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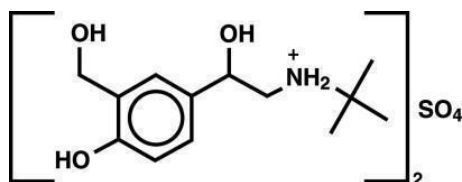
4 **PROVENTIL<sup>®</sup> HFA**  
5 **(albuterol sulfate)**  
6 **Inhalation Aerosol with Dose Indicator**

7 **FOR ORAL INHALATION ONLY**

8 **Prescribing Information**

9 **DESCRIPTION**

10 The active component of PROVENTIL<sup>®</sup> HFA (albuterol sulfate) Inhalation Aerosol is albuterol sulfate,  
11 USP racemic  $\alpha^1$  [(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene- $\alpha,\alpha'$ -diol sulfate (2:1)(salt), a relatively  
12 selective beta<sub>2</sub>-adrenergic bronchodilator having the following chemical structure:



14 Albuterol sulfate is the official generic name in the United States. The World Health Organization  
15 recommended name for the drug is salbutamol sulfate. The molecular weight of albuterol sulfate is 576.7,  
16 and the empirical formula is (C<sub>13</sub>H<sub>21</sub>NO<sub>3</sub>)<sub>2</sub>•H<sub>2</sub>SO<sub>4</sub>. Albuterol sulfate is a white to off-white crystalline  
17 solid. It is soluble in water and slightly soluble in ethanol. PROVENTIL HFA Inhalation Aerosol is a  
18 pressurized metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of  
19 albuterol sulfate in propellant HFA-134a (1,1,1,2-tetrafluoroethane), ethanol, and oleic acid.

20 Each actuation delivers 120 mcg albuterol sulfate, USP from the valve and 108 mcg albuterol sulfate,  
21 USP from the mouthpiece (equivalent to 90 mcg of albuterol base from the mouthpiece). Each canister  
22 provides 200 inhalations. It is recommended to prime the inhaler before using for the first time and in  
23 cases where the inhaler has not been used for more than 2 weeks by releasing four “test sprays” into the  
24 air, away from the face.

25 This product does not contain chlorofluorocarbons (CFCs) as the propellant.

26 **CLINICAL PHARMACOLOGY**

27 **Mechanism of Action** *In vitro* studies and *in vivo* pharmacologic studies have demonstrated that  
28 albuterol has a preferential effect on beta<sub>2</sub>-adrenergic receptors compared with isoproterenol. While it is  
29 recognized that beta<sub>2</sub>-adrenergic receptors are the predominant receptors on bronchial smooth muscle,  
30 data indicate that there is a population of beta<sub>2</sub>-receptors in the human heart existing in a concentration  
31 between 10% and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors has  
32 not been established. (See **WARNINGS, Cardiovascular Effects** section.)

33 Activation of beta<sub>2</sub>-adrenergic receptors on airway smooth muscle leads to the activation of adenylyclase  
34 and to an increase in the intracellular concentration of cyclic-3',5'-adenosine monophosphate (cyclic  
35 AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the  
36 phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation.  
37 Albuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles.

38 Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus  
39 protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also  
40 associated with the inhibition of release of mediators from mast cells in the airway.

41 Albuterol has been shown in most clinical trials to have more effect on the respiratory tract, in the form of  
42 bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer  
43 cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled  
44 albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some  
45 patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

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

50 Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac  
51 arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta<sub>2</sub>-agonist and  
52 methylxanthines were administered concurrently. The clinical significance of these findings is unknown.

53 Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (380-  
54 1300 times the maximum human exposure based on comparisons of AUC values), primarily producing  
55 ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related  
56 chlorofluorocarbons (CFCs), which have been used extensively in metered dose inhalers.

57 In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated,  
58 with an elimination half-life of 3 to 27 minutes in animals and 5 to 7 minutes in humans. Time to  
59 maximum plasma concentration (T<sub>max</sub>) and mean residence time are both extremely short, leading to a  
60 transient appearance of HFA-134a in the blood with no evidence of accumulation.

61 **Pharmacokinetics** In a single-dose bioavailability study which enrolled six healthy, male volunteers,  
62 transient low albuterol levels (close to the lower limit of quantitation) were observed after administration  
63 of two puffs from both PROVENTIL HFA Inhalation Aerosol and a CFC 11/12 propelled albuterol  
64 inhaler. No formal pharmacokinetic analyses were possible for either treatment, but systemic albuterol  
65 levels appeared similar.

66 **Clinical Trials** In a 12-week, randomized, double-blind, double-dummy, active- and placebo-controlled  
67 trial, 565 patients with asthma were evaluated for the bronchodilator efficacy of PROVENTIL HFA  
68 Inhalation Aerosol (193 patients) in comparison to a CFC 11/12 propelled albuterol inhaler (186 patients)  
69 and an HFA-134a placebo inhaler (186 patients).

70 Serial FEV<sub>1</sub> measurements (shown below as percent change from test-day baseline) demonstrated that  
71 two inhalations of PROVENTIL HFA Inhalation Aerosol produced significantly greater improvement in  
72 pulmonary function than placebo and produced outcomes which were clinically comparable to a CFC  
73 11/12 propelled albuterol inhaler.

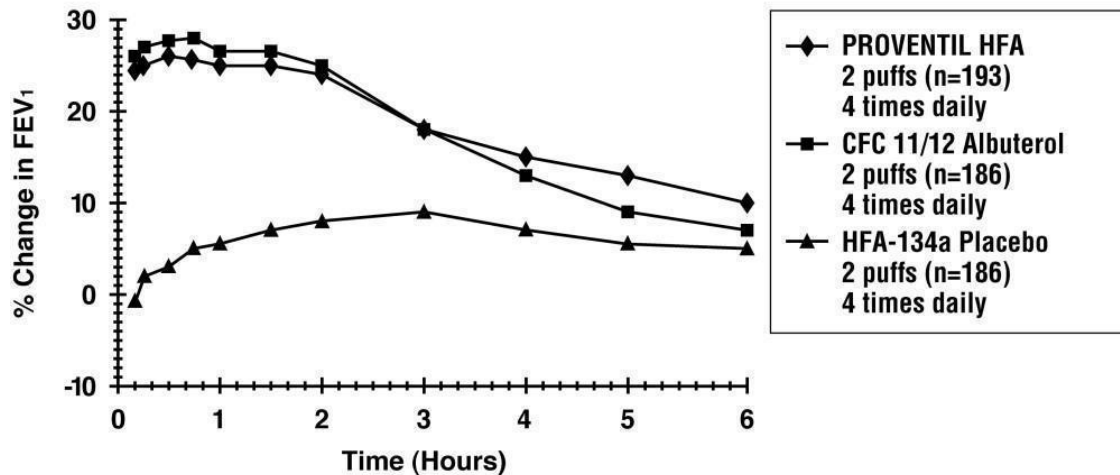
74 The mean time to onset of a 15% increase in FEV<sub>1</sub> was 6 minutes and the mean time to peak effect was  
75 50 to 55 minutes. The mean duration of effect as measured by a 15% increase in FEV<sub>1</sub> was 3 hours. In  
76 some patients, duration of effect was as long as 6 hours.

77 In another clinical study in adults, two inhalations of PROVENTIL HFA Inhalation Aerosol taken 30  
78 minutes before exercise prevented exercise-induced bronchospasm as demonstrated by the maintenance  
79 of FEV<sub>1</sub> within 80% of baseline values in the majority of patients.

80 In a 4-week, randomized, open-label trial, 63 children, 4 to 11 years of age, with asthma were evaluated  
81 for the bronchodilator efficacy of PROVENTIL HFA Inhalation Aerosol (33 pediatric patients) in  
82 comparison to a CFC 11/12 propelled albuterol inhaler (30 pediatric patients).

83

### FEV<sub>1</sub> as Percent Change from Predose in a Large 12-Week Clinical Trial



84

85 Serial FEV<sub>1</sub> measurements as percent change from test-day baseline demonstrated that two inhalations of  
86 PROVENTIL HFA Inhalation Aerosol produced outcomes which were clinically comparable to a CFC  
87 11/12 propelled albuterol inhaler.

88 The mean time to onset of a 12% increase in FEV<sub>1</sub> for PROVENTIL HFA Inhalation Aerosol was 7  
89 minutes and the mean time to peak effect was approximately 50 minutes. The mean duration of effect as  
90 measured by a 12% increase in FEV<sub>1</sub> was 2.3 hours. In some pediatric patients, duration of effect was as  
91 long as 6 hours.

92 In another clinical study in pediatric patients, two inhalations of PROVENTIL HFA Inhalation Aerosol  
93 taken 30 minutes before exercise provided comparable protection against exercise-induced bronchospasm  
94 as a CFC 11/12 propelled albuterol inhaler.

#### 95 INDICATIONS AND USAGE

96 PROVENTIL HFA Inhalation Aerosol is indicated in adults and children 4 years of age and older for the  
97 treatment or prevention of bronchospasm with reversible obstructive airway disease and for the  
98 prevention of exercise-induced bronchospasm.

#### 99 CONTRAINDICATIONS

100 PROVENTIL HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to  
101 albuterol or any other PROVENTIL HFA components.

#### 102 WARNINGS

- 103 1. **Paradoxical Bronchospasm:** Inhaled albuterol sulfate can produce paradoxical bronchospasm  
104 that may be life threatening. If paradoxical bronchospasm occurs, PROVENTIL HFA Inhalation  
105 Aerosol should be discontinued immediately and alternative therapy instituted. It should be

- 106 recognized that paradoxical bronchospasm, when associated with inhaled formulations,  
107 frequently occurs with the first use of a new canister.
- 108 2. **Deterioration of Asthma:** Asthma may deteriorate acutely over a period of hours or chronically  
109 over several days or longer. If the patient needs more doses of PROVENTIL HFA Inhalation  
110 Aerosol than usual, this may be a marker of destabilization of asthma and requires re-evaluation  
111 of the patient and treatment regimen, giving special consideration to the possible need for anti-  
112 inflammatory treatment, e.g., corticosteroids.
  - 113 3. **Use of Anti-inflammatory Agents:** The use of beta-adrenergic-agonist bronchodilators alone  
114 may not be adequate to control asthma in many patients. Early consideration should be given to  
115 adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.
  - 116 4. **Cardiovascular Effects:** PROVENTIL HFA Inhalation Aerosol, like other beta-adrenergic  
117 agonists, can produce clinically significant cardiovascular effects in some patients as measured by  
118 pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after  
119 administration of PROVENTIL HFA Inhalation Aerosol at recommended doses, if they occur, the  
120 drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG  
121 changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment  
122 depression. The clinical significance of these findings is unknown. Therefore, PROVENTIL HFA  
123 Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients  
124 with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and  
125 hypertension.
  - 126 5. **Do Not Exceed Recommended Dose:** Fatalities have been reported in association with excessive  
127 use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is  
128 unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic  
129 crisis and subsequent hypoxia is suspected.
  - 130 6. **Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions may occur after  
131 administration of albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash,  
132 bronchospasm, anaphylaxis, and oropharyngeal edema.

## 133 PRECAUTIONS

134 **General** Albuterol sulfate, as with all sympathomimetic amines, should be used with caution in patients  
135 with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension;  
136 in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are  
137 unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic  
138 blood pressure have been seen in individual patients and could be expected to occur in some patients after  
139 use of any beta-adrenergic bronchodilator.

140 Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and  
141 ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some  
142 patients, possibly through intracellular shunting, which has the potential to produce adverse  
143 cardiovascular effects. The decrease is usually transient, not requiring supplementation.

144 **Information for Patients** See illustrated [Patient's Instructions for Use](#). SHAKE WELL BEFORE  
145 USING. Patients should be given the following information:

146 It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has  
147 not been used for more than 2 weeks by releasing four "test sprays" into the air, away from the face.

148 KEEPING THE PLASTIC MOUTHPIECE CLEAN IS VERY IMPORTANT TO PREVENT  
149 MEDICATION BUILDUP AND BLOCKAGE. THE MOUTHPIECE SHOULD BE WASHED,  
150 SHAKEN TO REMOVE EXCESS WATER, AND AIR DRIED THOROUGHLY AT LEAST ONCE A  
151 WEEK. INHALER MAY CEASE TO DELIVER MEDICATION IF NOT PROPERLY CLEANED.

152 The mouthpiece should be cleaned (with the canister removed) by running warm water through the top  
153 and bottom for 30 seconds at least once a week. The mouthpiece must be shaken to remove excess water,  
154 then air dried thoroughly (such as overnight). Blockage from medication buildup or improper medication  
155 delivery may result from failure to thoroughly air dry the mouthpiece.

156 If the mouthpiece should become blocked (little or no medication coming out of the mouthpiece), the  
157 blockage may be removed by washing as described above.

158 If it is necessary to use the inhaler before it is completely dry, shake off excess water, replace canister,  
159 test spray twice away from face, and take the prescribed dose. After such use, the mouthpiece should be  
160 rewashed and allowed to air dry thoroughly.

161 The action of PROVENTIL HFA Inhalation Aerosol should last up to 4 to 6 hours. PROVENTIL HFA  
162 Inhalation Aerosol should not be used more frequently than recommended. Do not increase the dose or  
163 frequency of doses of PROVENTIL HFA Inhalation Aerosol without consulting your physician. If you  
164 find that treatment with PROVENTIL HFA Inhalation Aerosol becomes less effective for symptomatic  
165 relief, your symptoms become worse, and/or you need to use the product more frequently than usual,  
166 medical attention should be sought immediately. While you are taking PROVENTIL HFA Inhalation  
167 Aerosol, other inhaled drugs and asthma medications should be taken only as directed by your physician.

168 Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart  
169 rate, tremor, or nervousness. If you are pregnant or nursing, contact your physician about use of  
170 PROVENTIL HFA Inhalation Aerosol. Effective and safe use of PROVENTIL HFA Inhalation Aerosol  
171 includes an understanding of the way that it should be administered. Use PROVENTIL HFA Inhalation  
172 Aerosol only with the actuator supplied with the product. Discard the canister after 200 sprays have been  
173 used.

174 **In general, the technique for administering PROVENTIL HFA Inhalation Aerosol to children is**  
175 **similar to that for adults. Children should use PROVENTIL HFA Inhalation Aerosol under adult**  
176 **supervision, as instructed by the patient's physician. (See [Patient's Instructions for Use](#).)**

## 177 **Drug Interactions**

- 178 1. **Beta-Blockers:** Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of  
179 beta-agonists, such as PROVENTIL HFA Inhalation Aerosol, but may produce severe  
180 bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be  
181 treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after  
182 myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic  
183 blocking agents in patients with asthma. In this setting, cardioselective beta-blockers should be  
184 considered, although they should be administered with caution.
- 185 2. **Diuretics:** The ECG changes and/or hypokalemia which may result from the administration of  
186 nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by  
187 beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although  
188 the clinical significance of these effects is not known, caution is advised in the coadministration  
189 of beta-agonists with nonpotassium-sparing diuretics.
- 190 3. **Albuterol-Digoxin:** Mean decreases of 16% and 22% in serum digoxin levels were demonstrated  
191 after single-dose intravenous and oral administration of albuterol, respectively, to normal  
192 volunteers who had received digoxin for 10 days. The clinical significance of these findings for  
193 patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic  
194 basis is unclear; nevertheless, it would be prudent to carefully evaluate the serum digoxin levels  
195 in patients who are currently receiving digoxin and albuterol.
- 196 4. **Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:** PROVENTIL HFA Inhalation  
197 Aerosol should be administered with extreme caution to patients being treated with monoamine

198 oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such  
199 agents, because the action of albuterol on the cardiovascular system may be potentiated.

## 200 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

201 In a 2-year study in SPRAGUE-DAWLEY® rats, albuterol sulfate caused a dose-related increase in the  
202 incidence of benign leiomyomas of the mesovarium at the above dietary doses of 2 mg/kg (approximately  
203 15 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis and  
204 approximately 6 times the maximum recommended daily inhalation dose for children on a mg/m<sup>2</sup> basis).  
205 In another study this effect was blocked by the coadministration of propranolol, a nonselective beta-  
206 adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of  
207 tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1700 times the maximum  
208 recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis and approximately 800 times the  
209 maximum recommended daily inhalation dose for children on a mg/m<sup>2</sup> basis). In a 22-month study in  
210 Golden Hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50  
211 mg/kg (approximately 225 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup>  
212 basis and approximately 110 times the maximum recommended daily inhalation dose for children on a  
213 mg/m<sup>2</sup> basis).

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

216 Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg  
217 (approximately 340 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis).

## 218 **Pregnancy Teratogenic Effects Pregnancy**

219 Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice given albuterol sulfate  
220 subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the  
221 maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis) and in 10 of 108 (9.3%)  
222 fetuses at 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation dose for adults  
223 on a mg/m<sup>2</sup> basis). The drug did not induce cleft palate formation at a dose of 0.025 mg/kg (less than the  
224 maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis). Cleft palate also occurred in  
225 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg of isoproterenol (positive  
226 control).

227 A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when  
228 albuterol sulfate was administered orally at 50 mg/kg dose (approximately 680 times the maximum  
229 recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis).

230 In an inhalation reproduction study in SPRAGUE-DAWLEY rats, the albuterol sulfate/HFA-134a  
231 formulation did not exhibit any teratogenic effects at 10.5 mg/kg (approximately 70 times the maximum  
232 recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis).

233 A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-  
234 related material is transferred from the maternal circulation to the fetus.

235 There are no adequate and well-controlled studies of PROVENTIL HFA Inhalation Aerosol or albuterol  
236 sulfate in pregnant women. PROVENTIL HFA Inhalation Aerosol should be used during pregnancy only  
237 if the potential benefit justifies the potential risk to the fetus.

238 During worldwide marketing experience, various congenital anomalies, including cleft palate and limb  
239 defects, have been reported in the offspring of patients being treated with albuterol. Some of the mothers  
240 were taking multiple medications during their pregnancies. Because no consistent pattern of defects can  
241 be discerned, a relationship between albuterol use and congenital anomalies has not been established.

242 **Use in Labor and Delivery**

243 Because of the potential for beta-agonist interference with uterine contractility, use of PROVENTIL HFA  
244 Inhalation Aerosol for relief of bronchospasm during labor should be restricted to those patients in whom  
245 the benefits clearly outweigh the risk.

246 **Tocolysis:** Albuterol has not been approved for the management of preterm labor. The benefit:risk ratio  
247 when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including  
248 pulmonary edema, have been reported during or following treatment of premature labor with beta<sub>2</sub>-  
249 agonists, including albuterol.

250 **Nursing Mothers**

251 Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans,  
252 but it is not known whether the components of PROVENTIL HFA Inhalation Aerosol are excreted in  
253 human milk.

254 Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience  
255 with the use of PROVENTIL HFA Inhalation Aerosol by nursing mothers, a decision should be made  
256 whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug  
257 to the mother. Caution should be exercised when albuterol sulfate is administered to a nursing woman.

258 **Pediatrics**

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

261 **Geriatrics**

262 PROVENTIL HFA Inhalation Aerosol has not been studied in a geriatric population. As with other beta<sub>2</sub>-  
263 agonists, special caution should be observed when using PROVENTIL HFA Inhalation Aerosol in elderly  
264 patients who have concomitant cardiovascular disease that could be adversely affected by this class of  
265 drug.

266 **ADVERSE REACTIONS**

267 Adverse reaction information concerning PROVENTIL HFA Inhalation Aerosol is derived from a 12-  
268 week, double-blind, double-dummy study which compared PROVENTIL HFA Inhalation Aerosol, a CFC  
269 11/12 propelled albuterol inhaler, and an HFA-134a placebo inhaler in 565 asthmatic patients. The  
270 following table lists the incidence of all adverse events (whether considered by the investigator drug  
271 related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the PROVENTIL  
272 HFA Inhalation Aerosol treatment group and more frequently in the PROVENTIL HFA Inhalation  
273 Aerosol treatment group than in the placebo group. Overall, the incidence and nature of the adverse  
274 reactions reported for PROVENTIL HFA Inhalation Aerosol and a CFC 11/12 propelled albuterol inhaler  
275 were comparable.

276

**Adverse Experience Incidences (% of patients) in a Large 12-week Clinical Trial\***

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Body System/ Adverse Event (Preferred Term)		PROVENTIL HFA Inhalation Aerosol (N=193)	CFC 11/12 Propelled Albuterol Inhaler (N=186)	HFA-134a Placebo Inhaler (N=186)
Application Site Disorders	Inhalation Site Sensation	6	9	2
	Inhalation Taste Sensation	4	3	3
Body as a Whole	Allergic Reaction/Symptoms	6	4	<1
	Back Pain	4	2	3
	Fever	6	2	5
Central and Peripheral Nervous System	Tremor	7	8	2
Gastrointestinal System	Nausea	10	9	5
	Vomiting	7	2	3
Heart Rate and Rhythm Disorder	Tachycardia	7	2	<1
Psychiatric Disorders	Nervousness	7	9	3
Respiratory System Disorders	Respiratory Disorder (unspecified)	6	4	5
	Rhinitis	16	22	14
	Upper Resp Tract Infection	21	20	18
Urinary System Disorder	Urinary Tract Infection	3	4	2

\*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 PROVENTIL HFA Inhalation Aerosol group and more frequently in the PROVENTIL HFA Inhalation Aerosol group than in the HFA-134a placebo inhaler group.

277 Adverse events reported by less than 3% of the patients receiving PROVENTIL HFA Inhalation Aerosol,  
278 and by a greater proportion of PROVENTIL HFA Inhalation Aerosol patients than placebo patients,  
279 which have the potential to be related to PROVENTIL HFA Inhalation Aerosol include: dysphonia,  
280 increased sweating, dry mouth, chest pain, edema, rigors, ataxia, leg cramps, hyperkinesia, eructation,  
281 flatulence, tinnitus, diabetes mellitus, anxiety, depression, somnolence, rash. Palpitation and dizziness  
282 have also been observed with PROVENTIL HFA Inhalation Aerosol.

283 Adverse events reported in a 4-week pediatric clinical trial comparing PROVENTIL HFA Inhalation  
284 Aerosol and a CFC 11/12 propelled albuterol inhaler occurred at a low incidence rate and were similar to  
285 those seen in the adult trials.

286 In small, cumulative dose studies, tremor, nervousness, and headache appeared to be dose related.

287 Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported  
288 after the use of inhaled albuterol. In addition, albuterol, like other sympathomimetic agents, can cause  
289 adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, insomnia,  
290 headache, metabolic acidosis, and drying or irritation of the oropharynx.



## 291 OVERDOSAGE

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

297 Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death  
298 may be associated with abuse of PROVENTIL HFA Inhalation Aerosol. Treatment consists of  
299 discontinuation of PROVENTIL HFA Inhalation Aerosol together with appropriate symptomatic therapy.  
300 The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such  
301 medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial  
302 for overdosage of PROVENTIL HFA Inhalation Aerosol.

303 The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately 6800  
304 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis and approximately  
305 3200 times the maximum recommended daily inhalation dose for children on a mg/m<sup>2</sup> basis). In mature  
306 rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately  
307 3000 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis and  
308 approximately 1400 times the maximum recommended daily inhalation dose for children on a mg/m<sup>2</sup>  
309 basis). In young rats, the subcutaneous median lethal dose is approximately 2000 mg/kg (approximately  
310 14,000 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis and  
311 approximately 6400 times the maximum recommended daily inhalation dose for children on a mg/m<sup>2</sup>  
312 basis). The inhalation median lethal dose has not been determined in animals.

## 313 DOSAGE AND ADMINISTRATION

314 For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage  
315 for adults and children 4 years of age and older is two inhalations repeated every 4 to 6 hours. More  
316 frequent administration or a larger number of inhalations is not recommended. In some patients, one  
317 inhalation every 4 hours may be sufficient. Each actuation of PROVENTIL HFA Inhalation Aerosol  
318 delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouthpiece. It is  
319 recommended to prime the inhaler before using for the first time and in cases where the inhaler has not  
320 been used for more than 2 weeks by releasing four “test sprays” into the air, away from the face.

321 PROVENTIL HFA Inhalation Aerosol contains 200 inhalations per canister. The canister has an attached  
322 dose indicator, which indicates how many inhalations remain. The dose indicator display will move after  
323 every tenth actuation. When nearing the end of the usable inhalations, the background behind the number  
324 in the dose indicator display window changes to red at 20 actuations or lower. PROVENTIL HFA  
325 Inhalation Aerosol should be discarded when the dose indicator display window shows zero.

326 **Exercise Induced Bronchospasm Prevention:** The usual dosage for adults and children 4 years of age  
327 and older is two inhalations 15 to 30 minutes before exercise.

328 To maintain proper use of this product, it is important that the mouthpiece be washed and dried  
329 thoroughly at least once a week. The inhaler may cease to deliver medication if not properly cleaned and  
330 dried thoroughly (see **PRECAUTIONS, Information for Patients** section). Keeping the plastic  
331 mouthpiece clean is very important to prevent medication buildup and blockage. The inhaler may cease to  
332 deliver medication if not properly cleaned and air dried thoroughly. If the mouthpiece becomes blocked,  
333 washing the mouthpiece will remove the blockage.

334 If a previously effective dose regimen fails to provide the usual response, this may be a marker of  
335 destabilization of asthma and requires reevaluation of the patient and the treatment regimen, giving  
336 special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

337 **HOW SUPPLIED**

338 PROVENTIL HFA (albuterol sulfate) Inhalation Aerosol is supplied as a pressurized aluminum canister,  
339 with an attached dose indicator, a yellow plastic actuator and orange dust cap each in boxes of one. Each  
340 actuation delivers 120 mcg of albuterol sulfate from the valve and 108 mcg of albuterol sulfate from the  
341 mouthpiece (equivalent to 90 mcg of albuterol base). Canisters with a labeled net weight of 6.7 g contain  
342 200 inhalations (NDC 0085-1132-04).

343 **Rx only. Store between 15° - 25°C (59° - 77°F). Store the inhaler with the mouthpiece down. For**  
344 **best results, canister should be at room temperature before use.**

345 **SHAKE WELL BEFORE USING.**

346 **The yellow actuator supplied with PROVENTIL HFA Inhalation Aerosol should not be used with**  
347 **any other product canisters, and actuator from other products should not be used with a**  
348 **PROVENTIL HFA Inhalation Aerosol canister. The correct amount of medication in each canister**  
349 **cannot be assured after 200 actuations and when the dose indicator display window shows zero,**  
350 **even though the canister is not completely empty. The canister should be discarded when the**  
351 **labeled number of actuations have been used.**

352 **WARNING: Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate.**  
353 **Exposure to temperatures above 120°F may cause bursting. Keep out of reach of children.**

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

355

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 **MERCK & CO., INC.,** Whitehouse Station, NJ 08889, USA

356

357 Developed and Manufactured by:  
358 3M Health Care Limited  
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361 3M Drug Delivery Systems  
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