

1 **MEDICATION GUIDE**

2 **ADVAIR [ad'vair] DISKUS[®] 100/50**

3 **(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)**

4 **ADVAIR DISKUS[®] 250/50**

5 **(fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder)**

6 **ADVAIR DISKUS[®] 500/50**

7 **(fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder)**

8
9 Read the Medication Guide that comes with ADVAIR DISKUS before you start using it and
10 each time you get a refill. There may be new information. This Medication Guide does not take
11 the place of talking to your healthcare provider about your medical condition or treatment.

12
13 **What is the most important information I should know about ADVAIR DISKUS?**

14 **ADVAIR DISKUS can cause serious side effects, including:**

- 15 1. **People with asthma who take long-acting beta₂-adrenergic agonist (LABA) medicines,**
16 **such as salmeterol (one of the medicines in ADVAIR DISKUS), have an increased risk**
17 **of death from asthma problems.** It is not known whether fluticasone propionate, the other
18 medicine in ADVAIR DISKUS, reduces the risk of death from asthma problems seen with
19 salmeterol.
- 20 • **Call your healthcare provider if breathing problems worsen over time while using**
21 **ADVAIR DISKUS.** You may need different treatment.
 - 22 • **Get emergency medical care if:**
 - 23 • breathing problems worsen quickly and
 - 24 • you use your rescue inhaler medicine, but it does not relieve your breathing problems.
- 25 2. ADVAIR DISKUS should be used only if your healthcare provider decides that your asthma
26 is not well controlled with a long-term asthma control medicine, such as inhaled
27 corticosteroids.
- 28 3. When your asthma is well controlled, your healthcare provider may tell you to stop taking
29 ADVAIR DISKUS. Your healthcare provider will decide if you can stop ADVAIR DISKUS
30 without loss of asthma control. Your healthcare provider may prescribe a different asthma
31 control medicine for you, such as an inhaled corticosteroid.
- 32 4. Children and adolescents who take LABA medicines may have an increased risk of being
33 hospitalized for asthma problems.

34
35 **What is ADVAIR DISKUS?**

36 • ADVAIR DISKUS combines an inhaled corticosteroid medicine, fluticasone propionate (the
37 same medicine found in FLOVENT[®]), and a LABA medicine, salmeterol (the same medicine
38 found in SEREVENT[®]).

39 • Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the
40 lungs can lead to asthma symptoms.

41 • LABA medicines are used in people with asthma and chronic obstructive pulmonary
42 disease (COPD). LABA medicines help the muscles around the airways in your lungs
43 stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These
44 symptoms can happen when the muscles around the airways tighten. This makes it hard
45 to breathe. In severe cases, wheezing can stop your breathing and cause death if not
46 treated right away.

47 • ADVAIR DISKUS is used for asthma and COPD as follows:

48 **Asthma:**

49 ADVAIR DISKUS is used to control symptoms of asthma and to prevent symptoms such as
50 wheezing in adults and children aged 4 years and older.

51 ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT). LABA
52 medicines, such as salmeterol, increase the risk of death from asthma problems.

53 ADVAIR DISKUS is not for adults and children with asthma who are well controlled with
54 an asthma control medicine, such as a low to medium dose of an inhaled corticosteroid
55 medicine.

56 **COPD:**

57 COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both.

58 ADVAIR DISKUS 250/50 is used long term, 2 times each day to help improve lung function
59 for better breathing in adults with COPD. ADVAIR DISKUS 250/50 has been shown to
60 decrease the number of flare-ups and worsening of COPD symptoms (exacerbations).

61

62 **Who should not use ADVAIR DISKUS?**

63 Do not use ADVAIR DISKUS:

- 64 • to treat sudden, severe symptoms of asthma or COPD and
65 • if you have a severe allergy to milk proteins. Ask your doctor if you are not sure.

66

67 **What should I tell my healthcare provider before using ADVAIR DISKUS?**

68 **Tell your healthcare provider about all of your health conditions, including if you:**

- 69 • **have heart problems**
70 • **have high blood pressure**
71 • **have seizures**

- 72 • **have thyroid problems**
- 73 • **have diabetes**
- 74 • **have liver problems**
- 75 • **have osteoporosis**
- 76 • **have an immune system problem**
- 77 • **are pregnant or planning to become pregnant.** It is not known if ADVAIR DISKUS may
- 78 harm your unborn baby.
- 79 • **are breastfeeding.** It is not known if ADVAIR DISKUS passes into your milk and if it can
- 80 harm your baby.
- 81 • **are allergic to any of the ingredients in ADVAIR DISKUS, any other medicines, or food**
- 82 **products.** See the end of this Medication Guide for a complete list of the ingredients in
- 83 ADVAIR DISKUS.
- 84 • **are exposed to chickenpox or measles**

85 Tell your healthcare provider about all the medicines you take including prescription and
86 non-prescription medicines, vitamins, and herbal supplements. ADVAIR DISKUS and certain
87 other medicines may interact with each other. This may cause serious side effects. Especially,
88 tell your healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR[®] (ritonavir
89 capsules) Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA[®] (lopinavir/ritonavir)
90 Tablets contain ritonavir.

91 Know the medicines you take. Keep a list and show it to your healthcare provider and pharmacist
92 each time you get a new medicine.

93

94 **How do I use ADVAIR DISKUS?**

95 **See the step-by-step instructions for using ADVAIR DISKUS at the end of this Medication**
96 **Guide.** Do not use ADVAIR DISKUS unless your healthcare provider has taught you and you
97 understand everything. Ask your healthcare provider or pharmacist if you have any questions.

98 • Children should use ADVAIR DISKUS with an adult's help, as instructed by the child's
99 healthcare provider.

100 • Use ADVAIR DISKUS exactly as prescribed. **Do not use ADVAIR DISKUS more often**
101 **than prescribed.** ADVAIR DISKUS comes in 3 strengths. Your healthcare provider has
102 prescribed the one that is best for your condition.

103 • The usual dosage of ADVAIR DISKUS is 1 inhalation 2 times each day (morning and
104 evening). The 2 doses should be about 12 hours apart. Rinse your mouth with water after
105 using ADVAIR DISKUS.

106 • If you take more ADVAIR DISKUS than your doctor has prescribed, get medical help right
107 away if you have any unusual symptoms, such as worsening shortness of breath, chest pain,
108 increased heart rate, or shakiness.

- 109 • If you miss a dose of ADVAIR DISKUS, just skip that dose. Take your next dose at your
110 usual time. Do not take 2 doses at one time.
- 111 • Do not use a spacer device with ADVAIR DISKUS.
- 112 • Do not breathe into ADVAIR DISKUS.
- 113 • **While you are using ADVAIR DISKUS 2 times each day, do not use other medicines**
114 **that contain a LABA for any reason.** Ask your healthcare provider or pharmacist if any of
115 your other medicines are LABA medicines.
- 116 • Do not stop using ADVAIR DISKUS or other asthma medicines unless told to do so by your
117 healthcare provider because your symptoms might get worse. Your healthcare provider will
118 change your medicines as needed.
- 119 • ADVAIR DISKUS does not relieve sudden symptoms. Always have a rescue inhaler
120 medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting
121 bronchodilator, call your healthcare provider to have one prescribed for you.
- 122 • Call your healthcare provider or get medical care right away if:
 - 123 • your breathing problems worsen with ADVAIR DISKUS
 - 124 • you need to use your rescue inhaler medicine more often than usual
 - 125 • your rescue inhaler medicine does not work as well for you at relieving symptoms
 - 126 • you need to use 4 or more inhalations of your rescue inhaler medicine for 2 or more days
127 in a row
 - 128 • you use 1 whole canister of your rescue inhaler medicine in 8 weeks' time
 - 129 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers
130 that are right for you.
 - 131 • you have asthma and your symptoms do not improve after using ADVAIR DISKUS
132 regularly for 1 week

133

134 **What are the possible side effects with ADVAIR DISKUS?**

135 **ADVAIR DISKUS can cause serious side effects, including:**

- 136 • See “**What is the most important information I should know about ADVAIR**
137 **DISKUS?**”
- 138 • **serious allergic reactions.** Call your healthcare provider or get emergency medical care if
139 you get any of the following symptoms of a serious allergic reaction:
 - 140 • rash
 - 141 • hives
 - 142 • swelling of the face, mouth, and tongue
 - 143 • breathing problems
- 144 • **sudden breathing problems immediately after inhaling your medicine**

- 145 • **effects on heart**
- 146 • increased blood pressure
- 147 • a fast and irregular heartbeat
- 148 • chest pain
- 149 • **effects on nervous system**
- 150 • tremor
- 151 • nervousness
- 152 • **reduced adrenal function (may result in loss of energy)**
- 153 • **changes in blood (sugar, potassium, certain types of white blood cells)**
- 154 • **weakened immune system and a higher chance of infections**
- 155 • **lower bone mineral density.** This may be a problem for people who already have a higher
- 156 chance of low bone density (osteoporosis).
- 157 • **eye problems including glaucoma and cataracts.** You should have regular eye exams
- 158 while using ADVAIR DISKUS.
- 159 • **slowed growth in children.** A child's growth should be checked often.
- 160 • **pneumonia.** People with COPD have a higher chance of getting pneumonia. ADVAIR
- 161 DISKUS may increase the chance of getting pneumonia. Call your healthcare provider if you
- 162 notice any of the following symptoms:
- 163 • increase in mucus (sputum) production
- 164 • change in mucus color
- 165 • fever
- 166 • chills
- 167 • increased cough
- 168 • increased breathing problems

169 **Common side effects of ADVAIR DISKUS include:**

170 **Asthma:**

- 171 • upper respiratory tract infection
- 172 • throat irritation
- 173 • hoarseness and voice changes
- 174 • thrush in the mouth and throat
- 175 • bronchitis
- 176 • cough
- 177 • headache
- 178 • nausea and vomiting

179 In children with asthma, infections in the ear, nose, and throat are common.

180 **COPD:**

- 181 • thrush in the mouth and throat
- 182 • throat irritation
- 183 • hoarseness and voice changes
- 184 • viral respiratory infections
- 185 • headache
- 186 • muscle and bone pain

187 Tell your healthcare provider about any side effect that bothers you or that does not go away.

188 These are not all the side effects with ADVAIR DISKUS. Ask your healthcare provider or
189 pharmacist for more information.

190 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-
191 800-FDA-1088.

192

193 **How do I store ADVAIR DISKUS?**

- 194 • Store ADVAIR DISKUS at room temperature between 68° F to 77° F (20°C to 25° C). Keep
195 in a dry place away from heat and sunlight.
- 196 • Safely discard ADVAIR DISKUS 1 month after you remove it from the foil pouch, or after
197 the dose indicator reads “0”, whichever comes first.
- 198 • Keep ADVAIR DISKUS and all medicines out of the reach of children.

199

200 **General Information about ADVAIR DISKUS**

201 Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not
202 use ADVAIR DISKUS for a condition for which it was not prescribed. Do not give your
203 ADVAIR DISKUS to other people, even if they have the same condition that you have. It may
204 harm them.

205 This Medication Guide summarizes the most important information about ADVAIR DISKUS. If
206 you would like more information, talk with your healthcare provider or pharmacist. You can ask
207 your healthcare provider or pharmacist for information about ADVAIR DISKUS that was
208 written for healthcare professionals. You can also contact the company that makes ADVAIR
209 DISKUS (toll free) at 1-888-825-5249 or at www.advair.com.

210

211 **What are the ingredients in ADVAIR DISKUS?**

212 Active ingredients: fluticasone propionate, salmeterol xinafoate

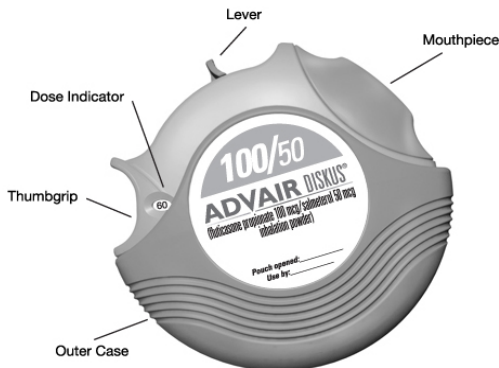
213 Inactive ingredient: lactose (contains milk proteins)

214

215

Instructions for Using ADVAIR DISKUS

216 Follow the instructions below for using your ADVAIR DISKUS. **You will breathe in (inhale)**
217 **the medicine from the DISKUS®**. If you have any questions, ask your healthcare provider or
218 pharmacist.



219

220 Take ADVAIR DISKUS out of the box and foil pouch. Write the “**Pouch opened**” and “**Use**
221 **by**” dates on the label on top of the DISKUS. **The “Use by” date is 1 month from date of**
222 **opening the pouch.**

- 223
- The DISKUS will be in the closed position when the pouch is opened.
 - The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose indicator number will decrease each time you use the DISKUS. After you have used 55 doses from the DISKUS, the numbers 5 to 0 will appear in **red** to warn you that there are only a few doses left (*see Figure 1*). If you are using a “sample” DISKUS, the numbers 5 to 0 will appear in red after 9 doses.
- 224
225
226
227
228



229

230

Figure 1

231 Taking a dose from the DISKUS requires the following 3 simple steps: Open, Click, Inhale.

232 **1. OPEN**

233 Hold the DISKUS in one hand and put the thumb of your other hand on the **thumbgrip**. Push
234 your thumb away from you as far as it will go until the mouthpiece appears and snaps into
235 position (*see Figure 2*).



236

237

Figure 2

238 **2. CLICK**

239 Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the **lever**
240 away from you as far as it will go until it **clicks** (*see Figure 3*). The DISKUS is now ready to
241 use.



242

243

Figure 3

244 Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a
245 decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the**
246 **DISKUS is ready:**

- 247
- **Do not close the DISKUS.**

- 248
- Do not tilt the DISKUS.
- 249
- Do not play with the lever.
- 250
- Do not move the lever more than once.

251 **3. INHALE**

252 Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding the
253 DISKUS level and away from your mouth (*see Figure 4*). **Remember, never breathe out**
254 **into the DISKUS mouthpiece.**



255

256

Figure 4

257 Put the mouthpiece to your lips (*see Figure 5*). Breathe in quickly and deeply through the
258 DISKUS. Do not breathe in through your nose.



259

260

Figure 5

261 Remove the DISKUS from your mouth. Hold your breath for about 10 seconds, or for as long
262 as is comfortable. Breathe out slowly.

263 The DISKUS delivers your dose of medicine as a very fine powder. Patients may or may not
264 taste or feel the powder. Do not use an extra dose from the DISKUS if you do not feel or
265 taste the medicine.

266 Rinse your mouth with water after breathing-in the medicine. Spit the water out. Do not
267 swallow.

268 **4.** Close the DISKUS when you are finished taking a dose so that the DISKUS will be ready for
269 you to take your next dose. Put your thumb on the thumbgrip and slide the thumbgrip back
270 towards you as far as it will go (*see Figure 6*). The DISKUS will click shut. The lever will
271 automatically return to its original position. The DISKUS is now ready for you to take your
272 next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4.)



273
274 **Figure 6**

273
274

275

276 **Remember:**

- 277 • Never breathe into the DISKUS.
- 278 • Never take the DISKUS apart.
- 279 • Always ready and use the DISKUS in a level, flat position.
- 280 • Do not use the DISKUS with a spacer device.
- 281 • After each dose, rinse your mouth with water and spit the water out. Do not swallow.
- 282 • Never wash the mouthpiece or any part of the DISKUS. **Keep it dry.**
- 283 • Always keep the DISKUS in a dry place.
- 284 • Never take an extra dose, even if you did not taste or feel the medicine.

285

286 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

287

288 ADAIR DISKUS, DISKUS, FLOVENT, and SEREVENT are registered trademarks of
289 GlaxoSmithKline.

290 The other brands listed are trademarks of their respective owners and are not trademarks of
291 GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse
292 GlaxoSmithKline or its products.

293

294



295

296 GlaxoSmithKline

297 Research Triangle Park, NC 27709

298

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300

301 Month Year

302 ADD:XMG

Appendix A:
Initial REMS Approval 04/2008
Most Recent Modification: 05/2011

NDA 21-077 ADVAIR DISKUS[®] (fluticasone propionate and salmeterol xinafoate) Inhalation Powder 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg

Corticosteroid and Long-Acting Beta₂-Adrenergic Agonist

GlaxoSmithKline, Five Moore Drive,

P.O. Box 13398, Research Triangle Park, NC 27709

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

1. To inform healthcare providers and prescribers of the increased risk of asthma-related death and serious outcomes with the long-acting beta₂-adrenergic agonists (LABA) including ADVAIR DISKUS.
2. To inform healthcare providers and prescribers of the appropriate use of long-acting beta₂-adrenergic agonists (LABA) including ADVAIR DISKUS.
3. To inform patients that long-acting beta₂-adrenergic agonists (LABA) medicines, such as salmeterol xinafoate, one of the active moieties in ADVAIR DISKUS, have been associated with an increased risk of death from asthma related events.
4. To inform patients of other serious risks associated with the use of ADVAIR DISKUS.

II. REMS ELEMENTS

A. MEDICATION GUIDE

A Medication Guide will be dispensed with each ADVAIR DISKUS inhalation powder prescription in accordance with 21 CFR 208.24.

B. COMMUNICATION PLAN

GSK will implement a communication plan to healthcare providers to support implementation of this REMS.

The communication plan will include:

1. A Dear Healthcare Professional Letter (DHCPL) that will be distributed to current and potential prescribers of LABAs: Allergists, Pulmonologists, Primary Care Physicians (Family Practice, General Practice and Internal Medicine), Pediatricians, and Allied Health (Nurse Practitioners and Physician Assistants)

Distribution of the DHCPL will be via direct mail, e-mail, or hand carry with the following timeline:

- a. Initial distribution within 60 days of REMS approval

Appendix A:
Initial REMS Approval 04/2008
Most Recent Modification: 05/2011

- b. Second distribution at or about 6 months' post-REMS approval.

The DHCPL will include the following safety information:

- a. Increased risk of asthma-related death in patients taking LABAs
 - b. New prescribing guidelines:
 - i. ADVAIR DISKUS should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA
 - ii. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue ADVAIR DISKUS) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.
 - iii. ADVAIR DISKUS should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
2. Printed or web-based information for healthcare providers will be posted on a GSK website within 30 days of the REMS approval. This information will remain on the website for 3 years. The content of the print or web-based material will, at a minimum, include the following:
- i. Information about the risk
 - ii. Key data regarding the risk (e.g. SMART, SNS)
 - iii. New prescribing guidelines
 - iv. Currently available LABAs and approved uses
 - v. Prescribing information for ADVAIR DISKUS
 - vi. Patient Counseling Information
 - vii. Medication Guide for ADVAIR DISKUS
 - viii. Questions and Answers
 - ix. DHCP letter (for a period of 1 year)
3. GSK will communicate via letter to the leadership of the following Professional Societies:
- American Academy of Allergy, Asthma & Immunology (AAAAI)
 - American College of Allergy, Asthma & Immunology (ACAAI)
 - American Thoracic Society (ATS)
 - American College of Chest Physicians (ACCP)
 - American Academy of Pediatrics (AAP)
 - American Academy of Family Physicians (AAFP)
 - American College of Physicians (ACP)
 - National Medical Association (NMA)
 - American Academy of Nurse Practitioners (AANP)
 - American Academy of Physician Assistants (AAPA)

Appendix A:
Initial REMS Approval 04/2008
Most Recent Modification: 05/2011

The communication to the professional societies will also include the information that is also available under Section II.B.2 above. GSK will request that these societies disseminate this information to their members. If available from professional societies, a total number of recipients will be communicated to the agency in the first modified REMS annual assessment.

The timeline for REMS communication materials to professional societies will parallel the direct mail, e-mail, or hand carry program:

- i. Initial distribution within 60 days of REMS approval;
- ii. Second distribution at or about 6 months' post-REMS approval.

The following materials are part of the REMS and are attached:

- i. DHCPL
- ii. Printed or web-based information
- iii. Dear (Medical Society) Letter

C. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

GSK will submit REMS assessments to FDA annually from the date of the approval of the modified REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. GSK will submit the assessment report so that it will be received by the FDA on or before the due date.

NDA 21-077; ADVAIR DISKUS

Attachment 1; Dear Healthcare Professional Letter

(GlaxoSmithKline Letterhead and Date)

Dear Healthcare Professional:

GlaxoSmithKline would like to inform you of important safety information for ADVAIR DISKUS[®] (fluticasone propionate and salmeterol xinafoate inhalation powder) and ADVAIR[®] HFA (fluticasone propionate and salmeterol xinafoate inhalation aerosol). ADVAIR DISKUS is a combination product containing a corticosteroid and a long acting beta₂-adrenergic agonist (LABA) indicated for the treatment of asthma in patients aged 4 years and older. ADVAIR DISKUS 250/50 is also indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema and to reduce exacerbations of COPD in patients with a history of exacerbations. ADVAIR HFA is a combination product containing a corticosteroid and a LABA indicated for treatment of asthma in patients aged 12 years and older. ADVAIR HFA is not indicated for the treatment of COPD. ADVAIR DISKUS/ADVAIR HFA is not indicated for the relief of acute bronchospasm.

Important safety information related to ADVAIR DISKUS/ADVAIR HFA includes:

- Increased risk of asthma-related death in patients taking LABAs.
- New prescribing guidelines.
 - ADVAIR DISKUS/ADVAIR HFA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.
 - Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS/ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.
 - ADVAIR DISKUS/ ADVAIR HFA should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

ADVAIR DISKUS/ADVAIR HFA has a risk evaluation and mitigation strategy (REMS) that consists of a Medication Guide and a communication program.

The ADVAIR DISKUS/ADVAIR HFA prescribing information includes a boxed warning to highlight the safety issue of asthma-related death.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR DISKUS/ADVAIR HFA, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT[®] Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out

NDA 21-077; ADVAIR DISKUS

Attachment 1; Dear Healthcare Professional Letter

of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS/ADVAIR HFA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS/ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS/ADVAIR HFA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Please note that ADVAIR DISKUS/ADVAIR HFA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma.

When prescribing ADVAIR DISKUS/ADVAIR HFA, please also provide the patient with an inhaled short-acting beta₂-agonist (e.g., albuterol) to be used as a rescue inhaler for treatment of acute symptoms. Increasing use of inhaled, short-acting beta₂-agonists is a marker for deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen.

Please instruct the patients to contact you if breathing problems worsen over time while using ADVAIR DISKUS/ADVAIR HFA and get emergency medical care if breathing problems worsen quickly and are not being relieved by the use of the rescue inhaler.

There is an increased risk of pneumonia in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS 250/50. Monitor patients for signs and symptoms of pneumonia as the clinical features of pneumonia and exacerbations frequently overlap.

Please take time to read the enclosed ADVAIR DISKUS and ADVAIR HFA Package Inserts for full prescribing information, for complete description of this important safety information and the new prescribing guidelines.

In addition, please review the attached Medication Guides with each patient who is prescribed ADVAIR DISKUS or ADVAIR HFA.

The Medication Guide will be enclosed in each carton packaging and must be provided by the authorized dispensers to each patient to whom the drug is dispensed.

To report adverse events potentially associated with ADVAIR DISKUS or ADVAIR HFA, please call GlaxoSmithKline at 1-888-825-5249.

NDA 21-077; ADVAIR DISKUS

Attachment 1; Dear Healthcare Professional Letter

Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by:

- Phone at 1-800-FDA-1088 (1-800-332-1088)
- Facsimile at 1-800-FDA-0178 (1-800-332-0178)
- Mail using FDA Form 3500 located at <http://www.fda.gov/medwatch>

Please contact GlaxoSmithKline at 1-888-825-5249 if you have any questions about ADVAIR DISKUS, ADVAIR HFA or the information in this letter.

Sincerely,

Ellen R. Strahlman, MD
Chief Medical Officer
GlaxoSmithKline

NDA 21-077; ADVAIR DISKUS®

Attachment 2; Print / Web-Based Information

Printed/Web-Based Information

The following content will be housed in a healthcare provider section of the product website.

- Information about the risk

Due to an increased risk of asthma-related death, FDA has mandated that all Long-Acting Beta Agonists (LABAs) and LABA-containing products, like ADVAIR DISKUS, carry a boxed warning. The boxed warning for ADVAIR DISKUS reads as follows:

WARNING: ASTHMA-RELATED DEATH

Long-acting beta2-adrenergic agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR DISKUS®, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

See the full Prescribing Information (link) for a more complete description of the risks associated with the use of ADVAIR DISKUS in the treatment of asthma.

- Key data regarding the risk of asthma-related death (e.g. SMART, SNS)

FDA's decision to require a Risk Evaluation and Mitigation Strategy (REMS) and class-labeling changes to the drug labels for Long-Acting Beta-Agonists (LABAs) is based on analyses from the Salmeterol Multi-center Asthma Research Trial (SMART), the Salmeterol Nationwide Surveillance study (SNS), and a meta-analysis conducted by FDA in 2008 and discussed at the joint Pulmonary Allergy Drugs, Drug Safety and Risk Management, and Pediatric Advisory Committees, held on December 10-11, 2008 (for complete safety reviews and background information discussed at this meeting see the following link: [December 10-11 2008 AC meeting](#)).

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SMART was a large, randomized, 28-week, placebo-controlled trial that evaluated patients 12 years of age and older receiving standard asthma therapy and the addition of either salmeterol or placebo. A total of 26,355 patients were evaluated in this study. Results showed that patients receiving salmeterol were at an increased risk for asthma-related death compared to patients receiving placebo. Subgroup analyses were also performed and found that asthma-related death in Caucasians and African Americans occurred at a higher rate in patients using salmeterol compared to placebo. See Table 1 below for results from SMART.

Table 1 SMART Results

SMART Patients	Asthma-Related Deaths in Salmeterol Group n (%)*	Asthma-Related Deaths in Placebo Group n (%)*	Relative Risk of Asthma-Related Death (95% Confidence Interval)	Excess Deaths Expressed per 10,000 Patients+ (95% Confidence Interval)
All Patients § Salmeterol: n = 13,176 Placebo: n = 13,179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Patients Salmeterol: n = 9,281 Placebo: n = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
African American Patients Salmeterol: n = 2,366 Placebo: n = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

* 28-week estimate, adjusted according to actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

+ Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

§ The Total Population includes Caucasian, African American, Hispanic, Asian, and "Other" and "not reported". No asthma-related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related

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death occurred in the placebo group in the subpopulation whose ethnic origin was "not reported" (salmeterol n = 130, placebo n = 127).

The SNS was a 16-week, double-blind study that compared the addition of salmeterol or albuterol to standard asthma therapy in 25,180 asthma patients who were 12 years of age and older. In the study, there was an increase in the number of respiratory and asthma-related deaths in the salmeterol group (0.07% [12 out of 16,787 patients]) compared to the albuterol group (0.02% [2 out of 8,393 patients] relative risk of 3.0, p=0.105).

In preparation for the December 2008 Advisory Committee, FDA conducted a meta-analysis of 110 studies evaluating the use of LABAs in 60,954 patients with asthma. The meta-analysis used a composite endpoint to measure severe exacerbation of asthma symptoms (asthma-related death, intubation, and hospitalization). The results of the meta-analysis suggested an increased risk for severe exacerbation of asthma symptoms in patients using LABAs compared to those not using LABAs. The largest risk difference per 1,000 treated patients was seen in children 4-11 years of age, see Table 2 below. The results of the meta-analysis were primarily driven by asthma-related hospitalizations. Other meta-analyses evaluating the safety of LABAs in the treatment of asthma have not shown a significant increase in the risk for severe asthma exacerbations.

Table 2 Meta-Analysis Results: Number of Patients Experiencing an Event*

Patient Population	LABA Patients experiencing an event	Non-LABA Patients experiencing an event	Risk Difference Estimate per 1000 treated patients	95% Confidence Interval
All Patients n = 30,148 LABA patients n = 30,806 non-LABA patients	381	304	2.80	1.11 – 4.49
Patients ages 12 to 17 years n = 3,103 LABA patients n = 3,289 non-LABA patients	48	30	5.57	0.21 – 10.92
Patients ages 4 to 11 years n = 1,626	61	39	14.83	3.24 – 26.43

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LABA patients n = 1,789 non-LABA patients				
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* Event defined as the composite endpoint (asthma-related death, intubation, and hospitalization)

At this time, there are insufficient data to conclude whether using LABAs with an inhaled corticosteroid reduces or eliminates the risk of asthma-related death and hospitalizations. FDA is requiring the manufacturers of LABAs to conduct studies evaluating the safety of LABAs when used in conjunction with an inhaled corticosteroid.

Based on the available information, FDA concludes there is an increased risk for severe exacerbation of asthma symptoms, leading to hospitalizations in pediatric and adult patients as well as death in some patients using LABAs for the treatment of asthma. The agency is requiring the REMS and class-labeling changes to improve the safe use of these products.

See [February 2010 LABA Drug Safety Communication](#) for more information.

Link:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm>

- New prescribing guidelines

Long-Acting Beta-Agonists (LABAs), a class of medications used for the treatment of asthma, now have new recommendations in their drug label intended to promote their safe use in the treatment of asthma.

In February 2010, the agency announced it was requiring manufacturers to revise their drug labels because of an increased risk of severe exacerbation of asthma symptoms, leading to hospitalizations, in pediatric and adult patients, as well as death in some patients using LABAs for the treatment of asthma (see [February 2010 LABA Drug Safety Communication](#)).

In June 2010, the agency issued updated recommendations on the appropriate use of LABAs. See [June 2010 LABA Drug Safety Communication](#) for more information.

Link:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm>

The new recommendations in the updated labels state:

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- Use of a LABA alone without use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated (absolutely advised against) in the treatment of asthma.
- LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
- LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.

FDA has stated its belief that when LABAs are used according to the recommendations outlined above and in the approved drug labels, the benefits of LABAs in improving asthma symptoms outweigh their risks of increasing severe asthma exacerbations and deaths from asthma.

- Currently available LABAs and their approved uses

FDA Approved Long-Acting Beta Agonists

Brand Name	LABA Active Ingredient	Corticosteroid Active Ingredient	FDA Approved Uses
ADVAIR DISKUS	Salmeterol	Fluticasone	Asthma, COPD
ADVAIR HFA	Salmeterol	Fluticasone	Asthma
SEREVENT DISKUS	Salmeterol	None	Asthma, COPD, Exercise-Induced Bronchospasm (EIB)
Brovana	Arformoterol	None	COPD
Foradil Aerolizer	Formoterol	None	Asthma, COPD, Exercise-Induced Bronchospasm (EIB)
Foradil Certihaler*	Formoterol	None	Asthma
Perforomist	Formoterol	None	COPD
Dulera Inhalation	Formoterol	Mometasone	Asthma

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Aerosol			
Symbicort	Formoterol	Budesonide	Asthma, COPD

* not currently marketed in the U.S.

See [June 2010 LABA Drug Safety Communication](#) for more information.

Link:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm>

- Prescribing information for ADVAIR DISKUS

LINK – http://us.gsk.com/products/assets/us_advair.pdf

- Patient Counseling Information

Patient Counseling Information

See USPI and Medication Guide

Asthma-Related Death

See Medication Guide

Patients should be informed that salmeterol, one of the active ingredients in ADVAIR DISKUS, increases the risk of asthma-related death. In pediatric and adolescent patients, salmeterol may increase the risk of asthma-related hospitalization. They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, the other component of ADVAIR DISKUS, or other long-term asthma control therapy mitigates or eliminates this risk. See Warnings and Precautions Section 5.1 of the full [Prescribing Information](#).

Not for Acute Symptoms

ADVAIR DISKUS is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta₂-agonist (the healthcare provider should prescribe a short-acting, beta₂-agonist and instruct the patient in how it should be used).

Patients should be instructed to seek medical attention immediately if they experience any of the following:

- If their symptoms worsen
- Significant decrease in lung function as outlined by the physician
- If they need more inhalations of a short-acting beta₂-agonist than usual

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Patients should be advised not to increase the dose or frequency of ADVAIR DISKUS. The daily dosage of ADVAIR DISKUS should not exceed one inhalation twice daily. If they miss a dose, they should be instructed to take their next dose at the same time they normally do. ADVAIR DISKUS provides bronchodilation for up to 12 hours.

Patients should not stop or reduce ADVAIR DISKUS therapy without physician/provider guidance since symptoms may recur after discontinuation. See Warnings and Precautions Section 5.2 of the full [Prescribing Information](#).

Do Not Use Additional Long-Acting Beta₂-Agonists

When patients are prescribed ADVAIR DISKUS, other long-acting beta₂-agonists should not be used. See Warnings and Precautions Section 5.3 of the full [Prescribing Information](#).

Risks Associated With Corticosteroid Therapy

Local Effects: Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with ADVAIR DISKUS therapy, but at times therapy with ADVAIR DISKUS may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised. See Warnings and Precautions Section 5.4 of the full [Prescribing Information](#).

Pneumonia in patients with COPD: Lower respiratory tract infections, including pneumonia, have been reported in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. See Warnings and Precautions Section 5.5 of the full [Prescribing Information](#).

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex. See Warnings and Precautions Section 5.6 of the full [Prescribing Information](#).

Hypercorticism and Adrenal Suppression: Patients should be advised that ADVAIR DISKUS may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to ADVAIR DISKUS/ADVAIR HFA. See Warnings and Precautions Section 5.8 of the full [Prescribing Information](#).

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and

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should be monitored and, where appropriate, be treated for this condition. See Warnings and Precautions Section 5.13 of the full [Prescribing Information](#).

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, a component of ADVAIR DISKUS, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of pediatric patients taking corticosteroids by any route. See Warnings and Precautions Section 5.14 of the full [Prescribing Information](#).

Glaucoma and Cataracts: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (glaucoma or cataracts); regular eye examinations should be considered. See Warnings and Precautions Section 5.15 of the full [Prescribing Information](#).

Risks Associated With Beta-Agonist Therapy

Patients should be informed that treatment with beta₂-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor or nervousness and death. See Warnings and Precautions Section 5.12 of the full [Prescribing Information](#).

- Medication Guide for ADVAIR DISKUS
LINK - http://us.gsk.com/products/assets/us_advair.pdf
- Questions and Answers

Questions about LABA Safety and Risk Evaluation and Mitigation Strategy (REMS) for LABAs

Q1. Why is FDA requiring LABA manufacturers to have a risk management program for these medicines?

Q2. What is the goal of the new risk management program for LABAs?

Q3. What are the key points people should know about the safe use of LABAs in patients with asthma?

Q4. What are the names of LABA-containing medicines used to treat asthma?

Q5. Why should LABAs only be used with a long-term asthma control medication, are they safer when used this way?

Q6. What information did FDA review to help the Agency decide to require a risk management program?

Questions about ADVAIR DISKUS Inhalation Powder

Q1. Why does ADVAIR DISKUS have a boxed warning?

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Q2. What should I tell patients about the risk of asthma-related death?

Q3. Can ADVAIR DISKUS be used for acute asthma symptoms?

Q4. Can additional LABAs be used with ADVAIR DISKUS?

Q5. What are the risks of Corticosteroid Therapy?

Q6. What are the risks of Beta-Agonist Therapy?

Questions about LABA safety

Q1. Why is FDA requiring LABA manufacturers to have a risk management program for these medicines?

A. Despite the benefits of long-acting beta₂-agonists (LABAs) in helping people with asthma, FDA's analyses indicate there is an increase in the risk of severe exacerbation of asthma symptoms leading to hospitalizations in pediatric and adult patients as well as death in some patients with asthma that use a LABA compared to patients with asthma that do not use a LABA. Because of this risk, FDA wants to make sure LABAs are used appropriately in patients with asthma. In order to ensure the safe use of these medicines, FDA is requiring the manufacturers of LABAs to develop this risk management program for healthcare professionals and patients.

Q2. What is the goal of the new risk management program for LABAs?

A. The risk management program for LABAs requires the manufacturers to better inform healthcare professionals and patients about the risk of LABAs for patients with asthma and ways to decrease that risk while maintaining the benefits of the drug. Under the program, patients who have a prescription filled for a LABA will receive a revised Medication Guide that explains the risks and benefits of the medicine. In addition manufacturers of LABAs will update the prescribing information they provide to healthcare professionals to include the latest recommendations for safe use of these important medicines.

Q3. What are the key points people should know about the safe use of LABAs in patients with asthma?

A. The key points are:

- Use of a LABA alone without use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated (absolutely advised against) in the treatment of asthma.
- LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

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- LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.

Q4. What are the names of LABA-containing medicines used to treat asthma?

Brand Name(s)	Generic Name(s)	Description
ADVAIR DISKUS	Salmeterol and Fluticasone	Salmeterol is a LABA and fluticasone is a corticosteroid long-term asthma control medicine
ADVAIR HFA	Salmeterol and Fluticasone	Salmeterol is a LABA and fluticasone is a corticosteroid long-term asthma control medicine
SEREVENT DISKUS	Salmeterol	Single ingredient LABA with no corticosteroid long-term asthma control medication
Foradil Aerolizer	Formoterol	Single ingredient LABA with no corticosteroid long-term asthma control medication
Dulera Inhalation Aerosol	Formoterol and Mometasone	Formoterol is a LABA and mometasone is a corticosteroid long-term asthma control medication
Symbicort Inhalation Aerosol	Formoterol and Budesonide	Formoterol is a LABA and budesonide is a corticosteroid long-term asthma control medication

Q5. Why should LABAs only be used with a long-term asthma control medication, are they safer when used this way?

A. At this time, there is no conclusive evidence that the combination of a long-term asthma control medication with a LABA decreases or eliminates the risk of a LABA. More study and analysis is required in this area. FDA is requiring the manufacturers of LABAs to conduct studies evaluating the safety of LABAs when used with an inhaled corticosteroid to better understand this issue.

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Because of the risks of LABAs, FDA recommends that a LABA should not be used for a patient whose asthma can be controlled with long-term asthma control medication, such as an inhaled corticosteroid. If a LABA needs to be added to that medicine, it should only be used until the patient's healthcare professional determines their asthma is under control, and then the LABA should be stopped if possible. This means it is always necessary for a patient to use a LABA in combination with a long-term asthma control medication.

Q6. What information did FDA review to help the Agency decide to require a risk management program?

A. FDA used a variety of studies and research in patients with asthma using a LABA. Two specific studies that provided valuable information were 1) the Salmeterol Multi-center Asthma Research Trial (SMART) and 2), the Serevent Nationwide Surveillance study (SNS). Salmeterol is the LABA in SEREVENT. Each of these studies showed a higher risk of death for patients with asthma that used a LABA (salmeterol) compared to patients with asthma that did not use a LABA. In addition, FDA used a research method called a meta-analysis to further understand the risks associated with the use of LABAs in patients with asthma. A meta-analysis uses data from multiple studies on a particular topic to enable scientists to combine information from those studies to make scientific conclusions or recommendations in that area. For more information on these specific studies, please see [February 2010 LABA Drug Safety Communication](#) for more information.

Questions about ADVAIR DISKUS

Q1. Why does ADVAIR DISKUS have a boxed warning?

A. Due to an increased risk of asthma-related death, FDA has mandated that all Long-Acting Beta-Agonists (LABAs) and LABA-containing products, like ADVAIR DISKUS, carry a boxed warning. The boxed warning for ADVAIR DISKUS reads as follows:

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR DISKUS®, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy

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(e.g., discontinue ADVAIR DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

See the full [Prescribing Information](#) for a more complete description of the risks associated with the use of ADVAIR DISKUS in the treatment of asthma.

Q2. What should I tell patients about the risk of asthma-related death?

A. Patients should be informed that salmeterol, one of the active ingredients in ADVAIR DISKUS, increases the risk of asthma-related death. In pediatric and adolescent patients, salmeterol may increase the risk of asthma-related hospitalization. They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids or other long-term asthma-control therapy mitigates this risk. See Warnings and Precautions Section 5.1 of the full [Prescribing Information](#).

Q3. Can ADVAIR DISKUS be used for acute asthma symptoms?

A. No. ADVAIR DISKUS is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta₂-agonist (the healthcare provider should prescribe a short-acting, beta₂-agonist and instruct the patient in how it should be used). Patients should be instructed to seek medical attention immediately if they experience any of the following:

- If their symptoms worsen
- Significant decrease in lung function as outlined by the physician
- If they need more inhalations of a short-acting beta₂-agonist than usual

Patients should be advised not to increase the dose or frequency of ADVAIR DISKUS. The daily dosage of ADVAIR DISKUS should not exceed one inhalation twice daily. If they miss a dose, they should be instructed to take their next dose at the same time they normally do. ADVAIR DISKUS provides bronchodilation for up to 12 hours.

Patients should not stop or reduce ADVAIR DISKUS therapy without physician/provider guidance since symptoms may recur after discontinuation. See Warnings and Precautions Section 5.2 of the full [Prescribing Information](#).

Q4. Can additional LABAs be used with ADVAIR DISKUS?

A. No. When patients are prescribed ADVAIR DISKUS, other long-acting beta₂-agonists should not be used. See Warnings and Precautions Section 5.3 of the full [Prescribing Information](#).

Q5 What are the risks of Corticosteroid Therapy

Local Effects: Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis

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develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with ADVAIR DISKUS therapy, but at times therapy with ADVAIR DISKUS may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised. See Warnings and Precautions Section 5.4 of the full [Prescribing Information](#).

Pneumonia in patients with COPD: Lower respiratory tract infections, including pneumonia, have been reported in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. See Warnings and Precautions Section 5.5 of the full [Prescribing Information](#).

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex. See Warnings and Precautions Section 5.6 of the full [Prescribing Information](#).

Hypercorticism and Adrenal Suppression: Patients should be advised that ADVAIR DISKUS may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to ADVAIR DISKUS/ADVAIR HFA. See Warnings and Precautions Section 5.8 of the full [Prescribing Information](#).

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and should be monitored and, where appropriate, be treated for this condition. See Warnings and Precautions Section 5.13 of the full [Prescribing Information](#).

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, a component of ADVAIR DISKUS, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of pediatric patients taking corticosteroids by any route. See Warnings and Precautions Section 5.14 of the full [Prescribing Information](#).

Glaucoma and Cataracts: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (glaucoma or cataracts); regular eye examinations should be considered. See Warnings and Precautions Section 5.15 of the full [Prescribing Information](#).

Q6. What are the risks of Beta-Agonist Therapy?

A. Patients should be informed that treatment with beta₂-agonists may lead to adverse events that include palpitations, chest pain, rapid heart rate, tremor or nervousness. See Warnings and Precautions Section 5.12 of the full [Prescribing Information](#).

This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>

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For more information:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm>

- DHCP Letter (for a period of 1 year)

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Attachment 3; Dear Medical Society Letter

(GlaxoSmithKline Letterhead and Date)

Dear (Medical Society):

GlaxoSmithKline would like to inform you of important safety information for ADVAIR DISKUS® (fluticasone propionate and salmeterol xinafoate inhalation powder) and ADVAIR® HFA (fluticasone propionate and salmeterol xinafoate inhalation aerosol). ADVAIR DISKUS is a combination product containing a corticosteroid and a long acting beta₂-adrenergic agonist (LABA) indicated for the treatment of asthma in patients aged 4 years and older. ADVAIR DISKUS 250/50 is also indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema and to reduce exacerbations of COPD in patients with a history of exacerbations. ADVAIR HFA is a combination product containing a corticosteroid and a LABA indicated for treatment of asthma in patients aged 12 years and older. ADVAIR HFA is not indicated for the treatment of COPD. ADVAIR DISKUS/ADVAIR HFA is not indicated for the relief of acute bronchospasm.

Important safety information related to ADVAIR DISKUS includes:

- Increased risk of asthma-related death in patients taking LABAs.
- New prescribing guidelines.
 - ADVAIR DISKUS/ADVAIR HFA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.
 - Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS/ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.
 - ADVAIR DISKUS/ ADVAIR HFA should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

ADVAIR DISKUS/ADVAIR HFA has a risk evaluation and a mitigation strategy (REMS) that consists of a Medication Guide and a communication program.

The ADVAIR DISKUS/ADVAIR HFA prescribing information includes a boxed warning to highlight the safety issue of asthma-related death.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR DISKUS/ADVAIR HFA, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176

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Attachment 3; Dear Medical Society Letter

patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS/ADVAIR HFA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS/ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS/ADVAIR HFA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Please note that ADVAIR DISKUS/ADVAIR HFA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma.

When prescribing ADVAIR DISKUS/ADVAIR HFA, the healthcare professional should be guided to also provide the patient with an inhaled short-acting beta₂-agonist (e.g., albuterol) to be used as a rescue inhaler for treatment of acute symptoms. Increasing use of inhaled, short-acting beta₂-agonists is a marker for deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen.

The healthcare professional should instruct the patients to contact them if breathing problems worsen over time while using ADVAIR DISKUS/ADVAIR HFA and get emergency medical care if breathing problems worsen quickly and are not being relieved by the use of the rescue inhaler.

There is an increased risk of pneumonia in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS 250/50. Monitor patients for signs and symptoms of pneumonia as the clinical features of pneumonia and exacerbations frequently overlap.

Please take time to read the enclosed ADVAIR DISKUS and ADVAIR HFA Package Inserts for full prescribing information, for complete description of this important safety information and the new prescribing guidelines. Visit [insert web link; alternative is to include reference to enclosed hard copies] for additional information about the risk of serious asthma outcomes and the safe use of LABAs.

We are asking you to share this communication with members of your society and advise practitioners prescribing ADVAIR DISKUS/ADVAIR HFA to discuss the benefits and risks of LABAs with their patients. They should also encourage each patient prescribed ADVAIR DISKUS/ADVAIR HFA to thoroughly review the enclosed Medication Guide prior to using.

NDA 21-077; ADVAIR DISKUS®

Attachment 3; Dear Medical Society Letter

The Medication Guide will be enclosed in each carton packaging and must be provided by the authorized dispensers to each patient to whom the drug is dispensed.

To report adverse events potentially associated with ADVAIR DISKUS/ADVAIR HFA, please call GlaxoSmithKline at 1-888-825-5249.

Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by:

- Phone at 1-800-FDA-1088 (1-800-332-1088)
- Facsimile at 1-800-FDA-0178 (1-800-332-0178)
- Mail using FDA Form 3500 located at <http://www.fda.gov/medwatch>

Please contact GlaxoSmithKline at 1-888-825-5249 if you have any questions about ADVAIR DISKUS/ADVAIR HFA or the information in this letter.

Sincerely,

Ellen R. Strahlman, MD
Chief Medical Officer
GlaxoSmithKline

1 **MEDICATION GUIDE**

2 **ADVAIR[®] HFA [ad' vair] 45/21 Inhalation Aerosol**
3 **(fluticasone propionate 45 mcg and salmeterol 21 mcg)**

4 **ADVAIR[®] HFA 115/21 Inhalation Aerosol**
5 **(fluticasone propionate 115 mcg and salmeterol 21 mcg)**

6 **ADVAIR[®] HFA 230/21 Inhalation Aerosol**
7 **(fluticasone propionate 230 mcg and salmeterol 21 mcg)**
8

9 Read the Medication Guide that comes with ADVAIR HFA Inhalation Aerosol before you start
10 using it and each time you get a refill. There may be new information. This Medication Guide
11 does not take the place of talking to your healthcare provider about your medical condition or
12 treatment.

13
14 **What is the most important information I should know about ADVAIR HFA?**

15 **ADVAIR HFA can cause serious side effects, including:**

- 16 1. **People with asthma who take long-acting beta₂-adrenergic agonist (LABA) medicines,**
17 **such as salmeterol (one of the medicines in ADVAIR HFA), have an increased risk of**
18 **death from asthma problems.** It is not known whether fluticasone propionate, the other
19 medicine in ADVAIR HFA, reduces the risk of death from asthma problems seen with
20 salmeterol.
- 21 • **Call your healthcare provider if breathing problems worsen over time while using**
22 **ADVAIR HFA.** You may need different treatment.
 - 23 • **Get emergency medical care if:**
 - 24 • breathing problems worsen quickly and
 - 25 • you use your rescue inhaler medicine, but it does not relieve your breathing problems.
- 26 2. ADVAIR HFA should be used only if your healthcare provider decides that your asthma is
27 not well controlled with a long-term asthma control medicine, such as inhaled
28 corticosteroids.
- 29 3. When your asthma is well controlled, your healthcare provider may tell you to stop taking
30 ADVAIR HFA. Your healthcare provider will decide if you can stop ADVAIR HFA without
31 loss of asthma control. Your healthcare provider may prescribe a different long-term asthma
32 control medicine for you, such as an inhaled corticosteroid.
- 33 4. Children and adolescents who take LABA medicines may have an increased risk of being
34 hospitalized for asthma problems.

35
36 **What is ADVAIR HFA?**

- 37 • ADVAIR HFA combines an inhaled corticosteroid medicine, fluticasone propionate (the
38 same medicine found in FLOVENT[®]), and a LABA medicine, salmeterol (the same medicine
39 found in SEREVENT[®]).
- 40 • Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the
41 lungs can lead to asthma symptoms.
- 42 • LABA medicines are used in people with asthma and chronic obstructive pulmonary
43 disease (COPD). LABA medicines help the muscles around the airways in your lungs
44 stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These
45 symptoms can happen when the muscles around the airways tighten. This makes it hard
46 to breathe. In severe cases, wheezing can stop your breathing and cause death if not
47 treated right away.
- 48 • ADVAIR HFA is used to control symptoms of asthma and to prevent symptoms such as
49 wheezing in adults and children aged 12 years and older.
- 50 • ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). LABA
51 medicines, such as salmeterol, increase the risk of death from asthma problems.

52 ADVAIR HFA is not for adults and children with asthma who are well controlled with an asthma
53 control medicine, such as a low to medium dose of an inhaled corticosteroid medicine.
54

55 **Who should not use ADVAIR HFA?**

56 Do not use ADVAIR HFA:

- 57 • to treat sudden, severe symptoms of asthma and
- 58 • if you are allergic to any of the ingredients in ADVAIR HFA. See the end of this
59 Medication Guide for a list of ingredients in ADVAIR HFA.
60

61 **What should I tell my healthcare provider before using ADVAIR HFA?**

62 **Tell your healthcare provider about all of your health conditions, including if you:**

- 63 • **have heart problems**
- 64 • **have high blood pressure**
- 65 • **have seizures**
- 66 • **have thyroid problems**
- 67 • **have diabetes**
- 68 • **have liver problems**
- 69 • **have osteoporosis**
- 70 • **have an immune system problem**
- 71 • **are pregnant or planning to become pregnant.** It is not known if ADVAIR HFA may
72 harm your unborn baby.

73 • **are breastfeeding.** It is not known if ADVAIR HFA passes into your milk and if it can
74 harm your baby.

75 • **are allergic to ADVAIR HFA or any other medicines**

76 • **are exposed to chickenpox or measles**

77 Tell your healthcare provider about all the medicines you take including prescription and
78 non-prescription medicines, vitamins, and herbal supplements. ADVAIR HFA and certain other
79 medicines may interact with each other. This may cause serious side effects. Especially, tell your
80 healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR[®] (ritonavir capsules)
81 Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA[®] (lopinavir/ritonavir) Tablets
82 contain ritonavir.

83 Know the medicines you take. Keep a list and show it to your healthcare provider and pharmacist
84 each time you get a new medicine.

85

86 **How do I use ADVAIR HFA?**

87 **See the step-by-step instructions for using ADVAIR HFA at the end of this Medication**
88 **Guide.** Do not use ADVAIR HFA unless your healthcare provider has taught you and you
89 understand everything. Ask your healthcare provider or pharmacist if you have any questions.

90 • Use ADVAIR HFA exactly as prescribed. **Do not use ADVAIR HFA more often**
91 **than prescribed.** ADVAIR HFA comes in 3 strengths. Your healthcare provider has
92 prescribed the one that is best for your condition.

93 • The usual dosage of ADVAIR HFA is 2 inhalations 2 times each day (morning and
94 evening). The 2 doses should be about 12 hours apart. Rinse your mouth with water after
95 using ADVAIR HFA.

96 • If you miss a dose of ADVAIR HFA, just skip that dose. Take your next dose at your
97 usual time. Do not take 2 doses at one time.

98 • **While you are using ADVAIR HFA 2 times each day, do not use other medicines**
99 **that contain a LABA for any reason.** Ask your healthcare provider or pharmacist if any of
100 your other medicines are LABA medicines.

101 • Do not stop using ADVAIR HFA or other asthma medicines unless told to do so by
102 your healthcare provider because your symptoms might get worse. Your healthcare provider
103 will change your medicines as needed.

104 • ADVAIR HFA does not relieve sudden symptoms. Always have a rescue inhaler
105 medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting
106 bronchodilator, call your healthcare provider to have one prescribed for you.

107 • Call your healthcare provider or get medical care right away if:

108 • your breathing problems worsen with ADVAIR HFA

- 109 • you need to use your rescue inhaler medicine more often than usual
- 110 • your rescue inhaler medicine does not work as well for you at relieving symptoms
- 111 • you need to use 4 or more inhalations of your rescue inhaler medicine for 2 or more
- 112 days in a row
- 113 • you use 1 whole canister of your rescue inhaler medicine in 8 weeks' time
- 114 • your peak flow meter results decrease. Your healthcare provider will tell you the
- 115 numbers that are right for you.
- 116 • you have asthma and your symptoms do not improve after using ADVAIR HFA
- 117 regularly for 1 week
- 118

119 **What are the possible side effects with ADVAIR HFA?**

120 **ADVAIR HFA can cause serious side effects, including:**

- 121 • **See “What is the most important information I should know about ADVAIR HFA?”**
- 122 • **serious allergic reactions.** Call your healthcare provider or get emergency medical
- 123 care if you get any of the following symptoms of a serious allergic reaction:
- 124 • rash
- 125 • hives
- 126 • swelling of the face, mouth, and tongue
- 127 • breathing problems
- 128 • **sudden breathing problems immediately after inhaling your medicine**
- 129 • **effects on heart**
- 130 • increased blood pressure
- 131 • a fast and irregular heartbeat
- 132 • chest pain
- 133 • **effects on nervous system**
- 134 • tremor
- 135 • nervousness
- 136 • **reduced adrenal function (may result in loss of energy)**
- 137 • **changes in blood (sugar, potassium, certain types of white blood cells)**
- 138 • **weakened immune system and a higher chance of infections**
- 139 • **lower bone mineral density.** This may be a problem for people who already have a
- 140 higher chance of low bone density (osteoporosis).
- 141 • **eye problems including glaucoma and cataracts.** You should have regular eye exams
- 142 while using ADVAIR HFA.
- 143 • **slowed growth in children.** A child's growth should be checked often.

- 144 • **throat tightness**
- 145 • **pneumonia.** ADVAIR HFA contains the same medicine found in ADVAIR DISKUS[®].
146 ADVAIR DISKUS is used to treat people with asthma and people with chronic obstructive
147 pulmonary disease (COPD). People with COPD have a higher chance of getting pneumonia.
148 ADVAIR DISKUS may increase the chance of getting pneumonia. ADVAIR HFA has not
149 been studied in people with COPD. Call your healthcare provider if you notice any of the
150 following symptoms:
- 151 • increase in mucus (sputum) production
 - 152 • change in mucus color
 - 153 • fever
 - 154 • chills
 - 155 • increased cough
 - 156 • increased breathing problems

157 **Common side effects of ADVAIR HFA include:**

- 158 • upper respiratory tract infection
- 159 • headache
- 160 • throat irritation
- 161 • musculoskeletal pain
- 162 • nausea and vomiting

163 Tell your healthcare provider about any side effect that bothers you or that does not go away.

164 These are not all the side effects with ADVAIR HFA. Ask your healthcare provider or
165 pharmacist for more information.

166 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-
167 800-FDA-1088.

168

169 **How do I store ADVAIR HFA?**

- 170 • Store at room temperature with the mouthpiece down.
- 171 • **Contents Under Pressure:** Do not puncture. Do not use or store near heat or open flame.
172 Exposure to temperatures above 120°F may cause bursting.
- 173 • Do not throw into fire or an incinerator.
- 174 • Keep ADVAIR HFA and all medicines out of the reach of children.

175

176 **General Information about ADVAIR HFA**

177 Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not
178 use ADVAIR HFA for a condition for which it was not prescribed. Do not give your ADVAIR
179 HFA to other people, even if they have the same condition that you have. It may harm them.

180 This Medication Guide summarizes the most important information about ADVAIR HFA. If you
181 would like more information, talk with your healthcare provider or pharmacist. You can ask your
182 healthcare provider or pharmacist for information about ADVAIR HFA that was written for
183 healthcare professionals. You can also contact the company that makes ADVAIR HFA (toll free)
184 at 1-888-825-5249 or at www.advair.com.

185

186 **What are the ingredients in ADVAIR HFA?**

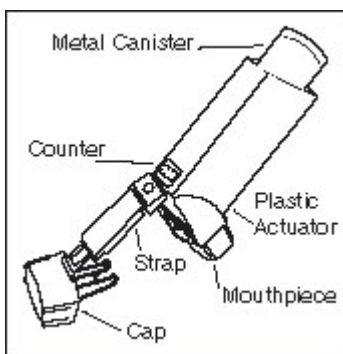
187 Active ingredients: fluticasone propionate, salmeterol xinafoate

188 Inactive ingredient: propellant HFA-134a

189

190 **How to use your ADVAIR HFA**

191 **The parts of your ADVAIR HFA:**



192

193

Figure 1

194 There are 2 main parts to your ADVAIR HFA inhaler—
195 the metal canister that holds the medicine and the purple
196 plastic actuator that sprays the medicine from the canister
197 (see Figure 1).

198 The inhaler also has a cap that covers the mouthpiece of
199 the actuator. The strap on the cap will stay attached to the
200 actuator.

201 **Do not use the actuator with a canister of medicine**
202 **from any other inhaler. Do not use an ADVAIR HFA**
203 **canister with an actuator from any other inhaler.**

204 The canister has a counter to show how many sprays of medicine you have left. The number
205 shows through a window in the back of the actuator.

206 The counter starts at 124, or at 064 if you have a sample or institutional canister. The number
207 will count down by 1 each time you spray the inhaler. The counter will stop counting at 000.

208 **Never try to change the numbers or take the counter off the metal canister.** The counter
209 cannot be reset, and it is permanently attached to the canister.

210 **Before using your ADVAIR HFA:**

211 Take the inhaler out of the foil pouch. Safely throw away the foil pouch and the drying packet
212 that comes inside the pouch. The counter should read 124, or 064 if you have a sample or
213 institutional canister.

214 The inhaler should be at room temperature before you use it.

215 Check each time to make sure the canister fits firmly in the plastic actuator. Also look into the
216 mouthpiece to make sure there are no foreign objects there, especially if the strap is no longer
217 attached to the actuator or if the cap is not being used to cover the mouthpiece.

218 **Priming your ADVAIR HFA:**

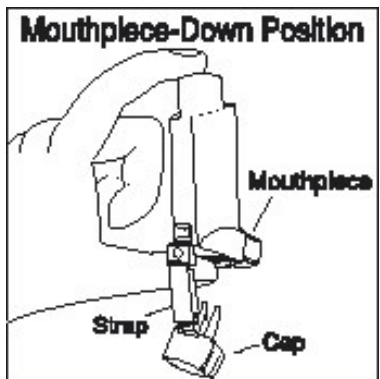
219 Before you use ADVAIR HFA for the first time, you must prime the inhaler so that you will
220 get the right amount of medicine when you use it. To prime the inhaler, take the cap off the

221 mouthpiece and shake the inhaler well for 5 seconds. Then spray it 1 time into the air away from
222 your face. Shake and spray the inhaler like this 3 more times to finish priming it. **Avoid**
223 **spraying in eyes.** The counter should now read 120, or 060 if you have a sample or institutional
224 canister.

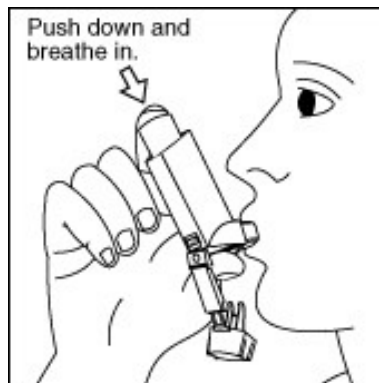
225 You must prime your inhaler again if you have not used it in more than 4 weeks or if you have
226 dropped it. Take the cap off the mouthpiece, shake the inhaler well for 5 seconds, and spray it
227 into the air away from your face. Shake and spray the inhaler like this 1 more time to finish
228 priming it.

229 **Instructions for taking a dose from your ADVAIR HFA:**

230 Read through the 7 steps below before using ADVAIR HFA. If you have any questions, ask
231 your doctor or pharmacist.



232
233 **Figure 2**



235
236 **Figure 3**

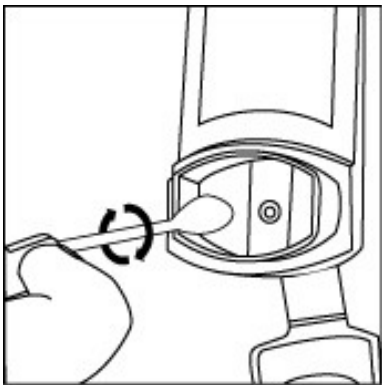
- 237 1. Take the cap off the mouthpiece of the actuator. **Shake the inhaler well** for 5 seconds before
238 each spray.
- 239 1. Hold the inhaler with the mouthpiece down (see Figure 2). **Breathe out through your mouth**
240 and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close
241 your lips around it.
- 242 2. **Push the top of the canister all the way down while you breathe in deeply and slowly**
243 **through your mouth** (see Figure 3). Right after the spray comes out, take your finger off the
244 canister. After you have breathed in all the way, take the inhaler out of your mouth and close
245 your mouth.
- 246 3. **Hold your breath as long as you can**, up to 10 seconds, then breathe normally.
- 247 4. Wait about 30 seconds and **shake** the inhaler again for 5 seconds. Repeat steps 2 through 4.
- 248 5. After you finish taking this medicine, rinse your mouth with water. Spit out the water. Do not
249 swallow it.
- 250 6. Put the cap back on the mouthpiece after every time you use the inhaler, and make sure it
251 snaps firmly into place.

252 **When to replace your ADVAIR HFA:**

- 253 • **When the counter reads 020**, you should refill your prescription or ask your doctor if you
254 need another prescription for ADVAIR HFA.
- 255 • **Throw the inhaler away** when the counter reads 000. You should not keep using the inhaler
256 when the counter reads 000 because you will not receive the right amount of medicine.
- 257 • **Do not use the inhaler** after the expiration date, which is on the packaging it comes in.

258 **How to clean your ADVAIR HFA:**

259 Clean the inhaler at least once a week after your evening dose. It is important to keep the
260 canister and plastic actuator clean so the medicine will not build-up and block the spray.



261 **Figure 4**

- 263 1. Take the cap off the mouthpiece. The strap on the cap
264 will stay attached to the actuator. Do not take the canister
265 out of the plastic actuator.
- 266 7. Use a dry cotton swab to clean the small circular
267 opening where the medicine sprays out of the canister.
268 Carefully twist the swab in a circular motion to take off
269 any medicine (see Figure 4).
- 270 8. Wipe the inside of the mouthpiece with a clean tissue
271 dampened with water. Let the actuator air-dry overnight.
- 272 9. Put the cap back on the mouthpiece after the actuator has
273 dried.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

ADVAIR, ADVAIR DISKUS, FLOVENT, and SEREVENT are registered trademarks of GlaxoSmithKline.

The other brands listed are trademarks of their respective owners and are not trademarks of GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse GlaxoSmithKline or its products.



GlaxoSmithKline
Research Triangle Park, NC 27709

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Month Year
ADH:XMG

Appendix A:
Initial REMS Approval 07/2008
Most Recent Modification: 05/2011

NDA 21-254 ADVAIR[®] HFA (fluticasone propionate and salmeterol) Inhalation Aerosol HFA 45/21, 115/21, 230/21

Corticosteroid and Long-Acting Beta₂-Adrenergic Agonist

GlaxoSmithKline, Five Moore Drive,

P.O. Box 13398, Research Triangle Park, NC 27709

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

1. To inform healthcare providers and prescribers of the increased risk of asthma-related death and serious outcomes with the long-acting beta₂-adrenergic agonists (LABA) including ADVAIR HFA.
2. To inform healthcare providers and prescribers of the appropriate use of long-acting beta₂-adrenergic agonists (LABA) including ADVAIR HFA.
3. To inform patients that long-acting beta₂-adrenergic agonists (LABA) medicines, such as salmeterol xinafoate, one of the active moieties in ADVAIR HFA, have been associated with an increased risk of death from asthma related events.
4. To inform patients of other serious risks associated with the use of ADVAIR HFA.

II. REMS ELEMENTS

A. MEDICATION GUIDE

A Medication Guide will be dispensed with each ADVAIR HFA Inhalation Aerosol prescription in accordance with 21 CFR 208.24.

B. COMMUNICATION PLAN

GSK will implement a communication plan to healthcare providers to support implementation of this REMS.

The communication plan will include:

1. A Dear Healthcare Professional Letter (DHCPL) that will be distributed to current and potential prescribers of LABAs: Allergists, Pulmonologists, Primary Care Physicians (Family Practice, General Practice and Internal Medicine), Pediatricians, and Allied Health (Nurse Practitioners and Physician Assistants)

Distribution of the DHCPL will be via direct mail, e-mail, or hand carry with the following timeline:

- a. Initial distribution within 60 days of REMS approval
- b. Second distribution at or about 6 months' post-REMS approval.

Appendix A:
Initial REMS Approval 07/2008
Most Recent Modification: 05/2011

The DHCPL will include the following safety information:

- a. Increased risk of asthma-related death in patients taking LABAs
- b. New prescribing guidelines:
 - i. ADVAIR HFA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA
 - ii. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue ADVAIR HFA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.
 - iii. ADVAIR HFA should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
2. Printed or web-based information for healthcare providers will be posted on a GSK website within 30 days of the REMS approval. This information will remain on the website for 3 years. The content of the print or web-based material will, at a minimum, include the following:
 - i. Information about the risk
 - ii. Key data regarding the risk (e.g. SMART, SNS)
 - iii. New prescribing guidelines
 - iv. Currently available LABAs and approved uses
 - v. Prescribing information for ADVAIR HFA
 - vi. Patient Counseling Information
 - vii. Medication Guide for ADVAIR HFA
 - viii. Questions and Answers
 - ix. DHCP letter (for a period of 1 year)
3. GSK will communicate via letter to the leadership of the following Professional Societies:
 - American Academy of Allergy, Asthma & Immunology (AAAAI)
 - American College of Allergy, Asthma & Immunology (ACAAI)
 - American Thoracic Society (ATS)
 - American College of Chest Physicians (ACCP)
 - American Academy of Pediatrics (AAP)
 - American Academy of Family Physicians (AAFP)
 - American College of Physicians (ACP)
 - National Medical Association (NMA)
 - American Academy of Nurse Practitioners (AANP)
 - American Academy of Physician Assistants (AAPA)

Appendix A:
Initial REMS Approval 07/2008
Most Recent Modification: 05/2011

The communication to the professional societies will also include the information that is also available under Section II.B.2 above. GSK will request that these societies disseminate this information to their members. If available from professional societies, a total number of recipients will be communicated to the agency in the first modified REMS annual assessment.

The timeline for REMS communication materials to professional societies will parallel the direct mail, e-mail, or hand carry program:

- i. Initial distribution within 60 days of REMS approval;
- ii. Second distribution at or about 6 months' post-REMS approval.

The following materials are part of the REMS and are attached:

- i. DHCPL
- ii. Printed or web-based information
- iii. Dear (Medical Society) Letter

C. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

GSK will submit REMS assessments to FDA annually from the date of the approval of the modified REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. GSK will submit the assessment report so that it will be received by the FDA on or before the due date.

NDA 21-254; ADVAIR HFA

Attachment 1; Dear Healthcare Professional Letter

(GlaxoSmithKline Letterhead and Date)

Dear Healthcare Professional:

GlaxoSmithKline would like to inform you of important safety information for ADVAIR DISKUS[®] (fluticasone propionate and salmeterol xinafoate inhalation powder) and ADVAIR[®] HFA (fluticasone propionate and salmeterol xinafoate inhalation aerosol). ADVAIR DISKUS is a combination product containing a corticosteroid and a long acting beta₂-adrenergic agonist (LABA) indicated for the treatment of asthma in patients aged 4 years and older. ADVAIR DISKUS 250/50 is also indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema and to reduce exacerbations of COPD in patients with a history of exacerbations. ADVAIR HFA is a combination product containing a corticosteroid and a LABA indicated for treatment of asthma in patients aged 12 years and older. ADVAIR HFA is not indicated for the treatment of COPD. ADVAIR DISKUS/ADVAIR HFA is not indicated for the relief of acute bronchospasm.

Important safety information related to ADVAIR DISKUS/ADVAIR HFA includes:

- Increased risk of asthma-related death in patients taking LABAs.
- New prescribing guidelines.
 - ADVAIR DISKUS/ADVAIR HFA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.
 - Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS/ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.
 - ADVAIR DISKUS/ADVAIR HFA should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

ADVAIR DISKUS/ADVAIR HFA has a risk evaluation and mitigation strategy (REMS) that consists of a Medication Guide and a communication program.

The ADVAIR DISKUS/ADVAIR HFA prescribing information includes a boxed warning to highlight the safety issue of asthma-related death.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR DISKUS/ADVAIR HFA, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT[®] Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out

NDA 21-254; ADVAIR HFA

Attachment 1; Dear Healthcare Professional Letter

of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS/ADVAIR HFA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS/ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS/ADVAIR HFA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Please note that ADVAIR DISKUS/ADVAIR HFA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma.

When prescribing ADVAIR DISKUS/ADVAIR HFA, please also provide the patient with an inhaled short-acting beta₂-agonist (e.g., albuterol) to be used as a rescue inhaler for treatment of acute symptoms. Increasing use of inhaled, short-acting beta₂-agonists is a marker for deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen.

Please instruct the patients to contact you if breathing problems worsen over time while using ADVAIR DISKUS/ADVAIR HFA and get emergency medical care if breathing problems worsen quickly and are not being relieved by the use of the rescue inhaler.

There is an increased risk of pneumonia in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS 250/50. Monitor patients for signs and symptoms of pneumonia as the clinical features of pneumonia and exacerbations frequently overlap.

Please take time to read the enclosed ADVAIR DISKUS and ADVAIR HFA Package Inserts for full prescribing information, for complete description of this important safety information and the new prescribing guidelines.

In addition, please review the attached Medication Guides with each patient who is prescribed ADVAIR DISKUS or ADVAIR HFA.

The Medication Guide will be enclosed in each carton packaging and must be provided by the authorized dispensers to each patient to whom the drug is dispensed.

To report adverse events potentially associated with ADVAIR DISKUS or ADVAIR HFA, please call GlaxoSmithKline at 1-888-825-5249.

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Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by:

- Phone at 1-800-FDA-1088 (1-800-332-1088)
- Facsimile at 1-800-FDA-0178 (1-800-332-0178)
- Mail using FDA Form 3500 located at <http://www.fda.gov/medwatch>

Please contact GlaxoSmithKline at 1-888-825-5249 if you have any questions about ADVAIR DISKUS, ADVAIR HFA or the information in this letter.

Sincerely,

Ellen R. Strahlman, MD
Chief Medical Officer
GlaxoSmithKline

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Attachment 2; Print / Web-Based Information

Printed/Web-Based Information

The following content will be housed in a healthcare provider section of the product website.

- Information about the risk

Due to an increased risk of asthma-related death, FDA has mandated that all Long-Acting Beta Agonists (LABAs) and LABA-containing products, like ADVAIR HFA, carry a boxed warning. The boxed warning for ADVAIR HFA reads as follows:

WARNING: ASTHMA-RELATED DEATH

Long-acting beta2-adrenergic agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR HFA®, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR HFA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

See the full Prescribing Information (link) for a more complete description of the risks associated with the use of ADVAIR HFA in the treatment of asthma.

- Key data regarding the risk of asthma-related death (e.g. SMART, SNS)

FDA's decision to require a Risk Evaluation and Mitigation Strategy (REMS) and class-labeling changes to the drug labels for Long-Acting Beta-Agonists (LABAs) is based on analyses from the Salmeterol Multi-center Asthma Research Trial (SMART), the Salmeterol Nationwide Surveillance study (SNS), and a meta-analysis conducted by FDA in 2008 and discussed at the joint Pulmonary Allergy Drugs, Drug Safety and Risk Management, and Pediatric Advisory Committees, held on December 10-11, 2008 (for complete safety reviews and background information discussed at this meeting see the following link: [December 10-11 2008 AC meeting](#)).

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SMART was a large, randomized, 28-week, placebo-controlled trial that evaluated patients 12 years of age and older receiving standard asthma therapy and the addition of either salmeterol or placebo. A total of 26,355 patients were evaluated in this study. Results showed that patients receiving salmeterol were at an increased risk for asthma-related death compared to patients receiving placebo. Subgroup analyses were also performed and found that asthma-related death in Caucasians and African Americans occurred at a higher rate in patients using salmeterol compared to placebo. See Table 1 below for results from SMART.

Table 1 SMART Results

SMART Patients	Asthma-Related Deaths in Salmeterol Group n (%)*	Asthma-Related Deaths in Placebo Group n (%)*	Relative Risk of Asthma-Related Death (95% Confidence Interval)	Excess Deaths Expressed per 10,000 Patients+ (95% Confidence Interval)
All Patients § Salmeterol: n = 13,176 Placebo: n = 13,179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Patients Salmeterol: n = 9,281 Placebo: n = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
African American Patients Salmeterol: n = 2,366 Placebo: n = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

* 28-week estimate, adjusted according to actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

+ Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

§ The Total Population includes Caucasian, African American, Hispanic, Asian, and "Other" and "not reported". No asthma-related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related

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death occurred in the placebo group in the subpopulation whose ethnic origin was "not reported" (salmeterol n = 130, placebo n = 127).

The SNS was a 16-week, double-blind study that compared the addition of salmeterol or albuterol to standard asthma therapy in 25,180 asthma patients who were 12 years of age and older. In the study, there was an increase in the number of respiratory and asthma-related deaths in the salmeterol group (0.07% [12 out of 16,787 patients]) compared to the albuterol group (0.02% [2 out of 8,393 patients] relative risk of 3.0, p=0.105).

In preparation for the December 2008 Advisory Committee, FDA conducted a meta-analysis of 110 studies evaluating the use of LABAs in 60,954 patients with asthma. The meta-analysis used a composite endpoint to measure severe exacerbation of asthma symptoms (asthma-related death, intubation, and hospitalization). The results of the meta-analysis suggested an increased risk for severe exacerbation of asthma symptoms in patients using LABAs compared to those not using LABAs. The largest risk difference per 1,000 treated patients was seen in children 4-11 years of age, see Table 2 below. The results of the meta-analysis were primarily driven by asthma-related hospitalizations. Other meta-analyses evaluating the safety of LABAs in the treatment of asthma have not shown a significant increase in the risk for severe asthma exacerbations.

Table 2 Meta-Analysis Results: Number of Patients Experiencing an Event*

Patient Population	LABA Patients experiencing an event	Non-LABA Patients experiencing an event	Risk Difference Estimate per 1000 treated patients	95% Confidence Interval
All Patients n = 30,148 LABA patients n = 30,806 non-LABA patients	381	304	2.80	1.11 – 4.49
Patients ages 12 to 17 years n = 3,103 LABA patients n = 3,289 non-LABA patients	48	30	5.57	0.21 – 10.92
Patients ages 4 to 11 years n = 1,626	61	39	14.83	3.24 – 26.43

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LABA patients n = 1,789 non-LABA patients				
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* Event defined as the composite endpoint (asthma-related death, intubation, and hospitalization)

At this time, there are insufficient data to conclude whether using LABAs with an inhaled corticosteroid reduces or eliminates the risk of asthma-related death and hospitalizations. FDA is requiring the manufacturers of LABAs to conduct studies evaluating the safety of LABAs when used in conjunction with an inhaled corticosteroid.

Based on the available information, FDA concludes there is an increased risk for severe exacerbation of asthma symptoms, leading to hospitalizations in pediatric and adult patients as well as death in some patients using LABAs for the treatment of asthma. The agency is requiring the REMS and class-labeling changes to improve the safe use of these products.

See [February 2010 LABA Drug Safety Communication](#) for more information.

Link:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm>

- New prescribing guidelines

Long-Acting Beta-Agonists (LABAs), a class of medications used for the treatment of asthma, now have new recommendations in their drug label intended to promote their safe use in the treatment of asthma.

In February 2010, the agency announced it was requiring manufacturers to revise their drug labels because of an increased risk of severe exacerbation of asthma symptoms, leading to hospitalizations, in pediatric and adult patients, as well as death in some patients using LABAs for the treatment of asthma (see [February 2010 LABA Drug Safety Communication](#)).

In June 2010, the agency issued updated recommendations on the appropriate use of LABAs. See [June 2010 LABA Drug Safety Communication](#) for more information.

Link:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm>

The new recommendations in the updated labels state:

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- Use of a LABA alone without use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated (absolutely advised against) in the treatment of asthma.
- LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
- LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.

FDA has stated its belief that when LABAs are used according to the recommendations outlined above and in the approved drug labels, the benefits of LABAs in improving asthma symptoms outweigh their risks of increasing severe asthma exacerbations and deaths from asthma.

- Currently available LABAs and their approved uses

FDA Approved Long-Acting Beta Agonists

Brand Name	LABA Active Ingredient	Corticosteroid Active Ingredient	FDA Approved Uses
ADVAIR DISKUS	Salmeterol	Fluticasone	Asthma, COPD
ADVAIR HFA	Salmeterol	Fluticasone	Asthma
SEREVENT DISKUS	Salmeterol	None	Asthma, COPD, Exercise-Induced Bronchospasm (EIB)
Brovana	Arformoterol	None	COPD
Foradil Aerolizer	Formoterol	None	Asthma, COPD, Exercise-Induced Bronchospasm (EIB)
Foradil Certihaler*	Formoterol	None	Asthma
Perforomist	Formoterol	None	COPD
Dulera Inhalation	Formoterol	Mometasone	Asthma

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Aerosol			
Symbicort	Formoterol	Budesonide	Asthma, COPD

* not currently marketed in the U.S.

See [June 2010 LABA Drug Safety Communication](#) for more information.

Link:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm>

- Prescribing information for ADVAIR HFA

LINK – http://us.gsk.com/products/assets/us_advair.pdf

- Patient Counseling Information

Patient Counseling Information

See USPI and Medication Guide

Asthma-Related Death

See Medication Guide

Patients should be informed that salmeterol, one of the active ingredients in ADVAIR HFA, increases the risk of asthma-related death. In pediatric and adolescent patients, salmeterol may increase the risk of asthma-related hospitalization. They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, the other component of ADVAIR HFA, or other long-term asthma control therapy mitigates or eliminates this risk. See Warnings section of the full [Prescribing Information](#).

Not for Acute Symptoms

ADVAIR HFA is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta₂-agonist (the healthcare provider should prescribe a short-acting, beta₂-agonist and instruct the patient in how it should be used).

Patients should be instructed to seek medical attention immediately if they experience any of the following:

- If their symptoms worsen
- Significant decrease in lung function as outlined by the physician
- If they need more inhalations of a short-acting beta₂-agonist than usual

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Patients should be advised not to increase the dose or frequency of ADVAIR HFA. The daily dosage of ADVAIR HFA should not exceed two inhalations twice daily. If they miss a dose, they should be instructed to take their next dose at the same time they normally do. ADVAIR HFA provides bronchodilation for up to 12 hours.

Patients should not stop or reduce ADVAIR HFA therapy without physician/provider guidance since symptoms may recur after discontinuation. See Warnings section of the full [Prescribing Information](#).

Do Not Use Additional Long-Acting Beta₂-Agonists

When patients are prescribed ADVAIR HFA, other long-acting beta₂-agonists should not be used. See Warnings section of the full [Prescribing Information](#).

Risks Associated With Corticosteroid Therapy

Local Effects: Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with ADVAIR HFA therapy, but at times therapy with ADVAIR HFA may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised. See Precautions section of the full [Prescribing Information](#).

Pneumonia in patients with COPD: Lower respiratory tract infections, including pneumonia, have been reported in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. See Warnings section of the full [Prescribing Information](#).

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex. See Warnings section of the full [Prescribing Information](#).

Hypercorticism and Adrenal Suppression: Patients should be advised that ADVAIR HFA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to ADVAIR DISKUS/ADVAIR HFA. See Warnings section of the full [Prescribing Information](#).

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and should be monitored and, where appropriate, be treated for this condition. See Precautions section of the full [Prescribing Information](#).

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Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, a component of ADVAIR HFA, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of pediatric patients taking corticosteroids by any route. See Precautions section of the full [Prescribing Information](#).

Glaucoma and Cataracts: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (glaucoma or cataracts); regular eye examinations should be considered. See Precautions section of the full [Prescribing Information](#).

Risks Associated With Beta-Agonist Therapy

Patients should be informed that treatment with beta₂-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor or nervousness and death. See Warnings and Precautions sections of the full [Prescribing Information](#).

- Medication Guide for ADVAIR HFA
LINK - http://us.gsk.com/products/assets/us_advair.pdf
- Questions and Answers

Questions about LABA Safety and Risk Evaluation and Mitigation Strategy (REMS) for LABAs

Q1. Why is FDA requiring LABA manufacturers to have a risk management program for these medicines?

Q2. What is the goal of the new risk management program for LABAs?

Q3. What are the key points people should know about the safe use of LABAs in patients with asthma?

Q4. What are the names of LABA-containing medicines used to treat asthma?

Q5. Why should LABAs only be used with a long-term asthma control medication, are they safer when used this way?

Q6. What information did FDA review to help the Agency decide to require a risk management program?

Questions about ADVAIR HFA Inhalation Aerosol

Q1. Why does ADVAIR HFA have a boxed warning?

Q2. What should I tell patients about the risk of asthma-related death?

Q3. Can ADVAIR HFA be used for acute asthma symptoms?

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Q4. Can additional LABAs be used with ADVAIR HFA?

Q5. What are the risks of Corticosteroid Therapy?

Q6. What are the risks of Beta-Agonist Therapy?

Questions about LABA safety

Q1. Why is FDA requiring LABA manufacturers to have a risk management program for these medicines?

A. Despite the benefits of long-acting beta₂-agonists (LABAs) in helping people with asthma, FDA's analyses indicate there is an increase in the risk of severe exacerbation of asthma symptoms leading to hospitalizations in pediatric and adult patients as well as death in some patients with asthma that use a LABA compared to patients with asthma that do not use a LABA. Because of this risk, FDA wants to make sure LABAs are used appropriately in patients with asthma. In order to ensure the safe use of these medicines, FDA is requiring the manufacturers of LABAs to develop this risk management program for healthcare professionals and patients.

Q2. What is the goal of the new risk management program for LABAs?

A. The risk management program for LABAs requires the manufacturers to better inform healthcare professionals and patients about the risk of LABAs for patients with asthma and ways to decrease that risk while maintaining the benefits of the drug. Under the program, patients who have a prescription filled for a LABA will receive a revised Medication Guide that explains the risks and benefits of the medicine. In addition manufacturers of LABAs will update the prescribing information they provide to healthcare professionals to include the latest recommendations for safe use of these important medicines.

Q3. What are the key points people should know about the safe use of LABAs in patients with asthma?

A. The key points are:

- Use of a LABA alone without use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated (absolutely advised against) in the treatment of asthma.
- LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
- LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if

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possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.

Q4. What are the names of LABA-containing medicines used to treat asthma?

Brand Name(s)	Generic Name(s)	Description
ADVAIR DISKUS	Salmeterol and Fluticasone	Salmeterol is a LABA and fluticasone is a corticosteroid long-term asthma control medicine
ADVAIR HFA	Salmeterol and Fluticasone	Salmeterol is a LABA and fluticasone is a corticosteroid long-term asthma control medicine
SEREVENT DISKUS	Salmeterol	Single ingredient LABA with no corticosteroid long-term asthma control medication
Foradil Aerolizer	Formoterol	Single ingredient LABA with no corticosteroid long-term asthma control medication
Dulera Inhalation Aerosol	Formoterol and Mometasone	Formoterol is a LABA and mometasone is a corticosteroid long-term asthma control medication
Symbicort Inhalation Aerosol	Formoterol and Budesonide	Formoterol is a LABA and budesonide is a corticosteroid long-term asthma control medication

Q5. Why should LABAs only be used with a long-term asthma control medication, are they safer when used this way?

A. At this time, there is no conclusive evidence that the combination of a long-term asthma control medication with a LABA decreases or eliminates the risk of a LABA. More study and analysis is required in this area. FDA is requiring the manufacturers of LABAs to conduct studies evaluating the safety of LABAs when used with an inhaled corticosteroid to better understand this issue.

Because of the risks of LABAs, FDA recommends that a LABA should not be used for a patient whose asthma can be controlled with long-term asthma control medication, such as an inhaled corticosteroid. If a LABA needs to be added to that medicine, it should only be used until the patient's healthcare professional determines their asthma is under control, and then the LABA should be stopped if possible. This means it is always

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necessary for a patient to use a LABA in combination with a long-term asthma control medication.

Q6. What information did FDA review to help the Agency decide to require a risk management program?

A. FDA used a variety of studies and research in patients with asthma using a LABA. Two specific studies that provided valuable information were 1) the Salmeterol Multi-center Asthma Research Trial (SMART) and 2), the Serevent Nationwide Surveillance study (SNS). Salmeterol is the LABA in SEREVENT. Each of these studies showed a higher risk of death for patients with asthma that used a LABA (salmeterol) compared to patients with asthma that did not use a LABA. In addition, FDA used a research method called a meta-analysis to further understand the risks associated with the use of LABAs in patients with asthma. A meta-analysis uses data from multiple studies on a particular topic to enable scientists to combine information from those studies to make scientific conclusions or recommendations in that area. For more information on these specific studies, please see [February 2010 LABA Drug Safety Communication](#) for more information.

Questions about ADVAIR HFA

Q1. Why does ADVAIR HFA have a boxed warning?

A. Due to an increased risk of asthma-related death, FDA has mandated that all Long-Acting Beta-Agonists (LABAs) and LABA-containing products, like ADVAIR HFA, carry a boxed warning. The boxed warning for ADVAIR HFA reads as follows:

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR HFA[®], increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT[®] Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR HFA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

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See the full [Prescribing Information](#) for a more complete description of the risks associated with the use of ADVAIR HFA in the treatment of asthma.

Q2. What should I tell patients about the risk of asthma-related death?

A. Patients should be informed that salmeterol, one of the active ingredients in ADVAIR HFA, increases the risk of asthma-related death. In pediatric and adolescent patients, salmeterol may increase the risk of asthma-related hospitalization. They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids or other long-term asthma-control therapy mitigates this risk. See Warnings section of the full [Prescribing Information](#).

Q3. Can ADVAIR HFA be used for acute asthma symptoms?

A. No. ADVAIR HFA is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta₂-agonist (the healthcare provider should prescribe a short-acting, beta₂-agonist and instruct the patient in how it should be used). Patients should be instructed to seek medical attention immediately if they experience any of the following:

- If their symptoms worsen
- Significant decrease in lung function as outlined by the physician
- If they need more inhalations of a short-acting beta₂-agonist than usual

Patients should be advised not to increase the dose or frequency of ADVAIR HFA. The daily dosage of ADVAIR HFA should not exceed two inhalations twice daily. If they miss a dose, they should be instructed to take their next dose at the same time they normally do. ADVAIR HFA provides bronchodilation for up to 12 hours.

Patients should not stop or reduce ADVAIR HFA therapy without physician/provider guidance since symptoms may recur after discontinuation. See Warnings section of the full [Prescribing Information](#).

Q4. Can additional LABAs be used with ADVAIR HFA?

A. No. When patients are prescribed ADVAIR HFA, other long-acting beta₂-agonists should not be used. See Warnings section of the full [Prescribing Information](#).

Q5 What are the risks of Corticosteroid Therapy

Local Effects: Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with ADVAIR HFA therapy, but at times therapy with ADVAIR HFA may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised. See Precautions section of the full [Prescribing Information](#).

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Pneumonia in patients with COPD: Lower respiratory tract infections, including pneumonia, have been reported in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. See Warnings section of the full [Prescribing Information](#).

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex. See Warnings section of the full [Prescribing Information](#).

Hypercorticism and Adrenal Suppression: Patients should be advised that ADVAIR HFA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to ADVAIR DISKUS/ADVAIR HFA. See Warnings section of the full [Prescribing Information](#).

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and should be monitored and, where appropriate, be treated for this condition. See Precautions section of the full [Prescribing Information](#).

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, a component of ADVAIR HFA, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of pediatric patients taking corticosteroids by any route. See Precautions section of the full [Prescribing Information](#).

Glaucoma and Cataracts: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (glaucoma or cataracts); regular eye examinations should be considered. See Precautions section of the full [Prescribing Information](#).

Q6. What are the risks of Beta-Agonist Therapy?

A. Patients should be informed that treatment with beta₂-agonists may lead to adverse events that include palpitations, chest pain, rapid heart rate, tremor or nervousness. See Warnings and Precautions sections of the full [Prescribing Information](#).

For more information:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm>

This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>

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Attachment 2; Print / Web-Based Information

- DHCP Letter (for a period of 1 year)

NDA 21-254; ADVAIR® HFA

Attachment 3; Dear Medical Society Letter

(GlaxoSmithKline Letterhead and Date)

Dear (Medical Society):

GlaxoSmithKline would like to inform you of important safety information for ADVAIR DISKUS® (fluticasone propionate and salmeterol xinafoate inhalation powder) and ADVAIR® HFA (fluticasone propionate and salmeterol xinafoate inhalation aerosol). ADVAIR DISKUS is a combination product containing a corticosteroid and a long acting beta₂-adrenergic agonist (LABA) indicated for the treatment of asthma in patients aged 4 years and older. ADVAIR DISKUS 250/50 is also indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema and to reduce exacerbations of COPD in patients with a history of exacerbations. ADVAIR HFA is a combination product containing a corticosteroid and a LABA indicated for treatment of asthma in patients aged 12 years and older. ADVAIR HFA is not indicated for the treatment of COPD. ADVAIR DISKUS/ADVAIR HFA is not indicated for the relief of acute bronchospasm.

Important safety information related to ADVAIR DISKUS/ADVAIR HFA includes:

- Increased risk of asthma-related death in patients taking LABAs.
- New prescribing guidelines.
 - ADVAIR DISKUS/ADVAIR HFA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.
 - Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS/ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.
 - ADVAIR DISKUS/ADVAIR HFA should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

ADVAIR DISKUS/ADVAIR HFA has a risk evaluation and a mitigation strategy (REMS) that consists of a Medication Guide and a communication program.

The ADVAIR DISKUS/ADVAIR HFA prescribing information includes a boxed warning to highlight the safety issue of asthma-related death.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR DISKUS/ADVAIR HFA, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176

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patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS/ADVAIR HFA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS/ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS/ADVAIR HFA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Please note that ADVAIR DISKUS/ADVAIR HFA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma.

When prescribing ADVAIR DISKUS/ADVAIR HFA, the healthcare professional should be guided to also provide the patient with an inhaled short-acting beta₂-agonist (e.g., albuterol) to be used as a rescue inhaler for treatment of acute symptoms. Increasing use of inhaled, short-acting beta₂-agonists is a marker for deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen.

The healthcare professional should instruct the patients to contact them if breathing problems worsen over time while using ADVAIR DISKUS/ADVAIR HFA and get emergency medical care if breathing problems worsen quickly and are not being relieved by the use of the rescue inhaler.

There is an increased risk of pneumonia in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS 250/50. Monitor patients for signs and symptoms of pneumonia as the clinical features of pneumonia and exacerbations frequently overlap.

Please take time to read the enclosed ADVAIR DISKUS and ADVAIR HFA Package Inserts for full prescribing information, for complete description of this important safety information and the new prescribing guidelines. Visit [insert web link; alternative is to include reference to enclosed hard copies] for additional information about the risk of serious asthma outcomes and the safe use of LABAs.

We are asking you to share this communication with members of your society and advise practitioners prescribing ADVAIR DISKUS/ADVAIR HFA to discuss the benefits and risks of LABAs with their patients. They should also encourage each patient prescribed ADVAIR DISKUS/ADVAIR HFA to thoroughly review the enclosed Medication Guide prior to using.

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The Medication Guide will be enclosed in each carton packaging and must be provided by the authorized dispensers to each patient to whom the drug is dispensed.

To report adverse events potentially associated with ADVAIR DISKUS/ADVAIR HFA, please call GlaxoSmithKline at 1-888-825-5249.

Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by:

- Phone at 1-800-FDA-1088 (1-800-332-1088)
- Facsimile at 1-800-FDA-0178 (1-800-332-0178)
- Mail using FDA Form 3500 located at <http://www.fda.gov/medwatch>

Please contact GlaxoSmithKline at 1-888-825-5249 if you have any questions about ADVAIR DISKUS/ADVAIR HFA or the information in this letter.

Sincerely,

Ellen R. Strahlman, MD
Chief Medical Officer
GlaxoSmithKline

MEDICATION GUIDE

SEREVENT[®] [*ser' uh-vent*] DISKUS[®] (salmeterol xinafoate inhalation powder)

Read the Medication Guide that comes with SEREVENT DISKUS before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about SEREVENT DISKUS?

SEREVENT DISKUS can cause serious side effects, including:

- 1. People with asthma who take long-acting beta₂-adrenergic agonist (LABA) medicines such as salmeterol (SEREVENT DISKUS), have an increased risk of death from asthma problems.**
 - Call your healthcare provider if breathing problems worsen over time while using SEREVENT DISKUS. You may need a different treatment.
 - Get emergency medical care if:
 - breathing problems worsen quickly, and
 - you use your rescue inhaler medicine, but it does not relieve your breathing problems.
- 2. Do not use SEREVENT DISKUS as your only asthma medicine. SEREVENT DISKUS must only be used with a long-term asthma-control medicine, such as an inhaled corticosteroid.**
3. When your asthma is well controlled, your healthcare provider may tell you to stop taking SEREVENT DISKUS. Your healthcare provider will decide if you can stop SEREVENT DISKUS without loss of asthma control. You will continue taking your long-term asthma-control medicine, such as an inhaled corticosteroid.
4. Children and adolescents who take LABA medicines may have an increased risk of being hospitalized for asthma problems.

What is SEREVENT DISKUS?

- SEREVENT DISKUS is a LABA medicine. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.
- SEREVENT DISKUS is used for asthma, exercise-induced bronchospasm (EIB), and chronic

obstructive pulmonary disease (COPD) as follows:

Asthma:

SEREVENT DISKUS is used in adults and children aged 4 years and older, with a long-term asthma control medicine, such as an inhaled corticosteroid:

- to control symptoms of asthma, and
- to prevent symptoms such as wheezing.

LABA medicines, such as SEREVENT DISKUS, increase the risk of death from asthma problems. SEREVENT DISKUS is not for adults and children with asthma who are well controlled with a long-term asthma-control medicine, such as a low to medium dose of an inhaled corticosteroid medicine.

Exercise-Induced Bronchospasm:

SEREVENT DISKUS is used to prevent wheezing caused by exercise in adults and children aged 4 years and older.

- If you have EIB only, your healthcare provider may prescribe only SEREVENT DISKUS for your condition.
- If you have EIB and asthma, your healthcare provider should also prescribe an asthma control medicine, such as an inhaled corticosteroid.

Chronic Obstructive Pulmonary Disease:

SEREVENT DISKUS is used long term, 2 times each day (morning and evening) to control symptoms of COPD and prevent wheezing in adults with COPD.

Who should not use SEREVENT DISKUS?

Do not take SEREVENT DISKUS:

- to treat your asthma without an asthma medicine known as an inhaled corticosteroid
- if you are allergic to salmeterol or any of the ingredients in SEREVENT DISKUS. Ask your healthcare provider if you are not sure. See the end of this Medication Guide for a complete list of ingredients in SEREVENT DISKUS.

What should I tell my healthcare provider before using SEREVENT DISKUS?

Tell your healthcare provider about all of your health conditions, including if you:

- have heart problems
- have high blood pressure
- have seizures
- have thyroid problems
- have diabetes
- have liver problems

- are pregnant or planning to become pregnant. It is not known if SEREVENT DISKUS may harm your unborn baby.
- are breastfeeding. It is not known if SEREVENT DISKUS passes into your milk and if it can harm your baby.
- are allergic to SEREVENT DISKUS, any other medicines, or food products. See the end of this Medication Guide for a complete list of ingredients in SEREVENT DISKUS.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. SEREVENT DISKUS and certain other medicines, especially those used to treat infections, may interact with each other. This may cause serious side effects.

Know the medicines you take. Keep a list and show it to your healthcare provider and pharmacist each time you get a new medicine.

How do I use SEREVENT DISKUS?

See the step-by-step instructions for using the SEREVENT DISKUS at the end of this Medication Guide. Do not use SEREVENT DISKUS unless your healthcare provider has taught you and you understand everything. Ask your healthcare provider or pharmacist if you have any questions.

- Children should use SEREVENT DISKUS with an adult's help, as instructed by the child's healthcare provider.
- Use SEREVENT DISKUS exactly as prescribed. Do not use SEREVENT DISKUS more often than prescribed.
- For asthma and COPD, the usual dose is 1 inhalation 2 times each day (morning and evening). The 2 doses should be about 12 hours apart.
- For preventing exercise-induced bronchospasm, take 1 inhalation at least 30 minutes before exercise. Do not use SEREVENT DISKUS more often than every 12 hours. Do not use extra SEREVENT DISKUS before exercise if you already use it 2 times each day.
- If you miss a dose of SEREVENT DISKUS, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.
- Do not use a spacer device with SEREVENT DISKUS.
- Do not breathe into SEREVENT DISKUS.
- While you are using SEREVENT DISKUS 2 times each day, do not use other medicines that contain a long-acting beta₂-agonist or LABA for any reason. Ask your healthcare provider or pharmacist for a list of these medicines.

- Do not stop using SEREVENT DISKUS or any of your asthma medicines unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- SEREVENT DISKUS does not relieve sudden symptoms. Always have a rescue inhaler medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.
- Call your healthcare provider or get medical care right away if:
 - your breathing problems worsen with SEREVENT DISKUS
 - you need to use your rescue inhaler medicine more often than usual
 - your rescue inhaler medicine does not work as well for you at relieving symptoms
 - you need to use 4 or more inhalations of your rescue inhaler medicine for 2 or more days in a row
 - you use 1 whole canister of your rescue inhaler medicine in 8 weeks' time
 - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
 - you have asthma and your symptoms do not improve after using SEREVENT DISKUS regularly for 1 week.
 - after a change in your asthma medicines you have any worsening of your asthma symptoms or an increase in the need for your rescue inhaler medicine.

What are the possible side effects with SEREVENT DISKUS?

SEREVENT DISKUS can cause serious side effects, including:

- **See “What is the most important information I should know about SEREVENT DISKUS?”**
- **serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
 - rash
 - hives
 - swelling of the face, mouth, and tongue
 - breathing problems.
- **sudden breathing problems immediately after inhaling your medicine**
- **effects on heart**
 - increased blood pressure
 - a fast and irregular heartbeat
 - chest pain
- **effects on nervous system**
 - tremor
 - nervousness

- **changes in blood (sugar, potassium)**

Common side effects of SEREVENT DISKUS include:

Asthma in adults and children:

- headache
- nasal congestion
- bronchitis
- throat irritation
- runny nose
- flu

Chronic obstructive pulmonary disease:

- headache
- musculoskeletal pain
- throat irritation
- cough
- respiratory infection

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with SEREVENT DISKUS. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store SEREVENT DISKUS?

- Store SEREVENT DISKUS at room temperature between 68°F to 77° F (20°C to 25° C). Keep in a dry place away from heat and sunlight.
- Safely discard SEREVENT DISKUS 6 weeks after you remove it from the foil pouch, or after the dose indicator reads “0”, whichever comes first.
- Keep SEREVENT DISKUS and all medicines out of the reach of children.

General Information about SEREVENT DISKUS

Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not use SEREVENT DISKUS for a condition for which it was not prescribed. Do not give your SEREVENT DISKUS to other people, even if they have the same condition that you have. It may harm them.

This Medication Guide summarizes the most important information about SEREVENT DISKUS. If you would like more information, talk with your healthcare provider or pharmacist.

You can ask your healthcare provider or pharmacist for information about SEREVENT DISKUS that was written for healthcare professionals. You can also contact the company that makes SEREVENT DISKUS (toll free) at 1-888-825-5249 or at www.serevent.com.

What are the ingredients in SEREVENT DISKUS?

Active ingredient: salmeterol xinafoate

Inactive ingredient: lactose (contains milk proteins)

Instructions for Using SEREVENT DISKUS

Follow the instructions below for using your SEREVENT DISKUS. **You will breathe in (inhale) the medicine from the DISKUS.** If you have any questions, ask your healthcare provider or pharmacist.



Take the SEREVENT DISKUS out of the box and foil pouch. Write the **“Pouch opened”** and **“Use by”** dates on the label on top of the DISKUS. **The “Use by” date is 6 weeks from date of opening the pouch.**

- The DISKUS will be in the closed position when the pouch is opened.
- The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose indicator number will decrease each time you use the DISKUS. After you have used 55 doses from the DISKUS, the numbers 5 to 0 will appear in **red** to warn you that there are only a few doses left (*see Figure 1*).



Figure 1

Taking a dose from the DISKUS requires the following 3 simple steps: Open, Click, Inhale.

1. OPEN

Hold the DISKUS in one hand and put the thumb of your other hand on the **thumbgrip**. Push your thumb away from you as far as it will go until the mouthpiece appears and snaps into position (*see Figure 2*).



Figure 2

2. CLICK

Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the **lever** away from you as far as it will go until it **clicks** (*see Figure 3*). The DISKUS is now ready to use.



Figure 3

Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the DISKUS is ready:**

- **Do not close the DISKUS.**
- **Do not tilt the DISKUS.**
- **Do not play with the lever.**
- **Do not move the lever more than once.**

3. INHALE

Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding the DISKUS level and away from your mouth (*see Figure 4*). **Remember, never breathe out into the DISKUS mouthpiece.**



Figure 4

Put the mouthpiece to your lips (*see Figure 5*). Breathe in quickly and deeply through the

DISKUS. Do not breathe in through your nose.



Figure 5

Remove the DISKUS from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable. Breathe out slowly.

The DISKUS delivers your dose of medicine as a very fine powder. Most patients can taste or feel the powder. Do not use another dose from the DISKUS if you do not feel or taste the medicine.

- 4. Close the DISKUS when you are finished taking a dose so that the DISKUS will be ready for you to take your next dose.** Put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go (*see Figure 6*). The DISKUS will click shut. The lever will automatically return to its original position. The DISKUS is now ready for you to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4.)



Figure 6

Remember:

- Never breathe into the DISKUS.
- Never take the DISKUS apart.
- Always ready and use the DISKUS in a level, flat position.
- Do not use the DISKUS with a spacer device.
- Never wash the mouthpiece or any part of the DISKUS. **Keep it dry.**
- Always keep the DISKUS in a dry place.
- Never take an extra dose, even if you did not taste or feel the medicine.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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GlaxoSmithKline
Research Triangle Park, NC 27709

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Month Year
SRD:XMG

Appendix A:
Initial REMS Approval 11/2010
Most Recent Modification: 05/2011

NDA 020692 SEREVENT[®] DISKUS[®]
(salmeterol xinafoate inhalation powder) 50 mcg

Long-Acting Beta₂-Adrenergic Agonist

GlaxoSmithKline, Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

1. To inform healthcare providers and prescribers of the increased risk of asthma-related death and serious outcomes with the long-acting beta₂-adrenergic agonists (LABAs), including SEREVENT DISKUS.
2. To inform healthcare providers and prescribers of the appropriate use of LABAs, including SEREVENT DISKUS.
3. To inform patients that people with asthma who take LABA medicines, such as salmeterol xinafoate, the active moiety in SEREVENT DISKUS, has been associated with an increased risk of death from asthma related events.
4. To inform patients of other serious risks associated with the use of SEREVENT DISKUS.

II. REMS ELEMENTS

A. MEDICATION GUIDE

A Medication Guide will be dispensed with each SEREVENT DISKUS inhalation powder prescription in accordance with 21 CFR 208.24.

Please see the appended Medication Guide.

B. COMMUNICATION PLAN

GSK will implement a communication plan to healthcare providers to support implementation of this REMS.

The communication plan will include:

1. A Dear Healthcare Professional Letter (DHCPL), that will be distributed to current and potential prescribers of LABAs: Allergists, Pulmonologists, Primary Care Physicians (Family Practice, General Practice and Internal Medicine), Pediatricians, and Allied Health (Nurse Practitioners and Physician Assistants).

Distribution of the DHCPL will be via direct mail, e-mail, or hand carry with the following timeline:

Appendix A:
Initial REMS Approval 11/2010
Most Recent Modification: 05/2011

- a. Initial distribution within 60 days of REMS approval
- b. Second distribution at or about 6 months post-REMS approval.

The DHCPL will include the following safety information:

- a. Increased risk of asthma-related death in patients taking LABAs
 - b. New prescribing guidelines:
 - i. SEREVENT DISKUS should only be used as concomitant therapy with a long-term asthma control medication, such as an inhaled corticosteroid (ICS), in patients aged 4 years and older with reversible obstructive airway disease.
 - ii. Use of SEREVENT DISKUS for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an ICS, is contraindicated.
 - iii. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an ICS.
 - iv. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS.
 - v. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose ICS.
 - vi. For pediatric and adolescent patients with asthma who require addition of a LABA to an ICS, a fixed-dose combination product containing both an ICS and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., ICS) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an ICS and a LABA is recommended.
2. Printed or web-based information for health care providers will be posted on a GSK website within 30 days of the REMS approval, Attachment 2. This information will remain on the website for 3 years. The content of the print or web-based material will, at a minimum, include the following:
- i. Information about the risk
 - ii. Key data regarding the risk (e.g. SMART, SNS)
 - iii. New prescribing guidelines
 - iv. Currently available LABAs and approved uses
 - v. Prescribing information for SEREVENT DISKUS
 - vi. Patient Counseling Information
 - vii. Medication Guide for SEREVENT DISKUS

Appendix A:
Initial REMS Approval 11/2010
Most Recent Modification: 05/2011

- viii. Questions and Answers
 - ix. DHCP letter (for a period of 1 year)
3. GSK will communicate via letter to the leadership of the following Professional Societies:
- American Academy of Allergy, Asthma & Immunology (AAAAI)
 - American College of Allergy, Asthma & Immunology (ACAAI)
 - American Thoracic Society (ATS)
 - American College of Chest Physicians (ACCP)
 - American Academy of Pediatrics (AAP)
 - American Academy of Family Physicians (AAFP)
 - American College of Physicians (ACP)
 - National Medical Association (NMA)
 - American Academy of Nurse Practitioners (AANP)
 - American Academy of Physician Assistants (AAPA)

The communication to the professional societies will also include the information that is also available under Section II.B.2 above. GSK will request that these societies disseminate this information to their members. If available from professional societies, a total number of recipients will be communicated to the agency at the first annual assessment.

The timeline for REMS communication materials to professional societies will parallel the direct mail, e-mail, or hand carry program:

- i. Initial distribution within 60-days of REMS approval;
- ii. Second distribution at or about 6 months post-REMS approval.

The following materials are part of the REMS and are attached:

- i. DHCPL
- ii. Dear (Medical Society) Letter
- iii. Printed or web-based information

C. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

GSK will submit REMS assessments to FDA annually from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. GSK will submit the assessment report so that it will be received by the FDA on or before the due date.

NDA 20-692; SEREVENT® DISKUS®

Attachment 1; Dear Healthcare Professional Letter

(GlaxoSmithKline Letterhead and Date)

Dear Healthcare Professional:

GlaxoSmithKline would like to inform you of important safety information for SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder). SEREVENT DISKUS is a long-acting beta₂-adrenergic agonist (LABA) indicated for treatment of asthma in the prevention of bronchospasm only as concomitant therapy with a long-term asthma control medication, such as an inhaled corticosteroid (ICS), in patients aged 4 years and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma. SEREVENT DISKUS is not indicated for the relief of acute bronchospasm.

Important safety information related to SEREVENT DISKUS includes:

- Increased risk of asthma-related death in patients taking LABAs.
- New prescribing guidelines.
- SEREVENT DISKUS should only be used as concomitant therapy with a long-term asthma control medication, such as an ICS, in patients aged 4 years and older with reversible obstructive airway disease.
- Use of SEREVENT DISKUS for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an ICS, is contraindicated.
- Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an ICS.
- Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS.
- Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose ICS.
- For pediatric and adolescent patients with asthma who require addition of a LABA to an ICS, a fixed-dose combination product containing both an ICS and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., ICS) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an ICS and a LABA is recommended.

SERVEVENT DISKUS has a risk evaluation and mitigation strategy (REMS) that consists of a Medication Guide and a communication program.

NDA 20-692; SEREVENT® DISKUS®

Attachment 1; Dear Healthcare Professional Letter

The SEREVENT DISKUS prescribing information includes a boxed warning to highlight the safety issue of asthma-related death.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABAs), such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs.

Because of this risk, use of SEREVENT DISKUS for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.

Please note that SEREVENT DISKUS should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma.

When prescribing SEREVENT DISKUS, please also provide the patient with an inhaled, short-acting beta₂-agonist (e.g., albuterol) to be used as a rescue inhaler for treatment of acute symptoms. Increasing use of inhaled, short-acting beta₂-agonists is a marker for deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen.

NDA 20-692; SEREVENT® DISKUS®

Attachment 1; Dear Healthcare Professional Letter

Please instruct the patients to contact you if breathing problems worsen over time while using SEREVENT DISKUS and get emergency medical care if breathing problems worsen quickly and are not being relieved by the use of the rescue inhaler.

Please take time to read the enclosed SEREVENT DISKUS Package Insert for full prescribing information for complete description of this important safety information and the new prescribing guidelines.

In addition, please review the attached Medication Guide with each patient who is prescribed SEREVENT DISKUS.

The Medication Guide will be enclosed in each carton packaging and must be provided by the authorized dispensers to each patient to whom the drug is dispensed.

To report adverse events potentially associated with SEREVENT DISKUS, please call GlaxoSmithKline at 1-888-825-5249.

Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by:

- Phone at 1-800-FDA-1088 (1-800-332-1088)
- Facsimile at 1-800-FDA-0178 (1-800-332-0178)
- Mail using FDA Form 3500 located at <http://www.fda.gov/medwatch>

Please contact GlaxoSmithKline at 1-888-825-5249 if you have any questions about SEREVENT DISKUS or the information in this letter.

Sincerely,

Ellen R. Strahlman, MD
Chief Medical Officer
GlaxoSmithKline

NDA 20-692; SEREVENT® DISKUS®

Attachment 2; Print / Web-Based Information

Printed/Web-Based Information

The following content will be housed in a healthcare provider section of the product website.

- Information about the risk

Due to an increased risk of asthma-related death, FDA has mandated that all long-acting beta-agonists (LABAs) carry a boxed warning. The boxed warning for SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder) reads as follows:

WARNING: ASTHMA RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABAs), such as salmeterol, the active ingredient in SEREVENT® DISKUS®, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs.

Because of this risk, use of SEREVENT DISKUS for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.

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See the full Prescribing Information (link) for a more complete description of the risks associated with the use of SEREVENT DISKUS in the treatment of asthma.

- Key data regarding the risk (e.g. SMART, SNS)

FDA’s decision to require a Risk Evaluation and Mitigation Strategy (REMS) and class-labeling changes to the drug labels for long-acting beta-agonists (LABAs) is based on analyses from the Salmeterol Multi-center Asthma Research Trial (SMART), the Salmeterol Nationwide Surveillance study (SNS), and a meta-analysis conducted by FDA in 2008 and discussed at the joint Pulmonary Allergy Drugs, Drug Safety and Risk Management, and Pediatric Advisory Committees, held on December 10-11, 2008 (for complete safety reviews and background information discussed at this meeting see the following link: [December 10-11 2008 AC meeting](#)).

SMART was a large, randomized, 28-week, placebo-controlled trial that evaluated patients 12 years of age and older receiving standard asthma therapy and the addition of either salmeterol or placebo. A total of 26,355 patients were evaluated in this study. Results showed that patients receiving salmeterol were at an increased risk for asthma-related death compared to patients receiving placebo. Subgroup analyses were also performed and found that asthma-related death in Caucasians and African Americans occurred at a higher rate in patients using salmeterol compared to placebo. See Table 1 below for results from SMART.

Table 1 SMART Results

SMART Patients	Asthma-Related Deaths in Salmeterol Group n (%*)	Asthma-Related Deaths in Placebo Group n (%*)	Relative Risk of Asthma-Related Death (95% Confidence Interval)	Excess Deaths Expressed per 10,000 Patients+ (95% Confidence Interval)
All Patients § Salmeterol: n = 13,176 Placebo: n = 13,179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Patients Salmeterol: n = 9,281 Placebo: n = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
African American Patients Salmeterol: n = 2,366 Placebo: n = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

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* 28-week estimate, adjusted according to actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

+ Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

§ The Total Population includes Caucasian, African American, Hispanic, Asian, and "Other" and "not reported". No asthma-related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death occurred in the placebo group in the subpopulation whose ethnic origin was "not reported" (salmeterol n = 130, placebo n = 127).

The SNS was a 16-week, double-blind study that compared the addition of salmeterol or albuterol to standard asthma therapy in 25,180 asthma patients who were 12 years of age and older. In the study, there was an increase in the number of respiratory and asthma-related deaths in the salmeterol group (0.07% [12 out of 16,787 patients]) compared to the albuterol group (0.02% [2 out of 8,393 patients] relative risk of 3.0, p=0.105).

In preparation for the December 2008 Advisory Committee, FDA conducted a meta-analysis of 110 studies evaluating the use of LABAs in 60,954 patients with asthma. The meta-analysis used a composite endpoint to measure severe exacerbation of asthma symptoms (asthma-related death, intubation, and hospitalization). The results of the meta-analysis suggested an increased risk for severe exacerbation of asthma symptoms in patients using LABAs compared to those not using LABAs. The largest risk difference per 1,000 treated patients was seen in children 4-11 years of age, see Table 2 below. The results of the meta-analysis were primarily driven by asthma-related hospitalizations. Other meta-analyses evaluating the safety of LABAs in the treatment of asthma have not shown a significant increase in the risk for severe asthma exacerbations.

Table 2 Meta-Analysis Results: Number of Patients Experiencing an Event*

Patient Population	LABA Patients experiencing an event	Non-LABA Patients experiencing an event	Risk Difference Estimate per 1000 treated patients	95% Confidence Interval
All Patients n = 30,148 LABA patients	381	304	2.80	1.11 – 4.49
n = 30,806 non-LABA patients				

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Patients ages 12 to 17 years n = 3,103 LABA patients n = 3,289 non-LABA patients	48	30	5.57	0.21 – 10.92
Patients ages 4 to 11 years n = 1,626 LABA patients n = 1,789 non-LABA patients	61	39	14.83	3.24 – 26.43

** Event defined as the composite endpoint (asthma-related death, intubation, and hospitalization)*

At this time, there are insufficient data to conclude whether using LABAs with an ICS reduces or eliminates the risk of asthma-related death and hospitalizations. FDA is requiring the manufacturers of LABAs to conduct studies evaluating the safety of LABAs when used in conjunction with an ICS.

Based on the available information, FDA concludes there is an increased risk for severe exacerbation of asthma symptoms, leading to hospitalizations in pediatric and adult patients as well as death in some patients using LABAs for the treatment of asthma. The agency is requiring the REMS and class labeling changes to improve the safe use of these products.

See [February 2010 LABA Drug Safety Communication](#) for more information.

Link:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm>

- New prescribing guidelines

Long-acting beta-agonists (LABAs), a class of medications used for the treatment of asthma, now have new recommendations in their drug label intended to promote their safe use in the treatment of asthma.

In February 2010, the agency announced it was requiring manufacturers to revise their drug labels because of an increased risk of severe exacerbation of asthma symptoms, leading to hospitalizations, in pediatric and adult patients, as well as death in some

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patients using LABAs for the treatment of asthma (see [February 2010 LABA Drug Safety Communication](#)).

In June 2010, the agency issued updated recommendations on the appropriate use of LABAs. See [June 2010 LABA Drug Safety Communication](#) for more information.

Link:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm>

The new recommendations in the updated labels state:

- LABAs should only be used as concomitant therapy with a long-term asthma control medication, such as an ICS.
- Use of LABA for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an ICS, is contraindicated.
- Use LABA only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an ICS.
- Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue LABA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS.
- Do not use LABA for patients whose asthma is adequately controlled on low- or medium-dose ICS.
- For pediatric and adolescent patients with asthma who require addition of a LABA to an ICS, a fixed-dose combination product containing both an ICS and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., ICS) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an ICS and a LABA is recommended.

FDA has stated its belief that when LABAs are used according to the recommendations outlined above and in the approved drug labels, the benefits of LABAs in improving asthma symptoms outweigh their risks of increasing severe asthma exacerbations and deaths from asthma.

- Currently available LABAs and their approved uses

FDA Approved Long-Acting Beta-Agonists

Brand Name	LABA Active Ingredient	Corticosteroid Active Ingredient	FDA Approved Uses
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SEREVENT DISKUS	Salmeterol	None	Asthma, COPD, Exercise-Induced Bronchospasm (EIB)
Brovana	Arformoterol	None	COPD
Foradil Aerolizer	Formoterol	None	Asthma, COPD, Exercise-Induced Bronchospasm (EIB)
Foradil Certihaler*	Formoterol	None	Asthma
Perforomist	Formoterol	None	COPD
ADVAIR DISKUS®	Salmeterol	Fluticasone	Asthma, COPD
ADVAIR® HFA	Salmeterol	Fluticasone	Asthma
Dulera Inhalation Aerosol	Formoterol	Mometasone	Asthma
Symbicort	Formoterol	Budesonide	Asthma, COPD

* not currently marketed in the U.S.

See [June 2010 LABA Drug Safety Communication](#) for more information.

Link:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm>

- Prescribing information for SEREVENT DISKUS
LINK - http://us.gsk.com/products/assets/us_serevent_diskus.pdf
- Patient Counseling Information

Patient Counseling Information

See USPI and Medication Guide

Asthma-Related Death

See Medication Guide

Patients should be informed that salmeterol, the active ingredients in SEREVENT

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DISKUS, increases the risk of asthma-related death. In pediatric and adolescent patients, salmeterol may increase the risk of asthma-related hospitalization. They should also be informed that data are not adequate to determine whether the concurrent use of ICS, or other long-term asthma-control therapy mitigates or eliminates this risk. See Warnings and Precautions Sections of the full [Prescribing Information](#).

Not for Acute Symptoms

SEREVENT DISKUS is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist (the health care provider should prescribe the patient with such medication and instruct the patient in how it should be used).

Patients should be instructed to seek medical attention immediately if they experience any of the following:

- If their symptoms worsen
- Significant decrease in lung function as outlined by the physician
- If they need more inhalations of a short-acting beta₂-agonist than usual

Patients should be advised not to increase the dose or frequency of SEREVENT DISKUS. The daily dosage of SEREVENT DISKUS should not exceed one inhalation twice daily. If they miss a dose, they should be instructed to take their next dose at the same time they normally do. SEREVENT DISKUS provides bronchodilation for up to 12 hours.

Patients should not stop or reduce SEREVENT DISKUS therapy without physician/provider guidance since symptoms may recur after discontinuation. See Warnings and Precautions Sections of the full [Prescribing Information](#).

Do Not Use Additional Long-Acting Beta₂-Agonists

When patients are prescribed SEREVENT DISKUS, other LABAs should not be used. See Warnings and Precautions sections of the full [Prescribing Information](#).

Risks Associated With Beta-Agonist Therapy

Patients should be informed that treatment with beta₂-agonists may lead to adverse events that include palpitations, chest pain, rapid heart rate, tremor or nervousness, and death. See Warnings and Precautions sections of the full [Prescribing Information](#).

- Medication Guide for SEREVENT DISKUS
LINK - http://us.gsk.com/products/assets/us_serevent_diskus.pdf
- Questions and Answers

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Attachment 2; Print / Web-Based Information

Questions about LABA Safety and Risk Evaluation and Mitigation Strategy (REMS) for LABAs

- Q1. Why is FDA requiring LABA manufacturers to have a risk management program for these medicines?**
- Q2. What is the goal of the new risk management program for LABAs?**
- Q3. What are the key points people should know about the safe use of LABAs in patients with asthma?**
- Q4. What are the names of LABA-containing medicines used to treat asthma?**
- Q5. Why should LABAs only be used with a long-term asthma control medication, are they safer when used this way?**
- Q6. What information did FDA review to help the Agency decide to require a risk management program?**

Questions about SEREVENT DISKUS

- Q1. Why does SEREVENT DISKUS have a boxed warning?**
- Q2. What should I tell patients about the risk of asthma-related death?**
- Q3. Can SEREVENT DISKUS be used for acute asthma symptoms?**
- Q4. Can additional LABAs be used with SEREVENT DISKUS?**
- Q5. What are the risks of Beta-Agonist Therapy?**

Questions about LABA safety

Q1. Why is FDA requiring LABA manufacturers to have a risk management program for these medicines?

A. Despite the benefits of long-acting beta₂-agonists (LABAs) in helping people with asthma, FDA's analyses indicate there is an increase in the risk of severe exacerbation of asthma symptoms leading to hospitalizations in pediatric and adult patients as well as death in some patients with asthma that use a LABA compared to patients with asthma that do not use a LABA. Because of this risk, FDA wants to make sure LABAs are used appropriately in patients with asthma. In order to ensure the safe use of these medicines, FDA is requiring the manufacturers of LABAs to develop this risk management program for healthcare professionals and patients.

Q2. What is the goal of the new risk management program for LABAs?

A. The risk management program for LABAs requires the manufacturers to better inform healthcare professionals and patients about the risk of LABAs for patients with asthma

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and ways to decrease that risk while maintaining the benefits of the drug. Under the program, patients who have a prescription filled for a LABA will receive a revised Medication Guide that explains the risks and benefits of the medicine. In addition manufacturers of LABAs will update the prescribing information they provide to healthcare professionals to include the latest recommendations for safe use of these important medicines.

Q3. What are the key points people should know about the safe use of LABAs in patients with asthma?

A. The key points are:

- LABAs should only be used as concomitant therapy with a long-term asthma control medication, such as an ICS.
- Use of LABA for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an ICS, is contraindicated.
- Use LABA only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an ICS.
- Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue LABA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS.
- Do not use LABA for patients whose asthma is adequately controlled on low- or medium-dose ICS.
- For pediatric and adolescent patients with asthma who require addition of a LABA to an ICS, a fixed-dose combination product containing both an ICS and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., ICS) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an ICS and a LABA is recommended.

Q4. What are the names of LABA-containing medicines used to treat asthma?

Brand Name(s)	Generic Name(s)	Description
SEREVENT DISKUS	Salmeterol	Single ingredient LABA with no corticosteroid long-term asthma control medication
Foradil Aerolizer	Formoterol	Single ingredient LABA with no corticosteroid long-term asthma control medication

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ADVAIR DISKUS	Salmeterol and Fluticasone	Salmeterol is a LABA and fluticasone is a corticosteroid long-term asthma control medicine
ADVAIR HFA	Salmeterol and Fluticasone	Salmeterol is a LABA and fluticasone is a corticosteroid long-term asthma control medicine
Dulera Inhalation Aerosol	Formoterol and Mometasone	Formoterol is a LABA and mometasone is a corticosteroid long-term asthma control medication
Symbicort Inhalation Aerosol	Formoterol and Budesonide	Formoterol is a LABA and budesonide is a corticosteroid long-term asthma control medication

Q5. Why should LABAs only be used with a long-term asthma control medication, are they safer when used this way?

A. At this time, there is no conclusive evidence that the combination of a long-term asthma control medication with a LABA decreases or eliminates the risk of a LABA. More study and analysis is required in this area. FDA is requiring the manufacturers of to conduct studies evaluating the safety of LABAs when used with an inhaled corticosteroid to better understand this issue. Because of the risks of LABAs, FDA recommends that a LABA should not be used for a patient whose asthma can be controlled with long-term asthma control medication, such as an ICS. If a LABA needs to be added to that medicine, it should only be used until the patient’s healthcare professional determines their asthma is under control, and then the LABA should be stopped if possible. This means it is always necessary for a patient to use a LABA in combination with a long-term asthma control medication.

Q6. What information did FDA review to help the Agency decide to require a risk management program?

A. FDA used a variety of studies and research in patients with asthma using a LABA. Two specific studies that provided valuable information were 1) the Salmeterol Multi-center Asthma Research Trial (SMART) and 2), the Serevent Nationwide Surveillance study (SNS). Salmeterol is the LABA in Serevent. Each of these studies showed a higher risk of death for patients with asthma that used a LABA (salmeterol) compared to patients with asthma that did not use a LABA. In addition, FDA used a research method called a meta-analysis to further understand the risks associated with the use of LABAs in patients with asthma. A meta-analysis uses data from multiple studies on a particular topic to enable scientists to combine information from those studies to make scientific conclusions or recommendations in that area. For more information on these specific

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studies, please see [February 2010 LABA Drug Safety Communication](#) for more information.

Questions about SEREVENT DISKUS

Q1. Why does SEREVENT DISKUS have a boxed warning?

A. Due to an increased risk of asthma-related death, FDA has mandated that all long-acting beta-agonists (LABAs), like SEREVENT DISKUS, and LABA-containing products carry a boxed warning. The boxed warning for SEREVENT DISKUS reads as follows:

WARNING: ASTHMA RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABAs), such as salmeterol, the active ingredient in SEREVENT® DISKUS®, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs.

Because of this risk, use of SEREVENT DISKUS for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.

See the full [Prescribing Information](#) for a more complete description of the risks associated with the use of SEREVENT DISKUS in the treatment of asthma.

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Q2. What should I tell patients about the risk of asthma-related death?

A. Patients should be informed that salmeterol, the active ingredients in SEREVENT DISKUS, increases the risk of asthma-related death. In pediatric and adolescent patients, salmeterol may increase the risk of asthma-related hospitalization. They should also be informed that data are not adequate to determine whether the concurrent use of ICS or other long-term asthma-control therapy mitigates this risk. See Warnings and Precautions Sections of the full [Prescribing Information](#).

Q3. Can SEREVENT DISKUS be used for acute asthma symptoms?

A. No. SEREVENT DISKUS is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta₂-agonist (the health care provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention immediately if they experience any of the following:

- If their symptoms worsen
- Significant decrease in lung function as outlined by the physician
- If they need more inhalations of a short-acting beta₂-agonist than usual

Patients should be advised not to increase the dose or frequency of SEREVENT DISKUS. The daily dosage of SEREVENT DISKUS should not exceed one inhalation twice daily. If they miss a dose, they should be instructed to take their next dose at the same time they normally do. SEREVENT DISKUS provides bronchodilation for up to 12 hours.

Patients should not stop or reduce SEREVENT DISKUS therapy without physician/provider guidance since symptoms may recur after discontinuation. See Warnings and Precautions Sections of the full [Prescribing Information](#).

Q4. Can additional LABAs be used with SEREVENT DISKUS?

A. No. When patients are prescribed SEREVENT DISKUS, other LABAs should not be used. See Warnings and Precautions Sections of the full [Prescribing Information](#).

Q5. What are the risks of Beta-Agonist Therapy?

A. Patients should be informed that treatment with beta₂-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor or nervousness. See Warnings and Precautions Sections of the full [Prescribing Information](#).

For more information:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm>

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- DHCP Letter (for a period of 1 year)

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Attachment 3; Dear Medical Society Letter

(GlaxoSmithKline Letterhead and Date)

Dear (Medical Society):

GlaxoSmithKline would like to inform you of important safety information for SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder). SEREVENT DISKUS is a long acting beta₂-adrenergic agonist (LABA) indicated for treatment of asthma in the prevention of bronchospasm only as concomitant therapy with a long-term asthma control medication, such as an inhaled corticosteroid (ICS), in patients aged 4 years and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma. SEREVENT DISKUS is not indicated for the relief of acute bronchospasm.

Important safety information related to SEREVENT DISKUS includes:

- Increased risk of asthma-related death in patients taking LABAs.
- New prescribing guidelines.
- SEREVENT DISKUS should only be used as concomitant therapy with a long-term asthma control medication, such as an ICS, in patients aged 4 years and older with reversible obstructive airway disease.
- Use of SEREVENT DISKUS for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an ICS, is contraindicated.
- Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an ICS.
- Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS.
- Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose ICS.
- For pediatric and adolescent patients with asthma who require addition of a LABA to an ICS, a fixed-dose combination product containing both an ICS and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., ICS) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an ICS and a LABA is recommended.

SERVEVENT DISKUS has a risk evaluation and a mitigation strategy (REMS) that consists of a Medication Guide and a communication program.

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Attachment 3; Dear Medical Society Letter

The SEREVENT DISKUS prescribing information includes a boxed warning to highlight the safety issue of asthma-related death.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABAs), such as salmeterol, the active ingredient in SEREVENT® DISKUS®, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs.

Because of this risk, use of SEREVENT DISKUS for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.

Please note that SEREVENT DISKUS should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma.

When prescribing SEREVENT DISKUS, please also provide the patient with an inhaled, short-acting beta₂-agonist (e.g., albuterol) to be used as a rescue inhaler for treatment of acute symptoms. Increasing use of inhaled, short-acting beta₂-agonists is a marker for deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen.

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Attachment 3; Dear Medical Society Letter

The healthcare professional should instruct the patients to contact them if breathing problems worsen over time while using SEREVENT DISKUS and get emergency medical care if breathing problems worsen quickly and are not being relieved by the use of the rescue inhaler.

Please take time to read the enclosed SEREVENT DISKUS Package Insert for full prescribing information for complete description of this important safety information and the new prescribing guidelines. Visit [insert web link; alternative is to include reference to enclosed hard copies] for additional information about the risk of serious asthma outcomes and the safe use of LABAs.

We are asking you to share this communication with members of your society and advise practitioners prescribing SEREVENT DISKUS to discuss the benefits and risks of LABAs with their patients. They should also encourage each patient prescribed SEREVENT DISKUS to thoroughly review the enclosed Medication Guide prior to using.

The Medication Guide will be enclosed in each carton packaging and must be provided by the authorized dispensers to each patient to whom the drug is dispensed.

To report adverse events potentially associated with SEREVENT DISKUS, please call GlaxoSmithKline at 1-888-825-5249.

Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by:

- Phone at 1-800-FDA-1088 (1-800-332-1088)
- Facsimile at 1-800-FDA-0178 (1-800-332-0178)
- Mail using FDA Form 3500 located at <http://www.fda.gov/medwatch>

Please contact GlaxoSmithKline at 1-888-825-5249 if you have any questions about SEREVENT DISKUS or the information in this letter.

Sincerely,

Ellen R. Strahlman, MD
Chief Medical Officer
GlaxoSmithKline