APPENDIX A: FORADIL AEROLIZER REMS Document

Initial REMS Approval: May 2011

NDA 20-831

FORADIL® AEROLIZER®
(formoterol fumarate inhalation powder)

Class of Product: Long-Acting Beta$_2$-adrenergic Agonist

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS:

- To inform healthcare providers and prescribers of the increased risk of asthma-related death and serious outcomes with the long-acting beta$_2$-adrenergic agonists (LABA) including FORADIL AEROLIZER.
- To inform healthcare providers and prescribers of the appropriate use of LABAs including FORADIL AEROLIZER.

II. REMS ELEMENTS

A. Communication Plan

Novartis, through its US licensee, will implement a Communication Plan to healthcare providers to support implementation of this REMS.
The communication plan will include the following:

1. A Dear Healthcare Professional Letter (DHCPL) (see Appendix B) will be distributed to current prescribers of LABAs, including Pulmonologists, Allergists/Immunologists, Primary Care Physicians (Family Practice, General Practice and Internal Medicine), Pediatricians Nurse Practitioners, and Physicians' Assistants.

Distribution of the DHCPL will be by direct mail or e-mail communication with the following timeline:

- Initial distribution within 60 days of the REMS approval.
- A 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. FORADIL AEROLIZER should only be used as concomitant therapy with a long-term asthma control medication, such as an inhaled corticosteroid (ICS), in patients aged 5 years and older with reversible obstructive airway disease.
   ii. Use of FORADIL AEROLIZER for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an ICS, is contraindicated.
   iii. Use FORADIL AEROLIZER only as additional therapy for patients 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 FORADIL AEROLIZER) if possible without loss of asthma control, and maintain the patient on a long term asthma control medication, such as an inhaled corticosteroid.
   v. Do not use FORADIL AEROLIZER for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.
   vi. For pediatric and adolescent patients who require addition of a LABA to an inhaled corticosteroid, a fixed dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure compliance. In cases where use of a separate asthma control medication and LABA is clinically indicated, appropriate steps must be taken to ensure adherence. If adherence cannot be assured, a fixed dose combination product containing both an inhaled corticosteroid and LABA is recommended.

2. A Dear Medical Society Letter

Novartis, through its US licensee will communicate via a letter to the leadership of the following professional associations:

American College of Allergy, Asthma & Immunology (ACAAI)
American Academy of Asthma Allergy & Immunology (AAAAI)
American Thoracic Society (ATS)
American College of Chest Physicians (ACCP)
American College of Physicians (ACP)
American Academy of Pediatricians (AAP)
American Academy of Family Physicians (AAFP)
National Medical Association (NMA)

American Academy of Nurse Practitioners (AANP)
American Academy of Physician Assistants (AAPA)

The communication to professional societies will also include a link to the website or hard copies of the educational information that are also available under number 3 below. The societies will be requested to disseminate this information to their members.

The timeline for REMS communication **materials** to professional societies will parallel the direct mail or e-mail DHCPL timeline:

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

3. Printed and web-based information

Printed **and web-based** information for healthcare providers will be posted on the product website within 30 days of the REMS approval and will remain on the website for 3 years. The content of the print or web-based materials include, at a minimum, 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 FORADIL AEROLIZER
vi. Patient Counseling Information for FORADIL AEROLIZER
vii. Questions and Answers
viii. DHCP Letter (for a period of 1 year)

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

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

B. Timetable for Submission of Assessments

Novartis will submit REMS Assessments to FDA annually from 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. Novartis will submit each assessment so that it will be received by the FDA on or before the due date.

APPENDIX B: FORADIL AEROLIZER

(Merck Letter head and date)

Dear Healthcare Provider Letter (DHCPL)

Dear Healthcare Professional

Merck would like to inform you of important safety information for FORADIL® AEROLIZER® (formoterol fumarate Inhaled Powder).

FORADIL AEROLIZER is a long-acting beta$_2$-agonist (LABA) indicated for the treatment of asthma in adults and children 5 years of age and older and chronic obstructive pulmonary disease (COPD).

New important safety information related to FORADIL AEROLIZER includes:

- Increased risk of asthma-related death in patients taking LABAs.
- New prescribing guidelines for asthma:
    - FORADIL AEROIZER should only be used as concomitant therapy with a long-term asthma control medication, such as an inhaled corticosteroid (ICS), in patients aged 5 years and older with reversible obstructive airway disease.
    - Use of FORADIL AEROLIZER for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an ICS, is contraindicated.
    - Use FORADIL AEROLIZER 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 FORADIL AEROLIZER) 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 FORADIL AEROLIZER for patients whose asthma is adequately controlled on low or medium dose ICS.

- Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure adherence with both medications. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and 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 LABA is recommended.

FORADIL has a risk evaluation and mitigation strategy (REMS) that consists of a communication plan.

The FORADIL AEROLIZER labeling includes a boxed warning to highlight the safety issue of asthma-related death.

WARNING: ASTHMA RELATED DEATH
See full prescribing information for complete boxed warning
Long-acting beta2-adrenergic agonists (LABA), such as formoterol the active ingredient in FORADIL AEROLIZER, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol (see WARNINGS in Prescribing Information). 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 LABA.

Because of this risk, use of FORADIL AEROLIZER for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use FORADIL AEROLIZER 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 FORADIL AEROLIZER) 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 FORADIL AEROLIZER 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 LABA 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 LABA should ordinarily be considered to ensure adherence with

both drugs. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and 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 LABA is recommended.

Please note that FORADIL AEROLIZER should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition.

When prescribing FORADIL AEROLIZER for asthma, please also provide the patients 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 FORADIL AEROLIZER 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 FORADIL AEROLIZER Package Insert for full prescribing information and complete description of this important safety information and the new prescribing guidelines.

In addition, please review the Medication Guide with each patient who is prescribed FORADIL AEROLIZER at the time of first dose or if the Medication Guide is materially changed.

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

To report adverse events potentially associated with FORADIL AEROLIZER, please call Merck & Co. at 1-800-444-2080.
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 Merck at 1-800-444-2080 if you have any questions about FORADIL AEROLIZER or the information in this letter.

Sincerely,

APPENDIX C: FORADIL AEROLIZER PRINTED / WEB MATERIALS

The following content will be housed in a health care 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 FORADIL AEROLIZER, carry a boxed warning. The boxed warning for FORADIL AEROLIZER reads as follows:

WARNING: ASTHMA RELATED DEATH
See full prescribing information for complete boxed warning
Long-acting beta2-adrenergic agonists (LABA), such as formoterol the active ingredient in FORADIL AEROLIZER, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol (see WARNINGS in Prescribing Information). 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 LABA.

Because of this risk, use of FORADIL AEROLIZER for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use FORADIL AEROLIZER 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 FORADIL AEROLIZER) 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 FORADIL AEROLIZER 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 LABA 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 LABA should ordinarily be considered to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and 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 LABA is recommended.

See the full Prescribing Information for a more complete description of the risks associated with the use of FORADIL 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 (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). 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 =	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)

9,361				
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 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 1000 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 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 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 implementation of a 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:

- LABAs should only be used as concomitant therapy with a long-term asthma control medication, such as an ICS.
- Use of a LABA for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an ICS, is contraindicated.
- Use LABAs 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 patients 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 FORADIL AEROLIZER for patients whose asthma is adequately controlled on low or medium dose ICS.

- For pediatric and adolescent patients who require the 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 approved uses

FDA Approved Long-Acting Beta Agonists

Brand Name	LABA active ingredient	Corticosteroid active ingredient	FDA Approved Uses
Serevent Diskus	Salmeterol	None	Asthma, COPD, exercise-induced bronchospasm
Foradil Aerolizer	Formoterol	None	Asthma, COPD, exercise-induced bronchospasm
Foradil Certihaler*	Formoterol	None	Asthma
Advair Diskus	Salmeterol	Fluticasone	Asthma, COPD
Advair HFA	Salmeterol	Fluticasone	Asthma
Symbicort	Formoterol	Budesonide	Asthma, COPD
DULERA Inhalation Aerosol	Formoterol	Mometasone	Asthma
Brovana	Arformoterol	None	COPD
Perforomist	Formoterol	None	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 FORADIL AEROLIZER

LINK - http://www.spfiles.com/piforadil.pdf

- Patient Counseling Information

Information for Patients

Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. Patients should be given the following information:

1. Patients should be informed that the active ingredient in FORADIL AEROLIZER increases the risk of asthma-related death and may increase the risk of asthma-related hospitalizations in pediatric and adolescent patients. 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 LABA. (See Warnings and Precautions Section 5.1 of the full Prescribing Information.)

2. FORADIL AEROLIZER 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).

3. 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

4. Patients should be advised not to increase the dose or frequency of FORADIL AEROLIZER without consulting the prescribing physician. Foradil Aerolizer provides bronchodilation for up to 12 hours.

5. Patients should be warned not to stop or reduce concomitant asthma therapy without medical advice.

6. Patients should be told that when FORADIL AEROLIZER is used for the prevention of exercise induced bronchospasm EIB, the contents of one capsule should be taken at least 15 minutes prior to exercise. Additional doses of FORADIL AEROLIZER should not be used for 12 hours. Prevention of EIB has not been studied in patients who are receiving chronic FORADIL AEROLIZER administration twice daily and these patients should not use additional FORADIL AEROLIZER for prevention of exercise induced bronchospasm (EIB).

7. 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.

8. Patients should be informed never to use FORADIL AEROLIZER with a spacer and never to exhale into the device.

9. Patients should avoid exposing the FORADIL capsules to moisture and should handle the capsules with dry hands. The AEROLIZER Inhaler should never be washed and should be kept dry. The patient should always use the new AEROLIZER Inhaler that comes with each refill.

10. Female patients should be advised to contact their physician if they become pregnant or if they are nursing.

11. Patients should be told that in rare cases, the gelatin capsule might break into small pieces. These pieces should be retained by the screen built into the AEROLIZER Inhaler. However, it remains possible that rarely, tiny pieces of gelatin might reach the mouth or throat after inhalation. The capsule is less likely to shatter when pierced if: storage conditions are strictly followed, capsules are removed from the blister immediately before use, and the capsules are only pierced once.

12. It is important that patients understand how to use the AEROLIZER Inhaler appropriately and how it should be used in relation to other asthma medications they are taking.

- 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 FORADIL AEROLIZER

Q1. Why does FORADIL have a boxed warning?

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

Q3. Can FORADIL be used for acute asthma symptoms?

Q4. Can LABAs be used as a substitute for corticosteroids in the treatment of asthma?

Q5. Should additional LABAs be used with FORADIL?

Q6. Are there special considerations with respect to the use of FORADIL in the treatment of EIB?

Q7. Can FORADIL be used with a spacer?

Q8. Are there special considerations with respect to the FORADIL capsules and the AEROLIZER device?

Q9. Can FORADIL capsules be swallowed?

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 beta$_2$-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 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.
- Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure adherence with both medications.

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

A. Below are the names of the LABA-containing medicines approved by FDA to treat asthma:

Brand Name(s)	Generic Name(s)	Description
Foradil Aerolizer	formoterol	single ingredient LABA with no corticosteroid long-term asthma control medication
Serevent Diskus	salmeterol	single ingredient LABA with no corticosteroid long-term asthma control medication
Advair Diskus, Advair HFA	salmeterol and fluticasone	salmeterol is a LABA and fluticasone 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
DULERA Inhalation Aerosol	formoterol and mometasone	formoterol is a LABA and mometasone 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 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.

For more information:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm

Questions about FORADIL

Q1. Why does FORADIL 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 FORADIL, carry a boxed warning. The boxed warning for FORADIL reads as follows:

WARNING: ASTHMA RELATED DEATH
See full prescribing information for complete boxed warning
Long-acting beta2-adrenergic agonists (LABA), such as formoterol the active ingredient in FORADIL AEROLIZER, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol (see WARNINGS in Prescribing Information). 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 LABA.

Because of this risk, use of FORADIL AEROLIZER for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use FORADIL AEROLIZER 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 FORADIL AEROLIZER) 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 FORADIL AEROLIZER 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 LABA 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 LABA should ordinarily be considered to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and 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 LABA is recommended.

See the full Prescribing Information for a more complete description of the risks associated with the use of FORADIL AEROLIZER in the treatment of asthma.

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

A. **Patients should be informed that long-acting beta2-adrenergic agonists (LABA), including formoterol, the active ingredient in FORADIL AEROLIZER, increase the risk of asthma-related death and may increase the risk of asthma-related hospitalizations in pediatric and adolescent patients. 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 LABA. Patients should be informed that FORADIL AEROLIZER should not be the only therapy for the treatment of asthma and must only be used as additional therapy when a long-term asthma control medication (e.g., inhaled corticosteroids) do not adequately control asthma symptoms. Patients should be informed that when FORADIL AEROLIZER is added to their treatment regimen they must continue to use their long-term asthma control medication**. See the Warnings and Precautions in the full Prescribing Information.

Q3. Can FORADIL be used for acute asthma symptoms?

A. No. FORADIL AEROLIZER 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 if:

-their symptoms worsen
-FORADIL AEROLIZER treatment becomes less effective
-they need more inhalations of a short-acting beta2-agonist than usual

Patients should not inhale more than the contents of one capsule at any one time. The daily dosage of FORADIL AEROLIZER should not exceed one capsule twice daily (24 mcg total daily dose). See the Warnings and Precautions in the full Prescribing Information.

Q4. Can LABAs be used as a substitute for corticosteroids in the treatment of asthma?

A. No. FORADIL AEROLIZER should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with FORADIL AEROLIZER

Q5. Should additional LABAs be used with FORADIL?

A. No. The active ingredient of FORADIL (formoterol fumarate) is a long-acting, bronchodilator used for the treatment of asthma, including nocturnal asthma, and for the prevention of exercise-induced bronchospasm. FORADIL AEROLIZER provides bronchodilation for up to 12 hours. Patients should be advised not to increase the dose or frequency of FORADIL AEROLIZER without consulting the prescribing physician. Patients should be warned not to stop or reduce concomitant asthma therapy without medical advice. In addition, no other LABAs or LABA-containing products should be used in conjunction with FORADIL. See the Warnings and Precautions in the full Prescribing Information.

Q6. Are there special considerations with respect to the use of FORADIL in the treatment of EIB?

A. When FORADIL AEROLIZER is used for the prevention of EIB, the contents of one capsule should be taken at least 15 minutes prior to exercise. Additional doses of FORADIL AEROLIZER should not be used for 12 hours. Prevention of EIB has not been studied in patients who are receiving chronic FORADIL AEROLIZER administration twice daily and these patients should not use additional FORADIL AEROLIZER for prevention of EIB.

Q7. Can FORADIL be used with a spacer?

A. Patients should be informed never to use FORADIL AEROLIZER with a spacer and never to exhale into the device.

Q8. Are there special considerations with respect to the FORADIL capsules and the AEROLIZER device?

A. Yes. Patients should avoid exposing the FORADIL capsules to moisture and should handle the capsules with dry hands. The AEROLIZER Inhaler should never be washed and should be kept dry. The patient should always use the new AEROLIZER Inhaler that comes with each refill. Patients should be told that in rare cases, the gelatin capsule

might break into small pieces. These pieces should be retained by the screen built into the AEROLIZER Inhaler. However, it remains possible that rarely, tiny pieces of gelatin might reach the mouth or throat after inhalation. The capsule is less likely to shatter when pierced if: storage conditions are strictly followed, capsules are removed from the blister immediately before use, and the capsules are only pierced once. It is important that patients understand how to use the AEROLIZER Inhaler appropriately and how it should be used in relation to other asthma medications they are taking.

Q9. Can FORADIL capsules be swallowed?

A. No. FORADIL capsules should only be used as inhaled therapy with the AEROLIZER device. Do not use FORADIL capsules with any other capsule inhaler, and do not use the AEROLIZER inhaler to take any other capsule medicine. **FORADIL capsules should not be ingested (i.e., swallowed) orally.**

APPENDIX D: Foradil Aerolizer

Dear Medical Society Letter

Dear Healthcare Professional/Professional Association:

Merck would like to inform you of important safety information for FORADIL® AEROLIZER® (formoterol fumarate inhaled powder).

FORADIL AEROLIZER is a long-acting beta$_2$-agonist (LABA) indicated for the treatment of asthma in adults and children 5 years of age and older and chronic obstructive pulmonary disease (COPD).
New important safety information related to FORADIL includes:

- Increased risk of asthma-related death in patients taking LABAs.

- New prescribing guidelines for asthma:

  - FORADIL AEROLIZER should only be used as concomitant therapy with a long-term asthma control medication, such as an inhaled corticosteroid (ICS), in patients aged 5 years and older with reversible obstructive airway disease.
    Use of FORADIL AEROLIZER for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an ICS, is contraindicated.

  - Use FORADIL AEROLIZER only as additional therapy for patients who are 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 FORADIL AEROLIZER) 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 FORADIL AEROLIZER for patients whose asthma is adequately controlled on low- or medium-dose ICS.

  - For pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid a fixed dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure compliance. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and LABA is clinically indicated, appropriate steps must be taken to ensure adherence. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.

FORADIL has a risk evaluation and mitigation strategy (REMS) that consists of a communication plan.

The FORADIL AEROLIZER labeling includes a boxed warning to highlight the safety issue of asthma-related death.

WARNING: ASTHMA RELATED DEATH
See full prescribing information for complete boxed warning
Long-acting beta2-adrenergic agonists (LABA), such as formoterol the active ingredient in FORADIL AEROLIZER, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol (see WARNINGS in Prescribing Information). 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 LABA.

Because of this risk, use of FORADIL AEROLIZER for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use FORADIL AEROLIZER 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 FORADIL AEROLIZER) 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 FORADIL AEROLIZER 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 LABA 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 LABA should ordinarily be considered to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and 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 LABA is recommended.

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

When prescribing FORADIL Aerolizer for asthma, please also provide the patients 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 Foradil Aerolizer 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 FORADIL AEROLIZER Package Insert for full prescribing information and complete description of this important safety information and the new prescribing guidelines.

In addition, please review the Medication Guide with each patient who is prescribed FORADIL AEROLIZER at the time of first dose or if the Medication Guide is materially changed.
To report adverse events potentially associated with FORADIL AEROLIZER, please call Merck & Co. at 1-800-444-2080.
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 Merck at 1-800-444-2080 if you have any questions about FORADIL AEROLIZER or the information in this letter.

Sincerely,

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY M SEYMOUR
05/18/2011