NDA 22007
PERFOROMIST® (formoterol fumarate)
Inhalation Solution

Class of Product: Long-acting beta$_2$-adrenergic agonist (LABA)

Dey Pharma, L.P.
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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of this REMS are to:

1. 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 PERFOROMIST® Inhalation Solution.

2. To inform healthcare providers and prescribers of the appropriate use of long-acting beta-2-adrenergic agonists (LABA) including PERFOROMIST® Inhalation Solution.

3. To inform patients with asthma who take long-acting beta-2-adrenergic agonists (LABA) medicines, such as formoterol fumarate, 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 PERFOROMIST® Inhalation Solution.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each PERFOROMIST® (formoterol fumarate) Inhalation Solution, 20 mcg/2ml prescription in accordance with 21 CFR 208.24.

The current Medication Guide is appended.

B. Communication Plan

Dey Pharma, L.P. 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 Provider Letter (DHCPL) will be distributed to current and potential prescribers of LABAs including pulmonologists, immunologists, allergists, general practitioners, internists, family practitioners, nurse practitioners, and physician assistants.

   Distribution of the DHCPL will be by direct mail or e-mail communication within 60 days of the REMS approval.

   The DHCPL will include the following safety information:
   a) Increased risk of asthma-related death in patients taking LABA for the treatment of asthma
   b) New prescribing guidelines including:
      i. All LABA, including PERFOROMIST® Inhalation Solution, are contraindicated in patients with asthma without use of a long-term asthma control medication.

2. A Dear Medical Society Letter will be distributed to the following professional societies:

   The American Academy of Allergy, Asthma, and Immunology (AAAAI)
   The American Thoracic Society (ATS)
   The American College of Chest Physicians (ACCP)
   The American Academy of Family Physicians (AAFP)
   The American College of Physicians (ACP)
   The American Academy of Nurse Practitioners (AANP)
   The American Academy of Physician Assistants (AAPA)
   The COPD Foundation
   The American College of Allergy, Asthma, and Immunology (ACAAI)
   The National Medical Association (NMA)

The communication to medical societies will also include a link to the website or hard copies of educational information that are also available under item 3 below. Dey Pharma, L.P. will request that these societies disseminate this information to their members.

The REMS communication materials to professional societies will parallel the direct mail or e-mail program and will be distributed within 60 days after REMS approval.

3. The product web site (perforomist.com) will be updated to reflect the new safety information. This information will be implemented within 30 days of the REMS approval date and will remain on the web site for 3 years. The content of the web-based material, at a minimum, will include the following:
    a. Information about the risk
    b. Key data regarding the risk (e.g. SMART, SNS)
    c. New prescribing guidelines
    d. Currently available LABAs and approved uses
    e. Prescribing information for PERFOROMIST®
    f. Patient Counseling Information
    g. Medication Guide for PERFOROMIST®
    h. Questions and Answers
    i. DHCPL (for a period of 1 year)
    j. Link to FDA web site for alerts on LABAs

The following are part of the REMS and are attached:

i. DHCPL
ii. Dear Medical Society Letter
iii. Educational or printed web-based information

C. Timetable for Submission of Assessments

Dey Pharma, L.P. will submit REMS assessments to FDA no less frequently than yearly from the date of 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 will conclude no earlier than 60 days before the submission date for that assessment. Dey will submit each assessment so that it will be received by FDA on or before the due date.

Attachments

Attachment A: PERFOROMIST® Medication Guide
Attachment B: Dear Healthcare Provider Letter
Attachment C: Web-based materials (perforomist.com)
Attachment D American Academy of Allergy, Asthma, and Immunology Letter
Attachment E: American Thoracic Society Letter
Attachment F: American College of Chest Physicians Letter
Attachment G: American Academy of Family Physicians Letter
Attachment H: American College of Physicians Letter
Attachment I: American Academy of Nurse Practitioners Letter
Attachment J: American Academy of Physician Assistants Letter
Attachment K: COPD Foundation Letter
Attachment L: American College of Allergy, Asthma, and Immunology Letter
Attachment M: National Medical Association Letter

Attachment B – Dear Healthcare Provider Letter

[Dey Pharma, L.P. letterhead]

[Date]

Dear Healthcare Professional:

Dey Pharma, L.P. would like to inform you of important safety-related changes to the PERFOROMIST® (formoterol fumarate) Inhalation Solution, 20 mcg/2mL prescribing information.

PERFOROMIST® is a long-acting $beta_2$-adrenergic agonist (LABA) indicated for long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

New important safety information related to PERFOROMIST® includes:

- Increased risk of asthma-related death in patients taking LABAs for treatment of asthma.
- New prescribing guideline.
    - All LABA, including PERFOROMIST®, are contraindicated in patients with asthma without the concomitant use of a long term asthma controller medication.

PERFOROMIST® is indicated for use in adults with COPD including chronic bronchitis and emphysema. PERFOROMIST® is not indicated for the treatment of asthma.

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

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

WARNING: ASTHMA-RELATED DEATH

Long-acting $beta_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting $beta_2$-adrenergic agonist (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, the active ingredient in PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS in the Prescribing information).

Attachment B – Dear Healthcare Provider Letter

Please note that PERFOROMIST® Inhalation Solution should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of PERFOROMIST® in this setting is inappropriate.

When prescribing PERFOROMIST®, please also provide the patient with an inhaled, short-acting beta2-agonist for treatment of COPD symptoms that occur acutely.

PERFOROMIST® should not be used in conjunction with other inhaled, long-acting $beta_2$-agonists. PERFOROMIST® should not be used with other medications containing long-acting $beta_2$-agonists.

When beginning treatment with PERFOROMIST®, patients who have been taking inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

Please instruct the patients to contact you if breathing problems worsen over time while using PERFOROMIST® 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 PERFOROMIST® Package Insert for full prescribing information, for complete description of this important safety information and the new prescribing guidelines.

PERFOROMIST® is not indicated for use in children. The safety and efficacy of PERFOROMIST® in pediatric patients have not been established.

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

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 PERFOROMIST® please call 1-877-446-3679. 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 Dey Medical Information at 1-800-429-7751 if you have any questions about PERFOROMIST® or the information in this letter.

Sincerely,

Sunil Mehra, MD, FRCP, FAAAAI
Chief Medical Officer
Dey Pharma, L.P.

The following content will be housed in a health care provider section of the product web site.

• 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 PERFOROMIST, carry a boxed warning. The boxed warning for PERFOROMIST reads as follows:

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (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, the active ingredient in PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS in the Prescribing Information).

See the full Prescribing Information for a more complete description of the risks associated with the use of PERFOROMIST.

• 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 a total of 26,355 patients 12 years of age and older receiving standard asthma therapy and the addition of either salmeterol or placebo. 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. 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 this study, there was an increase in the number of respiratory and asthma-related deaths in the salmeterol group compared to the albuterol group (0.07% [12 out of 16,787 patients]) compared to the albuterol group (0.02% [2 out of 8393 patients] relative risk of 3.0, p=0.105]).

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

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 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:

- All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication.

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

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

Attachment C – Web-based materials (perforomist.com)

Brand Name	LABA active ingredient	Corticosteroid active ingredient	FDA Approved Uses
Foradil Certihaler*	Formoterol	None	Asthma
Advair Diskus	Salmeterol	Fluticasone	Asthma, COPD
Advair HFA	Salmeterol	Fluticasone	Asthma
Symbicort	Formoterol	Budesonide	Asthma, COPD
Brovana	Arformoterol	None	COPD
Perforomist	Formoterol	None	COPD
Dulera Aerosol	Formoterol	Mometasone	Asthma

** 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

- **Patient Counseling Information**

See USPI and Medication Guide

Asthma-Related Death

Note: The safety and efficacy of PERFOROMIST in patients with asthma have not been established.

See Medication Guide
Patients should be informed that long acting beta agonist, such as PERFOROMIST, increase the risk of asthma-related death. All LABA, including PERFOROMIST, should not be used in patients with asthma without use of a long-term asthma control medication. See Warnings and Precautions Section 5.1 of the full Prescribing Information.

Acute Exacerbations or Deteriorations

PERFOROMIST Inhalation Solution is not indicated for relief of acute symptoms, and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist (the healthcare provider should provide 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 despite recommended doses of PERFOROMIST Inhalation Solution, if PERFOROMIST Inhalation Solution treatment becomes less effective, or if they need more inhalations of a short-acting beta$_2$-agonist than usual. See Warnings and Precautions Section 5.2 of the full Prescribing Information.

Appropriate Dosing

Patients should not stop using PERFOROMIST Inhalation Solution unless told to do so by a healthcare provider because symptoms may get worse. Patients should not inhale more than the prescribed number of vials at any one time. The daily dosage of PERFOROMIST Inhalation Solution should not exceed one vial twice daily (40 mcg total daily dose). Excessive use of sympathomimetics may cause significant cardiovascular effects, and may be fatal. See Dosage and Administration Section 2 of the full Prescribing Information.

Concomitant Therapy

Patients who have been taking inhaled, short-acting beta$_2$-agonists (e.g., albuterol) on a regular basis should be instructed to discontinue the regular use of these products and use them only for symptomatic relief of acute symptoms. PERFOROMIST Inhalation Solution should not be used in conjunction with other inhaled medications containing long-acting beta$_2$-agonists. Patients should be warned not to stop or change the dose of other concomitant COPD therapy without medical advice, even if symptoms improve after initiating treatment with PERFOROMIST Inhalation Solution.

Common Adverse Reactions with Beta$_2$-agonists

Patients should be informed that treatment with beta$_2$-agonists may lead to adverse reactions that include palpitations, chest pain, rapid heart rate, increased or decreased blood pressure, headache, tremor, nervousness, dry mouth, muscle cramps, nausea, dizziness, fatigue, malaise, low blood potassium, high blood sugar, high blood acid, or trouble sleeping . See Adverse Reactions Section 6.1 of the full Prescribing Information.

Instructions for Administration

It is important that patients understand how to use PERFOROMIST Inhalation Solution with a nebulizer appropriately [see Medication Guide]. Patients should be instructed not to mix other medications with PERFOROMIST Inhalation Solution or ingest PERFOROMIST Inhalation Solution. Patients should throw the plastic dispensing container away immediately after use. Due to their small size, the container and top pose a danger of choking to young children.

- Medication Guide for PERFOROMIST

Link - http://www.perforomist.com/pdf/Perforomist_Prescribing_Information.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 information did FDA review to help the Agency decide to require a risk management program?

Q5. What are the names of LABA-containing medicines used to treat asthma?

Q6. Why should LABAs only be used with a long-term asthma control medication, are they safer when used this way?

Q7. If LABAs are to be used with an asthma controller medicine, why aren't all LABA products required by FDA to be in a combination product with an asthma controller medicine?

Q8. Is the use of LABAs without the use of an asthma controller medication a big problem in the treatment of asthma?

Q9. Why is the new risk management program designed for patients with asthma and not for patients with COPD, aren't LABAs used to treat both conditions?

Questions about Perforomist® Inhalation Solution

Q1. Why does PERFOROMIST have a boxed warning?

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

Q3. Can PERFOROMIST be used for acute asthma symptoms or COPD?

Q4. Can additional LABAs be used with PERFOROMIST?

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 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.

Q4. 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 Multicenter 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.

Q5. 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
Advair Diskus, Advair HFA	salmeterol and fluticasone	salmeterol is a LABA and fluticasone is a corticosteroid asthma controller
Symbicort Inhalation Aerosol	formoterol and budesonide	formoterol is a LABA and budesonide is a corticosteroid asthma controller
Serevent Diskus	salmeterol	single ingredient LABA with no corticosteroid asthma controller
Foradil Aerolizer	formoterol	single ingredient LABA with no corticosteroid asthma controller
Dulera Aerosol	formoterol and mometasone	formoterol is a LABA and mometasone is a corticosteroid asthma controller

Q6. 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 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.

Q7. If LABAs are to be used with an asthma controller medicine, why aren't all LABA products required by FDA to be in a combination product with an asthma controller medicine?

A. There are several kinds of asthma controller medicines patients may use in combination with a LABA, but not all are able to be made into a combination product. For example, there are many different inhaled corticosteroids available and some pills, such as Singulair (montelukast) or prednisone, which patients may take with a LABA. This means that some single ingredient LABA products need to be available for patients whose other asthma controller medicine cannot be combined in the same inhaled dose. Additionally, single ingredient LABA products are used in the treatment of COPD.

Q8. Is the use of LABAs without the use of an asthma controller medication a big problem in the treatment of asthma?

A. No, currently, about 95% of patients using a LABA use an inhaled combination product that contains a LABA and a corticosteroid. However, discontinuation of the LABA once control of asthma is achieved is not currently a widespread practice; therefore, many patients who are using a combination LABA product may be unnecessarily exposed to the risks of LABAs. FDA is emphasizing its recommendation that when LABAs are needed that they be used for the shortest time possible to achieve asthma control and then be discontinued, if possible, to limit the long-term use.

Q9. Why is the new risk management program designed for patients with asthma and not for patients with COPD, aren't LABAs used to treat both conditions?

A. LABAs are used to treat both asthma and COPD, however, the studies reviewed by FDA included patients using LABAs for the treatment of asthma. These studies indicated an increased risk of severe exacerbation of asthma symptoms leading to hospitalization and death in these patients. There is no evidence to conclude that people with COPD who use LABAs are at any greater risk compared to people with COPD who do not use LABAs. FDA does not recommend any change in the use of LABAs for COPD.

Questions about PERFOROMIST

Q1. Why does PERFOROMIST 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 PERFOROMIST, carry a boxed warning. PERFOROMIST is not indicated in asthma, it is only indicated for use in COPD. The boxed warning for PERFOROMIST reads as follows:

> **WARNING: ASTHMA-RELATED DEATH**
> **Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (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, the active ingredient in PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication.**

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

A. Patients should be informed that formoterol, the active ingredient in PERFOROMIST, increases the risk of asthma-related death. In pediatric and adolescent patients, formoterol 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 PERFOROMIST be used for acute asthma symptoms or COPD?

A. No. **The safety and efficacy of PERFOROMIST in patients with asthma have not been established.** PERFOROMIST Inhalation Solution is not indicated for relief of acute symptoms of asthma or COPD, and extra doses should not be used for that purpose. Acute COPD symptoms should be treated with an inhaled, short-acting beta$_2$-agonist (the healthcare provider should provide 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 despite recommended doses of PERFOROMIST Inhalation Solution, if PERFOROMIST Inhalation Solution treatment becomes less effective, or if they need more inhalations of a short-acting beta$_2$-agonist than usual. See Warnings and Precautions Section in the full Prescribing Information.

Q4. Can additional LABAs be used with PERFOROMIST?

A. No. When patients are prescribed PERFOROMIST, other long-acting beta$_2$-agonists should not be used. See Warnings and Precautions Section 5.3 of the full Prescribing Information.

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

A. Patients should be informed that treatment with beta$_2$-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor or nervousness. See Warnings and Precautions Section 5.11 of the full Prescribing Information.

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

Attachment D – American Academy of Allergy, Asthma, and Immunology Letter

[Dey Pharma, L.P. letterhead]

[Date]

Kay Whalen, Executive Vice President
American Academy of Allergy, Asthma & Immunology
555 East Wells Street
Suite 1100
Milwaukee, WI 53202-3823

Dear Ms. Whalen:

Dey Pharma, L.P. would like to inform you of important safety-related changes to the PERFOROMIST® (formoterol fumarate) Inhalation Solution, 20 mcg/2mL prescribing information.

PERFOROMIST® is a long-acting beta$_2$-adrenergic agonist (LABA) indicated for long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

New important safety information related to PERFOROMIST® includes:

- Increased risk of asthma-related death in patients taking LABAs for treatment of asthma.
- New prescribing guideline.
    - All LABA, including PERFOROMIST® Inhalation Solution, are contraindicated in patients with asthma without the concomitant use of a long term asthma controller medication.

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

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (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, the active ingredient in

PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS in the Prescribing Information).

Please note that PERFOROMIST® Inhalation Solution should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of PERFOROMIST® in this setting is inappropriate.

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

PERFOROMIST® should not be used in conjunction with other inhaled, long-acting beta$_2$-agonists. PERFOROMIST® should not be used with other medications containing long-acting beta$_2$-agonists.

When beginning treatment with PERFOROMIST®, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

PERFOROMIST® should not be used in children as the safety and efficacy of PERFOROMIST® have not been established in pediatric patients.

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

Please share this communication with the members of your society and assure that they review the attached Medication Guide with each patient who is prescribed PERFOROMIST®.

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 PERFOROMIST® please call 1-877-446-3679. 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 Dey Medical Information at 1-800-429-7751 if you have any questions about PERFOROMIST® or the information in this letter.

Sincerely,

Sunil Mehra, MD, FRCP, FAAAAI
Chief Medical Officer
Dey Pharma, L.P.

Attachment E – American Thoracic Society Letter

[Dey Pharma, L.P. letterhead]

[Date]

Stephen C. Crane, PhD, MPH - Executive Director
American Thoracic Society
61 Broadway
4th Floor
New York, NY 10006-2755

Dear Dr. Crane

Dey Pharma, L.P. would like to inform you of important safety-related changes to the PERFOROMIST® (formoterol fumarate) Inhalation Solution, 20 mcg/2mL prescribing information.

PERFOROMIST® is a long-acting beta$_2$-adrenergic agonist (LABA) indicated for long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

New important safety information related to PERFOROMIST® includes:

- Increased risk of asthma-related death in patients taking LABAs for treatment of asthma.
- New prescribing guideline.
    - All LABA, including PERFOROMIST® Inhalation Solution, are contraindicated in patients with asthma without the concomitant use of a long term asthma controller medication.

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

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

WARNING: ASTHMA-RELATED DEATH

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PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS in the Prescribing Information).

Please note that PERFOROMIST® Inhalation Solution should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of PERFOROMIST® in this setting is inappropriate.

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

PERFOROMIST® should not be used in conjunction with other inhaled, long-acting beta2-agonists. PERFOROMIST® should not be used with other medications containing long-acting beta2-agonists.

When beginning treatment with PERFOROMIST®, patients who have been taking inhaled, short-acting beta2-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

PERFOROMIST® should not be used in children as the safety and efficacy of PERFOROMIST® have not been established in pediatric patients.

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

Please contact Dey Medical Information at 1-800-429-7751 if you have any questions about PERFOROMIST® or the information in this letter.

Sincerely,

Sunil Mehra, MD, FRCP, FAAAAI
Chief Medical Officer
Dey Pharma, L.P.

Attachment F – American College of Chest Physicians Letter

[Dey Pharma, L.P. letterhead]

[Date]

Paul A. Markowski, CAE - Executive Vice President and CEO
American College of Chest Physicians
3300 Dundee Road
Northbrook, IL 60062-2348

Dear Mr. Markowski:

Dey Pharma, L.P. would like to inform you of important safety-related changes to the PERFOROMIST® (formoterol fumarate) Inhalation Solution, 20 mcg/2mL prescribing information.

PERFOROMIST® is a long-acting beta$_2$-adrenergic agonist (LABA) indicated for long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

New important safety information related to PERFOROMIST® includes:

- Increased risk of asthma-related death in patients taking LABAs for treatment of asthma.
- New prescribing guideline.
    - All LABA, including PERFOROMIST® Inhalation Solution, are contraindicated in patients with asthma without the concomitant use of a long term asthma controller medication.

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

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

WARNING: ASTHMA-RELATED DEATH

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PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS in the Prescribing Information).

Please note that PERFOROMIST® Inhalation Solution should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of PERFOROMIST® in this setting is inappropriate.

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

PERFOROMIST® should not be used in conjunction with other inhaled, long-acting beta2-agonists. PERFOROMIST® should not be used with other medications containing long-acting beta2-agonists.

When beginning treatment with PERFOROMIST®, patients who have been taking inhaled, short-acting beta2-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

PERFOROMIST® should not be used in children as the safety and efficacy of PERFOROMIST® have not been established in pediatric patients.

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

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

Please contact Dey Medical Information at 1-800-429-7751 if you have any questions about PERFOROMIST® or the information in this letter.

Sincerely,

Sunil Mehra, MD, FRCP, FAAAAI
Chief Medical Officer
Dey Pharma, L.P.

Attachment G – American Academy of Family Physicians Letter

[Dey Pharma, L.P. letterhead]

[Date]

Douglas E. Henley, MD, FAAFP
American Academy of Family Physicians
P.O. Box 11210
Shawnee Mission, KS 66207-1210

Dear Dr. Henley:

Dey Pharma, L.P. would like to inform you of important safety-related changes to the PERFOROMIST® (formoterol fumarate) Inhalation Solution, 20 mcg/2mL prescribing information.

PERFOROMIST® is a long-acting beta$_2$-adrenergic agonist (LABA) indicated for long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

New important safety information related to PERFOROMIST® includes:

- Increased risk of asthma-related death in patients taking LABAs for treatment of asthma.
- New prescribing guideline.
    - All LABA, including PERFOROMIST® Inhalation Solution, are contraindicated in patients with asthma without the concomitant use of a long term asthma controller medication.

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

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

WARNING: ASTHMA-RELATED DEATH

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PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS in the Prescribing Information).

Please note that PERFOROMIST® Inhalation Solution should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of PERFOROMIST® in this setting is inappropriate.

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

PERFOROMIST® should not be used in conjunction with other inhaled, long-acting beta2-agonists. PERFOROMIST® should not be used with other medications containing long-acting beta2-agonists.

When beginning treatment with PERFOROMIST®, patients who have been taking inhaled, short-acting beta2-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

PERFOROMIST® should not be used in children as the safety and efficacy of PERFOROMIST® have not been established in pediatric patients.

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

Please share this communication with the members of your society and assure that they review the attached Medication Guide with each patient who is prescribed PERFOROMIST®.

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- Mail using FDA Form 3500 located at http://www.fda.gov/medwatch

Please contact Dey Medical Information at 1-800-429-7751 if you have any questions about PERFOROMIST® or the information in this letter.

Sincerely,

Sunil Mehra, MD, FRCP, FAAAAI
Chief Medical Officer
Dey Pharma, L.P.

Attachment H – American College of Physicians Letter

[Dey Pharma, L.P. letterhead]

[Date]

Steven E. Weinberger, MD, FACP
American College of Physicians
190 N Independence Mall West
Philadelphia, PA 19106-1572

Dear Dr. Weinberger:

Dey Pharma, L.P. would like to inform you of important safety-related changes to the PERFOROMIST® (formoterol fumarate) Inhalation Solution, 20 mcg/2mL prescribing information.

PERFOROMIST® is a long-acting beta$_2$-adrenergic agonist (LABA) indicated for long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

New important safety information related to PERFOROMIST® includes:

- Increased risk of asthma-related death in patients taking LABAs for treatment of asthma.
- New prescribing guideline.
    - All LABA, including PERFOROMIST® Inhalation Solution, are contraindicated in patients with asthma without the concomitant use of a long term asthma controller medication.

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

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

WARNING: ASTHMA-RELATED DEATH

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PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS in the Prescribing Information).

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Please contact Dey Medical Information at 1-800-429-7751 if you have any questions about PERFOROMIST® or the information in this letter.

Sincerely,

Sunil Mehra, MD, FRCP, FAAAAI
Chief Medical Officer
Dey Pharma, L.P.

Attachment I – American Academy of Nurse Practitioners Letter

[Dey Pharma, L.P. letterhead]

[Date]

Kay Todd, CAE, PhD, Executive Director
AANP National Administrative Office
PO Box 12846
Austin, TX 78711

Dear Dr. Todd:

Dey Pharma, L.P. would like to inform you of important safety-related changes to the PERFOROMIST® (formoterol fumarate) Inhalation Solution, 20 mcg/2mL prescribing information.

PERFOROMIST® is a long-acting beta$_2$-adrenergic agonist (LABA) indicated for long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

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- Increased risk of asthma-related death in patients taking LABAs for treatment of asthma.
- New prescribing guideline.
    - All LABA, including PERFOROMIST® Inhalation Solution, are contraindicated in patients with asthma without the concomitant use of a long term asthma controller medication.

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

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

WARNING: ASTHMA-RELATED DEATH

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PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS in the Prescribing Information).

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Please contact Dey Medical Information at 1-800-429-7751 if you have any questions about PERFOROMIST® or the information in this letter.

Sincerely,

Sunil Mehra, MD, FRCP, FAAAAI
Chief Medical Officer
Dey Pharma, L.P.

Attachment J – American Academy of Physician Assistants Letter

[Dey Pharma, L.P. letterhead]

[Date]

William Leinweber, CEO
American Academy of Physician Assistants
950 North Washington Street
Alexandria, VA 22314-1552

Dear Mr. Leinweber:

Dey Pharma, L.P. would like to inform you of important safety-related changes to the PERFOROMIST® (formoterol fumarate) Inhalation Solution, 20 mcg/2mL prescribing information.

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Please contact Dey Medical Information at 1-800-429-7751 if you have any questions about PERFOROMIST® or the information in this letter.

Sincerely,

Sunil Mehra, MD, FRCP, FAAAAI
Chief Medical Officer
Dey Pharma, L.P.

Attachment K – COPD Foundation Letter

[Dey Pharma, L.P. letterhead]

[Date]

John Walsh, President
COPD Foundation
50 F Street NW, Suite 950
Washington, DC 20001

Dear Mr. Walsh:

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- New prescribing guideline.
    - All LABA, including PERFOROMIST® Inhalation Solution, are contraindicated in patients with asthma without the concomitant use of a long term asthma controller medication.

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (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, the active ingredient in

PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS in the Prescribing Information).

Please note that PERFOROMIST® Inhalation Solution should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of PERFOROMIST® in this setting is inappropriate.

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

PERFOROMIST® should not be used in conjunction with other inhaled, long-acting beta2-agonists. PERFOROMIST® should not be used with other medications containing long-acting beta2-agonists.

When beginning treatment with PERFOROMIST®, patients who have been taking inhaled, short-acting beta2-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

PERFOROMIST® should not be used in children as the safety and efficacy of PERFOROMIST® have not been established in pediatric patients.

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

Please share this communication with the members of your society and assure that they review the attached Medication Guide with each patient who is prescribed PERFOROMIST®.

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 PERFOROMIST® please call 1-877-446-3679. 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 Dey Medical Information at 1-800-429-7751 if you have any questions about PERFOROMIST® or the information in this letter.

Sincerely,

Sunil Mehra, MD, FRCP, FAAAAI
Chief Medical Officer
Dey Pharma, L.P.

Attachment L – American College of Allergy, Asthma, and Immunology Letter

[Dey Pharma, L.P. letterhead]

[Date]

Rick Slawney, Executive Director
American College of Allergy, Asthma & Immunology
85 West Algonquin Road
Suite 550
Arlington Heights, IL 60005

Dear Mr. Slawney:

Dey Pharma, L.P. would like to inform you of important safety-related changes to the PERFOROMIST® (formoterol fumarate) Inhalation Solution, 20 mcg/2mL prescribing information.

PERFOROMIST® is a long-acting beta$_2$-adrenergic agonist (LABA) indicated for long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

New important safety information related to PERFOROMIST® includes:

- Increased risk of asthma-related death in patients taking LABAs for treatment of asthma.
- New prescribing guideline.
    - All LABA, including PERFOROMIST® Inhalation Solution, are contraindicated in patients with asthma without the concomitant use of a long term asthma controller medication.

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

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (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, the active ingredient in

PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS in the Prescribing Information).

Please note that PERFOROMIST® Inhalation Solution should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of PERFOROMIST® in this setting is inappropriate.

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

PERFOROMIST® should not be used in conjunction with other inhaled, long-acting beta2-agonists. PERFOROMIST® should not be used with other medications containing long-acting beta2-agonists.

When beginning treatment with PERFOROMIST®, patients who have been taking inhaled, short-acting beta2-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

PERFOROMIST® should not be used in children as the safety and efficacy of PERFOROMIST® have not been established in pediatric patients.

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

Please share this communication with the members of your society and assure that they review the attached Medication Guide with each patient who is prescribed PERFOROMIST®.

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To report adverse events potentially associated with PERFOROMIST® please call 1-877-446-3679. 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 Dey Medical Information at 1-800-429-7751 if you have any questions about PERFOROMIST® or the information in this letter.

Sincerely,

Sunil Mehra, MD, FRCP, FAAAAI
Chief Medical Officer
Dey Pharma, L.P.

Attachment M – National Medical Association Letter

[Dey Pharma, L.P. letterhead]

[Date]

Kweisi Mume, Executive Director
National Medical Association
8403 Colesville Road
Suite 920
Silver Spring, Maryland 20910

Dear Mr. Mume:

Dey Pharma, L.P. would like to inform you of important safety-related changes to the PERFOROMIST® (formoterol fumarate) Inhalation Solution, 20 mcg/2mL prescribing information.

PERFOROMIST® is a long-acting beta$_2$-adrenergic agonist (LABA) indicated for long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

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- Increased risk of asthma-related death in patients taking LABAs for treatment of asthma.
- New prescribing guideline.
    - All LABA, including PERFOROMIST® Inhalation Solution, are contraindicated in patients with asthma without the concomitant use of a long term asthma controller medication.

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (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, the active ingredient in

PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS in the Prescribing Information).

Please note that PERFOROMIST® Inhalation Solution should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of PERFOROMIST® in this setting is inappropriate.

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

PERFOROMIST® should not be used in conjunction with other inhaled, long-acting beta2-agonists. PERFOROMIST® should not be used with other medications containing long-acting beta2-agonists.

When beginning treatment with PERFOROMIST®, patients who have been taking inhaled, short-acting beta2-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

PERFOROMIST® should not be used in children as the safety and efficacy of PERFOROMIST® have not been established in pediatric patients.

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- 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 Dey Medical Information at 1-800-429-7751 if you have any questions about PERFOROMIST® or the information in this letter.

Sincerely,

Sunil Mehra, MD, FRCP, FAAAAI
Chief Medical Officer
Dey Pharma, L.P.

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

SUPPORTING DOCUMENT

NDA 22007
PERFOROMIST® (formoterol fumarate)
Inhalation Solution, 20 mcg/2ml

Class of Product: Long-acting beta$_2$-adrenergic agonist (LABA)

Dey Pharma, L.P.
110 Allen Road, 4th Floor
Basking Ridge, NJ 07920

REMS Contact: S. Wayne Talton, Vice President
Regulatory Affairs & Pharmacovigilance
North America
304.554.6551
wayne.talton@mylan.com

1. TABLE OF CONTENTS

2. BACKGROUND

2.1. Long-Acting Beta-Agonist Risk Evaluation and Mitigation Strategy

On September 27, 2007, the Food and Drug Administration Amendments Act of 2007 (FDAAA) was signed into law. Title IX, Subtitle A, section 901 of this statute created section 505-1 of the Food, Drug, and Cosmetic Act (FDCA). This new section authorized FDA to require holders of covered applications approved without a Risk Evaluation and Mitigation Strategy (REMS) to submit a proposed REMS if the FDA becomes aware of new safety information and determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug.

The term "new safety information" means information derived from:

- a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3)); or
- peer-reviewed biomedical literature; or
- data derived from the postmarket risk identification and analysis system under section 505(k); or
- other scientific data deemed appropriate by the Secretary of Health and Human Services about a serious risk or an unexpected serious risk associated with use of the drug of which the Secretary has become aware that may be based on a new analysis of existing information

On February 18, 2010, FDA announced the requirement of a REMS for Long-Acting Beta-Agonists (LABAs). The REMS will include a revised Medication Guide written specifically for patients and a plan to educate healthcare professionals about the appropriate use of LABAs, as well as a timetable of assessments. The agency is requiring the REMS and class-labeling changes to improve the safe use of these products.

LABAs are approved in the U.S. as single-entity products and in combination products with inhaled corticosteroids for the treatment of asthma and/or chronic obstructive pulmonary disease (COPD). LABAs work by relaxing muscles in the airway and lungs helping patients to breathe easier by relieving symptoms such as wheezing and shortness of breath. The new recommendations only apply to the use of LABAs in the treatment of asthma. There is no evidence to conclude that patients with COPD who use LABAs are at any greater risk compared to patients with COPD who do not use LABAs. Under this proposed REMS, FDA does not recommend any change in the use of LABAs for COPD.[1]

FDA has determined that the benefits of LABAs in asthma outweigh the potential risks when used appropriately with an asthma controller medication in patients who need the addition of a long-acting beta-agonist. FDA believes the additional safety measures recommended above will improve the safe use of LABAs for asthma. Note that PERFOROMIST® (formoterol fumarate) Inhalation Solution is not approved in asthma

and the prescribing information for this product will be updated to include a contraindication in asthma.

The proposed 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 provided to healthcare professionals to include the latest recommendations for safe use of these important medicines.

Based on multiple reviews of available information, FDA concluded 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 REMS and class-labeling changes are being implemented to improve the safe use of these products.

FDA's decision to require a 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 (SNS) study, and a meta-analysis conducted by FDA in 2008 and discussed at the joint meeting of the Pulmonary Allergy Drugs, Drug Safety and Risk Management, and Pediatric Advisory Committees held on December 10-11, 2008.[2]

Salmeterol (as Serevent® Inhalation Aerosol) was the first LABA approved in the U.S. Following the approval of salmeterol in 1994, GSK initiated the large safety study, SMART, in 1996. The SMART study was conducted at the Agency's request and was prompted by reports of serious asthma exacerbations and deaths in patients treated with salmeterol soon after its approval, as well as by findings of the Salmeterol Nationwide Surveillance (SNS) study that had been conducted in the United Kingdom in the mid 1990s.

The Serevent Nationwide Surveillance study (SNS)[3] was a 16-week, double-blind study that compared the addition of salmeterol or albuterol to standard asthma therapy in asthma patients who were 12 years of age and older. There were 25,180 patients randomized to treatment – 16,787 to salmeterol and 8,393 to albuterol. 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).

The 14 deaths from asthma were in patients with severe asthma either in the view of the general practitioner or in the view of the independent consultants appointed by the National Asthma Campaign. Five patients were taking oral steroids and an additional patient was taking nebulized beta-agonists. Yet another patient had previous attacks

described as catastrophic, but in this case inhaled steroids were stopped because of fear of growth suppression. All but two of the patients who died were taking two or more inhalers of a beta-agonist a month at the time of entry into the study.[3]

The Salmeterol Multicenter Asthma Research Trial (SMART)[4] was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, observational surveillance study conducted at 6,163 sites in the United States.

The primary end point was the occurrence of combined respiratory-related deaths or respiratory-related life-threatening experiences (defined as intubation and mechanical ventilation). Secondary end points included all-cause deaths, combined asthma-related deaths or life-threatening experiences, asthma-related deaths, respiratory-related deaths, combined all-cause deaths or life-threatening experiences, and all-cause hospitalizations. Other end points included the relative frequency of all-cause serious adverse events.

Following an interim analysis in 26,355 subjects, the study was terminated due to findings in African Americans and difficulties in enrollment. The occurrence of the primary outcome, respiratory-related deaths, or life-threatening experiences was low and not significantly different for salmeterol vs. placebo (50 vs. 36; relative risk [RR] = 1.40; 95% confidence interval [CI], 0.91 to 2.14). There was a small, significant increase in respiratory-related deaths (24 vs. 11; RR, 2.16; 95% CI, 1.06 to 4.41) and asthma-related deaths (13 vs. 3; RR, 4.37; 95% CI, 1.25 to 15.34), and in combined asthma-related deaths or life-threatening experiences (37 vs. 22; RR, 1.71; 95% CI, 1.01 to 2.89) in subjects receiving salmeterol vs. placebo. Subgroup analyses suggest the risk may be greater in African Americans compared with Caucasian subjects.

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. 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.[2]

Previous analyses of the SNS, SMART, and LABA postmarketing data led to several regulatory actions and labeling changes for LABA products.

On November 18, 2005, FDA alerted health care professionals and patients that several long-acting bronchodilator medicines have been associated with possible increased risk of worsening wheezing (bronchospasm) in some people, and requested that manufacturers update warnings in their existing product labeling.

On March 2, 2006, FDA approved new safety labeling and Medication Guides for Serevent Diskus (salmeterol xinafoate) and Advair Diskus (fluticasone propionate; salmeterol xinafoate). On June 19, 2006, FDA approved new safety labeling and a Medication Guide for Foradil (formoterol fumarate), and also approved Advair HFA.

On November 28, 2007, a Pediatric Advisory Committee meeting was held. At this meeting, FDA raised concerns about the safety of LABAs in pediatric patients with asthma. The Advisory Committee agreed with an FDA recommendation to continue assessment of the risks of LABAs and seek advice from a future advisory committee.

In January, 2008 FDA requested manufacturers of Advair Diskus®, Advair HFA®, Brovana® Inhalation Solution, Foradil® Aerolizer, PERFOROMIST® (formoterol fumarate) Inhalation Solution, Serevent® Diskus, and Symbicort® Inhalation Aerosol to provide information regarding controlled clinical studies conducted with these products in order to further evaluate the safety of LABAs when treating asthma.

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

2.2. PERFOROMIST® Inhalation Solution for COPD

PERFOROMIST® (formoterol fumarate) Inhalation Solution is a long-acting $beta_2$-agonist indicated for the long-term, twice-daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. PERFOROMIST® is a unique nebulized inhalation form of formoterol fumarate.

PERFOROMIST® was approved on May 11, 2007 under a 505(b)2 New Drug Application (NDA) that cross references the Foradil® (formoterol fumarate) dry powder inhaler NDA in support of safety and efficacy. Foradil®, unlike PERFOROMIST®, is also indicated for the 1) long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma, and 2) the acute prevention of exercise-induced bronchospasm (EIB) in adults and children 5 years of age and older, when administered on an occasional, as-needed basis.[5]

PERFOROMIST® was evaluated in a 12-week, double-blind, placebo- and active-controlled, randomized, parallel-group, multicenter trial conducted in the United States. Of a total enrollment of 351 adults (age range: 40 to 86 years; mean age: 63 years) with COPD who had a mean pre-bronchodilator FEV_1 of 1.34 liters (44% of predicted), 237 patients were randomized to PERFOROMIST® 20 mcg or placebo, administered twice

daily via a PARI-LC Plus® nebulizer with a PRONEB® Ultra compressor. The diagnosis of COPD was based upon a prior clinical diagnosis of COPD, a smoking history (at least 10 pack-years), age (at least 40 years), and spirometry results (pre-bronchodilator baseline FEV_1 at least 30% and less than 70% of the predicted value, and the FEV_1/FVC less than 70%). About 58% of patients had bronchodilator reversibility, defined as a 10% or greater increase in FEV_1 after inhalation of 2 actuations (180 mcg) of albuterol from a metered dose inhaler. About 86% (106) of patients treated with PERFOROMIST® and 74% (84) of placebo patients completed the trial.

PERFOROMIST® 20 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by serial FEV_1 for 12 hours post-dose; the primary efficacy analysis) compared to placebo when evaluated at endpoint (week 12 for completers and last observation for dropouts). Similar results were seen on Day 1 and at subsequent time points during the trial.

Mean FEV_1 measurements at Day 1 (Figure 1) and at endpoint (Figure 2) are shown below.

Figure 1
Mean* FEV_1 at Day 1

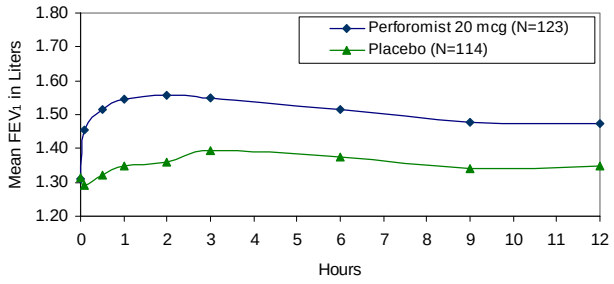
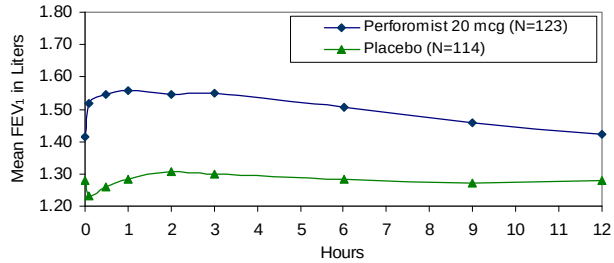


Figure 2
Mean* FEV_1 at Endpoint after 12 Weeks of Treatment



*Figures show least-squares means adjusted for baseline FEV_1

Patients treated with PERFOROMIST® used less rescue albuterol during the trial compared to patients treated with placebo.

Examination of age (≥ 65 or younger) and gender subgroups did not identify differences in response PERFOROMIST®. There were too few non-Caucasian subjects to assess differences in populations defined by race adequately.

In the 12 week study, 78% of subjects achieved a 15% increase from baseline FEV_1 following the first dose of PERFOROMIST® 20 mcg. In these subjects, the median time to onset of bronchodilation, defined as 15% increase in FEV_1, was 11.7 minutes. When defined as an increase in FEV_1 of 12% and 200 mL, the time to onset of bronchodilation was 13.1 minutes after dosing. The median time to peak bronchodilator effect was 2 hours after dosing.

ADVERSE EVENTS - CLINICAL TRIALS EXPERIENCE

Adults with COPD

The data described below reflect exposure to PERFOROMIST® 20 mcg twice daily by oral inhalation in 586 patients, including 232 exposed for 6 months and 155 exposed for at least 1 year. PERFOROMIST® was studied in a 12-week, placebo- and active-controlled trial (123 subjects treated with PERFOROMIST® Inhalation Solution) and a 52-week, active-controlled trial (463 subjects treated with PERFOROMIST® Inhalation Solution). Patients were mostly Caucasians (88%) between 40 and 90 years old (mean, 64 years old) and had COPD, with a mean FEV_1 of 1.33 L. Patients with significant concurrent cardiac and other medical diseases were excluded from the trials.

Table 1 shows adverse reactions from the 12-week, double-blind, placebo-controlled trial where the frequency was greater than or equal to 2% in the PERFOROMIST® group and where the rate in the PERFOROMIST® group exceeded the rate in the placebo group. In this trial, the frequency of patients experiencing cardiovascular adverse events was 4.1% for PERFOROMIST® and 4.4% for placebo. There were no frequently occurring specific cardiovascular adverse events for PERFOROMIST® (frequency greater than or equal to 1% and greater than placebo). The rate of COPD exacerbations was 4.1% for PERFOROMIST® and 7.9% for placebo.

TABLE 1
Number of patients with adverse reactions in the 12-week multiple-dose controlled clinical trial

Adverse Reaction	PERFOROMIST Inhalation Solution 20 mcg		Placebo	
	n	(%)	n	(%)
Total Patients	123	(100)	114	(100)
Diarrhea	6	(4.9)	4	(3.5)
Nausea	6	(4.9)	3	(2.6)
Nasopharyngitis	4	(3.3)	2	(1.8)
Dry Mouth	4	(3.3)	2	(1.8)
Vomiting	3	(2.4)	2	(1.8)
Dizziness	3	(2.4)	1	(0.9)
Insomnia	3	(2.4)	0	0

Patients treated with PERFOROMIST® 20 mcg twice daily in the 52-week open-label trial did not experience an increase in specific clinically significant adverse events above the number expected based on the medical condition and age of the patients.

POSTMARKETING EXPERIENCE WITH PERFOROMIST®

PERFOROMIST® received marketing approval on May 11, 2007 for the treatment of COPD. Since market launch, there have been no postmarketing deaths or life threatening adverse events received by the company from spontaneous sources. In addition, the sponsor has received no reports of asthma-related exacerbations associated with the use of PERFOROMIST®.

2.3. LABA REMS and Changes to PERFOROMIST® Prescribing Information and Medication Guide

FDA has determined that a REMS is necessary for PERFOROMIST® to ensure that the benefits of the drug continue to outweigh the risks based on the new safety information described above. The PERFOROMIST® REMS will consist of a:

- Medication Guide for patients' safe and effective use of PERFOROMIST®,
- Communication Plan targeting current and potential prescribers of PERFOROMIST® to support implementation during the first year after the REMS is approved, and
- Timetable for Submission of Assessments

3. GOALS

The goals of this REMS are to:

1. 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 PERFOROMIST® Inhalation Solution.

2. To inform healthcare providers and prescribers of the appropriate use of long-acting beta-2-adrenergic agonists (LABA) including PERFOROMIST® Inhalation Solution.

3. To inform patients with asthma who take long-acting beta-2-adrenergic agonists (LABA) medicines, such as formoterol fumarate, 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 PERFOROMIST® Inhalation Solution.

4. SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

4.1. Medication Guide

PERFOROMIST® Inhalation Solution, 20 mcg/2ml was initially approved with a Medication Guide. As part of the initial REMS request, the agency requested revisions to the PERFOROMIST® Medication Guide. Consistent with the agreed upon changes to the language included in the February 18, 2010, Safety Labeling Change Notification letter, and telephone facsimiles dated May 6, and 12, 2010, the Perforomist Medication Guide was revised and received approval on June 2, 2010. The current Medication Guide is appended.

The Medication Guide has been deemed necessary for patients' safe and effective use of PERFOROMIST®. FDA has determined that PERFOROMIST® is a product for which patient labeling could help prevent serious adverse effects. Further, PERFOROMIST® has serious risks (relative to the benefits) of which patients should be made aware because the information concerning the risks could affect patients' decisions to use, or continue to use PERFOROMIST®.

Under 21 CFR 208.24, Dey is responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed PERFOROMIST®. The PERFOROMIST® Medication Guide is included at the end of the prescribing information as a perforated attachment. The prescribing information and Medication Guide are both present in each PERFOROMIST® carton. PERFOROMIST® is supplied as a carton of 60 individually wrapped unit dose vials overwrapped in foil. The unit dose vials should always be stored in the foil pouch. Therefore, the carton is not intended to be divided.

Both the 60-vial commercial carton and the 15-vial sample carton bear the statement "Medication Guide For Patients Enclosed" prominently printed on the principal display panel of each carton.

4.2. Communication Plan

The intended audience for the Communication Plan is the likely prescribers of PERFOROMIST®. Dey has defined the likely prescribers to be all pulmonologists, recent PERFOROMIST® prescribers, and prescribers to whom Dey is actively marketing PERFOROMIST® ("targeted prescribers"). Recent and targeted prescribers would encompass pulmonologists and selected allergists, allergists/immunologists, general practitioners, nurse practitioners, physician assistants, internists, family practitioners, and otolaryngologists.

Pulmonologists will be identified from the AMA Physician Masterfile Codes for Self-Designation of Practice Specialties/Areas of Practice. Only pulmonologists with a valid US mailing address in the AMA Masterfile will be included in the pulmonologist distribution component. Recent prescribers will be defined as those identified as having written a PERFOROMIST® prescription within 12 months of the REMS approval date. Targeted prescribers will be identified from a company-maintained database.

The communication media will include a mailed Dear Healthcare Provider (DHCP) letter and an update to the product web site to include:

(1) Key information about the risk
(2) Key data regarding the risk (e.g. SMART, SNS)
(3) New prescribing guidelines
(4) Currently available LABAs and approved uses
(5) Prescribing information for Perforomist
(6) Patient Counseling Information
(7) Medication Guide for Perforomist
(8) Questions and Answers
(9) DHCP Letter (for a period of 1 year)
(10) Link to FDA web site for alerts on LABAs

The DHCP letter will provide the most extensive and rapid communication of the new prescribing guideline and safety information. This component will be completed within 60 days of the REMS approval. Finally, Dey will disseminate the new prescribing guidelines through professional societies and request that they distribute the safety notice to their membership following the REMS approval.

4.3. Elements to Assure Safe Use

The PERFOROMIST® REMS does not include Elements to Assure Safe Use.

4.4. Implementation System

Because this PERFOROMIST® REMS does not include Elements to Assure Safe Use, an implementation system is not required.

4.5. Timetable for Submission of Assessments of the REMS

Each year, within 60 days of the anniversary date, Dey will submit an assessment of the program by reviewing the following elements to measure whether the REMS goals are being met. This timetable has been pre-specified by FDA in the REMS request.

5. REMS ASSESSMENT PLAN

Each year, within 60 days of the anniversary date, Dey Pharma L.P. ("Dey") will submit an assessment of the program by reviewing the following elements to measure whether the REMS goals are being met. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. Based on the information reported, an assessment will be made as to whether the REMS is meeting its goals and whether modifications to the REMS are needed.

5.1. Physician Survey – Prescriber Understanding About the Safe Use of PERFOROMIST®

Dey will conduct a survey to evaluate prescribers' understanding about the safe use of PERFOROMIST®. Dey will submit the specific survey instrument and proposed survey methodology to FDA at least 90 days before the survey is scheduled to commence.

5.2. Patient Survey – Patient Knowledge of the Serious Risks Associated with Use of PERFOROMIST®

Dey will conduct a survey to evaluate patients' knowledge of the serious risks associated with use of the drug. Dey will submit the specific survey instrument and proposed survey methodology to FDA at least 90 days before the survey is scheduled to commence.

5.3. Review of Asthma-Related Deaths

The yearly assessment report will contain a case narrative for any asthma-related death associated with the use of PERFOROMIST®. Sources of case reports will include the Mylan Inc. (parent company of Dey Pharma, L.P.) worldwide pharmacovigilance database and the worldwide literature.

5.4. PERFOROMIST® Prescribing and Use Patterns

The yearly assessment will include the most current data available at the time of report writing for PERFOROMIST® prescribing and drug use patterns. Dey will include data on indication, prescriber specialty, and patient demographics. Existing third party databases will be evaluated to determine the most practical and feasible source for obtaining this data. Alternatively, Dey may explore the possibility of incorporating questions into the patient and physician surveys to collect the required data on drug use patterns. Dey will submit the methodology to FDA following selection of a third party vendor and at least 90 days prior to beginning the assessment process.

5.5. Distribution and Dispensing of PERFOROMIST® Medication Guide

Each carton of PERFOROMIST® Inhalation Solution, 20 mcg/2ml is shipped with a Medication Guide included at the end of the prescribing information as a perforated attachment. The carton is not intended to be divided. Therefore, periodic assessments of the distribution and dispensing of the Medication Guide are not required in accordance with 21 CFR 208.24.

5.6. Communication Plan

The following information pertaining to the Communication Plan will be included in the first REMS assessment:

- The date of launch of the communication plan (DHCP letter, web site, and communication to professional societies)
- The number of recipients of the DHCP letter distribution
- A copy of all the documents included in each distribution
- A listing of the professional societies that received the communication
- The information that the professional societies disseminated to its members and the timing for the dissemination (when available)

5.7. Overall Conclusions

Dey will review all assessment outcomes and make an overall evaluation on the effectiveness of the Communication Plan and Medication Guide in informing healthcare providers, prescribers, and patients about the serious risks associated with LABAs, including PERFOROMIST® and the appropriate use of LABAs. Based on the results, specific measures to increase awareness will be evaluated if the assessment plan reveals patients, healthcare providers and prescribers are not sufficiently aware of the appropriate use of PERFOROMIST® or the serious risks associated with use of PERFOROMIST®.

6. OTHER RELEVANT INFORMATION

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7. REFERENCES

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(3) DULERA™ Inhalation Aerosol Risk Evaluation and Mitigation Strategy (REMS). *US Food and Drug Administration. Last updated* 22 June 2010; Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM217719.pdf. Accessed 20 October 2010.

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(5) Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ.* 1993;306:1034-7.

(6) Fultz-Morris Y. Questions and Answers: New Safety Requirements for Long-Acting Asthma Medications called Long-Acting Beta Agonists (LABAs). *US Food and Drug Administration.* Last updated 18 February 2010; Available at: http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm201144.htm. Accessed 02 March 2010.

(7) Nelson H, Weiss S, Bleecker E, Yancey S, Dorinksy P. SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest.* 2006;(129):15-26.

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/s/

SALLY M SEYMOUR
02/01/2011