Initial REMA Approval : 06/2010
Most Recent Modificaion: 08/2011

NDA 022518 DULERA™ INHALATION AEROSOL
(mometasone furoate/formoterol fumarate)

Corticosteroid and Long-acting $Beta_2$-adrenergic Agonist

Schering Corporation a subsidiary of Merck & Co., Inc
2000 Galloping Hill Rd. Kenilworth, NJ 07033

Marty Huber, MD, Vice-President of Global Safety

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS:

1. To inform healthcare providers and prescribers of the increased risk of asthma-related death and serious outcomes with the long-acting $beta_2$-adrenergic agonists (LABA) including DULERA.
2. To inform healthcare providers and prescribers of the appropriate use of long-acting $beta_2$-adrenergic agonists (LABA) including DULERA.

II. REMS ELEMENTS:

A. Communication Plan

Schering Corporation 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, Pulmonologists, Allergists/Immunologists, and select primary care physicians.
   Distribution of the Dear Healthcare Professional Letter will be by direct mail or e-mail communication with the following timeline:

   a) Initial distribution via mail or e-mail within 60 days of REMS approval
   b) Second distribution via mail or e-mail at or about 6 months post-marketing approval.

   The DHCPL will include the following safety information:
   a) Increased risk of asthma-related death in patients taking LABAs
   b) New prescribing guidelines:
      i. DULERA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an

inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA

ii. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.

iii. DULERA should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

2. Printed or web-based information for health care providers will be posted on a Merck website within 10 days of the REMS approval. This information will remain on the website for 3 years. The content of the print or web-based material will, at a minimum, include the following:
    i. Information about the risk
    ii. Key data regarding the risk (e.g. SMART, SNS)
    iii. New prescribing guidelines
    iv. Currently available LABAs and approved uses
    v. Prescribing information for DULERA
    vi. Patient Counseling Information
    vii. Medication Guide for DULERA
    viii. Questions and Answers
    ix. DHCP letter (for a period of 1 year)

3. Schering Corporation will communicate via a letter to the leadership of the following professional societies:
    American College of Allergy, Asthma & Immunology (ACAAI)
    American Academy of Asthma Allergy & Immunology (AAAAI)
    American Thoracic Society (ATS)
    American College of Chest Physicians (ACCP)
    American College of Physicians (ACP)
    National Medical Association (NMA)
    American Academy of Nurse Practioners (AANP)
    American Academy of Physician Assistants (AAPA)

    The communication to medical societies will also include the information that is also available on the under 2) above. Schering Corporation will request that these societies disseminate this information to their members. A total number of recipients will be communicated to the agency prior to product launch.

    The timeline for REMS communication materials to professional societies will parallel the direct mail or e-mail program:
        i. Initial distribution at product approval
        ii. Second distribution at or about 6 months post-marketing approval

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

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

C. Timetable for Submission of Assessments

Schering Corporation will submit REMS Assessments to FDA annually from approval of the initial REMS (June 22, 2010). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Schering Corporation will submit each assessment so that it will be received by the FDA on or before the due date.

Attachment 1:
(Schering Corporation a subsidiary of Merck & Co. letterhead)

Dear Healthcare Professional:

Schering Corporation a subsidiary of Merck & Co., would like to inform you of important safety information for DULERA™ (mometasone furoate/formoterol fumarate). DULERA is a combination product containing a corticosteroid and a long acting $beta_2$-adrenergic agonist (LABA) indicated for treatment of asthma, in adults and patients 12 years of age and older. DULERA is not indicated for the relief of acute bronchospasm.

Important safety information related to DULERA includes:

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

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

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

WARNING: ASTHMA-RELATED DEATH
See full prescribing information for complete boxed warning
Long-acting $beta_2$-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. 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 the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, DULERA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for

patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

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

When prescribing DULERA, please also provide the patient with an inhaled, short-acting $beta_2$-agonist (e.g., albuterol) to be used as a rescue inhaler for treatment of acute symptoms. Increasing use of inhaled, short-acting $beta_2$-agonists is a marker for deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen.

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

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

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 DULERA, please call Schering Corporation at 1-800-672-6372

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 Schering Plough at 1-800-672-6372 if you have any questions about DULERA or the information in this letter.

Sincerely,

Marty Huber, MD
Vice President, Global Safety
Schering Corporation a subsidiary of Merck & Co.

Attachment 2:
(Schering Corporation a subsidiary of Merck & Co. letterhead)

Dear (Medical Society):

Schering Corporation a subsidiary of Merck & Co., would like to inform you of the U.S. Food and Drug Administration approval of DULERA™ (mometasone furoate/formoterol fumarate) a combination product containing a corticosteroid and a long acting $beta_2$-adrenergic agonist (LABA) indicated for treatment of asthma, in adults and patients 12 years of age and older. DULERA is not indicated for the relief of acute bronchospasm.

Important safety information related to DULERA includes:

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

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

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

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corticosteroids.

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

When prescribing DULERA, the healthcare professional should be guided to also provide the patient with an inhaled, short-acting $beta_2$-agonist (e.g., albuterol) to be used as a rescue inhaler for treatment of acute symptoms. Increasing use of inhaled, short-acting $beta_2$-agonists is a marker for deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen

The healthcare professional should instruct the patients to contact them if breathing problems worsen over time while using DULERA 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 DULERA 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 DULERA.

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 DULERA, please call Schering Corporation at 1-800-672-6372

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

- Phone at 1-800-FDA-1088 (1-800-332-1088)
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Please contact Schering Corporation at 1-800-672-6372 if you have any questions about DULERA or the information in this letter.

Sincerely,

Marty Huber, MD
Vice President, Global Safety
Schering Corporation a subsidiary of Merck & Co.

Attachment 3:
Printed / Web-based information:

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

- Information about the risk

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

WARNING: ASTHMA RELATED DEATH
See full prescribing information for complete boxed warning
Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigate the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

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

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

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

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

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

Table 1. SMART Results

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

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

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

[§] *The Total Population includes Caucasian, African American, Hispanic, Asian, and "Other" and "not reported". No asthma-related deaths occurred in the Hispanic*

(salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death occurred in the placebo group in the subpopulation whose ethnic origin was "not reported" (salmeterol n = 130, placebo n = 127).

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

In preparation for the December 2008 Advisory Committee, FDA conducted a meta-analysis of 110 studies evaluating the use of LABAs in 60,954 patients with asthma. The meta-analysis used a composite endpoint to measure severe exacerbation of asthma symptoms (asthma-related death, intubation, and hospitalization). The results of the meta-analysis suggested an increased risk for severe exacerbation of asthma symptoms in patients using LABAs compared to those not using LABAs. The largest risk difference per 1000 treated patients was seen in children 4-11 years of age, see table 2 below. The results of the meta-analysis were primarily driven by asthma-related hospitalizations. Other meta-analyses evaluating the safety of LABAs in the treatment of asthma have not shown a significant increase in the risk for severe asthma exacerbations.

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

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

Patients ages 4 to 11 years n = 1,626 LABA patients n = 1,789 non-LABA patients	61	39	14.83	3.24 – 26.43

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

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

Based on the available information, FDA concludes there is an increased risk for severe exacerbation of asthma symptoms, leading to hospitalizations in pediatric and adult patients as well as death in some patients using LABAs for the treatment of asthma. The agency is requiring the 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:

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

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

- Currently available LABAs and approved uses

FDA Approved Long-Acting Beta Agonists

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

Symbicort	Formoterol	Budesonide	Asthma, COPD
Brovana	Arformoterol	None	COPD
Perforomist	Formoterol	None	COPD

* not currently marketed in the U.S.

See June 2010 LABA Drug Safety Communication for more information.

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

- Prescribing information for DULERA

LINK - http://www.spfiles.com/pidulera.pdf (will be live once product is approved)

- Patient Counseling Information

Patient Counseling Information

See USPI and Medication Guide

Asthma-Related Death
See Medication Guide
Patients should be informed that formoterol, one of the active ingredients in DULERA, 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, the other component of DULERA, or other long-term asthma-control therapy mitigates or eliminates this risk. See Warnings and Precautions Section 5.1 of the full Prescribing Information.

Not for Acute Symptoms
DULERA is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta$_2$-agonist (the health care provider should prescribe the patient with such medication and instruct the patient in how it should be used).

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

- If their symptoms worsen
- Significant decrease in lung function as outlined by the physician
- If they need more inhalations of a short-acting beta$_2$-agonist than usual

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

Patients should not stop or reduce DULERA therapy without physician/provider guidance since symptoms may recur after discontinuation. See Warnings and Precautions Section 5.2 of the full Prescribing Information.

Do Not Use Additional Long-Acting Beta$_2$-Agonists
When patients are prescribed DULERA, other long-acting beta$_2$-agonists should not be used. See Warnings and Precautions Section 5.3 of the full Prescribing Information.

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

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex. See Warnings and Precautions Section 5.5 of the full Prescribing Information.

Hypercorticism and Adrenal Suppression: Patients should be advised that DULERA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to DULERA. See Warnings and Precautions Section 5.7 of the full Prescribing Information.

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and should be monitored and, where appropriate, be treated for this condition. See Warnings and Precautions Section 5.12 of the full Prescribing Information.

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, a component of DULERA, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of pediatric patients taking corticosteroids by any route. See Warnings and Precautions Section 5.13 of the full Prescribing Information.

Glaucoma and Cataracts: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (glaucoma or cataracts); regular eye examinations should be

considered. See Warnings and Precautions Section 5.14 of the full Prescribing Information.

Risks Associated With Beta-Agonist Therapy
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 and death. See Warnings and Precautions Section 5.11 of the full Prescribing Information.

- Medication Guide for DULERA

LINK - http://www.spfiles.com/mgdulera.pdf (will be live at product approval)

- Questions and Answers

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

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

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

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

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

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

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

Questions about DULERA Inhalation Aerosol

Q1. Why does DULERA have a boxed warning?

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

Q3. Can DULERA be used for acute asthma symptoms?

Q4. Can additional LABAs be used with DULERA?

Q5. What are the risks of corticosteroid therapy?

Q6. What are the risks of Beta-Agonist Therapy

Questions about LABA safety

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

A. Despite the benefits of long-acting $beta_2$-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 about the risk of LABAs for patients with asthma and ways to decrease that risk while maintaining the benefits of the drug. 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 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
DULERA Inhalation Aerosol	formoterol and mometasone	formoterol is a LABA and mometasone is a corticosteroid long-term asthma control medication
Advair Diskus, Advair HFA	salmeterol and fluticasone	salmeterol is a LABA and fluticasone is a corticosteroid long-term asthma control medication
Symbicort Inhalation Aerosol	formoterol and budesonide	formoterol is a LABA and budesonide is a corticosteroid long-term asthma control medication
Serevent Diskus	salmeterol	single ingredient LABA with no corticosteroid long-term asthma control medication
Foradil Aerolizer	formoterol	single ingredient LABA with no corticosteroid long-term asthma control medication

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

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

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

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

A. FDA used a variety of studies and research in patients with asthma using a LABA. Two specific studies that provided valuable information were 1) the Salmeterol Multi-center Asthma Research Trial (SMART) and 2), the Serevent Nationwide Surveillance

study (SNS). Salmeterol is the LABA in Serevent. Each of these studies showed a higher risk of death for patients with asthma that used a LABA (salmeterol) compared to patients with asthma that did not use a LABA. In addition, FDA used a research method called a meta-analysis to further understand the risks associated with the use of LABAs in patients with asthma. A meta-analysis uses data from multiple studies on a particular topic to enable scientists to combine information from those studies to make scientific conclusions or recommendations in that area. For more information on these specific studies, please see February 2010 LABA Drug Safety Communication for more information.

Questions about DULERA

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

WARNING: ASTHMA RELATED DEATH
See full prescribing information for complete boxed warning
Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

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

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

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

A. Patients should be informed that formoterol, one of the active ingredients in DULERA, 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, the other component of DULERA, or other long-term asthma-control therapy mitigates this risk. See Warnings and Precautions Section 5.1 of the full Prescribing Information.

Q3. Can DULERA be used for acute asthma symptoms?
A. No. DULERA is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta$_2$-agonist (the health care provider should prescribe the patient with such medication and instruct the patient in how it should be used).
Patients should be instructed to seek medical attention immediately if they experience any of the following:

- If their symptoms worsen
- Significant decrease in lung function as outlined by the physician
- If they need more inhalations of a short-acting beta$_2$-agonist than usual

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

Patients should not stop or reduce DULERA therapy without physician/provider guidance since symptoms may recur after discontinuation. See Warnings and Precautions Section 5.2 of the full Prescribing Information.

Q4. Can additional LABAs be used with DULERA?
A. No. When patients are prescribed DULERA, 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 Corticosteroid Therapy?

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

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex. See Warnings and Precautions Section 5.5 of the full Prescribing Information.

Hypercorticism and Adrenal Suppression: Patients should be advised that DULERA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to DULERA. See Warnings and Precautions Section 5.7 of the full Prescribing Information.

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and should be monitored and, where appropriate, be treated for this condition. See Warnings and Precautions Section 5.12 of the full Prescribing Information.

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, a component of DULERA, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of pediatric patients taking corticosteroids by any route. See Warnings and Precautions Section 5.13 of the full Prescribing Information.

Glaucoma and Cataracts: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (glaucoma or cataracts); regular eye examinations should be considered. See Warnings and Precautions Section 5.14 of the full Prescribing Information.

Q6. 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

- DHCP letter (for a period of 1 year)

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/s/

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08/18/2011

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08/18/2011