

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22518Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: June 22, 2010  
To: Badrul Chowdhury, M.D., PhD., Director  
Division of Pulmonary, Allergy, and  
Rheumatology Products (DPARP)

Through: Mary Willy, Ph D.,  
Deputy Division Director  
Division of Risk Management (DRISK)

From: Scientific Lead  
Yasmin Choudhry, M.D. Medical Officer, DRISK  
Dulera REMS Review Team  
Marcia Britt, Ph. D., Health Education Reviewer,  
DRISK  
Jodi Duckhorn, MA, Social Science Reviewer,  
DRISK  
Michelle Marsh, B.S., CSO, OC  
Roberta Szydlo, R.Ph., DDMAC

Subject: Review of Proposed Risk Evaluation and  
Mitigation Strategy (REMS)

Drug Name(s): Dulera (mometasone furoate/formoterol  
fumarate) Inhalation Aerosol

Indication: For the treatment of asthma in patients with 12  
years of age and older

Application Type/Number: NDA 22-518

Applicant/Sponsor: Schering Plough

OSE RCM #: 2009-1099

## **EXECUTIVE SUMMARY**

Dulera (mometasone furoate/formoterol fumarate) is a combination of a long-acting beta-agonist (LABA) and a corticosteroid that was originally submitted for review May 21, 2009. Dulera is indicated for the treatment of asthma in patients 12 years of age and older. On February 18, 2010, FDA issued a Prior Approval Supplement Request (for the approved LABAS) notifying Sponsors of the FDA's determination of new safety information with the use of the class of long-acting beta agonists and required the Sponsors to submit a Risk Evaluation and Mitigation Strategy (REMS) amendment. Schering Plough was notified at that time to submit a REMS amendment for Dulera.

The Sponsor submitted a proposed REMS on March 5, 2010, The Division of Pulmonary, Allergy and Rheumatology Products (DPARP), the Office of Surveillance and Epidemiology (OSE), Office of Compliance (OC) and Division of Drug Marketing, Advertising and Communication (DDMAC) reviewed the proposed REMS and provided a series of interim comments to Schering Plough.

The proposed REMS includes a Medication Guide, Communication Plan and a Timetable for Submission of Assessment of the REMS. The REMS review team finds the proposed REMS submitted on June 21, 2010 to be acceptable.

### **1. BACKGROUND**

Dulera (mometasone furoate/formoterol fumarate) is a combination of a long-acting beta-agonist (LABA) and a corticosteroid, indicated for the treatment of asthma in patients 12 years of age and older. The Sponsor submitted the original NDA May 21, 2009. Since the May 2009 submission, FDA determined that serious asthma outcomes (asthma related death, intubations, and hospitalizations) were associated with the use of LABAS; this information was based on the Salmeterol Multi-Center Asthma Research Trial (SMART) and the clinical trial data presented as meta-analysis at the December 10-11, 2008, joint meeting of the Pulmonary Allergy Drugs, Drug Safety and Risk Management, and Pediatric Advisory Committees.

In accordance with section 505-1 of the FDCA, the Agency determined that a REMS is necessary for approved LABAs as well as Dulera to ensure that the benefits of the drug outweigh the risks of the identified serious asthma outcomes. On February 18, 2010, FDA issued a Prior Approval Supplement Request (for the approved LABAS) notifying Sponsors of the FDA's determination of new safety information with the use of the class of long-acting beta agonists (LABAS). Schering Plough was notified at the same time to submit a REMS amendment for Dulera.

The February 18, 2010 letter to Schering Plough specifically requested the following be included in the REMS:

- A Medication Guide as specified in the notification letter.

- A communication plan targeted to healthcare providers who are likely to prescribe Dulera. The communication plan must provide dissemination of information about the risks of LABAs, including the increased risk of asthma-related deaths and new prescribing guidelines for adult, adolescent and pediatric populations. The communication plan must include, at a minimum, the following:
  - A Dear Healthcare Provider (DHCP) letter to be distributed within 60 days of the REMS approval.
  - Other printed or web-based materials to be directed at healthcare providers.
  - A description of the audience for the communication plan and how often the materials will be distributed.
  - A plan for disseminating information through professional societies to include a list of the professional societies targeted and details on how professional societies will convey the information to their members.
- A timetable for submission of assessments no less frequently than annually from the date of the approval of the revised REMS.

On March 5, 2010, Schering Plough submitted the Dulera REMS amendment to the FDA. The initial REMS for Dulera was submitted voluntarily by the Sponsor on May 21, 2009 along with the original NDA application.

The first set of REMS interim comments sent to the Sponsor on June 4, 2010 were regarding rewording of the REMS goals, submission of the actual web-based educational materials, updating the list of professional societies/prescribers to be targeted, REMS assessment plan, and the first revision of the REMS document.

A second set of comments sent to the Sponsor on June 11, 2010 (in response to the Sponsor's response dated June 9, 2010) addressed the insufficiency of the educational materials such as: a letter to the professional societies informing them of the key messages regarding the safety of Dulera; timelines for the DHCP and the medical society letters; and the REMS assessment plan (Sponsor had eliminated some previously agreed upon elements). The web/print materials were insufficient (only the Package Insert and the MG constituted the web materials) therefore DRISK recommended the following:

- a. The content of the print or web-based material must include 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)

We also told the Sponsor that some optional pieces could include:

- Resource list of future meetings and peer reviewed journal articles related to LABAs
- Links to FDA Alert(s) for the LABAs

A third set of comments dated June 15, 2010 provided additional comments. In the June 17, 2010 submission, the Sponsor sufficiently addressed most of the items of concern regarding the Dulera REMS and incorporated all communication materials, including the Dear Medical Society Letter and the web-based materials as recommended by DRISK in the June 11, 2010 and June 15, 2010 FDA comments; REMS comments generated by FDA after June 15, 2010 were mostly editorial. A fourth set of comments were sent June 18, 2010 that identified some additional minor editorial corrections. The Sponsor submitted a revised proposed REMS on June 21, 2010 and a final version of the REMS on June 22, 2010 that included recommendations made by DPARP on June 21, 2010.

## **2. MATERIALS REVIEWED**

The Dulera REMS proposal was reviewed for responsiveness to Agency comments that were communicated to the applicant and for conformance with the Food and Drug Administration Amendments Act of 2007. The following REMS related submissions were reviewed:

- Dulera (NDA 22-518) Proposed REMS, Submission eCTD 0000, dated May 21, 2009
- Dulera REMS Notification Letter dated February 18, 2010
- Dulera (NDA 22-518) Proposed REMS Amendment, Submission eCTD 0023, dated March 5, 2010
- FDA's Interim REMS Comments for Dulera sent (via email) to Schering Plough on June 4, 2010; June 11, 2010; June 15, 2010; June 18, 2010, and June 21, 2010.
- Revised Dulera REMS submission received via email on June 9, 2010; educational materials including revised DHCPL and web-based materials received June 17, 2010; and educational materials relating to snap shots received June 18, 2010; REMS submission dated June 21, 2010 and June 22, 210.
- Clinical reviews, Susan Limb, M.D., Medical Officer, Division of Pulmonary, Allergy and Rheumatology Products (DPARP), dated January 22, 2010 and May 19, 2010.

## **3. RESULTS REVIEW OF PROPOSED REMS**

The following REMS proposal for Dulera submitted on June 21, 2010 reflect revisions based upon the FDA comments sent to Schering Plough during the course of the REMS review. See Appendix A for the final Dulera REMS with our track changes.

### **3.1 GOALS**

The REMS goals for DULERA Inhalation Aerosol are:

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.
3. To inform patients that people with asthma who take long-acting beta-2-adrenergic agonists (LABA) medicines, such as formoterol fumarate, one of the active moieties in Dulera, 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 Dulera.

## **3.2 REMS ELEMENTS**

### **3.2.1 Medication Guide**

A Medication Guide (MG) will be dispensed with each Dulera prescription as part of the packaging for each product carton in compliance with 21 CFR 208.24.

- Schering Corporation will ensure a Dulera Inhalation Aerosol Medication Guide will be enclosed in each carton packaging of Dulera Inhalation Aerosol to ensure that the Medication Guide is given to each patient with each new prescription and refill.
- The Medication Guide will be available on a Merck website within 10 days of approval.
- The Dulera Inhalation Aerosol carton of each package will include a prominent and conspicuous instruction alerting authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed. It will be stated as follows: “Attention Health Care Professional: Dispense the enclosed Medication Guide to each patient.”

### **3.2.2 Communication Plan**

Schering Plough will implement a communication plan to the healthcare providers (HCPs) to support implementation of the REMS. The communication plan includes:

- Dear Healthcare Provider Letter (DHCPL)
- Dear Medical Society Letter
- Print or web-based materials

The initial distribution of the DHCPL will be by direct mail or e-mail at product approval followed by a second distribution at or about 6 months post-marketing approval.

The Dear Medical Society Letter will be distributed to the leadership of the various professional societies at the same timeline as the DHCPL; this letter is similar in content as the DHCPL. Schering Plough will ensure that the professional societies disseminate this information to their members.

Schering Plough will post the Dulera printed or web-based materials on Merck's website within 10 days and will keep this information on the website for 3 years. The content of Schering Plough's web-based educational materials for Dulera include: the risk information, key risk data from clinical trials, the new prescribing guidelines, current LABAs on the market and approved uses, prescribing information for Dulera, patient counseling information, the Medication Guide for Dulera, and questions and answers for the HCPs.

For the Dulera communication plan, Schering Plough will target pulmonologists, allergists/immunologists, primary care physicians, nurse practitioners, and physician assistants; the list of professional societies to be targeted includes the major organizations that include prescribers of LABAs in their membership.

### **3.2.3 Elements to Assure Safe Use**

The Dulera REMS does not have any elements to assure safe use.

### **3.3 Implementation System**

An implementation system is not a required element of the proposed Dulera REMS since there are no elements to assure safe use.

### **3.4 Timetable for Submission of Assessments**

Schering Plough will submit REMS Assessments to FDA annually from the REMS approval. The reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

### **3.5 REMS Assessment Plan**

Information needed for assessments is included in the Dulera REMS Supporting Document. The Sponsor provides the following information in the REMS supporting document.

1. An evaluation of the patients' understanding of the serious risks of Dulera including the increased risk of asthma-related deaths.
2. An analysis of the prescriber understanding of the increased risk of asthma related deaths and the safe use of LABAs.
3. A description of specific measures that would be taken to increase awareness if the assessment of the prescribers indicates that the prescribers' awareness is not adequate.
4. A narrative summary with analysis of all reported asthma-related deaths during the reporting period.

5. Drug use patterns (reasons for use, patient demographics, length of therapy, prescribing medical specialties)
6. With regard to the communication plan: the date of launch of the communication plan, the number of recipients of the DCHP letter, dates of distribution of the DHCP letter, a copy of all documents included in each distribution, the professional societies that they communicated to, and the information that the professional societies disseminated to its members and the timing for the dissemination.
7. Based on the information reported, an assessment of and conclusion regarding whether the REMS is meeting its goal and whether modifications to the REMS are needed.
8. The evaluation protocol will be outlined and submitted to the Agency 90 days prior to the patient evaluation schedule to gain acceptance for planned survey activities. Recruitment will be described in the protocol submission.

#### **4. DISCUSSION AND CONCLUSION**

DRISK/OSE finds the proposed REMS for Dulera to be acceptable and recommends approval of this REMS as submitted on March 5, 2010 with final revisions on June 21, 2010.

Schering Plough's proposed REMS for Dulera addresses the requirements stipulated by FDA in the February 18, 2010 notification letter and includes a MG and a communication plan with a DHCPL, a Dear Medical Society Letter, and printed/web-based educational materials, a timeline for distribution of the educational materials, and a description of the intended audience. The DHCP and the Dear Medical Society letters address the safety concerns with Dulera use and the new prescribing guidelines for Dulera appropriately. The printed/web-based materials (also reviewed by DPARP for accuracy) provides an in depth information about Dulera and includes questions and answers for the prescribers education on the subject.

22 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

---

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

---

/s/

---

YASMIN A CHOUDHRY  
06/22/2010

MARY E WILLY  
06/22/2010  
I concur

**Dulera REMS Interim Review Comments**

<p><b>Drug Name:</b> Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol</p> <p><b>Indication:</b> Asthma</p> <p><b>Sponsor:</b> Schering Plough</p>	<p><b>NDA:</b> 22-518</p> <p><b>PDUFA Date:</b> 6-22-10</p>	<p><b>Date:</b> 6-11-10</p> <p><b>Comment Set # 2</b></p>
<p><b>DRISK Scientific Lead:</b></p> <p>Yasmin Choudhry, M. D., Medical Officer, Division of Risk Management (DRISK)</p>		<p><b>DRISK Reviewers:</b></p> <p>Marcia Britt, Ph. D., Health Education Reviewer</p> <p>Jodi Duckhorn, MA., Social Science Reviewer</p> <p>Claudia Karwoski, Pharm D., Division Director</p>
<p><b>RCM #:</b> 2009-1099</p>	<p><b>OC Reviewers</b></p> <p>Michelle Marsh, CSO</p> <p><b>DDMAC Reviewers</b></p> <p>Roberta Szydlo, Regulatory Review Officer</p> <p>Lisa Hubbard, Professional Reviewers Group Leader</p>	

**Introduction:**

This interim review provides comments on the proposed Risk Evaluation and Mitigation Strategy (REMS) amendment for Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol submitted via email by Schering Plough on June 9, 2010 in response to the FDA Information Request letter dated June 4, 2010.

**Materials Reviewed:**

- REMS Notification Letter to Schering Plough dated February 18, 2010
- FDA Information Request Letter sent to Schering Plough on June 4, 2010
- Dulera NDA 22-518 Proposed REMS and REMS Supporting Document Submission submitted via email on June 9, 2010

**Background:**

Please see our Dulera REMS Interim Review Comments #1 for additional fuller background regarding the proposed REMS for Dulera.

Schering Plough resubmitted their proposed REMS for Dulera via email on June 9, 2010 in response our interim comments on their March 5, 2010 REMS proposal. Specifically, in the FDA IR letter we have comments on the following elements of their proposed REMS:

- Revisions to the Dulera REMS goals
- Regarding the communication plan:
  - We provided interim comments on the DHCP letter
  - We asked the sponsor to submit the materials planned for the website as well as the materials that would be provided to the professional societies
  - We asked the company to provides specifics about how they plan to distribute communication plan materials the timeframes for the communication plan
  - We told them the that additional professional societies would need to be targeted
- Regarding the REMS Assessment Plan:
  - We ask them to include the additional information in the REMS assessment plan
  - We provided guidance on their proposed surveys

**Brief Summary of the REMS Proposal and comments to DPARP:**

As with the March 5, 2010 submission, the proposed REMS submission of June 9, 2010 includes the following elements:

1. Medication Guide
2. Communication Plan
  - a. Dear Healthcare Provider Letter
  - b. Website
  - c. Outreach to professional societies
3. Timetable for submission of assessment of the REMS that is annually for years 1 through 3 and at 7 years.

Our biggest concern at this time is that the sponsor's planned communication plan is limited to a DHCP letter that will be sent to HCPs likely to prescribe LABAs and some type of communication or outreach, not otherwise specified to the agreed upon professional societies. They propose to post the DHCP and approved labeling on the website for a period of one year. We believe that this is insufficient is not in the spirit of the elements laid out in the original REMS Notification Letter.

We propose printed materials or preferably a website that includes information on risk of serious asthma outcomes and the safe use of LABAs. This information should be required to be posted for a period of at least 3 years following the approval of the REMS. The information should include the following:

- Information about the risk
- Key data regarding the risk (e.g. SMART, SNS)
- New prescribing guidelines

**\*\*\*Pre-decisional Agency Information\*\*\***

- Currently available LABAs and approved uses
- Prescribing information for Dulera
- Patient Counseling Information
- Medication Guide for Dulera
- Questions and Answers
- DHCP Letter (for a period of 1 year)

We further propose a similar approach for the other approved LABA products and our future comments will reflect the above recommendations.

Below are our comments on the revised proposal. Please let us know if you would like a meeting to discuss any of our comments prior to sending to the Applicant. Please request that the Sponsor respond to these comments and questions ASAP upon receipt.

**Comments for the Sponsor:**

1. See the appended Dulera REMS proposal (Appendix A) for track changes corresponding to comments in this review.
2. **REMS Goals:** The first three goals of your REMS are acceptable, however since the communication plan is not targeted to patients, the only source of information that patients will be receiving is the Medication Guide which is specific to your product. Revise your 4<sup>th</sup> goal as follows:

*To inform patients of the other serious risks associate with the use of Dulera*

**3. Medication Guide:**

We have no additional comments on the Medication Guide at this time. See the appended REMS for editorial comments on this section of the REMS.

**4. Communication Plan:**

- a. Your proposed website materials are not sufficient. Your communication plan must include printed or preferably web-based material that includes information on the risk of serious asthma outcomes and the safe use of LABAs and will be required to be posted or provided for a period of at least 3 years following the approval of the REMS. The content of the print or web-based material must include 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)

Some optional pieces could include:

- Resource list of future meetings and peer reviewed journal articles related to LABAs
  - Links to FDA Alert(s) for the LABAs
- b. Submit a letter for review that is to be directed to the leadership of the professional societies. You may consider the ESA letters to the professional societies as an example when drafting these letters. You can find the Aranesp or Epogen REMS on the FDA website. In addition to the letter, your communication to the professional societies must include a link to the website or if hard copies of the pre-printed materials (see above).
- c. We have no additional comments on your DHCP letter at this time, however additional comments may follow. The DHCP letter should be also be available on your website for a period of 1 year after approval of the REMS.
- d. The communication plan materials including the website presentation, the DHCP, and the communication materials to professionals' societies must be submitted for review ASAP. These materials are part of the final approved REMS.
5. **Timetable for Submission of Assessments:** Your timetable for submission of assessments is acceptable. Please see the appended REMS for editorial comments to this section of the REMS.

**6. REMS Assessments Plan:**

- a. You have eliminated elements of your REMS Assessment Plan previously agreed upon. Since your REMS includes a communication plan to HCPs, you will need to assess whether your communication plan has been effective in assessing the goals of your REMS: Your REMS Assessment Plan will include at minimum the following information:
- i. An evaluation of patients' understanding of the serious risks of Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol, including the increased risk of asthma-related deaths.
  - ii. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
  - iii. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
  - iv. An analysis of prescribers' understanding of the increased risk of asthma-related deaths and the safe use of LABAs.
  - v. A description of specific measures that would be taken to increase awareness if the assessment of healthcare prescribers indicates that prescriber awareness is not adequate.

- vi. A narrative summary with analysis of all reported asthma-related deaths during the reporting period.
  - vii. Drug use patterns (reasons for use, patient demographics, length of therapy, prescribing medical specialties)
  - viii. With regard to the communication plan:
    1. The date of launch of the communication plan (DHCP letter, website, and communication to professional societies)
    2. The number of recipients of the DCHP letter distribution
    3. Date(s) of distribution of the DHCP letter
    4. A copy of all documents included in each distribution
    5. The professional societies that you communicated to
    6. The information that the professional societies disseminated to its members and the timing for the dissemination
  - ix. Based on the information reported, an assessment of and conclusion regarding whether the REMS is meeting its goal and whether modifications to the REMS are needed.
- b. We acknowledge your comment to submit your survey methodology 90 days prior to the evaluation of patients understanding of the risks and safe use of Dulera. You should also submit your prescriber survey 90 days prior to your evaluation of prescribers' knowledge and understanding of the risks and safe use of LABAs.

**7. General comments:**

- Submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. All REMS materials should be free of promotional language and tone.
- Consider these comments interim comments. You will receive additional comments on your proposed REMS, REMS materials, and REMS supporting document as we continue our review of the application.

5 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

---

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

---

/s/

---

MARY J DEMPSEY  
06/11/2010

CLAUDIA B KARWOSKI  
06/11/2010  
concur

**Dulera REMS Interim Review Comments**

<b>Drug Name:</b> Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol  <b>Indication:</b> Asthma  <b>Sponsor:</b> Schering Plough	<b>NDA:</b> 22-518  <b>PDUFA Date:</b> 6-22-10	<b>Date:</b> 6-4-10  <b>Comment Set # 1</b>
<b>DRISK Scientific Lead:</b>  Yasmin Choudhry, M. D., Medical Officer, Division of Risk Management (DRISK)	<b>DRISK Reviewers:</b> Marcia Britt, Ph. D., Health Education Reviewer Jodi Duckhorn, MA., Social Science Reviewer Claudia Karwoski, Pharm D., Division Director	
<b>RCM #:</b> 2009-1099	<b>OC Reviewers</b> Michelle Marsh, B.S., CSO  <b>DDMAC Reviewers</b> Roberta Szydlo, Regulatory Review Officer Lisa Hubbard, Professional Reviewers Group Leader	

**Introduction:**

This interim review provides comments on the proposed Risk Evaluation and Mitigation Strategy (REMS) amendment for Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol submitted by Schering Plough on March 5, 2010 in response to the REMS Notification dated February 18, 2010.

**Materials Reviewed:**

- REMS Notification Letter to Schering Plough dated February 18, 2010
- Dulera NDA 22-518 Proposed REMS and REMS Supporting Document Submission eCTD #0000, submitted on May 21, 2009 (voluntarily submitted with NDA)
- Dulera NDA 22-518 Proposed REMS amendment and REMS Supporting Document Submission eCTD #0023, dated March 3, 2010 (submitted in response to REMS Notification Letter)

**Background:**

Schering Plough voluntarily submitted a proposed REMS for Dulera on May 21, 2009 as part of the NDA 22-518 (currently under review in DPARP) that consisted of a Medication Guide, a communication plan to healthcare providers and patients, and a timetable of submission of assessments.

On February 18, 2010, the Agency issued Prior Approval Supplement Request Letters to all of the sponsors of long acting beta agonists (LABAs) notifying them to submit safety labeling changes (SLC) and a proposed REMS. The letters were issued to address the risk of serious asthma outcomes associated with the use of these products. Schering Plough was notified at the same time to submit a REMS amendment for Dulera.

Specifically, the February 18, 2010 letter requested the following:

- Revisions to the Medication Guide as specified in the notification letter.
- A communication plan targeted to healthcare providers who are likely to prescribe Dulera. The communication plan must provide dissemination of information about the risks of LABAs, including the increased risk of asthma-related deaths and new prescribing guidelines for adult, adolescent and pediatric populations. The communication plan must include, at a minimum, the following:
  - A Dear Healthcare Provider (DHCP) letter to be distributed within 60 days of the REMS approval.
  - Other printed or web-based materials to be directed at healthcare providers.
  - A description of the audience for the communication plan and how often the materials will be distributed.
  - A plan for disseminating information through professional societies to include a list of the professional societies targeted and details on how professional societies will convey the information to their members.
- A timetable for submission of assessments no less frequently than annually from the date of the approval of the revised REMS.

**Brief Summary of the REMS Proposal:**

On March 5, 2010, Schering Plough submitted a proposed REMS amendment for Dulera that includes:

1. Medication Guide
2. Communication Plan
  - a. Dear Healthcare Provider Letter
  - b. Website.
3. Timetable for submission of assessment of the REMS that is annually for years 1 through 3 and at 7 years.

Schering Plough proposes, as part of the Communication Plan, to distribute a DHCP letter to the HCPs within 60 days of the REMS approval and to post printed or web-based educational materials (including the new prescribing guidelines) on a Merck's web site within 10 days of the REMS approval. The DHCP letter was included in this REMS

**\*\*\*Pre-decisional Agency Information\*\*\***

submission; the actual web-based education materials and the actual communication materials to be distributed by the professional societies have not been submitted.

The targeted audience for the proposed communication plan includes pulmonologists, allergists/immunologists, and select primary care physicians.

The targeted professional societies for Dulera REMS include the American College of Allergy, Asthma & Immunology, the American Academy of Asthma, Allergy & Immunology, and the American Thoracic Society.

**Comments to DPARP:**

We have a number of interim comments to the sponsor below, including adding the following professional societies to their communication plan:

- American College of Chest Physicians (ACCP)
- American College of Physicians (ACP)
- National Medical Association (NMA)
- American Academy of Nurse Practitioners (AANP)
- American Academy of Physician Assistants (AAPA).

We recommend you review the DHCPL for concurrence and accuracy. We have highlighted the areas of the DHCPL in yellow and green; the yellow highlighted items are the additions from us that we want the Sponsor to include in the DHCPL; the information about the Salmeterol study (highlighted in green) was included by the Sponsor and we would like you to review this and inform us if this information is accurate and necessary to include in the DHCPL.

Please let us know if you would like a meeting to discuss any of our comments prior to sending to the Applicant. Please request that the Sponsor respond to these comments and questions ASAP upon receipt. We would like the Sponsor to submit the response by Tuesday of next week.

**Comments and Questions for the Sponsor:**

**1. REMS Goals:**

Revise the goals of the REMS as follows:

The goals of this REMS are:

- To inform healthcare providers and prescribers about:
  - a. the increased risk of asthma-related death and other serious outcomes associated with the long acting beta<sub>2</sub>-adrenergic agonists (LABA), including Dulera.
  - b. the appropriate use of the long acting beta<sub>2</sub>-adrenergic agonists (LABA), including Dulera.
- To inform patients:
  - a. that people with asthma who take long-acting beta<sub>2</sub>-adrenergic agonist (LABA) medicines, such as formoterol fumarate (one of the medicines

**\*\*\*Pre-decisional Agency Information\*\*\***

in Dulera), have been associated with a higher risk of death from asthma problems.

b. about the other serious risks associated with the use of Dulera.

**2. Medication Guide:**

Comments on the Medication Guide will be sent separately. Your Medication Guide distribution plan is acceptable.

**3. Communication Plan:**

1. Submit the REMS communication materials to be distributed by the professional societies. Clarify if these are different from the printed and web-based material.
  - i. Describe and submit in the REMS and the REMS Supporting Document the actual materials being communicated from professional societies to the targeted prescribers.
2. You propose to make available the educational programs and materials through the Merck web site within 10 days of the REMS approval.
  - i. Specify the length of time this material will be posted on the website.
  - ii. Specify what control you have over the content of the Dulera Communication Plan on the Merck website.
  - iii. Submit the actual web-based educational material intended on the website
3. You propose to distribute the DHCPL to the HCPs within 60 days of the modified REMS approval. This is acceptable. Specify:
  - i. How you plan to distribute the DHCPL e.g., via direct mail etc.
  - ii. How often the DHCPL will be distributed; submit a timeline for the DHCPL distribution.
  - iii. See our preliminary comments on the DHCPL in Appendix A
4. Your proposed targeted audience for the Dulera Communication Plan includes: allergists, immunologists and pulmonologists, and select primary care physicians.
  - i. Specify which primary care physicians you plan to include in the list.
5. Submit a timeline for distributing REMS communication material from the professional societies to the targeted prescribers.

**4. Timetable for Submission of Assessments:**

Your proposal to submit the Dulera REMS assessments to FDA annually for 3 years after approval of the REMS and then at 7 years from the date of approval is not acceptable. As per February 18, 2010 REMS Notification Letter, you are required to submit the REMS assessments annually. You will be notified if the Agency at some point determines if the REMS assessments on an annual basis is no longer needed.

## **5. REMS Assessments Plan:**

- a. Your REMS Assessment Plan should also include the following information:
  - a. The date of launch of the communication plan
  - b. The number of recipients in the DCHP letter distribution
  - c. Date(s) of distribution of the DHCP letter
  - d. A copy of all documents included in each distribution
  
- b. Regarding the physicians' and patients' surveys:

The submitted methodology lacks sufficient detail to complete a review. Submit for review the detailed plan that will be used to evaluate patients' understanding about the risks associated with and safe use of Dulera. This information does not need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence." The submission should include all methodology and instruments that will be used to evaluate the patients' knowledge about the risks associated with and safe use of Dulera.
  
- i. Your proposal includes an assessment of healthcare providers' comprehension of communication and education regarding Dulera. While we encourage you to study healthcare provider comprehension, this is not a necessary component of your Medication Guide –only REMS assessment.
  
- ii. Your proposal includes an assessment of patients' comprehension of educational activities, including the Medication Guide. While we encourage you to study patients' comprehension of the Medication Guide, this is not a necessary component of your REMS assessment.

The assessment is to evaluate the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of Dulera. The assessment is not to evaluate consumer comprehension of the Medication Guide.

Respondents should not be offered an opportunity to read or see the Medication Guide again prior to taking the survey.
  
- iii. Recruit respondents using a multi-modal approach. For example, patients could be recruited online, through physicians' offices, through pharmacies, managed care providers, or through consumer panels.

Explain how often non-respondent follow-up or reminders will be completed, and the planned frequency.

Explain how an incentive or honorarium will be offered, and the intended amount.

Explain how recruitment sites will be selected.

Submit for review any recruitment advertisements.
  
- iv. Define the sample size and confidence associated with that sample size.
  
- v. Define the expected number of patients to be surveyed, and how the sample will be determined (selection criteria)

**\*\*\*Pre-decisional Agency Information\*\*\***

- vi. Explain the inclusion criteria; that is, who is an eligible respondent. For example, patient respondents might be:
- Age 18 or older
  - Currently taking Dulera or have taken in past 3 months
  - Not currently participating in a clinical trial involving Dulera
  - Not a healthcare provider
- Submit any screener instruments, and if any quotas will be used.
- vii. Explain how surveys will be administered, and the intended frequency. Offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy population. For example, surveys could be completed online or through email, in writing or by mail, over the phone, or in person. Explain how surveyors will be trained. Explain controls used to compensate for the limitations or bias associated with the methodology
- viii. The patient sample should be demographically representative of the patients who use Dulera. If possible and appropriate, sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geography
- ix. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey. Potential respondents should be told that their answers will not affect their ability to receive or take Dulera, and that their answers and personal information will be kept confidential and anonymous.
- x. Respondents should not be eligible for more than one wave of the survey.
- xi. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
- xii. The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event. Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about Dulera?" section of the Medication Guide. The questions should be about understanding the risk, the symptoms, and what to do if the event occurs. The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option. The order of the multiple choice responses should be randomized on each survey.
- xiii. The order of the questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide.

**\*\*\*Pre-decisional Agency Information\*\*\***

Demographic questions should be collected last or as part of any screener questions.

Respondents should not have the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

- xiv. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.
- xv. Just prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,  
Now we are going to ask you some questions about the Medication Guide you may have received with Dulera. The Medication Guide is a paper handout that contains important information about the risks associated with use of Dulera and how to use Dulera safely. Medication Guides always include the title “Medication Guide”.
- xvi. Use the following (or similar) questions to assess receipt and use of the Medication Guide.
- Who gave you the Medication Guide for Dulera? (Select all that apply)
    - a) My doctor or someone in my doctor’s office
    - b) My pharmacist or someone at the pharmacy
    - c) Someone else - please explain: \_\_\_\_\_
    - d) I did not get a Medication Guide for Dulera
  - Did you read the Medication Guide?
    - All,
    - Most,
    - Some,
    - None
  - Did you understand what you read in the Medication Guide?
    - All,
    - Most,
    - Some,
    - None
  - Did someone offer to explain to you the information in the Medication Guide?
    - Yes, my doctor or someone in my doctor’s office
    - Yes, my pharmacist or someone at the pharmacy
    - Yes, someone else – please explain:  
\_\_\_\_\_
    - No
  - Did you accept the offer? Yes or No
  - Did you understand the explanation that was given to you?
    - All,
    - Most,
    - Some,

**\*\*\*Pre-decisional Agency Information\*\*\***

- None
- Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA
- xvii. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

Data may be stratified by any relevant demographic variable, and also presented in aggregate. We encourage you to submit with your assessments all methodology and instruments that were used to evaluate the effectiveness of the REMS.

Please let us know if you have any questions.

**6. General comments:**

- Submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. All REMS materials should be free of promotional language and tone.
- Consider these comments interim comments. You will receive additional comments on your proposed REMS, REMS materials, and REMS supporting document as we continue our review of the application.

3 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

<p><b>Drug Name:</b> Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol</p> <p><b>Indication:</b> Asthma</p> <p><b>Sponsor:</b> Schering Plough</p>	<p><b>NDA:</b> 22-518</p> <p><b>PDUFA Date:</b> 6-22-10</p>	<p><b>Date:</b> 6-7-10</p> <p><b>Comment Set # 2</b></p> <p>Summary of the comments on the Dulera DHCPL</p>
<p><b>DRISK Scientific Lead:</b></p> <p>Yasmin Choudhry, M. D., Medical Officer, Division of Risk Management (DRISK)</p>		<p><b>DRISK Reviewers:</b> Marcia Britt, Ph. D., Health Education Reviewer Jodi Duckhorn, MA., Social Science Reviewer Claudia Karwoski, Pharm D., Division Director</p> <p><b>OC Reviewers</b> Michelle Marsh, B.S., CSO</p> <p><b>DDMAC Reviewers</b> Roberta Szydlo, Regulatory Review Officer Lisa Hubbard, Professional Reviewers Group Leader</p>

**Summary of Comments on the Dulera DHCPL:**

This interim review is an addendum to the Dulera Interim Comments entered into DARRTS and sent to the Sponsor on June 4, 2010. The new prescribing guidelines for the LABAS drafted by Dr. Sally Seymour have been added to the Dulera Dear Healthcare Provider Letter in addition to the safety information (see the DHCPL below); we concur with the new prescribing guidelines.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

---

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

---

/s/

---

YASMIN A CHOUDHRY

06/07/2010

Dulera REMS Review and the Addendum are included in this review.

CLAUDIA B KARWOSKI

06/07/2010

concur



NDA 022518

**REMS NOTIFICATION**

Schering-Plough Corporation  
2000 Galloping Hill Road  
Kenilworth, NJ 07033-0530 USA

Attention: Michael Belman  
Director, Regulatory Affairs

Dear Mr. Belman:

Please refer to your new drug application (NDA) dated May 21, 2009, and received on May 22, 2009, under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol.

We note that you voluntarily submitted a proposed Risk Evaluation and Mitigation Strategy (REMS) in your NDA submission.

We are reviewing your submission and have the following comments. We request a prompt response in order to continue our evaluation of your application.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Dulera Inhalation Aerosol to ensure that the benefits of the drug outweigh the risks of serious asthma outcomes (asthma related death, intubations, and hospitalizations) associated with the use of the class of long acting beta agonists (LABAs).

Your proposed REMS must include the following:

- a) **Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Dulera Inhalation Aerosol poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Dulera Inhalation Aerosol. FDA has determined that Dulera Inhalation Aerosol is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of

which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Dulera Inhalation Aerosol. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Dulera Inhalation Aerosol.

- b) **Communication Plan:** We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Dulera Inhalation Aerosol will support implementation of the elements of your REMS during the first year after the REMS is approved. The communication plan must provide for the dissemination of information about the risks of LABAs, including the increased risk of asthma-related deaths and new prescribing guidelines for adult, adolescent and pediatric populations.

The communication plan must include, at minimum, the following:

1. A Dear Healthcare Provider Letter to be distributed within 60 days of the REMS approval. This letter should introduce the following safety information to current and potential prescribers of LABAs:
    - a) Increased risk of asthma-related deaths in patients taking LABAs
    - b) New prescribing guidelines:
      - i. LABAs should be discontinued once asthma control has been achieved and patients should be maintained on an asthma controller medication, such as inhaled corticosteroids.
      - ii. Do not use LABAs for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
  2. Other printed or web-based materials to inform healthcare providers about the occurrence of the increased risk of asthma-related deaths in patients taking LABAs and the new prescribing guidelines.
  3. A description of the audience for the communication plan, stating specifically the types and specialties of healthcare providers to whom the communication materials will be directed. Information must also be included on how often these materials will be distributed.
  4. A plan for disseminating information about the serious risks associated with the use of LABAs and the new prescribing guidelines through professional societies. Include in your proposal a list of the professional societies you aim to target and the details of how the professional societies will convey the information to their members.
- c) **Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than yearly after the

REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. 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. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Dulera Inhalation Aerosol. Additionally, all relevant proposed REMS materials including communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include but may not be limited to:

- a. An evaluation of patients' understanding of the risks associated with Dulera Inhalation Aerosol including the increased risk of asthma-related deaths.
- b. An analysis of physicians' understanding of the increased risk of asthma-related deaths and the safe use of LABAs.
- c. A description of specific measures that would be taken to increase awareness if the assessment of healthcare prescribers indicates that prescriber awareness is not adequate.
- d. A narrative summary with analysis of all reported asthma-related deaths during the reporting period.
- e. Drug use patterns (reasons for use, patient demographics, length of therapy, prescribing medical specialties)
- f. Based on the information reported, an assessment of and conclusion regarding whether the REMS is meeting its goal and whether modifications to the REMS are needed.

If the Medication Guide is not included in unit-of-use packaging with the Medication Guide attached to packaging, the REMS assessment plan should also include:

- g. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

- h. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Before we can continue our evaluation of this NDA, you will need to submit the proposed REMS. The REMS you have already submitted does not contain all of the elements we are requiring, as discussed above, and is not adequate.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend that you use one of the following two statements depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- a) “Dispense the enclosed Medication Guide to each patient.” or
- b) “Dispense the accompanying Medication Guide to each patient.”

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022518  
PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA022518  
PROPOSED REMS-AMENDMENT**

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, call Eunice Chung, Regulatory Project Manager, at (301)796-4006.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22518

-----  
ORIG-1

-----  
SCHERING CORP

-----  
MOMETASONE  
FUROATE/FORMOTEROL  
FUMARATE

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

/s/  
-----

BADRUL A CHOWDHURY

02/18/2010

## Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
Office of New Drugs  
Office of Drug Evaluation II  
Division of Pulmonary and Allergy Products (DPAP)

---

**NDA/BLA #:** NDA 022518  
**Product:** Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol  
**APPLICANT:** Schering Plough  
**FROM:** Badrul Chowdhury, MD, PhD, Division Director, DPAP  
**DATE:** February 18, 2010

---

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol outweigh the risks of serious asthma outcomes (asthma related death, intubations, and hospitalizations) associated with the use of the class of long acting beta agonists (LABAs). Our information was obtained from the Salmeterol Multi-Center Asthma Research Trial (SMART) and clinical trial data presented as a meta-analysis at the December 10-11, 2008, joint meeting of the Pulmonary Allergy Drugs, Drug Safety and Risk Management, and Pediatric Advisory Committees, and the discussion at the joint Advisory Committee meeting, which raised concerns regarding the use of LABAs without concomitant asthma controller therapy, particularly in pediatric and adolescent patients. In reaching this determination we considered the following:

- A. Asthma is a chronic inflammatory disorder of the airways characterized by episodic and reversible airflow obstruction and airway hyperresponsiveness. Clinical manifestations include wheezing, coughing, and shortness of breath. Although the

pathophysiology of asthma is fairly well understood, the exact etiology is not. Estimates from CDC's 2002 Asthma Surveillance Summary indicate that asthma 12-month period prevalence was 5.5% in 1996, an increase from 3.0% of the population in 1970.<sup>1</sup> The prevalence of patients with moderate to severe persistent disease who may be candidates for treatment with an inhaled corticosteroid and LABA combination product is unknown.

- B. Left untreated, persistent asthma results in significant morbidity as well as mortality. For the 3-year period 2001-2003, an average annual 4,210 deaths from asthma occurred, with relatively few deaths in persons aged <18 years (200) and approximately 50% in persons aged  $\geq 65$  years.<sup>1</sup>
- C. Inhaled corticosteroids (ICS) are anti-inflammatory medications approved for the maintenance treatment of asthma and are considered the most effective treatment of asthma. LABAs are bronchodilators. ICS and LABA combination products are approved based upon an improvement in lung function as measured by the forced expiratory volume in one second (FEV1). ICS and LABA combination products improve lung function and improve symptoms of asthma. ICS and LABA combination products are products of convenience approved for the maintenance treatment of asthma and these products are widely used for the treatment of persistent asthma.
- D. Because asthma is a chronic disease with waxing and waning of symptoms, the expected duration of therapy with ICS and LABA combination products may be indefinite.
- E. LABAs increase the risk of asthma related death especially when used without concomitant asthma controller therapy. The primary source of this information is from the controlled clinical trial, Salmeterol Multi-Center Asthma Research Trial (SMART). SMART was a randomized, double-blind study to assess the safety of salmeterol (Serevent Inhalation Aerosol) twice daily over 28 weeks compared to placebo when added to usual asthma therapy in 26,355 patients with asthma. The results showed that patients receiving salmeterol were at increased risk for fatal asthma events with a relative risk of 4.4 (95% CI: 1.3-15.3) compared to placebo. In addition, a meta-analysis of all placebo controlled clinical trial data with LABAs was presented at the December 10-11, 2008 Pulmonary Allergy Drug Advisory Committee meeting. This meta-analysis showed an increased risk of asthma hospitalizations with LABAs, especially in pediatric and adolescent patients. Furthermore, the following potential serious adverse events are included in labeling for LABAs: paradoxical bronchospasm, cardiovascular effects (increase pulse rate, blood pressure, and/or symptoms, ECG changes), hypokalemia, hyperglycemia, and immediate hypersensitivity reactions. In terms of the background rate for asthma related death, according to National Vital Statistics System, the rate of death from asthma in 2004 was 1.9 per 10,000 persons with asthma over a 12 month period.

---

<sup>1</sup> Moorman, JE, Rudd, RA, et al. National Surveillance for Asthma - United States, 1980-2004. MMWR 56(SS08);1-14;18-54; October 19, 2007.

F. Dulera Inhalation Aerosol is not a new molecular entity (or comprised of new molecular entities).

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Dulera Inhalation Aerosol. FDA has determined that Dulera Inhalation Aerosol poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Dulera Inhalation Aerosol. FDA has determined that Dulera Inhalation Aerosol is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Dulera Inhalation Aerosol.

The elements of the REMS will be a Medication Guide, Communication Plan and a timetable for submission of assessments of the REMS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

---

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

---

/s/

---

EUNICE H CHUNG  
02/18/2010

BADRUL A CHOWDHURY  
02/18/2010