NDA 22-383

ARCAPTA™ NEOHALER™

(indacaterol maleate)

Long-acting beta$_2$-adrenergic agonist

Novartis Pharmaceuticals, One Health Plaza, East Hanover, N.J. 07936-1080

Risk Evaluation and Mitigation Strategy (REMS)

I Goals

- To inform healthcare providers and prescribers of the increased risk of asthma related death and serious outcomes with the long-acting beta$_2$-adrenergic agonists (LABAs) including ARCAPTA NEOHALER when used to treat asthma.
- To inform healthcare providers and prescribers of the appropriate use of ARCAPTA NEOHALER, and its approved indication (COPD).

II REMS Elements

A. Communication Plan

Novartis Pharmaceuticals Corporation will implement a communication plan to healthcare providers to support the implementation of this REMS. This communication plan will include the following:

1. A Dear Healthcare Provider Letter (DHCPL) will be distributed to potential prescribers of ARCAPTA NEOHALER including pulmonologists, allergist/immunologists, primary care providers, nurse practitioners, and physician assistants.

   Distribution of the Dear Healthcare Provider Letter will be by direct mail or email communication at least one month prior to first product availability. The DHCPL will include the following safety information:

   a. Increased risk of asthma-related death in patients with asthma taking LABAs.
   b. New prescribing guidelines
      i. All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication. Arcapta Neohaler is not indicated for the treatment of asthma.
      ii. ARCAPTA NEOHALER is indicated for the treatment of COPD. ARCAPTA NEOHALER is not indicated for the relief of acute bronchospasm and should not be initiated in patients during rapidly deterioration or potentially life-threatening episodes of COPD

2. Printed or web-based information for health care providers will be posted on a Novartis 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, for example, include the following:
    a. Information about the risk in asthma and COPD
    b. Key data regarding the risk (e.g. SMART, SNS)
    c. New prescribing guidelines
    d. Currently available LABAs and approved uses
    e. Prescribing information for ARCAPTA NEOHALER
    f. Patient Counseling Information for ARCAPTA NEOHALER
    g. Questions and Answers
    h. DHCP letter (for a period of 1 year)
    i. Link to FDA website for alerts on LABAs

3. Novartis Pharmaceuticals 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 Physician (ACCP)
    - American College of Physicians (ACP)
    - National Medical Association (NMA)
    - American Academy of Nurse Practitioners (AANP)
    - American Academy of Physician Assistants (AAPA)
    - American Academy of Family Physicians (AAFP)
    - The COPD Foundation

The communication to medical societies will also include a link to the website or hard copies of the educational information that are also available under 2) above. Novartis will request that these societies disseminate this information to their members.

The REMS communication materials to professional societies will parallel the direct mail or e-mail program and will be distributed at least one month prior to first product availability.

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

i. DHCPL (Appendix A)
ii. Dear (Medical Society) Letter (Appendix B)
iii. Educational printed or web-based information (Appendix C)

B. Timetable for Submission of Assessments

Novartis will submit REMS Assessments to FDA annually from approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to

prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Novartis will submit each assessment so that it will be received by the FDA on or before the due date.

Appendix A: ARCAPTA NEOHALER DHCPL

Novartis Letter Head

IMPORTANT DRUG WARNING

<<date>>

Subject: Important information in the ARCAPTA™ NEOHALER™ Prescribing Information – regarding safety of long-acting beta-agonists.

Dear Healthcare Professional:

Novartis Pharmaceuticals Corporation would like to inform you of important safety information contained in the package insert for ARCAPTA NEOHALER (indacaterol inhalation powder).

ARCAPTA NEOHALER is a long-acting beta$_2$-agonist (LABA) indicated for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

New important safety information related to ARCAPTA NEOHALER includes:

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

ARCAPTA NEOHALER is indicated for use in adults with COPD including chronic bronchitis and emphysema. ARCAPTA NEOHALER is NOT indicated to treat asthma.

ARCAPTA NEOHALER has a risk evaluation and mitigation strategy (REMS) that consists of a communication program.

The ARCAPTA NEOHALER Prescribing Information includes a boxed warning highlighting an increased risk of asthma-related deaths observed in patients taking LABAs for the treatment of asthma.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta2-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy

showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including indacaterol, the active ingredient in ARCAPTA NEOHALER. The safety and efficacy of ARCAPTA NEOHALER in patients with asthma have not been established. ARCAPTA NEOHALER is not indicated for the treatment of asthma. [See Contraindications (4), Warnings and Precautions (5.1)].

See the full Prescribing Information for a more complete description. References within the boxed warning refer to sections within the full Prescribing Information.

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

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

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

ARCAPTA NEOHALER is not indicated for the relief of acute bronchospasm.

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

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

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

To report adverse events potentially associated with ARCAPTA NEOHALER, please call Novartis Pharmaceuticals Corporation at 1-800-XXX-XXXX.

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 Novartis at 1-800-XXX-XXXX or go to http://www.arcapta.com if you have any questions about ARCAPTA NEOHALER or this information.

Sincerely,
XXXX

Appendix B: Dear Medical Society Letter

<Novartis Letter Head>

IMPORTANT DRUG WARNING

<<date>>

Subject: Important information in the ARCAPTA™ NEOHALER™ Prescribing Information regarding safety of long-acting beta$_2$-agonists

<date>
<Medical Society contact>
<Medical Society>
<Medical Society address>

Dear <Medical Society contact>:

Novartis Pharmaceuticals Corporation would like to inform you of important safety information contained in the package insert for ARCAPTA NEOHALER (indacaterol inhalation powder). ARCAPTA NEOHALER is a long-acting beta$_2$-agonist (LABA) indicated for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

New important safety information related to ARCAPTA NEOHALER includes:

- Increased risk of asthma-related death in patients taking LABAs for treatment of asthma.
- New prescribing guidelines.
    - All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication.

ARCAPTA NEOHALER is indicated for use in adults with COPD including chronic bronchitis and emphysema. Arcapta Neohaler is NOT indicated to treat asthma.

ARCAPTA NEOHALER has a risk evaluation and mitigation strategy (REMS) that consists of a communication program.

The ARCAPTA NEOHALER Prescribing Information includes a boxed warning highlighting an increased risk of asthma-related deaths observed in patients taking LABAs for the treatment of asthma.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta2-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including indacaterol, the active ingredient in ARCAPTA NEOHALER. The safety and efficacy of ARCAPTA NEOHALER in patients with asthma have not been established. ARCAPTA

NEOHALER is not indicated for the treatment of asthma. [See Contraindications (4), Warnings and Precautions (5.1)].

See the full Prescribing Information for a more complete description. References within the boxed warning refer to sections within the full Prescribing Information.

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

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

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

ARCAPTA NEOHALER is not indicated for the relief of acute bronchospasm.

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

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

Please take time to read the enclosed ARCAPTA NEOHALER Package Insert for full prescribing information, for complete description of this important safety information and the 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 ARCAPTA NEOHALER.

To report adverse events potentially associated with ARCAPTA NEOHALER, please call Novartis Pharmaceuticals Corporation at 1-800-XXX-XXXX.

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 Novartis at 1-800-XXX-XXXX or go to http://www.arcapta.com if you have any questions about ARCAPTA NEOHALER or this information.
Sincerely,

XXXX

Appendix C: ARCAPTA NEOHALER printed/web materials

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

- **Information about the risk in asthma**

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta2-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including indacaterol, the active ingredient in ARCAPTA NEOHALER. The safety and efficacy of ARCAPTA NEOHALER in patients with asthma have not been established. ARCAPTA NEOHALER is not indicated for the treatment of asthma. [See Contraindications (4), Warnings and Precautions (5.1)].

- **Information about the risk in COPD**

See the full Prescribing Information for a more complete description of both the safety and efficacy associated with the use of ARCAPTA NEOHALER in the treatment of COPD.

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

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

SMART was a large, randomized, 28-week, placebo-controlled trial that evaluated patients 12 years of age and older receiving standard asthma therapy and the addition of either salmeterol or placebo. A total of 26,355 patients were evaluated in this study. Results showed that patients receiving salmeterol were at an increased risk for asthma-related death compared to patients receiving placebo (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). Subgroup analyses were also performed and found that asthma-related death in Caucasians and African Americans occurred at a higher rate in patients using salmeterol compared to placebo.

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. 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.

For full details regarding each of these studies and additional detailed educational materials regarding serious risks associated with the use of LABAs in the treatment of asthma including asthma-related death, please see the information provided by the FDA at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm.

Based on the available information from these studies in asthma, 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. However, the FDA is requiring the implementation of a REMS and class-labeling changes to improve the safe use of these products.

- **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 FDA 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.).

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

Link:

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

The new recommendations in the updated labels state:
• All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication. ARCAPTA NEOHALER is not indicated for the treatment of asthma.

ARCAPTA (indacaterol maleate) NEOHALER is indicated for the long term, once daily maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary

disease (COPD), including chronic bronchitis and emphysema. Novartis Pharmaceuticals Corporation does not promote or recommend the use of ARCAPTA NEOHALER for the treatment of asthma. ARCAPTA NEOHALER is not indicated for the treatment of asthma.

See the full Prescribing Information for a more complete description of both the safety and efficacy associated with the use of ARCAPTA NEOHALER in the treatment of COPD.

- **Currently available LABAs and approved uses**

For reference, the following table summarizes the currently available LABAs and their approved uses:

FDA Approved Long-Acting Beta Agonists

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

* not currently marketed in the U.S.

See June 2010 LABA Drug Safety Communication for more information.

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

- **Prescribing information for ARCAPTA NEOHALER**

See the full Prescribing Information for ARCAPTA NEOHALER at http://www.arcapta.com.

- **Patient Counseling Information**

Information for Patients

See ARCAPTA NEOHALER Medication Guide at http://www.arcapta.com

Asthma-Related Death

Patients should be informed that LABA, such as ARCAPTA NEOHALER, increase the risk of asthma-related death. ARCAPTA NEOHALER is not indicated for the treatment of asthma.

Instructions for Administering ARCAPTA NEOHALER

It is important for patients to understand how to correctly administer ARCAPTA capsules using the NEOHALER device [see Instructions for use at the end of the Medication Guide]. Patients should be instructed that ARCAPTA capsules should only be administered via the NEOHALER device and the NEOHALER device should not be used for administering other medications. **The contents of ARCAPTA capsules are for oral inhalation only and must not be swallowed.**

ARCAPTA capsules should always be stored in sealed blisters. Only one ARCAPTA capsule should be removed immediately before use, or its effectiveness may be reduced. Additional ARCAPTA capsules that are exposed to air (i.e. not intended for immediate use) should be discarded.

Not for Acute Symptoms

ARCAPTA NEOHALER is not meant to relieve acute symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist such as albuterol. (The healthcare provider should provide the patient with such medication and instruct the patient in how it should be used.)

Patients should be instructed to notify their physician immediately if they experience any of the following:

- Worsening of symptoms
- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician.

Patients should not stop therapy with ARCAPTA NEOHALER without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting Beta$_2$-Agonists

Patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis should be instructed to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

When patients are prescribed ARCAPTA NEOHALER, other inhaled medications containing long-acting beta$_2$-agonists should not be used. Patients should not use more than the recommended once daily dose of ARCAPTA NEOHALER. Excessive use of sympathomimetics may cause significant cardiovascular effects, and may be fatal.

Risks Associated With Beta-Agonist Therapy

Patients should be informed of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

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

Q6. Why is the risk management program designed for patients with asthma and not for patients with COPD, aren't LABAs used to treat both conditions?

Questions about ARCAPTA NEOHALER

Q1. Why does ARCAPTA NEOHALER have a boxed warning?

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

Q3. Can ARCAPTA NEOHALER be used for acute COPD symptoms?

Q4. Can additional LABAs be used with ARCAPTA NEOHALER?

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

Questions about LABA safety

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

A. Despite the benefits of long-acting beta$_2$-agonists (LABAs) in helping people with asthma, FDA's analyses indicate there is an increase in the risk of severe exacerbation of asthma symptoms leading to hospitalizations in pediatric and adult patients as well as death in some patients with asthma that use a LABA compared to patients with asthma that do not use a LABA. Because of this risk, FDA wants to make sure LABAs are used appropriately in patients with asthma. In order to ensure the safe use of these medicines, FDA is requiring the manufacturers of LABAs to develop this risk management program for healthcare professionals, regardless of whether or not the individual LABA is indicated for use in asthma. ARCAPTA NEOHALER is indicated for the treatment of COPD and not for the treatment of asthma.

Q2. What is the goal of the 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, the prescribing information being provided to healthcare professionals includes 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
Foradil Aerolizer	formoterol	single ingredient LABA with no corticosteroid long-term asthma control medication
Serevent Diskus	salmeterol	single ingredient LABA with no corticosteroid long-term asthma control medication
Advair Diskus, Advair HFA	salmeterol and fluticasone	salmeterol is a LABA and fluticasone is a corticosteroid long-term asthma control medication
Symbicort Inhalation Aerosol	formoterol and budesonide	formoterol is a LABA and budesonide is a corticosteroid long-term asthma control medication
Dulera Inhalation Aerosol	formoterol and mometasone	formoterol is a LABA and mometasone is a corticosteroid long-term asthma control medication

Q5. 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 asthma 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 http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm for more information.

ARCAPTA NEOHALER is not indicated for patients with asthma.

Q6. Why is the risk management program designed for patients with asthma and not for patients with COPD, aren't LABAs used to treat both conditions?

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

Questions about ARCAPTA NEOHALER

Q1. Why does ARCAPTA NEOHALER have a boxed warning?

A. ARCAPTA NEOHALER belongs to a class of drugs known as long-acting beta agonists (LABAs). As a safety measure, the FDA has requested that the Boxed Warning and other

labeling sections, as well as the Medication Guide, for all LABA, like ARCAPTA NEOHALER, include language indicating that LABA increase the risk of asthma-related death. **Please note that ARCAPTA NEOHALER is not indicated for asthma**.

The boxed warning for ARCAPTA NEOHALER reads as follows:

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including indacaterol, the active ingredient in ARCAPTA NEOHALER. The safety and efficacy of ARCAPTA NEOHALER in patients with asthma have not been established. ARCAPTA NEOHALER is not indicated for the treatment of asthma. [see Contraindications (4), Warnings and Precautions (5.1)].

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

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

A. Patients with asthma should be informed that ARCAPTA NEOHALER has been approved for COPD only. In patients with asthma, long-acting beta$_2$-agonist (LABA) medicines may increase the chance of death from asthma problems. In a large asthma study, more patients who used another LABA medicine died from asthma problems compared with patients who did not use that LABA medicine. See the Warnings and Precautions section of the full Prescribing Information.

Q3. Can ARCAPTA be used for acute COPD symptoms?

A. No. ARCAPTA NEOHALER is not indicated to relieve acute respiratory 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 if:

- their symptoms worsen
- ARCAPTA NEOHALER treatment becomes less effective
- they need more inhalations of a short-acting beta$_2$-agonist than usual

Patients should not inhale more than the contents of one capsule at any one time. The daily dosage of ARCAPTA NEOHALER should not exceed one capsule once daily. See the Warnings and Precautions in the full Prescribing Information.

Q4. Can additional LABAs be used with ARCAPTA NEOHALER?

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

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

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

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

/s/

CAROL F HILL
07/01/2011

CURTIS J ROSEBRAUGH
07/01/2011