

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022472Orig1s000

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

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUGS
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS**

NDA/BLA #s: 022472
Products: Afrezza (insulin human) Inhalation Powder
APPLICANT: MannKind Corporation
FROM: Jennifer R. Pippins, M.D., M.P.H.
DATE: June 27, 2014

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 for Afrezza (insulin human) Inhalation Powder to ensure that the benefits of the drug outweigh the risk of acute bronchospasm in patients with chronic lung disease. In reaching this determination, we considered the following:

- A. In 2010 diabetes affected 25.8 million people in the United States, of which 18.8 million were diagnosed and 7.0 million were undiagnosed.¹
- B. Patients with diabetes are at risk for a variety of complications including heart disease, stroke, blindness, kidney failure, nervous system damage, amputations, and death if untreated.
- C. In patients with inadequately controlled type 1 diabetes, Afrezza (insulin human) Inhalation Powder administered at mealtime and in combination with basal insulin over 24 weeks provides a mean reduction in hemoglobin A1c meeting a pre-specified non-inferiority margin of 0.4% compared to the combination of mealtime insulin aspart and basal insulin. In

¹ <http://www.cdc.gov/diabetes/pubs/factsheet11/fastfacts.htm>; accessed March 28, 2014.

patients with inadequately controlled type 2 diabetes, Afrezza (insulin human) Inhalation Powder administered at mealtime and in combination with oral anti-diabetic agents over 24 weeks has been shown to achieve a mean placebo-adjusted reduction in hemoglobin A1c of 0.4%. Some of the complications listed above can be prevented or delayed with good glycemic control. Afrezza (insulin human) Inhalation Powder is an option for patients with either type 1 or type 2 diabetes. Afrezza (insulin human) Inhalation Powder is not a substitute for long-acting insulin, and must be used in combination with long-acting insulin in patients with type 1 diabetes. Afrezza (insulin human) Inhalation Powder is not recommended for the treatment of diabetic ketoacidosis, and is also not recommended in patients who smoke or who have recently stopped smoking. Afrezza (insulin human) Inhalation Powder is contraindicated in patients known to have lung disease.

- D. The expected duration of therapy is over a patient's lifetime.
- E. In addition to the serious risk of acute bronchospasm, Afrezza (insulin human) Inhalation Powder is associated with hypoglycemia, decline in pulmonary function, and diabetic ketoacidosis, and is potentially associated with lung cancer, systemic allergic reactions, hypokalemia, and fluid retention and heart failure with concomitant use of PPAR-gamma agonists.
- F. Afrezza (insulin human) Inhalation Powder is not a new molecular entity.

The elements of the REMS will be a communication plan and a timetable for submission of assessments of the REMS.

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/s/

JENNIFER R PIPPINS
06/27/2014

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVALUATION AND MITIGATION STRATEGY REVIEW

Date:	June 24, 2014
Reviewer(s)	Joyce Weaver, Pharm.D., Risk Management Analyst Division of Risk Management (DRISK) Anahita Tavakoli, M.A., Health Communication Analyst, DRISK
Team Leader	Doris Auth, Pharm.D., Acting Team Leader, DRISK
Division Director:	Claudia Manzo, Pharm.D., Acting OMEPRM Director
Subject:	Review recommending REMS approval
Drug Name(s):	AFREZZA® (insulin human) Inhalation Powder
Therapeutic class & dosage form:	Antidiabetic Inhalation
OND Review Division	Division of Metabolism and Endocrinology Products
Application Type/Number:	NDA 022472, DARRTS Supporting Document #96
Submission received	June 20, 2014
PDUFA/Action Date	July 15, 2014
Applicant/sponsor:	MannKind Corporation
OSE RCM #:	2013-2342
TSI #:	n/a

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) provides the final review of the Afrezza REMS.

Agency comments on the proposed communication plan REMS were sent to the sponsor June 17, 2014. The sponsor responded with a modified REMS proposal, incorporating Agency comments. The modified REMS, REMS Supporting Document, and REMS materials were submitted June 20, 2014.

Afrezza is ultra-fast acting insulin administered via inhalation. The application has received two prior reviews from the Agency. The Agency issued a second complete response (CR) letter for this application on January 18, 2011. On October 15, 2013, MannKind Corporation resubmitted the application. The application is on a 6-month review schedule, extended by 3 months for a major amendment.

2 MATERIALS REVIEWED

We reviewed the following submitted June 20, 2014:

- Revised Risk Evaluation and Mitigation Strategy (REMS), DARRTS Supporting Document #96

2.1 PREVIOUS DRISK REMS REVIEWS

- November 23, 2009; M. Williams
- December 9, 2009; M. Williams
- October 24, 2011; J. Weaver
- March 25, 2014; J. Weaver
- June 13, 2014; J. Weaver
- June 17, 2014; J. Weaver

3 RESULTS OF REVIEW

The sponsor incorporated all Agency comments. The REMS submitted June 20, 2014 is acceptable.

4 RECOMMENDATION

DRISK recommends approval of the REMS.

NDA 022472 AFREZZA® (insulin human) Inhalation Powder

MannKind Corporation
61 South Paramus Road
Paramus, NJ 07652
Phone: (201) 983-5000

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of the Afrezza REMS is to mitigate the risk of acute bronchospasm associated with Afrezza by:

- Informing healthcare providers that there is risk of acute bronchospasm associated with AFREZZA in patients with chronic lung disease
- Informing healthcare providers that acute bronchospasm has been observed with AFREZZA in patients with asthma and COPD
- Informing healthcare providers that AFREZZA is contraindicated in patients with chronic lung disease
- Informing healthcare providers of the need to evaluate patients for lung disease before starting on AFREZZA

II. REMS ELEMENTS

A. Communication Plan

MannKind Corporation will implement the following communication plan to healthcare providers likely to prescribe AFREZZA. The communication plan will include:

1. REMS Letters

MannKind Corporation will send a *REMS Letter for Healthcare Providers* and *REMS Letter for Professional Societies* within 60 days of this REMS approval (June 2014) and again after one year from the date of the REMS approval. If the commercial launch of AFREZZA occurs later than 90 days following REMS approval, an additional issuance of REMS Letters will be sent within 30 days of product launch. The REMS Letters will address the risk of acute bronchospasm in patients with chronic lung disease, including the fact that acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA, that AFREZZA is contraindicated in patients with chronic lung disease, and that healthcare providers should evaluate all patients for lung disease (a detailed medical history, physical examination, and spirometry [FEV₁] to identify potential lung disease) before starting on AFREZZA.

REMS Letters will be distributed by electronic mail (email).

Email will be the primary method to disseminate the REMS Letters. If an email is marked as unopened, a second email will be sent within 14 calendar days. If the second email is marked as unopened, the REMS Letter will be mailed within 14 calendar days. If a healthcare

provider's or professional society's email address is not available or if the email is undeliverable, the REMS Letter will be mailed within 14 calendar days.

MannKind will make the *REMS Letter for Healthcare Providers* available via a link from the AFREZZA REMS website and through MannKind's sales and medical representatives upon request for one year after the approval of the REMS (June 2014). A copy of or a link to the Prescribing Information (PI) and REMS Factsheet will accompany each REMS Letter for Healthcare Providers.

a. REMS Letter for Healthcare Providers

The intended audience for the *REMS Letter for Healthcare Providers* will be healthcare providers likely to prescribe AFREZZA and healthcare providers targeted by AFREZZA marketing activities.

b. REMS Letter for Professional Societies

MannKind Corporation will send the *REMS Letter for Professional Societies* to the following professional societies and organizations requesting the risk information in the letter be provided to their membership:

- American Diabetes Association
- American Association of Clinical Endocrinologists
- American Medical Association
- American College of Physicians
- Society of General Internal Medicine
- American Academy of Family Physicians
- National Medical Association
- Endocrine Society
- American College of Osteopathic Family Physicians
- American Association of Diabetes Educators
- American Association of Nurse Practitioners
- American Society of Health System Pharmacists
- American Pharmacists Association
- National Community Pharmacists Association
- American College of Clinical Pharmacy
- Association of Managed Care Pharmacy
- National Association of Managed Care Physicians

2. REMS Factsheet

A *REMS Factsheet* will be distributed with the REMS Letter for Healthcare Providers and made available to healthcare providers through MannKind Corporation's sales and medical representatives during the initial discussion with healthcare providers during the first 12 months after approval of this AFREZZA REMS. If the commercial launch of Afrezza occurs later than 90 days after REMS approval, distribution of the *REMS Factsheet* will continue during the initial discussion with healthcare providers during the first 18 months after approval of the REMS.

3. REMS Website

The AFREZZA REMS website for healthcare professionals (www.AfrezzaREMS.com) will include a prominent REMS-specific link and will continue for the duration of the REMS.

The REMS website will include the option to print versions of the PI, *REMS Letter for Healthcare Providers*, and the *REMS Factsheet*.

4. Dissemination of REMS information at scientific meetings

The *AFREZZA REMS Factsheet* will be prominently displayed at relevant scientific meetings where MannKind Corporation has a presence (e.g., booth) for the duration of the REMS.

The following are part of the REMS and are appended:

- *AFREZZA REMS Letter for Healthcare Providers* (print version)
- *AFREZZA REMS Letter for Healthcare Providers* (email version)
- *AFREZZA REMS Letter for Professional Societies* (print version)
- *AFREZZA REMS Letter for Professional Societies* (email version)
- *AFREZZA REMS Factsheet*
- *AFREZZA REMS Website* (www.AfrezzaREMS.com)

B. Timetable for Submission of Assessments

MannKind Corporation will submit REMS Assessments to FDA at 18 months, 3 years, and 7 years from the date of the approval of the initial REMS (June 2014). 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. MannKind Corporation will submit each assessment so that it will be received by the FDA on or before the due date.



AFREZZA[®] REMS

FDA Required REMS Safety Information

- **Risk of acute bronchospasm in patients with chronic lung disease**
 - Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA
- **Contraindicated in patients with chronic lung disease such as asthma or COPD**
- **Need to evaluate all patients for lung disease before starting AFREZZA**
Before initiating AFREZZA, perform
 - a detailed medical history
 - physical examination, and
 - spirometry (FEV₁)

Important Safety Notice

The FDA has required this safety notice as part of the AFREZZA REMS (Risk Evaluation and Mitigation Strategy) to inform healthcare providers (HCPs) about the following **serious risks of AFREZZA**:

- **Risk of Acute Bronchospasm in Patients with Chronic Lung Disease.**
 - Counsel patients to inform their HCP if they have a history of lung disease. Do not use in patients with chronic lung disease
- **Appropriate Patient Selection.** AFREZZA is contraindicated in patients with:
 - Chronic lung disease such as asthma or chronic obstructive pulmonary disease (COPD)
- **Patient Evaluation Before Initiating Therapy.**
 - Before initiating, prescribers must perform a detailed medical history, physical examination, and spirometry (FEV₁) in all patients to identify potential underlying lung disease

A non-promotional factsheet, reviewed by the FDA, with more detailed safety information on these risks, and a link to the Prescribing Information including the BOXED WARNING are available at www.AfrezzaREMS.com.

Indication: AFREZZA (insulin human) Inhalation Powder is a rapid acting inhaled insulin indicated to improve glycemic control in adult patients with diabetes mellitus.

Important limitations of use:

- Not a substitute for long-acting insulin. In patients with type 1 diabetes, must use with a long-acting insulin
- Not recommended for the treatment of diabetic ketoacidosis
- Not recommended in patients who smoke or have recently stopped smoking

Please visit www.AfrezzaREMS.com for more information.

This letter does not contain the complete safety profiling for AFREZZA. Please see the Prescribing Information and Medication Guide, enclosed.

Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to MannKind Corporation at 1-877-323-8505 and/or the FDA www.fda.gov/medwatch, or call 1-800-FDA-1088.

Signature,

From: MannKind
To: Healthcare Provider
Subject: Risk of acute bronchospasm with AFREZZA in patients with chronic lung disease



AFREZZA[®] REMS

FDA Required REMS Safety Information

- **Risk of acute bronchospasm in patients with chronic lung disease**
 - Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA
 - **Contraindicated in patients with chronic lung disease such as asthma or COPD**
 - **Need to evaluate all patients for lung disease before starting AFREZZA**
- Before initiating AFREZZA, perform**
- a detailed medical history
 - physical examination, and
 - spirometry (FEV₁)

Important Safety Notice

The FDA has required this safety notice as part of the AFREZZA REMS (Risk Evaluation and Mitigation Strategy) to inform healthcare providers about the following **serious risks of AFREZZA**:



- **Risk of acute bronchospasm in patients with chronic lung disease**
- **Contraindicated in patients with chronic lung disease such as asthma or COPD**
- **Need to evaluate patients for lung disease before starting AFREZZA**

A non-promotional factsheet, reviewed by the FDA, with more detailed safety information on these risks, and a link to the Prescribing Information including the BOXED WARNING are available at www.AfrezzaREMS.com.

Indication

AFREZZA (insulin human) Inhalation Powder is a rapid acting inhaled insulin indicated to improve glycemic control in adult patients with diabetes mellitus.

Important limitations of use

- Not a substitute for long-acting insulin. In patients with type 1 diabetes, must use with a long-acting insulin
- Not recommended for the treatment of diabetic ketoacidosis
- Not recommended in patients who smoke or have recently stopped smoking

This email does not contain the complete safety profile for AFREZZA. To review the Prescribing Information and Medication Guide, see links below:

[Prescribing Information](#)

[Medication Guide](#)

Please visit www.AfrezzaREMS.com for more information.

Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to MannKind Corporation at 1-877-323-8505 and/or the FDA www.fda.gov/medwatch, or call 1-800-FDA-1088.

Signature,



AFREZZA[®] REMS

FDA Required REMS Safety Information

- **Risk of acute bronchospasm in patients with chronic lung disease**
 - Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA
- **Contraindicated in patients with chronic lung disease such as asthma or COPD**
- **Need to evaluate all patients for lung disease before starting AFREZZA**
Before initiating AFREZZA, perform
 - a detailed medical history
 - physical examination, and
 - spirometry (FEV₁)

Important Safety Notice

The FDA has required MannKind Corporation to distribute this safety notice to your organization as part of the AFREZZA REMS (Risk Evaluation and Mitigation Strategy) program. We request that you inform your members about the following **serious risks of AFREZZA**:

- **Risk of Acute Bronchospasm in Patients with Chronic Lung Disease.** Prescribers should counsel their patients to inform them if they have a history of lung disease. AFREZZA should not be used in patients with chronic lung disease
- **Appropriate Patient Selection.** AFREZZA is contraindicated in patients with chronic lung disease such as asthma or chronic obstructive pulmonary disease (COPD)
- **Patient Evaluation Before Initiating Therapy.** Before initiating, prescribers must perform a detailed medical history, physical examination, and spirometry (FEV₁) in all patients to identify potential underlying lung disease

A non-promotional factsheet, reviewed by the FDA, with more detailed safety information on these risks, and a link to the Prescribing Information including the BOXED WARNING are available at www.AfrezzaREMS.com.

Indication: AFREZZA (insulin human) Inhalation Powder is a rapid acting inhaled insulin indicated to improve glycemic control in adult patients with diabetes mellitus.

Important limitations of use:

- Not a substitute for long-acting insulin. In patients with type 1 diabetes, must use with a long-acting insulin
- Not recommended for the treatment of diabetic ketoacidosis
- Not recommended in patients who smoke or have recently stopped smoking

This letter does not contain the complete safety profile for AFREZZA. Please visit www.AfrezzaREMS.com for more information.

Signature,

From: MannKind
To: Professional Societies
Subject: Risk of acute bronchospasm with AFREZZA in patients with chronic lung disease



AFREZZA[®] REMS

FDA Required REMS Safety Information

- **Risk of acute bronchospasm in patients with chronic lung disease**
 - Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA
 - **Contraindicated in patients with chronic lung disease such as asthma or COPD**
 - **Need to evaluate all patients for lung disease before starting AFREZZA**
- Before initiating AFREZZA, perform**
- a detailed medical history
 - physical examination, and
 - spirometry (FEV₁)

Important Safety Notice

The FDA has required MannKind to distribute this safety notice to your organization as part of their AFREZZA REMS (Risk Evaluation and Mitigation Strategy) program. We request that you inform your members about the following **serious risks of AFREZZA**:



- **Risk of acute bronchospasm in patients with chronic lung disease**
- **Contraindicated in patients with chronic lung disease such as asthma or COPD**
- **Need to evaluate patients for lung disease before starting AFREZZA**

A non-promotional factsheet, reviewed by the FDA, with more detailed safety information on these risks, and a link to the Prescribing Information including the BOXED WARNING are available at www.AfrezzaREMS.com.

Indication:

AFREZZA (insulin human) Inhalation Powder is a rapid acting inhaled insulin indicated to improve glycemic control in adult patients with diabetes mellitus.

Important limitations of use:

- Not a substitute for long-acting insulin. In patients with type 1 diabetes, must use with a long-acting insulin
- Not recommended for the treatment of diabetic ketoacidosis
- Not recommended in patients who smoke or have recently stopped smoking

This email does not contain the complete safety profile for AFREZZA. To review the Prescribing Information and Medication Guide, see links below:

[Prescribing Information](#)

[Medication Guide](#)

Please visit www.AfrezzaREMS.com for more information.

Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to MannKind Corporation at 1-877-323-8505 and/or the FDA www.fda.gov/medwatch, or call 1-800-FDA-1088.

Signature,



AFREZZA[®] (insulin human) Inhalation Powder REMS (Risk Evaluation and Mitigation Strategy)

FDA Required REMS* Safety Information

- **Risk of acute bronchospasm in patients with chronic lung disease**
 - Acute Bronchospasm has been observed in patients with asthma and COPD using AFREZZA
- **Contraindicated in patients with chronic lung disease such as asthma or COPD**
- **Need to evaluate all patients for lung disease before starting AFREZZA**
Before initiating AFREZZA, perform
 - a detailed medical history
 - physical examination, and
 - spirometry (FEV1)

Risk of Acute Bronchospasm in Patients with Chronic Lung Disease

- Counsel patients to inform their HCP if they have a history of lung disease
- Do not use in patients with chronic lung disease

Appropriate Patient Selection

AFREZZA is contraindicated in patients with chronic lung disease such as asthma or chronic obstructive pulmonary disease (COPD)

Patient Evaluation Before Initiating Therapy

- Before initiating, perform a detailed medical history, physical examination, and spirometry (FEV1) in all patients, to identify potential underlying lung disease

Indication

AFREZZA (insulin human) Inhalation Powder is a rapid acting inhaled insulin indicated to improve glycemic control in adult patients with diabetes mellitus

Important limitations of use:

- Not a substitute for long-acting insulin. In patients with type 1 diabetes, must use with a long-acting insulin
- Not recommended for the treatment of diabetic ketoacidosis
- Not recommended in patients who smoke or have recently stopped smoking

BOXED WARNING- Risk of Acute Bronchospasm in Patients with Chronic Lung Disease

- Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA
- AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD.
- Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV1) to identify potential lung disease in all patients



*What is the AFREZZA REMS?

A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. FDA has determined that a REMS is necessary to ensure that the benefits of AFREZZA outweigh the risks of acute bronchospasm in patients. This factsheet is required by the FDA as part of the AFREZZA REMS program. Please visit www.AfrezzaREMS.com for further information.

Reporting Adverse Events:

To report adverse events contact:

- MannKind Corporation at 1-877-323-8505 and/or
- FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

This factsheet does not contain the complete safety profile for AFREZZA. Please refer to the Prescribing Information, including Boxed Warning, for further information.

afrezza
(insulin human) Inhalation Powder

[Prescribing Information Including Boxed Warning](#)

[Medication Guide](#)

AFREZZA REMS (Risk Evaluation and Mitigation Strategy)

What is the AFREZZA REMS?

A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the Food and Drug Administration (FDA) to manage known or potential serious risks associated with a drug product.

The purpose of the AFREZZA REMS is to inform healthcare providers about the following risks of AFREZZA:

- Risk of acute bronchospasm in patients with chronic lung disease
- Contraindicated in patients with chronic lung disease such as asthma or COPD
- Need to evaluate all patients for lung disease before starting AFREZZA

Before initiating AFREZZA, perform

- a detailed medical history
- physical examination, and
- spirometry (FEV1)

A non-promotional factsheet, reviewed by the FDA, with more detailed safety information on these risks is available in the box to the right.

Materials for Healthcare Provider



AFREZZA REMS
Safety Information for
Providers Factsheet



REMS Letter to
Healthcare Providers



You are encouraged to report negative side effects of prescription drugs to MannKind Corporation at (1-877-323-8505) or FDA at (1-800-FDA-1088) or www.fda.gov/medwatch

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/s/

JOYCE P WEAVER
06/24/2014

CLAUDIA B MANZO
06/24/2014
concur

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

RISK EVALUATION AND MITIGATION STRATEGY REVIEW

Date:	June 19, 2014
Reviewer(s)	Joyce Weaver, Pharm.D., Risk Management Analyst Division of Risk Management (DRISK) Anahita Tavakoli, M.A., Health Communication Analyst, DRISK
Team Leader	Doris Auth, Pharm.D., Acting Team Leader, DRISK
Subject:	Review to provide REMS comments to the sponsor
Drug Name(s):	AFREZZA® (insulin human) Inhalation Powder
Therapeutic class & dosage form:	Antidiabetic Inhalation
OND Review Division	Division of Metabolism and Endocrinology Products
Application Type/Number:	NDA 022472, DARRTS Supporting Document #95
Submission received	June 17, 2014
PDUFA/Action Date	July 15, 2014
Applicant/sponsor:	MannKind Corporation
OSE RCM #:	2013-2342
TSI #:	n/a

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) provides comments to the sponsor on the modified REMS submission June 17, 2014.

Agency comments on the proposed communication plan REMS were sent to the sponsor June 13, 2014. The sponsor responded with a modified REMS proposal, incorporating most Agency comments. The modified REMS, REMS Supporting Document, and REMS materials were submitted June 17, 2014.

Afrezza is ultra-fast acting insulin administered via inhalation. The application has received two prior reviews from the Agency. The Agency issued a second complete response (CR) letter for this application on January 18, 2011. On October 15, 2013, MannKind Corporation resubmitted the application. The application is on a 6-month review schedule, extended by 3 months for a major amendment.

2 MATERIALS REVIEWED

We reviewed the following submitted June 17, 2014:

- Revised Risk Evaluation and Mitigation Strategy (REMS), DARRTS Supporting Document #95

2.1 PREVIOUS DRISK REMS REVIEWS

- November 23, 2009; M. Williams
- December 9, 2009; M. Williams
- October 24, 2011; J. Weaver
- March 25, 2014; J. Weaver
- June 13, 2014; J. Weaver

3 RESULTS OF REVIEW

We have additional comments and edits to the REMS, REMS materials, and REMS Supporting Document.

4 RECOMMENDATION

The comments below and the appended REMS document and materials should be sent to the sponsor. The sponsor should resubmit the REMS, REMS materials, and REMS Supporting Document with the changes requested by close of business Monday, June 23, 2014.

Comments for the sponsor:

- 1) Language in all REMS materials must reflect what is in final approved labeling.
- 2) We remind you that REMS materials are not appropriate to be used in a promotional manner.
- 3) The REMS Factsheet you submitted is not consistent with the other REMS materials. The REMS Factsheet we provided previously should be used instead of the REMS Factsheet you submitted June 17, 2014.
- 4) The timetable for submission of assessments as outlined in the REMS document, will not be adjusted if the launch of Afrezza is delayed.
- 5) REMS Supporting Document—The REMS Supporting Document should be edited to be consistent with final agreed-upon labeling.
- 6) See our edits on the REMS, the REMS materials, and the REMS Supporting Document. Make the required changes and submit the REMS, the REMS materials, and the REMS Supporting Document by close of business Monday, June 23, 2014.

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/s/

JOYCE P WEAVER
06/19/2014

DORIS A AUTH
06/19/2014

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

RISK EVALUATION AND MITIGATION STRATEGY REVIEW

Date: June 13, 2014

Reviewer(s) Joyce Weaver, Pharm.D., Risk Management Analyst
Division of Risk Management (DRISK)
Anahita Tavakoli, M.A., Health Communication Analyst,
DRISK

Team Leader Cynthia LaCivita, Pharm.D., Acting Director, DRISK

Division Director: Claudia Manzo, Pharm.D., Acting Director, Office of
Medication Error Prevention and Risk Management
(OMEPRM)

Subject: Review to document Afrezza REMS decision and to provide
REMS comments to the sponsor

Drug Name(s): AFREZZA® (insulin human) Inhalation Powder

Therapeutic class &
dosage form: Antidiabetic
Inhalation

OND Review Division Division of Metabolism and Endocrinology Products

Application Type/Number: NDA 022472

Application received October 10, 2013

PDUFA/Action Date July 15, 2014

Applicant/sponsor: MannKind Corporation

OSE RCM #: 2013-2342

TSI #: n/a

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) documents the Agency decision regarding the need for a Risk Evaluation and Mitigation Strategy (REMS) for Afrezza (insulin human) Inhalation Powder, a drug-device combination product. The application was the subject of an April 1, 2014 meeting of the FDA's Endocrinologic and Metabolic Drugs Advisory Committee. The committee endorsed approval of the application, but expressed concern regarding the safety issues associated with the product. The committee members expressed concern about the risk of bronchospasm in patients with chronic lung disease, the potential risk of lung cancer, and the potential risk of pulmonary function decline over time with long-term use.

Afrezza (insulin human) Inhalation Powder is a dry powder formulation of recombinant human insulin. The proposed indication for Afrezza is to improve glycemic control in adults with type 1 or type 2 diabetes mellitus. The applicant, MannKind Corporation, proposed a REMS comprising a communication plan for the product to address the risk of acute bronchospasm when used by patients with chronic lung disease.

1.1 BACKGROUND

Afrezza is ultra-fast acting insulin administered via inhalation. The application has received two prior reviews from the Agency. The Agency issued a second complete response (CR) letter for this application on January 18, 2011. On October 15, 2013, MannKind Corporation resubmitted the application. The application is on a 6-month review schedule, extended by 3 months for a major amendment.

1.2 REGULATORY HISTORY

The following are regulatory milestones for this application.

- Application submitted March 16, 2009; the application included a REMS comprising a Medication Guide and a communication plan.
- CR letter issued March 12, 2010 citing deficiencies in clinical (failure to demonstrate noninferiority), clinical pharmacology, chemistry, and device data in the submission

The CR letter cited a need for a REMS (required REMS elements not specified) to ensure that the benefits of the drug outweigh the risks of respiratory difficulty immediately post-inhalation, especially in patients with undiagnosed chronic lung disease, the risk of pulmonary function decline over time, and the potential risk of harm due to use by inappropriate patient populations, i.e., smokers and patients with chronic lung disease.

- Application resubmitted June 29, 2010; the resubmission included a Medication Guide-only REMS

- CR letter issued January 18, 2011 citing deficiencies in the clinical (failure to submit data for the device to be marketed,), inadequate adverse event data clinical pharmacology, product quality, and device data in the submission; the CR letter restated the need for a REMS, as stated in the previous CR letter
- Application resubmitted October 15, 2013
- Agency notified applicant October 28, 2013 that the October 15, 2013 submission was a complete, class 2 response to the action letter of January 18, 2011, and that the user fee goal date is April 15, 2014.
- April 1, 2014 meeting of the FDA’s Endocrinologic and Metabolic Drugs Advisory Committee to consider the application; the committee endorsed approval of the application
- Agency notified the applicant April 8, 2014 that the February 8, 2014 and February 28, 2014 submissions constituted a major amendment to the application, and the user fee goal date was extended to July 15, 2014

2 MATERIALS REVIEWED

We reviewed the following from the resubmission of October 15, 2013:

- Proposed Risk Evaluation and Mitigation Strategy (REMS)
- Technosphere Insulin Inhalation Powder 2013 Resubmission Safety Update
- Technosphere Insulin Inhalation System Human Factors Study Report
- Proposed draft labeling
- Discipline handouts and slides from the January 14, 2014 Mid-cycle Meeting for the application
- FDA background briefing document for the April 1, 2014 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee
- Sponsor background briefing document for the April 1, 2014 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee
- Slide sets for the April 1, 2014 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee
- NDA22472 Afrezza: Post Marketing Document; signed in DARRTS May 30, 2014 by R. Whitehead

Additionally, we reviewed the following:

- Applicant’s REMS submissions of March 16, 2009 (Medication Guide + communication plan REMS proposal), December 31, 2009 (response to OSE’s interim comments), and June 16, 2010 (Medication Guide REMS proposal)
- CR letters of March 12, 2010 and January 18, 2011
- Afrezza REMS Memo, March 5, 2010

- Afrezza Clinical Reviews, Lisa Yanoff, M.D., Division of Metabolic and Endocrine Products, December 24, 2009, and December 10, 2010
- Afrezza Cross Discipline Team Leader Clinical Review, Hylton V. Joffe, M.D., March 11, 2010
- Pulmonary Safety of Afrezza, consult from Banu Karimi-Shah, MD, Division of Pulmonary, Allergy, and Rheumatology Products, December 28, 2009 and December 13, 2010
- End-of-Review Meeting Package, March 15, 2011
- Division of Epidemiology Review of Exubera Cancer Risk, May 20, 2008
- Office of Prescription Drug Promotion (OPDP) review of REMS materials, Ankur Kalola, June 10, 2014

2.1 PREVIOUS DRISK REMS REVIEWS

- November 23, 2009; M. Williams
- December 9, 2009; M. Williams
- October 24, 2011; J. Weaver
- March 25, 2014; J. Weaver

3 RESULTS OF REVIEW

3.1 EFFICACY

An overview of the Afrezza development program and a summary of the efficacy findings were presented in DRISK's March 25, 2014 review. At the April 1, 2014 advisory committee meeting, the committee was asked to focus on two new efficacy trials submitted with the October 2013 resubmission. In the first trial, Afrezza was shown to be better than placebo in lowering HbA1c in patients with type 2 diabetes. In the second trial, Afrezza was inferior to insulin aspart in lowering HbA1c in patients with type 1 diabetes. A lack of Afrezza dose-response, a greater incidence of diabetic ketoacidosis in Afrezza-treated patients, and a lower incidence of hypoglycemia in Afrezza-treated patients were considered by the committee as potential efficacy issues with Afrezza.

3.2 SAFETY CONCERNS

The safety concerns for Afrezza were presented in our March 25, 2014 review. The risks previously described, and discussed at the April 1, 2014 advisory committee meeting, include acute bronchospasm immediately post-inhalation, especially in patients with undiagnosed chronic lung disease, pulmonary function decline over time with chronic use of Afrezza, and lung cancer.

There are insufficient data to draw conclusions concerning the potential risks of lung cancer and pulmonary function decline over time. These issues will be addressed with

post-marketing requirements (PMRs), and the preliminary information concerning these issues will be presented in the *Warnings and Precautions* section of the labeling.

A safety issue of concern with the possible widespread use of Afrezza is acute bronchospasm, especially in patients with chronic lung disease. A boxed warning is proposed to address this issue.

The proposed boxed warning¹ states, in part:

WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE

- Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA. (5.1)
- AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD. Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV₁) to identify potential lung disease in all patients. (2.1), (4), (5.1)

The draft language of Section 5.1 of the labeling states the following:

Because of the risk of acute bronchospasm, AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD [see *Contraindications* (4)].

(b) (4) initiating therapy with AFREZZA, evaluate all patients with a medical history, physical examination and spirometry (FEV₁) to identify potential underlying lung disease.

Acute bronchospasm, (b) (4). In this study, bronchoconstriction and wheezing following AFREZZA dosing was reported in 29% (5 out of 17) and 0% (0 out of 13) of patients with and without a diagnosis of asthma, respectively. (b) (4)

(b) (4) The long-term safety and efficacy of AFREZZA in patients with chronic lung disease has not been established.

3.3 RISK MANAGEMENT PROPOSED BY THE APPLICANT

The applicant proposed a REMS comprising a communication plan. The REMS included the following goals:

(b) (4)

The applicant proposes issuing a Dear Healthcare Provider Letter (DHCPL) to healthcare providers and professional societies involved in the treatment of patients with diabetes. The applicant proposes that the DHCPL convey the following key risk messages:

¹ Afrezza labeling is still being negotiated with the sponsor.

They propose that the letter be available on REMS website for (b) (4) from the date of the mailing.

DRISK reviewer comment: The proposed REMS addresses the risks cited in the previous CR letters. Following discussion at the advisory committee meeting, subsequent discussion within the Agency has focused the risk to be addressed in the REMS on the risk of acute bronchospasm in patients with underlying chronic lung disease, a risk that will be presented in a boxed warning. The REMS goal should be changed as below to reflect the risk that will be in the boxed warning:

The goal of the Afrezza REMS is to mitigate the risk of acute bronchospasm associated with Afrezza by:

- *informing healthcare providers that there is risk of acute bronchospasm associated with Afrezza in patients with chronic lung disease*
- *informing healthcare providers that acute bronchospasm has been observed with Afrezza in patients with asthma and COPD*
- *informing healthcare providers that Afrezza is contraindicated in patients with chronic lung disease*
- *informing healthcare providers of the need to evaluate patients for lung disease before starting on Afrezza*

To be consistent with the DRISK's current approach to communication plan REMS, the communication materials should comprise a REMS Letter for Healthcare Providers (print and electronic versions), a REMS Letter for Professional Societies (print and electronic versions), a REMS Factsheet, and a REMS website.

4 CONSIDERATION OF A REMS FOR AFREZZA

Although the advisory committee supported approval of the application, committee members expressed concern about the safety issues with the product. Following the advisory committee meeting, OND and OSE met to discuss risk mitigation for Afrezza. Team members were concerned that the use of Afrezza outside a clinical trial² would

² the protocols for the clinical trials included screening patients for lung disease and excluding patients with chronic lung disease

result in patients with chronic lung disease receiving the drug. Additionally, team members expressed concern that prescribers of insulin do not routinely need to consider lung function when prescribing insulin. Consideration of lung function when prescribing an insulin will be a change in practice for prescribers who prescribe Afrezza.

There was agreement among team members that a REMS comprising a communication plan would inform prescribers of the risk of acute bronchospasm if used by patients with chronic lung disease. The communication plan REMS would help ensure that the benefits of Afrezza outweigh its risks, without imposing undue access burden on prescribers and patients. A REMS with ETASU was considered, but the team believed a communication plan REMS would be sufficient to ensure that the benefits of Afrezza outweigh its risks, and an ETASU REMS was not warranted.

Risk messages

The primary risk message for HCPs is the risk presented in the boxed warning:

- There is risk of acute bronchospasm associated with Afrezza in patients with chronic lung disease.

Supporting risk messages are:

- Acute bronchospasm has been observed in patients with asthma and COPD using Afrezza.
- Afrezza is contraindicated in patients with chronic lung disease.
- HCPs should evaluate all patients for lung disease (a detailed medical history, physical examination, and spirometry (FEV1) to identify potential lung disease) before starting on Afrezza.

REMS goal

The Agency's proposed goals match the risk messages.

REMS communication pieces

The Agency proposes that the REMS include the following:

- *Afrezza REMS Letter for Healthcare Providers* (print and email versions, distributed within 60 days of REMS approval, and again after 1 year)
- *Afrezza REMS Letter for Professional Societies* (print and email versions, distributed within 60 days of REMS approval, and again after 1 year)
- *Afrezza REMS Factsheet* (distributed with the REMS letters, during detailing for a year after approval of the REMS, and at scientific meetings at which MannKind Corporation has a presence [i.e., booth])
- Afrezza REMS Website (www.AfrezzaREMS.com)

Timetable for submission of assessments

The sponsor will submit REMS Assessments to FDA at 18 months, 3 years, and 7 years from the date of the approval of the initial REMS.

Assessment plan

The REMS assessment plan should include the following:

1. REMS communication plan activities:
 - a. Number of healthcare providers and professional societies targeted by the REMS.
 - b. Number of REMS letters sent to healthcare providers and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via email because the mailed letter was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
 - c. Number of REMS Factsheets distributed to healthcare providers by sales representatives and medical liaisons during the reporting period.
 - d. Date the REMS website went live and number of total and unique site visits during the assessment period.
 - e. Names and dates of all scientific meetings during which REMS materials (REMS letters, REMS Factsheet) were distributed

2. Evaluation of healthcare providers' understanding of:
 - a. The risk of acute bronchospasm associated with Afrezza in patients with chronic lung disease
 - b. Acute bronchospasm has been observed in patients with asthma and COPD using Afrezza
 - c. Afrezza is contraindicated in patients with chronic lung disease
 - d. HCPs should evaluate all patients for lung disease (a detailed medical history, physical examination, and spirometry (FEV1) to identify potential lung disease) before starting on Afrezza

3. Afrezza utilization information including, but not limited to, indication for use and type of prescriber (i.e., endocrinologist, general practitioner, internist, etc.).

4. Safety surveillance:
 - a. Analysis of serious postmarketing case reports of bronchospasm received during the reporting period. Include in the analysis information on whether or not the patient was evaluated for lung disease before receiving Afrezza, and how the patient was evaluated for chronic lung disease (e.g., baseline FEV1, past medical history, physical examination)

- b. Analysis of postmarketing case reports of serious respiratory adverse events reported for patients with chronic lung disease during the reporting period. Include in the analysis information on whether or not the patient was evaluated for lung disease before receiving Afrezza, and how the patient was evaluated for chronic lung disease (e.g., baseline FEV1, past medical history, physical examination)

5 RECOMMENDATION

The comments below and the appended REMS document and materials should be sent to the sponsor. The sponsor should resubmit the REMS with the changes requested within one week.

Comments for the sponsor:

- 1) Language in all REMS materials must reflect what is in final approved labeling.
- 2) We remind you that REMS materials are not appropriate to be used in a promotional manner.
- 3) The REMS risk messages for healthcare providers within the REMS should be as follows—

The primary risk message is:

- There is risk of acute bronchospasm associated with Afrezza in patients with chronic lung disease.

Supporting risk messages are:

- Acute bronchospasm has been observed in patients with asthma and COPD using Afrezza.
- Afrezza is contraindicated in patients with chronic lung disease.
- HCPs should evaluate all patients for lung disease (a detailed medical history, physical examination, and spirometry (FEV1) to identify potential lung disease) before starting on Afrezza.

- 4) The REMS goal should be as follows—

The goal of the Afrezza REMS is to mitigate the risk of acute bronchospasm associated with Afrezza by:

- informing healthcare providers that there is risk of acute bronchospasm associated with Afrezza in patients with chronic lung disease
- informing healthcare providers that acute bronchospasm has been observed with Afrezza in patients with asthma and COPD

- informing healthcare providers that Afrezza is contraindicated in patients with chronic lung disease
 - informing healthcare providers of the need to evaluate patients for lung disease before starting on Afrezza
- 5) REMS communication materials (REMS letters, REMS Factsheet, and a REMS website).
- a) REMS Letters—Replace the standard Dear Healthcare Provider (DHCP) letter with concise, risk-focused REMS letters addressed to HCPs and relevant Professional Societies. The REMS letters should be formatted in two different ways: print and electronic versions. The electronic version of the REMS letters should be email- and handheld device-friendly. The objective of these changes is to improve the communication of the risk message among the growing HCP population of hand-held device users. The subject of the emails should be “Risk of acute bronchospasm with Afrezza in patients with chronic lung disease”. The outside of the mailed envelopes should state: "FDA Required REMS Safety Information: it should be printed in red, bolded, and a minimum size 14 font. It may be on two lines and should be boxed, for example:

**FDA Required REMS
Safety Information**

See proposed print and electronic REMS letter templates attached.

- b) REMS Factsheet for HCPs. This REMS Factsheet must be in a user-friendly format, including coloring, and any logos from Afrezza's REMS program; include bullets, boxes, and bold text to highlight important information; should have plenty of white space and a font size of at least 12; be printed on thicker card stock paper; be only one sheet with information on both sides of paper and heading should read: FDA Required Afrezza REMS Safety Information.

Key messages to include on fact sheet include a brief REMS explanation and the risks from the boxed warning, including:

The primary risk message for HCPs is—

- There is risk of acute bronchospasm associated with Afrezza in patients with chronic lung disease.

Supporting risk messages are —

- Acute bronchospasm has been observed in patients with asthma and COPD using Afrezza.
- Afrezza is contraindicated in patients with chronic lung disease.

- HCPs should evaluate all patients for lung disease (a detailed medical history, physical examination, and spirometry (FEV1) to identify potential lung disease) before starting on Afrezza.
- c) REMS Website—Ensure the REMS website is independent of links to the promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the REMS website back to the commercial website. The REMS website should also be accessible directly through a search engine. The REMS website, including all REMS materials (REMS letters, REMS factsheet) will be available for the duration of the REMS.

Submit screen shots and actual layout for the Afrezza REMS website.

We ask you to use bullets, moderate white space, short line lengths, and few lines of text when possible when developing your website. The following is a link to helpful guidelines developed by HHS that you may consider in developing your website.

http://www.usability.gov/sites/default/files/documents/guidelines_book.pdf?post=yes

See proposed REMS website template attached.

6) REMS Assessment Reports—

The REMS assessment plan should include the following:

a. REMS communication plan activities:

- i. Number of healthcare providers and professional societies targeted by the REMS.
- ii. Number of REMS letters sent to healthcare providers and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via email because the mailed letter was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
- iii. Number of REMS Factsheets distributed to healthcare providers by sales representatives and medical liaisons during the reporting period.
- iv. Date the REMS website went live and number of total and unique site visits during the assessment period.
- v. Names and dates of all scientific meetings during which REMS materials (REMS letters, REMS Factsheet) were distributed

b. Evaluation of healthcare providers' understanding of:

- i. The risk of acute bronchospasm associated with Afrezza in patients with chronic lung disease
- ii. Acute bronchospasm has been observed in patients with asthma and COPD using Afrezza
- iii. Afrezza is contraindicated in patients with chronic lung disease

- iv. HCPs should evaluate all patients for lung disease (a detailed medical history, physical examination, and spirometry (FEV1) to identify potential lung disease) before starting on Afrezza
 - c. Afrezza utilization information including, but not limited to, indication for use and type of prescriber (i.e., endocrinologist, general practitioner, internist, etc.).
 - d. Safety surveillance:
 - i. Analysis of serious postmarketing case reports of bronchospasm received during the reporting period. Include in the analysis information on whether or not the patient was evaluated for lung disease before receiving Afrezza, and how the patient was evaluated for chronic lung disease (e.g., baseline FEV1, past medical history, physical examination)
 - ii. Analysis of postmarketing case reports of serious respiratory adverse events reported for patients with chronic lung disease during the reporting period. Include in the analysis information on whether or not the patient was evaluated for lung disease before receiving Afrezza, and how the patient was evaluated for chronic lung disease (e.g., baseline FEV1, past medical history, physical examination)
- 7) REMS Supporting Document—The REMS Supporting Document should be edited to be consistent with labeling and the REMS. The REMS Assessment Plan should be included in the REMS Supporting Document.

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/s/

JOYCE P WEAVER
06/13/2014

CLAUDIA B MANZO
06/13/2014
concur

Internal Consult

Pre-decisional Agency Information

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Anahita Tavakoli, Health Communications Analyst, DRISK

From: Ankur Kalola, Regulatory Review Officer

CC: Ankur Kalola, Regulatory Review Officer
Adora Ndu, Acting Team Leader
Lyle Canida, SRPM, OSE
Cynthia LaCivita, Team Leader, DRISK
Joyce Weaver, Risk Management Analyst, DRISK
Kate Heinrich Oswell, Health Communications Analyst, DRISK
Carole Broadnax, CDER-OPDP-RPM
Michael Wade, RPM, OPDP

Date: June 10, 2014

Re: NDA 022472
Afrezza[®] (insulin human) Inhalation Powder
Comments on draft Risk Evaluation and Mitigation Strategies (REMS)
Materials (Submission date: June 4, 2014)

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for Afrezza:

- Healthcare Provider (HCP) REMS Materials:
 - REMS letter for Healthcare Professionals (print version)

- REMS letter for Professional Societies (print version)
- REMS letter for Healthcare Professionals and Professional Societies (email versions)
- Afrezza REMS Fact Sheet
- Afrezza REMS Website Landing Page

The version of the draft REMS materials used in this review was emailed by Anahita Tavakoli on June 4, 2014, and is attached to the end of this review.

The version of the proposed draft Prescribing Information (PI) used in this review, entitled "draft-labeling-text-word_MannKind Edits 30 may 2014," was obtained from Microsoft SharePoint on June 5, 2014, and is attached to the end of this review.

OPDP offers the following comments on these draft REMS materials for Afrezza.

General Comment

Please remind MannKind Corporation (MannKind) that REMS materials are not appropriate for use in a promotional manner.

OPDP notes that the Afrezza PI is still being reviewed and modified. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved PI.

OPDP cannot comment on place holders such as "www.AfrezzaREMS.com" or "taglines/logos" (located on the website landing page). However, we recommend that these items not be promotional in tone and that any links represent a direct link to only REMS related information. Furthermore, we remind MannKind that the REMS specific website should not be the sole source of approved REMS materials.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- REMS letter for Healthcare Professionals (print version)
- REMS letter for Professional Societies (print version)
- REMS letter for Healthcare Professionals and Professional Societies (email versions)
- Afrezza REMS Fact Sheet
- Afrezza REMS Website Landing Page

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising or deleting them from the REMS piece:

- **REMS letter for Healthcare Professionals (print version), REMS letter for Professional Societies (print version), REMS letter for Healthcare Professionals and Professional Societies (email versions), and REMS Fact Sheet**

- OPDP is concerned that the section of these REMS materials entitled **“Important Limitations of Use”** (emphasis original) implies that these are the full limitations for use for Afrezza; however, it omits material information from the full limitations of use for Afrezza. Specifically, the Indications and Usage section of the draft PI states the following (in pertinent part; emphasis added):

- AFREZZA is not a substitute for long-acting insulin.
- The safety and efficacy of AFREZZA in patients who smoke has not been established. The use of AFREZZA is not recommended in patients who smoke or have recently stopped smoking.

OPDP recommends revising the **“Important Limitations of Use”** (emphasis original) section of these REMS materials to communicate this material information.

- OPDP is also concerned that these materials minimize the risks associated with Afrezza by omitting important material information from the PI regarding the risk of acute bronchospasm in patients with chronic lung disease. Specifically, the Warnings and Precautions section of the PI states, “In this study, bronchoconstriction and wheezing following AFREZZA dosing was reported in 29% (5 out of 17) and 0% (0 out of 13) of patients with and without a diagnosis of asthma, respectively.” OPDP recommends revising these materials to include this important material information in a manner consistent with the draft PI.

- **REMS letter for Healthcare Professionals (print version), REMS letter for Professional Societies (print version), REMS letter for Healthcare Professionals and Professional Societies (email versions), REMS Website Landing Page**

- (b) (4)
(emphasis original)

- OPDP is concerned that this statement minimizes the risks associated with Afrezza by omitting important material information from draft PI regarding the risk of acute bronchospasm in patients with chronic lung disease.

Specifically, the Boxed Warning in the PI states, “**Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA**” (bolded emphasis original; underlined emphasis added). OPDP recommends revising these materials to include this important material information in a manner consistent with the draft PI.

- **REMS letter for Healthcare Professionals (print version), REMS letter for Professional Societies (print version), REMS letter for Healthcare Professionals and Professional Societies (email versions)**

- OPDP is concerned that these REMS materials may minimize the risks associated with Afrezza by omitting important material information from draft PI regarding the risk of acute bronchospasm in patients with chronic lung disease. Specifically, the Boxed Warning in the draft PI is titled “RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE” (emphasis original). Because these REMS materials fail to include this title, OPDP is concerned that these materials may not clearly convey that this risk is associated with all chronic lung diseases and is not just limited to asthma or COPD. Therefore, OPDP recommends revising these materials to include this important material information in a manner consistent with the draft PI.

- **REMS letter for Healthcare Professionals (print version), REMS letter for Professional Societies (print version) and REMS Fact Sheet**

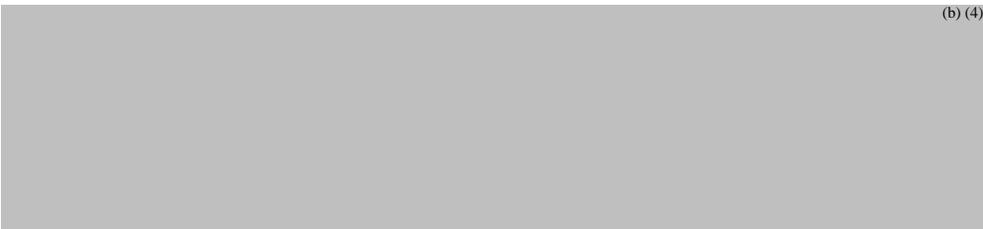
- “ (b) (4) **Patient Selection.** (b) (4)
[Redacted]

- OPDP is concerned that the header (b) (4) **Patient Selection**” in conjunction with the contraindication statement may imply that Afrezza is only contraindicated in patients with chronic lung disease. However, as stated in the Contraindications section of the PI, Afrezza is also contraindicated during episodes of hypoglycemia and in patients with hypersensitivity. We are also concerned that the header does not alert the reader that important risk information regarding the contraindication for Afrezza will follow. Therefore, OPDP recommends revising this presentation.

- **REMS letter for Healthcare Professionals and Professional Societies (email versions)**

-  (b) (4)
 - OPDP is concerned that this statement minimizes the risks associated with Afrezza by omitting important material information from draft PI regarding the risk of acute bronchospasm in patients with chronic lung disease. Specifically, the Boxed Warning in the PI states, “**Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV1) to identify potential lung disease in all patients**” (emphasis original). OPDP recommends revising these materials to include this important material information in a manner consistent with the draft PI.

- **REMS letter for Healthcare Professionals and Professional Societies (email versions); REMS letter for Professional Societies (print version)**

-  (b) (4)
- 
- OPDP is concerned that these statements imply that the Fact Sheet and the “www.AfrezzaREMS.com” website will provide a more comprehensive presentation of all of the risks associated with the drug; however, the Fact Sheet and website only disclose some risk information from the draft PI regarding the potential risk of acute bronchospasm in patients with chronic lung disease. OPDP recommends revising these statements to more accurately communicate the risk information that is conveyed in the Fact Sheet and website.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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/s/

ANKUR S KALOLA
06/10/2014

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
RISK EVALUATION AND MITIGATION STRATEGY REVIEW**

Date: March 25, 2014

Reviewer(s) Joyce Weaver, Pharm.D., Risk Management Analyst
Division of Risk Management (DRISK)

Team Leader Cynthia LaCivita, Pharm.D., Team Leader, DRISK

Division Director: Claudia Manzo, Pharm.D., Director, DRISK

Subject: Review to determine if a REMS is necessary

Drug Name(s): Afrezza (Technosphere Insulin Inhalation System)

Therapeutic class & dosage form: Antidiabetic
Inhalation

OND Review Division Division of Metabolism and Endocrinology Products

Application Type/Number: NDA 022472

Application received October 10, 2013

PDUFA/Action Date April 10, 2014

Applicant/sponsor: MannKind Corporation

OSE RCM #: 2013-2342

TSI #: n/a

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) provides a preliminary assessment of the need for a Risk Evaluation and Mitigation Strategy (REMS) for Afrezza (insulin human [rDNA origin]) Inhalation Powder, the Afrezza Technosphere Insulin Inhalation System. The application will be the subject of the April 1, 2014 meeting of the FDA's Endocrinologic and Metabolic Drugs Advisory Committee. DRISK will consider the advice of the Advisory Committee and the issue of a REMS for this product again following this meeting.

Afrezza Technosphere Insulin Inhalation Powder is a dry powder formulation of recombinant human insulin that contains the excipient, fumaric acid dihydrate (FDKP). The proposed indication for Afrezza is to improve glycemic control in adults with type 1 or type 2 diabetes mellitus. The applicant, MannKind Corporation, proposed a REMS comprising a communication plan for the product.

1.1 BACKGROUND

Afrezza is ultra-fast acting insulin administered via inhalation. The application has received two prior reviews from the Agency. The Agency issued a second complete response (CR) letter for this application on January 18, 2011. On October 15, 2013, MannKind Corporation resubmitted the application. The application is on a 6-month review schedule.

1.2 REGULATORY HISTORY

The following are regulatory milestones for this application.

- Application submitted March 16, 2009; the application included a REMS comprising a Medication Guide and a communication plan.
- CR letter issued March 12, 2010 citing deficiencies in clinical (failure to demonstrate noninferiority), clinical pharmacology, chemistry, and device data in the submission

The CR letter cited a need for a REMS (required REMS elements not specified) to ensure that the benefits of the drug outweigh the risks of respiratory difficulty immediately post-inhalation, especially in patients with undiagnosed chronic lung disease, the risk of pulmonary function decline over time, and the potential risk of harm due to use by inappropriate patient populations, i.e., smokers and patients with chronic lung disease.

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Additionally, we reviewed the following:

- Applicant's REMS submissions of March 16, 2009 (Medication Guide + communication plan REMS proposal), December 31, 2009 (response to OSE's interim comments), and June 16, 2010 (Medication Guide REMS proposal)
- DRISK REMS reviews of November 23, 2009 (interim comments) and January 22, 2010 (deferral memo)
- DRISK Memo to File October 24, 2011
- CR letters of March 12, 2010 and January 18, 2011
- Afrezza REMS Memo, March 5, 2010
- Afrezza Clinical Reviews, Lisa Yanoff, M.D., Division of Metabolic and Endocrine Products, December 24, 2009, and December 10, 2010
- Afrezza Cross Discipline Team Leader Clinical Review, Hylton V. Joffe, M.D., March 11, 2010
- Pulmonary Safety of Afrezza, consult from Banu Karimi-Shah, MD, Division of Pulmonary, Allergy, and Rheumatology Products, December 28, 2009 and December 13, 2010.
- End-of-Review Meeting Package, March 15, 2011
- Division of Epidemiology Review of Exubera Cancer Risk, May 20, 2008.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF DEVELOPMENT PROGRAM¹

Safety and efficacy were assessed in trials using endpoints of hemoglobin A1c, fasting blood glucose, post-prandial glucose, hypoglycemia, and changes in body weight. The previously submitted efficacy trials are presented in Dr. Yanoff's clinical reviews of December 24, 2009, and December 10, 2010. Two new efficacy trials with the to-be-marketed device were submitted to support the resubmission, one trial conducted in patients with type 1 diabetes, and the other trial conducted in patients with type 2 diabetes. As in the previous Afrezza trials, the trials excluded current smokers and patients with chronic lung disease.

Afrezza (n=174) was compared to subcutaneously administered insulin aspart (n=170) in patients with type 1 diabetes. All patients also received long acting basal insulin. At the end of 24 weeks, the reductions in hemoglobin A1c in the Afrezza patients were non-inferior to the insulin aspart group. The fasting blood glucose and the hypoglycemic event rate were lower in the Afrezza-treated group. Between group weight difference was -1.32 kg in the Afrezza group.

Afrezza (n=177) was compared to placebo (n=176) in adult patients with type 2 diabetes "suboptimally controlled on optimal/maximally tolerated doses of metformin only, or 2 or more oral antidiabetic (OAD) agents." At the end of the 24-week study period, the mean change in hemoglobin A1c in the Afrezza group was statistically superior to the placebo group. The reduction in fasting glucose was 7.42 mg/dL lower in the Afrezza group. Patients receiving Afrezza gained weight (1.62 kg difference between the groups) compared to patients receiving placebo. The hypoglycemic event rate was higher in patients receiving Afrezza.

3.2 SAFETY CONCERNS

Safety concerns (other than pulmonary concerns) for Afrezza are presented in Dr. Yanoff's clinical reviews of December 24, 2009, and December 10, 2010. Pulmonary safety concerns were reviewed by Banu Karimi-Shah, MD, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) in reviews of December 28, 2009 and December 13, 2010. Most of the data currently available were reviewed in the 2009 reviews.

Dr. Yanoff focused her 2009 safety review on hypoglycemia, cardiovascular events, neoplasms, and immunogenicity. She found that the rates of hypoglycemia were comparable between Afrezza and insulin comparators except for in one trial in which the rate of severe hypoglycemia was lower for Afrezza. She found no safety signal for cardiovascular risk. No safety signal for any type of malignancy was seen in the clinical development program, although she noted that a lack of a neoplasm signal in the clinical development program did not dispel the concern for this event, because a possible signal had been observed in Exubera inhaled insulin data. Dr. Yanoff did not change her assessment of the safety of Afrezza in her 2010 review.

¹ Information on efficacy from resubmission supplied by applicant.

Dr. Karimi-Shah focused on serious pulmonary adverse events occurring in the trials. Such events in patients with type 1 diabetes included bronchial obstruction, cough, and hemoptysis. Serious pulmonary adverse events reported in patients with type 2 diabetes included asthma, atelectasis, dyspnea, pulmonary edema, respiratory failure, pneumonia, and pulmonary tuberculosis. There were no serious pulmonary adverse events that occurred in more than one subject in the Afrezza group and more commonly than in the comparator group. Analysis of the respiratory serious adverse events did not demonstrate a pulmonary safety signal with use of Afrezza.

In 2010, Dr. Karimi-Shah reviewed the pulmonary safety data submitted for the second review cycle for this application. Dr. Karimi-Shah did not find a pulmonary signal in the resubmission, but the lack of data in the submission with the to-be-marketed device rendered a full safety evaluation impossible. She recommended additional safety data with the to-be-marketed device.

The CR letters issued in 2009 and 2010 cited a need for a REMS (required REMS elements not specified) to ensure that the benefits of the drug outweigh the risks of

- respiratory difficulty immediately post-inhalation, especially in patients with undiagnosed chronic lung disease
- pulmonary function decline over time
- potential risk of harm due to use by inappropriate patient populations, i.e., smokers and patients with chronic lung disease

Respiratory difficulty immediately post-inhalation, especially in patients with undiagnosed chronic lung disease

The applicant found 8 of 1026 patients with type 1 diabetes in the pivotal trial experienced wheezing, bronchospasm, or throat tightness post-inhalation. All the patients experienced the events in trials with the previous, not-to-be-marketed device. No patients experienced these events in the small trials with the to-be-marketed device (overall, 351 patients were exposed to Afrezza in the two trials with the to-be-marketed device).

Nineteen of 2,281 patients with type 2 diabetes experienced such events, with 2 of the patients experiencing the events with the to-be-marketed device. Overall, in trials for type 1 diabetes and type 2 diabetes, wheezing was the most frequently occurring event, with 17 patients experiencing wheezing. The applicant assessed these events as not being related to hypersensitivity, but rather likely caused by locally irritating effects of inhaling a dry powder.

Dr. Karimi-Shah concluded that Afrezza causes cough and occasional bronchospasm, particularly in patients with underlying lung disease, such as asthma. Cough was the most common adverse event in the clinical trials, occurring in 25-30% of patients using Afrezza. Although cough was generally mild, and decreased over time, cough was the reason for discontinuation in approximately 3% of patients treated with Afrezza.

There were a number of other respiratory adverse events reported that suggested irritation of the upper respiratory tract including, asthma, bronchial hyperreactivity, bronchospasm, dyspnea, laryngospasm, throat irritation, throat tightness, and wheezing. Dr. Karimi-Shah noted in her 2009 review that [REDACTED] ^{(b) (4)} the excipient FDKP might contribute to airway irritation and cough.

The applicant conducted serial pulmonary testing starting immediately post-inhalation of Afrezza in a small number of patients with underlying pulmonary disease. They followed 22 asthmatic patients for 2 hours, and 8 patients with chronic obstructive pulmonary disease (COPD) for 4 hours, and they compared these patients to patients without underlying pulmonary disease. In patients without asthma, a mean decline in forced expiratory volume in 1 second (FEV1) up to 90mL-138mL after inhalation of Afrezza was noted. Dr. Karimi-Shah noted that this decline in FEV1 is not large enough to cause symptoms in someone without lung disease.

In asthmatic patients, FEV1 declined approximately 400 mL when measured 15 minutes after administering Afrezza. When measured at 2 hours, the FEV1 had recovered to close to baseline. Patients with COPD had a smaller decline in FEV1 (200 mL) which recovered over 4 hours toward baseline.

In 2009, the applicant attempted to more thoroughly evaluate Afrezza in subjects with asthma and COPD, beyond this preliminary exploration of Afrezza exposure in a small number of patients with asthma and COPD. The local data safety monitoring board (DSMB) with oversight for the trial was concerned about the potential risks for acute bronchoconstriction and pulmonary exacerbations associated with this product in this subpopulation of patients. On May 28, 2009, the DSMB recommended that the applicant stop enrollment of patients with underlying lung disease.

Pulmonary function decline over time

The data showed larger declines in FEV1 in patients with both type 1 and type 2 diabetes treated with Afrezza compared to control patients. The treatment differences were small (40-50 mL). The differences appeared within the first 3 months of treatment and persisted for the 2-year observation period, with a mean treatment difference of -40 mL at 2 years. It is not clear whether or not this decline in FEV1 is reversible.

Potential risk of harm due to use by inappropriate patient populations, i.e., smokers and patients with chronic lung disease

Although preliminary testing that the applicant conducted using serial pulmonary testing post-inhalation of Afrezza in a small number of patients with underlying pulmonary disease showed a potential for compromise of pulmonary function in such patients, there are insufficient data to establish the risks and benefits of Afrezza for patients with underlying chronic lung disease. A 2009 trial was halted after the DSMB recommended that the applicant stop enrollment of patients with underlying lung disease.

Similar to insufficient data for safety and effectiveness in patients with underlying pulmonary disease, there are insufficient data for safety and effectiveness in smokers because current smokers were excluded from the pivotal clinical trials. Smoking up to 6

months prior to study entry was an exclusion criterion for the clinical trials; however, former smokers with a more remote smoking history were enrolled. Twenty-nine percent of patients in the clinical development program were past smokers. There was not an analysis comparing pulmonary adverse event data for the patients with a remote smoking history compared to patients who never smoked.

Concerns about use of Afrezza by smokers are:

1. Altered bioavailability of Afrezza in smokers; according to testing conducted in a few smokers (n=12 smokers compared to n=12 non-smokers), smoking increases the exposure to insulin by about 25%. This could possibly lead to hypoglycemic events for some patients. The clinical pharmacology reviewer, Dr. Sang Chung, recommended that the labeling include a statement for cautious dose titration in smokers to prevent hypoglycemic events.
2. Exacerbation of underlying pulmonary disease in smokers; underlying pulmonary disease is more likely in smokers. As noted previously, there are few data relevant to patients with underlying pulmonary disease, including in smokers.
3. Development of lung tumors or stimulation of occult lung tumors in smokers; concern over a cancer risk for Afrezza is based on the occurrence of a cancer signal for Exubera, a previously marketed inhaled insulin. The following information is from a 2008 review by Dr. Cynthia Kornegay from the Division of Epidemiology, Office of Surveillance and Epidemiology:

“At the time of approval of Exubera there were three cases of malignant neoplasm of the lung in individuals exposed to Exubera versus one in a non-exposed patient. In December 2007, the sponsor submitted an information update for clinical trials that described nine cases of lung cancer, eight of which were in patients exposed to inhaled insulin. Of these eight cases, six are thought to be potentially directly associated with Exubera exposure.”

Dr. Kornegay characterized the data as “somewhat compelling” but “quite preliminary.”

The following warning about cancer was added to Exubera’s labeling:

"In clinical trials of Exubera, there have been 6 newly diagnosed cases of primary lung malignancies among Exubera-treated patients, and 1 newly diagnosed case among comparator-treated patients. There has also been 1 postmarketing report of a primary lung malignancy in an Exubera-treated patient. In controlled clinical trials of Exubera, the incidence of new primary lung cancer per 100 patient-years of study drug exposure was 0.13 (5 cases over 3800 patient-years) for Exubera-treated patients and 0.03 (1 case over 3900 patient-years) for comparator-treated patients. There were too few cases to determine whether the emergence of these events is related to Exubera. All patients who were diagnosed with lung cancer had a prior history of cigarette smoking."

The Follow-Up Study of patients previously enrolled in Exubera controlled clinical trials (FUSE), an observational study funded by Pfizer found a non-significant trend toward increased risk of lung cancer in patients exposed to the inhaled insulin Exubera, compared to control patients.²

Dr. Patricia Bright, an epidemiologist with the Division of Epidemiology 1 summarized the findings from the FUSE study.³

Exubera (Insulin Human [rDNA origin] Inhalation Powder) was approved by the FDA in January 2006 to improve glycemic control in adults with type 1 and type 2 diabetes. Exubera was later withdrawn by the sponsor (Pfizer) due to lower than expected sales.

At the time of the NDA filing in 2006, there was a known imbalance in lung cancers in Exubera-exposed participants in clinical trials. By 2008, this imbalance had increased to 5 cases of incident lung cancer per 3,846 person-years (PYs) in Exubera-exposed patients and 1 case of incident lung cancer per 3,925 PYs in comparator patients, yielding a crude hazard ratio (HR) of 5.1 (95% CI: 0.71 - 121.4). Comparator patients across 17 trials had been randomized to standard of care (ranging from no treatment to subcutaneous insulin). All of the patients who developed lung cancer had type 2 diabetes mellitus (DM), were over 55 years of age, and were previous smokers.

The sponsor suggested that the imbalance may have resulted, in part, from detection bias. Most of the 17 trials were open label (not blinded to exposure) since Exubera use required a novel route of administration, and cough was a common side effect – which could have led to more thorough or frequent pulmonary assessments in exposed patients.

To further assess lung cancer risk, the sponsor conducted a follow-up study (referred to as FUSE) of participants who had been exposed to Exubera and comparison medications in pre-approval clinical trials and to standard of care after trial completion.

Study results are based on the final study report submitted to the FDA and Pfizer slides⁴ from an August 24, 2012, presentation on FUSE. The study results included the following:

- Overall, 7,439 subjects contributed retrospective data to the study; however, only 2,536 (34%) of original participants completed the FUSE prospective portion.
- Smoking history was generally balanced across the prospective 1,356 Exubera patients and 1,271 comparators for percentage of former smokers and pack-years.

² <http://clinicaltrials.gov/show/NCT00734591>. Accessed December 31, 2013.

³ Dr. Bright; March 4, 2014.

⁴ Source: Gatto NM, Koralek DO, Bracken MB, Duggan WT, Lem J, Klioze SS, Jackson NC. Comparative lung cancer mortality with inhaled insulin or comparator: FUSE final results. ICPE, August 24, 2012.

- Primary lung cancer mortality – Six cases were reported in 12,605.9 PYs in the Exubera group and 2 cases in 11,802.5 PYs in the comparator group. The incidence density ratio (IDR) was 2.81 (95% CI: 0.50 - 28.46).
- Primary lung cancer incidence – Twelve cases were reported in 11,180.7 PYs in the Exubera group and 3 cases in 10,467.9 PYs in the comparator group. The IDR was 3.75 (95% CI: 1.01 - 20.68).
- All-cause mortality -- The estimated rate was 6.0 per 1,000 PYs (76 deaths in 12,605.9 PYs) in the Exubera group and 7.4 per 1000 PYs (87 deaths in 11,802.5 PYs) in the comparator group. The hazard ratio (HR) was 0.81 (95% CI: 0.60 - 1.10).

Study limitations included the low participation of sites and patients, potential for detection and reporting biases, and the small number of cases.

3.3 RISK MANAGEMENT PROPOSED BY THE APPLICANT

The applicant proposed a REMS comprising a communication plan. The REMS included the following goals:

(b) (4)

The applicant proposes issuing a Dear Healthcare Provider Letter (DHCPL) to healthcare providers and professional societies involved in the treatment of patients with diabetes. The applicant proposes that the DHCPL convey the following key risk messages:

(b) (4)

They propose that the letter be available on REMS website for (b) (4) from the date of the mailing.

DRISK reviewer comment: The proposed REMS addresses the risks cited in the previous CR letters.

4 DISCUSSION OF A REMS FOR AFREZZA

Several risk management approaches were discussed and included; no REMS, boxed warning and no REMS, and a communication plan in the absence of a risk requiring a boxed warning. There was agreement that the risks do not require a REMS with ETASU at this time. The Food and Drug Amendments Act of 2007 gives the Agency the authority to require a REMS if the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) together determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks. A REMS may be required if labeling alone will not be sufficient to mitigate the risks, and use of a REMS will favorably affect the risk–benefit balance of the drug to allow approval of the drug.

The applicant's proposed labeling does not include

(b) (4)

Although the clinical review of the safety data is not complete, at this time medical officers reviewing the data believe that the *Contraindications* and the *Warnings and Precautions* sections of the labeling will be used to relay the risk information summarized above. At this time the medical officers consulted in the Division of Pulmonary, Allergy, and Rheumatology Products do not believe that these risks rise to the level of a boxed warning. Despite the preliminary assessment that none of the risks are serious enough to merit a boxed warning, the medical officers believe a REMS with a communication plan should be considered because the pulmonary risks addressed by the proposed REMS are risks that would be unusual for prescribers of antidiabetic products to consider and manage.

DRISK's experiences to date with REMS show that it is challenging to mitigate serious drug risks with communication plans in general. We believe it is additionally challenging when the risk messages are not supported with strong labeling or when the risk messages are unclear. REMS with communication plans were used for serious risks of the anti-diabetic agents, exenatide (Byetta, and Bydureon), and liraglutide (Victoza), each with a theoretical risk for thyroid C-cell tumors and an established risk of pancreatitis. The REMS assessments for these REMS show low prescriber awareness of REMS materials, including the DHCPLs distributed within the REMS. The REMS for romiplostim (Nplate) changed from a REMS with ETASU to a communication plan. The awareness of the risk messages fell after the requirement for prescriber training on the risks was removed from the REMS.

The risks of Afrezza and the measures needed to manage the risks were considered in a meeting that included the review team and senior CDER management on March 18, 2014. The risks to be addressed in the REMS would include the pulmonary risks. There was agreement that there is insufficient evidence of a cancer signal for Afrezza to include cancer in the REMS. Members of the group voiced differing opinions on the most

appropriate strategy to manage the risk. Several options were discussed and included; no REMS, boxed warning and no REMS, and a communication plan in the absence of a risk requiring a boxed warning. There was consensus that the risks do not warrant ETASU at this time.

5 CONCLUSION/RECOMMENDATION

A final determination has not been made about the risk management appropriate for Afrezza. The application will be the subject of an FDA Advisory Committee discussion April 1, 2014. We will address the issue of a REMS for this product again following the discussion at the advisory committee.

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/s/

JOYCE P WEAVER
03/25/2014

CLAUDIA B MANZO
03/25/2014
concur

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

REMS MEMO TO FILE

Date: October 24, 2011

Subject: Risk Evaluation and Mitigation Strategy (REMS)
Considerations

Drug Name (Established Name): Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler

Therapeutic Class: Antidiabetic

Dosage and Route: Titrated to insulin requirement, administered via oral inhalation before meals

Application Type/Number: NDA 22-472

Applicant: MannKind Corporation

OSE RCM #: 2011-1334

SUMMARY

This document considers risk evaluation and mitigation strategies (REMS) for Afrezza, an inhaled insulin product that has received two previous complete response letters. The REMS strategies should be considered should an application for Afrezza be submitted in the future.

The safety issues that have been identified as possibly requiring mitigation are:

- potential risk of decline in lung function with chronic use
- potential risk of malignancy
- possibility that patients with undiagnosed underlying lung disease could develop bronchospasm with initial use.

REMS may not be as effective if the risk is not clearly characterized (e.g., decline in lung function with chronic use and malignancy) and the risk message is tentative. When developing risk mitigation strategies consider whether informing, educating or creating a process that changes behavior or creates elements to assure safe use will ultimately be able to mitigate a potential risk.

Additionally, it is not clear that the benefit of inhaled insulin outweighs any risks serious enough to warrant a REMS. In clinical testing, Afrezza plus a long-acting injected insulin was inferior to the combination of a short-acting injected insulin plus a long-acting injected insulin. Although use of Afrezza decreases the number of injections required to treat diabetic patients with insulin, the use of Afrezza does not eliminate the need to inject long-acting insulin.

Should Afrezza be approved, the risk of bronchospasm with initial use might be mitigated with a REMS. The pulmonary clinical reviewer believed that patients should receive pulmonary function testing (PFT) prior to use of the product. The level of REMS to be implemented for this risk depends on the urgency of PFTs prior to use of Afrezza, and whether the first dose should be medically supervised, as recommended by the pulmonary safety clinical reviewer. To be assured that PFTs are conducted prior to patients receiving Afrezza, or to be assured that the first dose is medically supervised, a REMS with restricted distribution and ETASU element D (“Afrezza dispensed to patients with evidence or other documentation of safe-use conditions”) would likely be needed. The burden that this requirement would place on patients and prescribers should be considered.

1 INTRODUCTION

This review provides REMS considerations to be used by DMEP and DRISK if Afrezza is re-submitted for review.

Background

Afrezza is an ultra-fast acting insulin administered via inhalation. The NDA has received two complete response (CR) letters. The first letter issued March 12, 2010 for the submission of March 16, 2009. The deficiencies cited included clinical deficiencies, deficiencies in a bioequivalence study, and unresolved device issues. The applicant submitted a response June 29, 2010. The applicant had changed the inhalation delivery device, but they had not performed phase 3 studies establishing the safety and efficacy of the new device/drug system. In the second complete response letter for the application, issued January 18, 2011, the applicant was advised that two randomized controlled trials must be conducted using the new inhaler.

REMS Regulatory History

The applicant voluntarily submitted a REMS comprising a Medication Guide, a communication plan, and a timetable for submission of assessments with the original application. A March 5, 2010 REMS Memo stated that a REMS comprising a Medication Guide, communication plan, and timetable for submission of assessments was needed. The first CR letter stated that a REMS would be needed if Afrezza was eventually approved:

We have determined that a REMS will be necessary for Afrezza (insulin human [rDNA] origin) inhalation powder, if it is approved, to ensure that the benefits of the drug outweigh the risks of respiratory difficulty immediately post-inhalation, especially in patients with undiagnosed chronic lung disease, the risk of pulmonary function decline over time, and the potential risk of harm due to use by inappropriate patient populations, i.e., smokers and patients with chronic lung disease.

In the complete response to the action letter, submitted June 29, 2010 by the applicant, a Medication Guide-only REMS was proposed. The need for REMS was reiterated in the CR letter issued January 18, 2011:

As described in our letter dated March 12, 2010, in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) will be necessary for Afrezza (insulin human [rDNA] origin) inhalation powder, if it is approved, to ensure that the benefits of the drug outweigh the risks of respiratory difficulty immediately post-inhalation, especially in patients with undiagnosed chronic lung disease, the risk of pulmonary function decline over time, and the potential risk of harm due to use by inappropriate patient populations, i.e., smokers and patients with chronic lung disease.

We acknowledge the receipt of your proposed REMS included in your initial NDA submission and amended on January 8 and June 29, 2010. The proposed REMS, as amended, contains a Medication Guide and a timetable for submission of assessments of the REMS. The REMS, should it be approved, will create enforceable obligations.

We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

DRISK has written three memos for this application. The first, REMS Interim Review Comments, dated November 23, 2009, provided preliminary comments on the initial REMS proposal. The second review, a REMS Review Deferral memo, written January 22, 2010, closed the REMS consult without a full review when the extent of the deficiencies with the application became clear, and the decision was made to send a CR letter. The third DRISK review, written January 5, 2011, deferred the review of patient labeling submitted with the resubmission of the application.

2 DATA AND INFORMATION SOURCES

- Applicant's REMS submissions of February 17, 2009 (Medication Guide + communication plan REMS proposal), December 31, 2009 (response to OSE's interim comments), and June 16, 2010 (Medication Guide REMS proposal)
- DRISK reviews of November 23, 2009 (interim comments) and January 22, 2010 (deferral memo)
- Complete Response letters of March 12, 2010 and January 18, 2011
- Afrezza REMS Memo, March 5, 2010
- Afrezza Clinical Reviews, Lisa Yanoff, M.D., Division of Metabolic and Endocrine Products, December 24, 2009, and December 10, 2010
- Afrezza Cross Discipline Team Leader Clinical Review, Hylton V. Joffe, M.D., March 11, 2010
- Pulmonary Safety of Afrezza, consult from Banu Karimi-Shah, MD, Division of Pulmonary, Allergy, and Rheumatology Products, December 28, 2009 and December 13, 2010
- End-of-Review Meeting Package, March 15, 2011
- Division of Epidemiology Review of Exubera Cancer Risk, May 20, 2008.

3 REVIEW OF DATA

Overview of Clinical Program

Afrezza was studied in type 1 and type 2 diabetes. Two trials were conducted in type 1 diabetics, one 12-week phase 2 trial and one 52-week phase 3 trial. Both studies were open-label trials that compared pre-meal inhaled Afrezza with pre-meal insulin aspartate in patients receiving insulin glargine at bedtime. Six trials were conducted in type 2 diabetics, including two phase 2, double-blind, placebo-controlled trials and three phase 3, open-label, active comparator-controlled trials. The sixth study, a phase 2 trial, had only 15 patients in the control arm. The maximum duration of exposure in the clinical trials was two years. A limited number (n=229) type 2 diabetics received the product for four years in an open-label extension trial.

Dr. Lisa Yanoff, the clinical reviewer for the application, made the following statements about efficacy, based on her 2009 review of the efficacy data.

- For Type 2 diabetic patients there is clear evidence that Afrezza is functioning as exogenous insulin (efficacy compared to placebo).
- Afrezza plus a long-acting injected insulin is non-inferior to twice-daily injected premixed insulin analogue therapy (Novolog 70/30) and, in combination with the oral antidiabetic drug metformin is non-inferior to the combination of metformin and an oral secretagogue.
- Afrezza plus a long-acting injected insulin *is inferior* to the combination of a short-acting injected insulin plus a long-acting injected insulin (called basal/bolus injected therapy).

Dr. Yanoff stated that the finding of inferiority of Afrezza versus basal/bolus injected therapy in Type 2 diabetes patients should not preclude approval of Afrezza because, with its novel route of delivery, Afrezza should not be required to be as good as the most effective injected insulin therapy available, but instead should be required to show at least substantial benefit without excess risk.

Safety Concerns

Three safety concerns of note were described in clinical reviews of Afrezza; these safety concerns are pulmonary function decline with chronic use, acute onset of bronchospasm, and development of lung malignancies.

Chronic and Acute Changes in Pulmonary Function

The data concerning pulmonary risk was reviewed by Banu Karimi-Shah, M.D., Division of Pulmonary, Allergy, and Rheumatology Products. Dr. Karimi-Shah noted that > 600 type 1 diabetics and > 1700 type 2 diabetics in clinical testing of inhaled insulin with the original inhaler, the MedTone inhaler. (This device was subsequently replaced in the clinical development program.) Of the 2300 subjects, 538 type 1 diabetics and 1334 type 2 diabetics were exposed for up to 2 years in controlled trials.

Dr Karimi-Shah believed that the number of patients exposed and the duration of exposure were sufficient to assess pulmonary safety in patients without underlying pulmonary disease.

Cough was experienced by 25-30% of subjects receiving Afrezza. This resulted in discontinuation of Afrezza in 3% of trial subjects. Other, less frequently occurring events indicative of respiratory irritation were bronchospasm (n=2), dyspnea (n=10), laryngospasm (n=1), throat irritation (n=4), throat tightness (n=1), and wheezing (n=2).

A small chronic decrease in forced expiratory volume in one second (FEV1) in pulmonary function testing occurred in subjects receiving Afrezza. This statistically significant decrease averaged about 40-50 mL, and was assessed by Dr. Karimi-Shah as generally not clinically significant for patients with normal pulmonary function. The decrease in FEV1 manifested within the first three months of therapy, and persisted throughout therapy. Data on chronic decreases in FEV1 in subjects with underlying pulmonary disease are not available.

The application contained data to assess acute decreases in FEV1. In subjects without asthma, an acute decrease in FEV1 of 90-138 mL was observed, compared to a 200 mL decrease in subjects with chronic obstructive pulmonary disease (COPD), and a 400 mL decrease in asthmatic subjects. Acute changes in FEV1 resolved over several hours.

Similar pulmonary findings were observed in testing with fewer subjects and for shorter duration with other device models, although the chronic decrease in FEV1 appeared to be smaller (about 20-40 mL) with a later device model, the inhaler intended for marketing.

The testing with the device intended for marketing was insufficient to support efficacy and safety, and the need for two randomized, controlled, phase 3 trials with the device intended for marketing was a deficiency cited in the CR letter of January 18, 2011.

Malignancy

Because post-marketing cases of lung malignancy were reported for Exubra, a previously marketed inhaled insulin, the clinical trial data were reviewed for malignant events. Based on the available data for Exubra, there is concern of the development of lung malignancies in patients who use inhaled insulin, especially for those patients with a history of smoking.

A pulmonary malignancy signal was not noted in Afrezza clinical testing; however, the trials were likely underpowered for examining this issue. Twelve of 2409 subjects receiving Afrezza in clinical testing developed malignancies, none of which was a primary lung malignancy. There was one case in an Afrezza-treated subject of a neuroendocrine tumor with lung involvement (Oat cell cancer). Seven of 1944 subjects in the comparator group developed malignancies, none of which was a primary lung malignancy. There was one case of a reported primary lung malignancy in a patient enrolled in an uncontrolled extension trial.

Applicant's Proposed Risk Evaluation and Mitigation Strategy

The applicant proposed two different REMS for Afrezza, one proposal comprising a Medication Guide, a communication plan, and a timetable for submission of assessments, proposed with the initial submission. A second REMS proposal, comprising a Medication Guide, and a timetable for submission of assessments, was proposed with the resubmission of the application.

Goals

The goals of the first REMS proposed (MG + CP) were:

(b) (4)

The goals of the REMS proposed (MG) with the resubmission were:

(b) (4)

Medication Guide

Both REMS proposals included a Medication Guide.

Communication Plan

The first REMS proposed included a communication plan. (b) (4)

(b) (4)

Details about the communication plan had not been worked out at the time of the CR action letter.

¹ Afresa was an earlier proposed name for the inhaled insulin product.

Timetable for Submission of Assessments

The sponsor proposed the standard timetable for submission of assessments, 18 months, 3 years, and 7 years following approval of the REMS.

Information Needed for Assessment

The proposal included reporting of the results of surveys of knowledge, attitude, and behavior of prescribers, other HCPs, and patients, and adverse event reporting.

Proposed Postmarketing Studies

The sponsor proposed conducting an observational study of about (b) (4) patients receiving Afrezza for at least (b) (4) to investigate neoplasms, use in patients with lung disease, cardiovascular events, all cause mortality, and hypoglycemic events.

4 DISCUSSION

The safety issues for the product that might be addressed with a REMS are possible decline in lung function with chronic use, bronchospasm with initial use, particularly in patients with undiagnosed lung disease, and potential for development of malignancies, especially in patients with smoking history. There is an issue of correct use of the product (i.e., without patient error), but this issue is best approached by product design and clear directions for use, not by the use of a REMS. The Division of Medication Error Prevention and Analysis (DMEPA) has been involved with the issue of the usability of the product, and DMEPA's involvement will continue to be important in this regard as this product is considered for approval within the FDA.

It is not clear that any excess risk should be tolerated for inhaled insulin. The use of this inhaled insulin would not eliminate the patients' need to receive injections because they would still need to receive injections of long-acting insulin. There appears to be little advantage of using inhaled insulin except to reduce the number of daily injections needed. It appears that serious safety issues, including unresolved safety issues, should be viewed as issues to resolve prior to approving Afrezza, rather than issues that can be mitigated with REMS. However, should Afrezza be approved, the considerations for REMS for each risk is presented below.

Decline in lung function with chronic use

It does not appear that the issue of periodic PFT is critical to the use of the product in patients without underlying lung disease, except to provide individual patient monitoring for chronic use of Afrezza to use individual patient monitoring for an area of clinical uncertainty, as this issue was not addressed in the clinical study of Afrezza. The data show a small decrease in FEV1 in patients without underlying lung disease over the course of a 2-year study. There are no data establishing the effect on lung function with longer use in a sufficient number of patients. A post-marketing requirement to study this

question is likely needed. It is not clear that a REMS to amplify the labeling about periodic PFT of patients is needed unless there is evidence that Afrezza is associated with clinically significant pulmonary function decline.

The effect of inhaled insulin on the course of underlying lung disease is not known. It is logical to suspect that an inhaled product will cause adverse pulmonary events. In addition, adequate clinical trial data on the new inhalation device is not available and this delivery system may positively or negatively impact this risk. Given these factors and unknowns, it does not appear that it would be useful to use a REMS to amplify the uncertainty and concern that will be presented in the labeling about this risk. Therefore, based on the available data, we would likely recommend that this risk be managed with appropriate labeling and required post-marketing safety studies.

Malignancy

Regarding malignancy, there is an uninvestigated concern that inhaled insulin could promote the growth of occult tumors, especially in high-risk patients, e.g., smokers. Dr. Cynthia Kornegay from the Division of Epidemiology (DEPI) looked at the data regarding malignancy concerning Exubra, a previously marketed inhaled insulin:

“At the time of approval of Exubera there were three cases of malignant neoplasm of the lung in individuals exposed to Exubera versus one in a non-exposed patient. In December 2007, the sponsor submitted an information update for clinical trials that described nine cases of lung cancer, eight of which were in patients exposed to inhaled insulin. Of these eight cases, six are thought to be potentially directly associated with Exubera exposure. The data, while somewhat compelling, are quite preliminary. Details on the individual studies where the cases arose are not provided, so the study data could not be pooled and analyzed in a more rigorous manner. While cases originated in the US, Canada, and Europe, the only lung cancer background rates available were those for the US. Since the number of US study participants was not provided, it is not clear if the lung cancer rate seen in US Exubera study participants would be in excess of the US lung cancer background rate.”

Information concerning the potential risk of malignancy was added to the WARNINGS section of the Exubera labeling. A REMS comprising a Medication Guide and a communication plan was requested for Exubera. Exubera was voluntarily removed from the market before the REMS was implemented.

The Agency has considered how to mitigate a potential risk of cancer for other products. A REMS containing a Medication Guide and a communication plan was implemented for Victoza (liraglutide), an anti-diabetic product associated with medullary thyroid cancer. REMS with ETASU have been used for other products associated with possible malignancies (e.g., Nplate [romiplostim], Promacta [eltrombopag]), and some products associated with possible malignancies do not have REMS addressing the risk (e.g., Neoral [cyclosporine]).

The applicant has proposed establishing a post marketing registry to evaluate the long-term safety of Afrezza, including the potential malignancy risk. They propose to study approximately (b) (4) patients receiving Afrezza for at least (b) (4) compared with a larger cohort of similar patients who did not receive Afrezza. The endpoints to be examined include malignancies, lung disease, cardiovascular events (myocardial infarct, stroke), all-cause mortality, and severe hypoglycemia leading to medical utilization. Review of the proposed registry by the DEPI is needed to assess whether the proposed registry would answer the question of the malignant potential of Afrezza. DEPI input could be useful as well to define the study needed to resolve the safety issues before marketing.

Based on the lack of available data regarding malignancy, the level of concern regarding this risk is not known. It is questionable that it would be useful to use a REMS to amplify the uncertainty and concern that will be presented in the labeling about this issue while the question is being studied. It appears this risk could be managed with appropriate labeling (i.e., a contraindication for use in patients with smoking history) and required post-marketing safety studies.

Bronchospasm/hyperreactivity

Most data about hyperreactivity are contained in the safety data submitted in 2009 with the previously used device, a device that will not be marketed. Seventeen of 2409 subjects in the safety database evaluated by Dr. Karimi-Shah in her 2009 review experienced some type of hyperreactivity reaction that resulted in discontinuation of the study drug. These reactions were described as dyspnea, asthma, bronchial hyperactivity, bronchospasm, wheezing, and bronchial obstruction. In one phase 3 trial conducted in patients with asthma or COPD, 5/17 (29%) patients with asthma had bronchoconstriction, wheezing, or asthma exacerbation acutely after inhalation of this product. The respiratory events in the five patients resolved without intervention.

Dr. Karimi-Shah recommended that, if approved, Afrezza should be contraindicated in patients who smoke, and in patients with unstable or poorly controlled lung disease. She additionally advised that the labeling include a recommendation that Afrezza not be used by patients with any underlying lung disease. Dr. Karimi-Shah expressed concern about development of bronchospasm in patients, especially in patients with previously unknown lung disease, who would not know they could be at risk. Because of the concern for a hyperreactivity reaction, she recommended that patients receive the first dose of Afrezza in a medical office, and that they receive PFT prior to receiving Afrezza. Dr. Yanoff believed that administering the first dose in a medical office would be problematic because of the necessity to time the dose with a meal.

At this time, it is not clear what risk management measures should be used for to address this risk. The following information would be informative:

- The issue of hyperreactivity with the device to be marketed should be explored when the application is resubmitted. The data should be reviewed for
 - the incidence and seriousness of hyperreactivity reactions

- whether such reactions could be predicted by PFT
- whether such reactions can occur with subsequent dosing if no reaction occurred with the first dose
- time to onset.

This risk should be revisited when the safety data are submitted with the device to be marketed with the following considerations

- If PFT is imperative to ensuring that the benefits of Afrezza outweigh its risks, implementing a REMS with ETASU might be needed. This would be especially so if administering the first dose under medical supervision is needed. The Agency should consider whether the benefits of Afrezza outweigh these risks, and outweigh the burden on stakeholders to mitigate the risk, even with a REMS in place.
- If PFT is not imperative, but strongly advised, and it is determined that labeling, including a boxed warning would be insufficient to deliver the message to prescribers about this recommended testing, then amplification of the information in the labeling concerning this risk with a communication plan-based REMS might be appropriate.

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/s/

JOYCE P WEAVER
10/24/2011

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION II
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS**

NDA/BLA #s: 022472
Products: AFREZZA® (insulin human [rDNA origin]) Inhalation Powder, 15 and 30 units
APPLICANT: MannKind Corporation
FROM: Mary H. Parks, M.D.
DATE: 5 March 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 for AFREZZA (insulin human [rDNA origin]) to ensure that the benefits of the drug outweigh the risks of respiratory difficulty immediately post-inhalation, especially in patients with undiagnosed chronic lung disease, the risk of pulmonary function decline over time, and the potential risk of harm due to use by inappropriate patient populations, i.e., smokers and patients with chronic lung disease. In reaching this determination, we considered the following:

- A. The number of people in the United States with diabetes mellitus (type 1 and type 2) is estimated to be greater than 23 million. Although type 2 diabetics may initially be treated with a variety of oral and injectable anti-diabetic agents as monotherapy or in combination, many will ultimately require insulin therapy due to the progressive nature of the disease. Insulin is a life-sustaining treatment for type 1 diabetic patients.
- B. Patients with diabetes are at risk for a variety of complications including heart disease, stroke, blindness, kidney failure, nervous system damage, amputations, and death.

- C. AFREZZA (insulin human [rDNA origin]) has been shown to help diabetic patients achieve glycemic control, as assessed by hemoglobin A1c. Some of the complications listed above can be prevented or delayed with good glycemic control. AFREZZA (insulin human [rDNA origin]) is an option for patients with type 2 diabetes who are inadequately treated with lifestyle modification and other anti-diabetic therapies. AFREZZA (insulin human [rDNA origin]) is an option for patients with type 1 diabetes as an alternative to injected prandial insulin therapy.
- D. The expected duration of therapy is over a patient's lifetime.
- E. In addition to the risk of respiratory difficulty immediately post-inhalation, the risk of pulmonary function decline over time, and the potential risk of harm due to use by inappropriate patient populations AFREZZA (insulin human [rDNA origin]) is associated with other adverse effects, including hypoglycemia, diabetic ketoacidosis (in patients with type 1 diabetes) and allergy.
- F. AFREZZA (insulin human [rDNA origin]) is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for AFREZZA (insulin human [rDNA origin]). FDA has determined that AFREZZA (insulin human [rDNA origin]) 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 AFREZZA (insulin human [rDNA origin]). FDA has determined that AFREZZA (insulin human [rDNA origin]) 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 AFREZZA (insulin human [rDNA origin]).

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANKIND CORP	Afrezza (insulin) inhalation powder

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/s/

LISA B YANOFF
03/16/2010

MARY H PARKS
03/16/2010

**REMS Interim Review Comments for the
Division of Metabolic and Endocrine Products (DMEP)**

Drug Name: AFRESA (insulin monomer human [rDNA origin]) Inhalation System	BLA/NDA: 22-472	Date: 11/23/2009
		Comment Set # [1]
DRISK Scientific Lead: Marcia Britt, PhD	Reviewers: Yasmin Choudhry, MD, Medical Officer, DRISK Gita Toyserkani, Pharm.D., MBA, Risk Management Analyst (Acting) TL, DRISK Kendra Jones, Regulatory Review Officer, DDMAC Sam Skariah, PharmD., Regulatory Review Officer, DDMAC	
RCM #: 2009-593		

Introduction:

AFRESA is an ultra-rapid acting prandial insulin delivered via pulmonary route. The proposed indication is for the treatment of hyperglycemia in adults with Type 1 or Type 2 diabetes. MannKind Corporation (MKC) voluntarily submitted a Risk Evaluation Mitigation Strategy (REMS) for AFRESA on July 22, 2009. The REMS proposal consists of a Medication Guide and a Communication Plan. MKC describes the purpose of the AFRESA REMS

[REDACTED] (b) (4)

The Sponsor has not described in the REMS document or the Supporting Document (SD) the serious risk for which a REMS is necessary to ensure that the benefits outweigh the risks. DRISK met with DMEP on September 15, 2009 and October 26, 2009 to discuss the serious risks associated with the use of AFRESA. DMEP is currently reviewing the application to determine the safety risks associated with the use of AFRESA.

The comments below are DRISK's preliminary review of the REMS proposal for AFRESA. The REMS, SD, and material may be affected as the serious risk is more clearly elucidated. The comments provided may also need to be revised according to the identified risks. DDMAC will comment on the proposed REMS materials at a later date, when the revised REMS materials are submitted.

Please request the Sponsor respond to these preliminary comments and questions within 2 weeks upon receipt.

Material included and reviewed:

REMS
Supporting Document
Pharmacovigilance Plan



Brief Summary for DMEP:

MKC characterizes the risk with AFRESA in their Pharmacovigilance Plan document as those generally associated with insulin treatment and with the inhalation of a dry powder. The indentified risks include hypoglycemia and cough. Additionally, there is the potential risk of hypo- and hyperglycemia during treatment initiation (i.e. titration of AFRESA and changes in subcutaneous insulin dosing). Other potential risks include using AFRESA in patients, in whom the safety has not been established, including patients with underlying lung disease, smokers, pediatrics, pregnancy and lactating women, and patients with hepatic or renal impairment.

- **REMS Goal and Objectives**

The Sponsor has proposed the following goals:



.The Sponsor has not described the serious risk for which a REMS is necessary to ensure that the benefits outweigh the risks. REMS goals should target the achievement of a particular health outcomes or knowledge related to known safety risks.

- **Medication Guide**

MKC proposes that a Medication Guide will be available for each AFRESA prescription. It will also be available through Regional Medical Liaisons, sales representatives, through the MKC's toll free information number and on the AFRESA website. MKC will directly provide, or provide the means to produce Medication Guides in sufficient numbers to distributors, packers, or authorized dispensers of AFRESA as required by 21 CFR 208.24.

A review of the Medication Guide will be provided under separate cover.

- **Communication Plan (CP)**

The sponsor proposes a CP that utilizes education and outreach to HCPs () with targeted materials (e.g., Prescriber Information, Medication Guide and Instructions for Use) to reinforce important safety information

regarding the correct administration of AFRESA in the appropriate patient population.

(b) (4)

(b) (4)

- **Timetable for Submission of Assessments**

MKC proposes to evaluate the effectiveness of the AFRESA REMS at 18 months, 3 years and 7 years after REMS approval. Pending a complete review of the final proposed REMS, we find the timetable for submission of assessments appropriate.

Comments for the Sponsor:

1. A REMS is intended to ensure that the benefits outweigh the risks of the drug. The serious risks for which a REMS is warranted need to be clearly identified in the REMS and REMS Supporting Document (SD).
2. REMS goals should target the achievement of a particular health outcomes or knowledge related to known safety risks. The goals of the proposed REMS should be revised to include goals that mitigate the identified serious risks associated with the use of AFRESA. Include these risks in the AFRESA communication and educational material.

The use of AFRESA in the appropriate patient population is currently a goal of the AFRESA Inhalation System REMS. The REMS and SD provide limited information about patient selection. Revise the REMS and SD to describe important factors healthcare professionals should consider before prescribing AFRESA for their patients.

3. Clarify the target audience (b) (4)
4. Refer to the REMS format provided by the Food and Drug Administration (Appendix A) when determining the headings and subheadings for the proposed AFRESA REMS. Delete (b) (4) from the proposed REMS. This heading is not an approved heading in the REMS template.

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

5. Remove [REDACTED] (b) (4)
6. [REDACTED] (b) (4)
7. Revise the REMS [REDACTED] (b) (4)
8. Section 3.1.6.1 of the REMS Supporting Document states [REDACTED] (b) (4)
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 - b. The introductory letter for health professionals is not intended to continue over the lifetime of the product; it will function only to inform prescribers of the serious risk associated with AFRESA for a period of time. Provide a timeline in ‘months’ or ‘years’ that MKC intends to provide the introductory letters for health professionals.
9. Include the AFRESA risk information in the Introductory Letter for Healthcare Professionals realizing that this information may change once the final labeling is completed and the risks are more clearly identified.
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12. [REDACTED] (b) (4)

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These comments will be provided with the full review of the REMS.
14. Submit for review a detailed plan to evaluate the providers' and patients' understanding of the safe use of AFRESA to FDA 90 days prior to conducting the survey. The submission should include, but is not limited to:
- *Sample size and confidence interval associated with that sample size*
 - *How the sample will be determined (selection criteria)*
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 - *The Sponsor should submit the survey instruments (questionnaires and moderator's guide) for review.*
 - *Provide any background information on testing survey questions and the correlation to the educational materials, and explain what will be done with the resulting data from the surveys.*
15. Submit the revised proposed REMS with appended materials and the REMS Supporting Document. Provide a track changes and clean version of all revised materials and documents. Submit your proposed REMS and other materials in WORD format. It is preferable that the entire REMS and appended materials be a single WORD document.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANKIND CORP	INSULIN HUMAN (RDNA ORIG)INH POWDER

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/s/

MARCIA BRITT
12/09/2009

December 10, 2009

Please refer to the corrected AFRESA Interim Review dated 12/9/2009.

**REMS Interim Review Comments for the
Division of Metabolic and Endocrine Products (DMEP)**

Drug Name: AFRESA (insulin monomer human [rDNA origin]) Inhalation System	BLA/NDA: 22-472	Date: 11/23/2009
		Comment Set # [1]
DRISK Scientific Lead: Marcia Britt, PhD	Reviewers: Yasmin Choudhry, MD, Medical Officer, DRISK Gita Toyserkani, Pharm.D., MBA, Risk Management Analyst (Acting) TL, DRISK Kendra Jones, Regulatory Review Officer, DDMAC Sam Skariah, PharmD., Regulatory Review Officer, DDMAC	
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Material included and reviewed:

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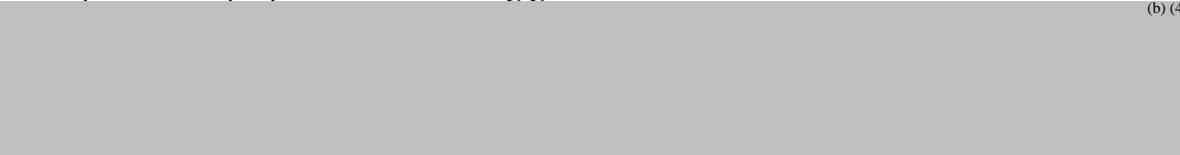


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/s/

MARCIA BRITT
11/23/2009

MARY E WILLY
11/23/2009