

Initial REMS approval: 06/2014

Most recent modification: 04/2015

NDA 022472 AFREZZA® (insulin human) Inhalation Powder

Sanofi-aventis U.S.
55 Corporate Boulevard
Bridgewater, New Jersey 08807
Phone: 1-800-633-1610

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

Sanofi-aventis will implement the following communication plan to healthcare providers likely to prescribe AFREZZA. The communication plan will include:

1. REMS Letters

Sanofi-aventis 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.

Sanofi-aventis will make the *REMS Letter for Healthcare Providers* available via a link from the AFREZZA REMS website and through Sanofi-aventis 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

Sanofi-aventis 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 Sanofi-aventis 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 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*. The

Afrezza product website will include a prominent REMS-specific link to the Afrezza REMS Website.

4. Dissemination of REMS information at scientific meetings

The *AFREZZA REMS Factsheet* will be prominently displayed at relevant scientific meetings where Sanofi-aventis 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

Sanofi-aventis 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. Sanofi-aventis 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 type1 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 Sanofi US at 1-800-633-1610 and/or the FDA www.fda.gov/medwatch, or call 1-800-FDA-1088.

Signature,



Charles Hugh-Jones, M.D.
Vice President and Chief Medical Officer, North America Pharmaceuticals
Sanofi US

US.HUM.14.10.004



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**
- **Contraindicated in patients with chronic lung disease as asthma or COPD**
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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 of AFREZZA. To review the Prescribing Information and Medication Guide, see links below:

[Prescribing information](#)

[Medication Guide](#)

Please visit www.AfrezzaREMS.com for more information.

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Signature,



Charles Hugh-Jones, M.D.

Vice President and Chief Medical Officer, North America Pharmaceuticals
Sanofi US



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 Sanofi US to distribute this safety notice to your organization as part of the AFREZZA REMS (R*isk* E*valuation* and M*itigation* S*trategy*) 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

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Indication: AFREZZA[®] (insulin human) Inhalation Powder is a rapid acting inhaled insulin of action 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 see the Prescribing Information and Medication Guide, enclosed.

Signature,

A handwritten signature in black ink, appearing to read 'CHJ', written in a cursive style.

Charles Hugh-Jones, M.D.
Vice President and Chief Medical Officer, North America Pharmaceuticals
Sanofi US

From: Sanofi US
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 Sanofi US 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 you 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 as asthma or COPD**
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[Prescribing information](#)

[Medication Guide](#)

Please visit www.AfrezzaREMS.com for more information.

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Signature,



Charles Hugh-Jones, M.D.
Vice President and Chief Medical Officer, North America Pharmaceuticals
Sanofi US



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
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- 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

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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:

- Sanofi US at 1-800-633-1610 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.



[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

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- physical examination, and
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Materials for Healthcare Provider

 [AFREZZA REMS Safety Information for Providers Factsheet](#)

 [REMS Letter to Healthcare Providers](#)