

Initial REMS Approval: 12/2008
Most Recent Modification: 5/2014

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Single, Shared System for Rosiglitazone-Containing Medicines

I. GOAL

The goal of the Rosiglitazone REMS Program for the rosiglitazone-containing medicines (hereafter referred to as rosiglitazone) is to provide training to likely prescribers of rosiglitazone medicines about the current state of knowledge concerning the cardiovascular risks of these medicines.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Training will be provided to healthcare providers who are likely to prescribe rosiglitazone medicines of the current state of knowledge on the medicines' cardiovascular risk.
 - a. Rosiglitazone REMS Sponsors will ensure healthcare providers who are likely to prescribe rosiglitazone are provided training, for the duration of the REMS. Training materials on the current state of knowledge concerning the cardiovascular risk of these medicines will be available on the Rosiglitazone REMS website (www.rosiglitazonerems.com).

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

- training slide deck

In order to facilitate prescriber training

b. A *Dear Healthcare Provider Letter* (DHCP letter) will be distributed via direct mail within 14 working days of the approval of the REMS Modification (May 2014). The target audience for this communication will be likely prescribers, defined as prescribers who had written a prescription for rosiglitazone one year prior to the implementation of the original restricted distribution of the REMS program in June 2011. In addition, this letter will be sent by electronic mail to those prescribers currently enrolled in the REMS program.

Rosiglitazone REMS Sponsors will send the *Dear Healthcare Provider Letter* to MedWatch prior to the time the letter is disseminated to the target audience.

c. A *Dear Professional Society Letter* will be distributed to the leadership of the following societies via direct mail or electronic mail within 14 working days of the approval of the REMS Modification (May 2014):

- American Association of Clinical Endocrinologists (AACE)

- Endocrine Society (ES)
- American Association of Family Physicians (AAFP)
- American College of Physicians (ACP)
- Society of General Internal Medicine (SGIM)
- National Medical Association (NMA)
- American Heart Association (AHA)
- American College of Cardiologists (ACC)
- American Academy of Nurse Practitioners (AANP)
- American Academy of Physician Assistants (AAPA)
- American College of Clinical Pharmacy (ACCP)
- American Society of Health-System Pharmacists (ASHP)
- American Pharmacists Association (APhA)

d. The Rosiglitazone REMS Sponsors will make the following materials available on a REMS website (www.rosiglitazonerems.com) for the duration of the REMS following approval of this REMS modification:

1. Prescriber training materials (the training slide deck)
2. *Dear Healthcare Provider Letter*
3. Prescribing Information and Medication Guides for all rosiglitazone-containing medicines (branded and generic versions) that are approved
4. Contact information for the manufacturers of approved rosiglitazone-containing medicines

The *Dear Healthcare Provider Letter*, *Dear Professional Society Letter*, and REMS website are part of the REMS and are appended.

Based on monitoring and evaluation of these elements to assure safe use, Rosiglitazone REMS Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the Rosiglitazone REMS Program requirements, as applicable.

D. Timetable for Submission of Assessments

Rosiglitazone NDA Sponsor(s) will submit REMS assessments to FDA 6 months, 12 months, and annually from the date of initial approval of this REMS with ETASU (May 18, 2011). 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. Rosiglitazone NDA Sponsor(s) will submit each assessment so that it will be received by the FDA on or before the due date.

Rosiglitazone REMS Program

Introduction

- This training updates prescribers on what is known about the ischemic cardiovascular risk of rosiglitazone
- Data are inconsistent regarding the ischemic cardiovascular risk with rosiglitazone. However, overall, a review of data has led to the following actions by FDA:
 - Updating of the labeling including removal of myocardial infarction from the boxed warning in the labeling for rosiglitazone products
 - Removal of the requirement that prescribers of rosiglitazone be certified in the Risk Evaluation and Mitigation Strategy (REMS) program
 - Removal of the requirement that patients receiving rosiglitazone be enrolled in the REMS program
 - Removal of the requirement that pharmacies that dispense rosiglitazone be certified in the REMS program

Rosiglitazone REMS Program

Synopsis

- Data from long-term, prospective, randomized, controlled clinical trials of rosiglitazone versus metformin or sulfonylureas, particularly a cardiovascular outcome trial (RECORD), **observed no difference in overall mortality or in major adverse cardiovascular events (MACE) and its components**
- Meta-analysis of mostly short-term trials **suggested increased risk for myocardial infarction with rosiglitazone compared to placebo**

The Cardiovascular Outcome Trial: RECORD

- Randomized, open label, prospectively designed cardiovascular outcome trial with a mean follow-up of 5.5 years in 4,447 patients
- Compared addition of rosiglitazone to metformin or to a sulfonylurea vs. a control group receiving metformin plus sulfonylurea in patients with type 2 diabetes for the primary composite endpoint of cardiovascular hospitalization or cardiovascular death

The Cardiovascular Outcome Trial: RECORD

- Data from RECORD, a long-term clinical trial of rosiglitazone versus other antidiabetes agents (metformin or sulfonylureas) **observed no difference in overall mortality or in major adverse cardiovascular events (MACE) and its components** (stroke, myocardial infarction, cardiovascular death)

Hazard Ratios:

- Composite of cardiovascular hospitalization or cardiovascular death: HR=0.99 (95% CI: 0.85-1.16)
- Stroke: HR=0.72 (95% CI: 0.49, 1.06)
- Myocardial infarction: HR=1.14 (95% CI: 0.80, 1.63)
- Cardiovascular death: HR=0.84 (95% CI: 0.59, 1.18)

Rosiglitazone REMS Program

Data from ADOPT and DREAM

2 Long Term Randomized Controlled Trials

Rosiglitazone REMS Program

Data from ADOPT (A Diabetes Outcome Progression Trial)

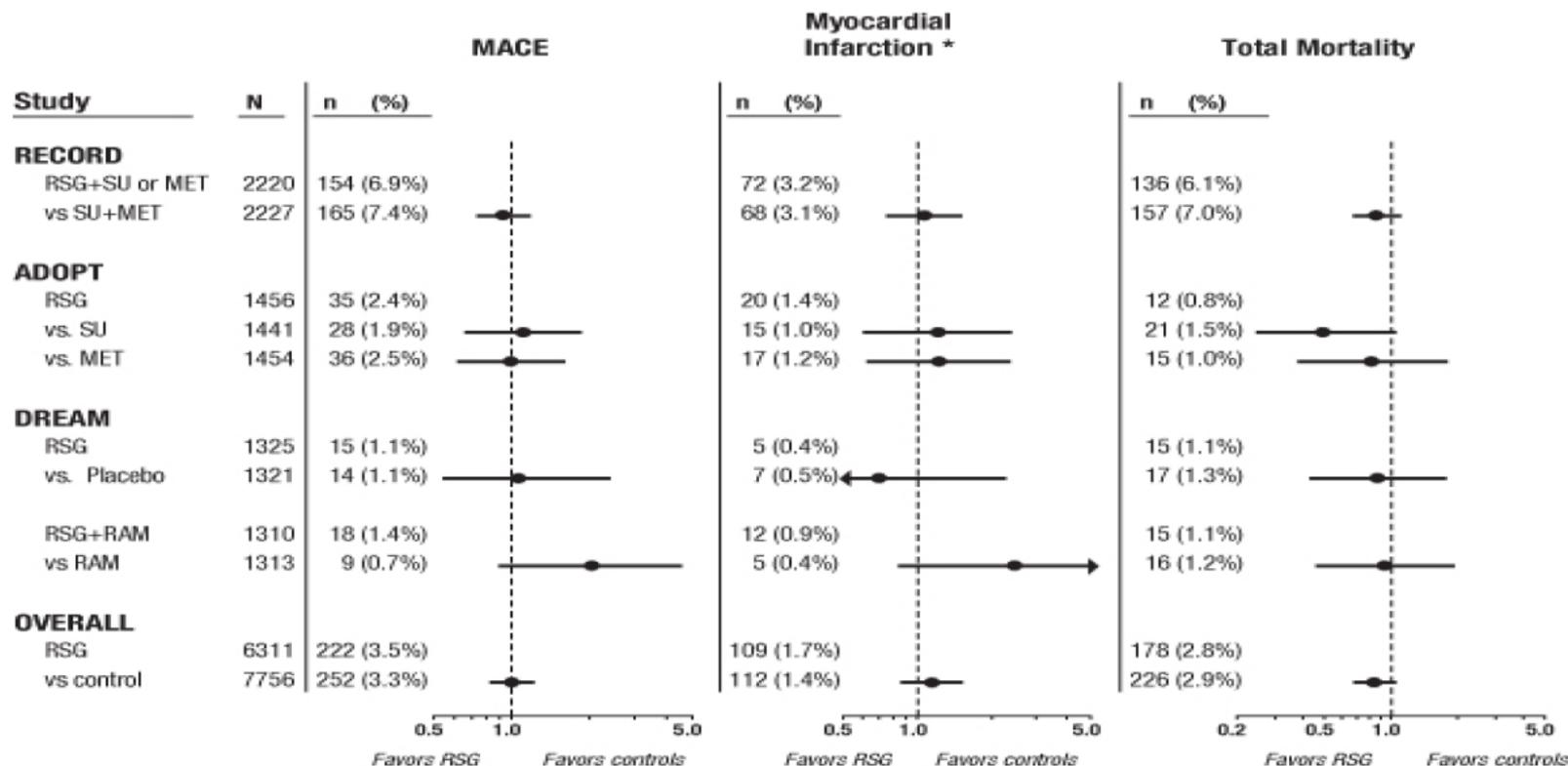
- Multicentre, double-blind, controlled trial with duration over 3 years
- Rosiglitazone was compared to metformin and to sulfonylurea in 4351 drug naive subjects recently diagnosed with type 2 diabetes
- **No statistically significant differences for MACE and its components** (stroke, myocardial infarction, cardiovascular death) between rosiglitazone and metformin or a sulfonylurea

Data From the DREAM Study

- Prospective assessment of treatment with either ramipril and/or rosiglitazone in 5,269 subjects with Impaired Glucose Tolerance or Impaired Fasting Glucose
- **Incidence of cardiovascular events was higher in subjects who were randomized to rosiglitazone in combination with ramipril than in subjects randomized to ramipril alone**
- **No statistically significant differences for MACE and its components** (stroke, myocardial infarction, cardiovascular death) for rosiglitazone vs. placebo

Rosiglitazone REMS Program

Forest Plots for 3 Long Term Studies**



RSG = rosiglitazone; SU = sulfonylurea; MET = metformin; RAM = ramipril
 * Myocardial infarction includes fatal and non-fatal MI plus sudden death

** Hazard Ratios for the Risk of MACE, Myocardial Infarction, and Total Mortality With Rosiglitazone Compared With a Control Group in Long-term Trials

Rosiglitazone REMS Program

52 Clinical-Trial Meta-analysis

- A meta-analysis was conducted of 52 double blind, randomized, controlled clinical trials (mean duration 6 months) designed to assess glucose lowering efficacy in type 2 diabetes

Rosiglitazone REMS Program

Data from 52 Clinical-Trial Meta-Analysis

- **Overall:** statistically significant increased risk of myocardial infarction with rosiglitazone vs. pooled comparators (active and placebo) and a statistically non-significant increased risk of MACE with rosiglitazone versus pooled comparators
 - **Placebo-controlled trials:**
 - **Statistically significant increased risk of myocardial infarction**
 - Statistically non-significant increased risk of MACE
 - **Active-controlled trials:**
 - **No increased risk of myocardial infarction or MACE**

Odds Ratios (OR):

- **Rosiglitazone vs. pooled comparators**
 - Myocardial infarction: rosiglitazone vs. pooled comparators (active & placebo) 0.4% vs. 0.3%; (OR) 1.8, (95% CI 1.03, 3.25)
 - MACE with rosiglitazone versus pooled comparators (OR 1.44, 95% CI 0.95, 2.20)
- **Rosiglitazone vs. placebo**
 - Myocardial infarction: 0.4% vs. 0.2%, OR 2.23 (95% CI 1.14, 4.64)
 - MACE: 0.7% vs. 0.5%, OR 1.53 (95% CI 0.94, 2.54).

Rosiglitazone REMS Program

Summary

- Data from long-term, prospective, randomized, controlled clinical trials of rosiglitazone versus metformin or sulfonylureas, particularly a cardiovascular outcome trial (RECORD), **observed no difference in overall mortality or in major adverse cardiovascular events (MACE) and its components**
- Meta-analysis of mostly short-term trials **suggested increased risk for myocardial infarction with rosiglitazone compared to placebo**

Rosiglitazone REMS Program

Conclusion

- **This training updates prescribers on what is known about the ischemic cardiovascular risk of rosiglitazone**
- **Data are inconsistent regarding the ischemic cardiovascular risk with rosiglitazone. However, overall, a review of data has led to the following actions by FDA:**
 - Updating of the labeling including removal of myocardial infarction from the boxed warning in the labeling for rosiglitazone products
 - Removal of the requirement that prescribers of rosiglitazone be certified in the Risk Evaluation and Mitigation Strategy (REMS) program
 - Removal of the requirement that patients receiving rosiglitazone be enrolled in the REMS program
 - Removal of the requirement that pharmacies that dispense rosiglitazone be certified in the REMS program

Rosiglitazone REMS Program

Approved Rosiglitazone Products

- Avandia[®] (rosiglitazone maleate)
- Avandamet[®] (rosiglitazone maleate/metformin hydrochloride)
- Avandaryl[®] (rosiglitazone maleate/glimepiride)
- Generic rosiglitazone products

Rosiglitazone REMS Program

END OF TRAINING
Thank you for your time

Rosiglitazone REMS Program

Date: *To be inserted locally*

Rosiglitazone Risk Update and REMS Program Changes

- Change in current state of knowledge on cardiovascular risk of rosiglitazone – containing medicines; new training available
- Elimination of the prescriber, patient and pharmacy enrollment/certification requirements in Rosiglitazone REMS Program

Dear Healthcare Provider:

The US Food and Drug Administration (FDA) has eliminated the restricted distribution requirements of the Rosiglitazone REMS Program based on new understanding of cardiovascular risk of rosiglitazone-containing medicines.

Approved rosiglitazone-containing medicines:

- Avandamet® (rosiglitazone maleate/metformin hydrochloride)
- Avandaryl® (rosiglitazone maleate/glimepiride)
- Avandia® (rosiglitazone maleate)
- Generic rosiglitazone products

New cardiovascular risk information

Training on the current state of knowledge of the cardiovascular risk of rosiglitazone-containing medicines is available at <https://www.rosiglitazonerems.com>. The training includes more details on the following:

- Data from long-term, prospective, randomized, controlled clinical trials of rosiglitazone versus metformin or sulfonylureas, particularly the cardiovascular outcome trial RECORD, **observed no difference in overall mortality or in major adverse cardiovascular events (MACE)** and its components.
- A meta-analysis of mostly short-term trials **suggested an increased risk for myocardial infarction with rosiglitazone compared to placebo.**

Within the rosiglitazone Prescribing Information, the WARNINGS AND PRECAUTIONS section has been revised. **Please see enclosed Prescribing Information for rosiglitazone maleate.**

What are the key changes to the REMS Program?

Indicated Population:

Rosiglitazone- containing medicines are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

- Rosiglitazone is no longer limited to patients already on rosiglitazone-containing medicines who are benefiting from the medicine or to new patients who are unable to be controlled on other diabetes medications.

Prescribers

- No longer need to be certified within the Rosiglitazone REMS Program

Patients

- No longer need to be enrolled in the Rosiglitazone REMS Program in order to receive rosiglitazone-containing medicines

Pharmacies

- No longer need to be specially certified in order to dispense rosiglitazone-containing medicines

What should I tell my patients about the changes in the Rosiglitazone REMS Program?

Patients previously or currently enrolled in the Rosiglitazone REMS Program should be informed of the following:

1. The elimination of enrollment requirements
2. Availability of rosiglitazone-containing medicines through local pharmacies

What about records I collected for the Rosiglitazone REMS Program?

Enrolled prescribers and pharmacies should maintain patient and Rosiglitazone REMS Program records in accordance with state and local records retention requirements.

Further information

Should you have additional questions about the Rosiglitazone REMS Program, contact the Coordinating Center at 1-800-282-6342

Sincerely,

Rosiglitazone REMS Sponsors

Rosiglitazone REMS Program

Date: *To be inserted locally*

Rosiglitazone Risk Update and REMS Program Changes

- Change in current state of knowledge on cardiovascular risk of rosiglitazone – containing medicines; New training available
- Elimination of the prescriber, patient and pharmacy enrollment/certification requirements in Rosiglitazone REMS Program

Dear Professional Society Leader:

The FDA has required Rosiglitazone REMS sponsors to distribute this notice to your organization. The FDA has eliminated the restricted distribution requirements of the Rosiglitazone REMS Program based on new understanding of cardiovascular risk of rosiglitazone-containing medicines. We request that you inform your members about the following **update and REMS Program changes**.

New cardiovascular risk information

Training on the current state of knowledge of the cardiovascular risk of rosiglitazone-containing medicines is available at <https://www.rosiglitazonerems.com>. The training includes more details on the following:

- Data from long-term, prospective, randomized, controlled clinical trials of rosiglitazone versus metformin or sulfonylureas, particularly the cardiovascular outcome trial RECORD, **observed no difference in overall mortality or in major adverse cardiovascular events (MACE)** and its components.
- A meta-analysis of mostly short-term trials **suggested an increased risk for myocardial infarction with rosiglitazone compared to placebo**.

Within the rosiglitazone Prescribing Information, the WARNINGS AND PRECAUTIONS section has been revised. **Please see enclosed Prescribing Information for rosiglitazone maleate.**

What are the key changes to the REMS Program?

Indicated Population:

Rosiglitazone-containing medicines are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

- Rosiglitazone is no longer limited to patients already on rosiglitazone-containing medicines who are benefiting from the medicine or to new patients who are unable to be controlled on other diabetes medications.

Prescribers:

- No longer need to be certified within the Rosiglitazone REMS Program

Patients:

- No longer need to be enrolled in the Rosiglitazone REMS Program in order to receive rosiglitazone-containing medicines

Pharmacies

- No longer need to be specially certified in order to dispense rosiglitazone-containing medicines

What do patients need to know about the changes in the Rosiglitazone REMS Program?

Patients previously or currently enrolled in the Rosiglitazone REMS Program should be informed of the following: :

1. The elimination of enrollment requirements
2. Availability of rosiglitazone-containing medicines through local pharmacies

What happens to records collected for the Rosiglitazone REMS Program?

Enrolled prescribers and pharmacies should maintain patient and Rosiglitazone REMS Program records in accordance with state and local records retention requirements.

Rosiglitazone product information

Approved rosiglitazone-containing medicines:

- Avandamet® (rosiglitazone maleate/metformin hydrochloride)
- Avandaryl® (rosiglitazone maleate/glimepiride)
- Avandia® (rosiglitazone maleate)
- Generic rosiglitazone products

Within the rosiglitazone Prescribing Information, the WARNINGS AND PRECAUTIONS section has been revised to include additional data on the risks. **Please review the Prescribing Information for rosiglitazone maleate.**

Further information

Should you have additional questions about the Rosiglitazone REMS Program, contact the Coordinating Center at 1-800-282-6342

Sincerely,

Rosiglitazone REMS Sponsors

Rosiglitazone REMS Program

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Rosiglitazone Risk Evaluation and Mitigation Strategy (REMS) Program

What is the Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy)?

The Rosiglitazone REMS is a training program designed to inform prescribers of the current state of knowledge concerning the cardiovascular risk of rosiglitazone-containing medicines. This program is required by The Food and Drug Administration (FDA) to ensure the benefits of rosiglitazone containing medicines outweigh the risks.

[Approved Rosiglitazone Products and Manufacturers](#)

To review the training materials for healthcare providers, please click here.

[TRAINING MATERIALS:
US Prescribers click here](#)[TRAINING MATERIALS:
If you are not a US Prescriber click here](#)[Dear Healthcare Provider Letter](#)[Frequently Asked Questions](#)

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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Important Safety Information

Prescribing Information

Medication Guide

Rosiglitazone REMS Program

AVANDIA®

AVANDAMET®

AVANDARYL®

ROSIGLITAZONE MALEATE

ROSIGLITAZONE MALEATE AND METFORMIN HYDROCHLORIDE

AVANDIA®

AVANDAMET®

AVANDARYL®

ROSIGLITAZONE MALEATE

ROSIGLITAZONE MALEATE AND METFORMIN HYDROCHLORIDE

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FREQUENTLY ASKED QUESTIONS

CONTACT INFORMATION FOR ROSIGLITAZONE REMS PROGRAM

Rosiglitazone Risk Evaluation and Mitigation Strategy (REMS) Program

What is the Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy)?

The Rosiglitazone REMS is a training program designed to inform prescribers of the current state of knowledge concerning the cardiovascular risk of rosiglitazone-containing medicines. This program is required by The Food and Drug Administration (FDA) to ensure the benefits of rosiglitazone containing medicines outweigh the risks.

[Approved Rosiglitazone Products and Manufacturers](#)

To review the training materials for healthcare providers, please click here.

TRAINING MATERIALS:
[US Prescribers click here](#)

TRAINING MATERIALS:
[If you are not a US Prescriber click here](#)

[Dear Healthcare Provider Letter](#)

[Frequently Asked Questions](#)

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Frequently Asked Questions

Do I have to be enrolled in the Rosiglitazone REMS in order to prescribe rosiglitazone-containing medicines?

No. Prescribers do not need to enroll in the Rosiglitazone REMS in order to prescribe rosiglitazone-containing medicines

Do I need to enroll my patients in the Rosiglitazone REMS Program for them to receive rosiglitazone-containing medicines?

No. Patients do not need to be enrolled in the Rosiglitazone REMS Program to receive rosiglitazone containing medicines

Do I have to review the training materials before I can prescribe rosiglitazone containing medicines?

Healthcare providers are encouraged to complete the Prescriber Training to be informed about the current state of knowledge concerning the cardiovascular risk of rosiglitazone-containing medicines

Will my patients be able to receive rosiglitazone-containing medicines through their local pharmacies?

Rosiglitazone-containing medicines are no longer under restricted distribution and are available for order by local pharmacies

Who do I contact if I have additional questions about the Rosiglitazone REMS Program?

Contact the Rosiglitazone REMS Coordinating Center at 1-800-282-6342 if you have additional questions about the Rosiglitazone REMS Program

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Please call the Rosiglitazone REMS Program Coordinating Center with questions about the Rosiglitazone REMS Program.

Phone: 1-800-282-6342

Hours of Operation:

Monday through Friday from 8:30 AM to 5:00 PM ET

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PDFs to be accessed through the Rosiglitazone REMS Program website:

1. Dear Healthcare Provider Letter
2. Prescriber Training Materials
3. Prescribing Information for approved rosiglitazone medicines:
 - a. AVANDIA[®]
 - b. AVANDAMET[®]
 - c. AVANDARYL[®]
 - d. ROSIGLITAZONE MALEATE
 - e. ROSIGLITAZONE MALEATE AND METFORMIN HYDROCHLORIDE
4. Medication Guide for approved rosiglitazone medicines:
 - a. AVANDIA[®]
 - b. AVANDAMET[®]
 - c. AVANDARYL[®]
 - d. ROSIGLITAZONE MALEATE
 - e. ROSIGLITAZONE MALEATE AND METFORMIN HYDROCHLORIDE
5. Contact Information for Manufacturers of approved rosiglitazone medicines
6. Important Safety Information

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

/s/

JEAN-MARC P GUETTIER
05/07/2014