Initial REMS Approval: 12/2008
Initial REMS with ETASU Approval: 05/18/2011
Most Recent Modification xx/2012

NDA 21-071 AVANDIA (rosiglitazone maleate) Tablets
NDA 21-410 AVANDAMET (rosiglitazone maleate and metformin hydrochloride) Tablets
NDA 21-700 AVANDARYL (rosiglitazone maleate and glimepiride) Tablets

A thiazolidinedione agonist for peroxisome proliferator-activated receptor gamma

SmithKline Beecham (Cork) Ltd d/b/a GlaxoSmithKline
Currabinny, Carrigaline, County Cork, Ireland

2301 Renaissance Boulevard
Mail Code RN 0420
King of Prussia, PA 19406-2772
610-787-3566

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

GOALS

The goals of the Avandia-Rosiglitazone Medicines Access Program (hereafter referred to as the Rosiglitazone REMS Program) are:

1. To restrict access to rosiglitazone-containing medicines (Avandia, Avandamet, Avandaryl) so that only prescribers who acknowledge the potential increased risk of myocardial infarction associated with the use of rosiglitazone are prescribing rosiglitazone.

2. To restrict access to patients who have been advised by a healthcare provider about the potential increased risk of myocardial infarction associated with the use of rosiglitazone and are one of the following:

   - either already taking rosiglitazone or

   - if not already taking rosiglitazone, they are unable to achieve glycemic control on other medications and, in consultation with their healthcare provider, have decided not to take pioglitazone for medical reasons

REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each rosiglitazone prescription in accordance with 21 CFR 208.24.

The Medication Guide for each product is part of the REMS and is appended.

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe rosiglitazone-containing medicines for outpatient or long-term care use are specially certified

a. GlaxoSmithKline will ensure healthcare providers who prescribe rosiglitazone for outpatient or long-term care use are specially certified. GlaxoSmithKline will begin enrolling prescribers no later than 60 days after initial approval of the REMS.

b. To become specially certified to prescribe rosiglitazone, prescribers will be required to enroll in the Rosiglitazone REMS Program and must:

   1) Review the Rosiglitazone REMS *Prescriber Overview* and the Full Prescribing Information, including the *Medication Guide*.

   2) Complete and sign the *Prescriber Enrollment Form* and submit it to the Rosiglitazone REMS Program.

   3) Agree to complete and sign a Rosiglitazone REMS *Patient Enrollment Form* for each patient enrolled.

   4) Agree to provide and review the *Medication Guide* for the prescribed rosiglitazone medicine with the patient or caregiver.

   5) Agree to provide a completed, signed copy of the *Patient Enrollment Form* to the patient, retain a copy for my records, and submit a copy to the Rosiglitazone REMS Program.

c. GlaxoSmithKline will inform enrolled prescribers following substantial changes to the Rosiglitazone REMS or REMS Program. Substantial changes include: 1) significant changes to the operation of the Program or 2) Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of rosiglitazone.

d. GlaxoSmithKline will:

   1) Ensure that prescriber enrollment can be completed via the *Rosiglitazone REMS Program website*, by phone, or by faxing the forms.

   The website is part of the Rosiglitazone REMS Program and is appended.

   2) Ensure that, as part of the enrollment process, prescribers receive the following materials that are part of the Rosiglitazone REMS
   a) Prescriber Overview

b) Prescriber Enrollment Form
c) Patient Enrollment Form
d) Medication Guide

3) Ensure that the *Prescriber Enrollment Form* is complete before activating a prescriber's enrollment in the REMS Program

4) Ensure that prescribers are notified when they have been successfully enrolled in the Rosiglitazone REMS program, and therefore, certified to prescribe rosiglitazone.

2. Rosiglitazone will be dispensed only by specially certified pharmacies.

GlaxoSmithKline will ensure that rosiglitazone will only be dispensed by certified pharmacies. To become certified to dispense rosiglitazones, each pharmacy must be enrolled in the Rosiglitazone REMS Program**.**

To be certified, the pharmacy must agree to the following:

a. To have a system in place to be able to verify that the prescriber (if the prescriber has prescribed rosiglitazone for outpatient or long-term care use) and patient are enrolled in the Rosiglitazone REMS Program prior to dispensing each time rosiglitazone is prescribed. If the patient and prescriber are not enrolled, rosiglitazone cannot be dispensed.

b. To educate all pharmacy staff involved in the dispensing of rosiglitazone on the program requirements of the REMS.

c. To provide a Medication Guide each time rosiglitazone is dispensed

d. To be audited to ensure that all processes and procedures are in place and are being followed for the Rosiglitazone REMS.

3. Rosiglitazone will only be dispensed to patients with evidence or other documentation of safe-use conditions

GlaxoSmithKline will ensure that rosiglitazone will only be dispensed if there is documentation in the Rosiglitazone REMS Program system that the dispensing pharmacy, prescriber (if the prescriber will prescribe rosiglitazone for outpatient or long-term care use), and patient are all enrolled in the Program. To become enrolled, each patient must review the Medication Guide and sign the *Patient Enrollment Form or VA Patient Enrollment Form* with their prescriber.

The *Patient Enrollment Form* and the *VA Patient Enrollment Form* are appended and part of the REMS.

C. Implementation System

1. GlaxoSmithKline will ensure that pharmacies (including pharmacy distributors) dispensing rosiglitazone are specially certified using the criteria described above.

2. GlaxoSmithKline will ensure that distributors who distribute rosiglitazone are specially certified. Specially certified distributors will agree to:

   a. Distribute rosiglitazone medicines only to pharmacies certified in the Rosiglitazone REMS Program. In the case of patients in longterm care facilities or hospitals, specially certified distributors will provide rosiglitazone on a named patient basis.

   b. Put processes and procedures in place to ensure that the requirements of the Rosiglitazone REMS are followed.

   c. Be audited to ensure that rosiglitazone medicines are distributed according to the REMS

3. GlaxoSmithKline will ensure that all rosiglitazone medicines are withdrawn from uncertified pharmacies within 6 months after the initial approval of the REMS. GlaxoSmithKline will monitor distribution of rosiglitazone to check that these products are being shipped only to certified pharmacies.

4. GlaxoSmithKline will maintain a secure, validated, interactive, web-based database of all enrolled entities (prescribers, pharmacies, patients, and distributors). The database allows certified prescribers to enroll themselves and to enroll patients. Certified pharmacies can access the database to verify patient and prescriber enrollment status as required by the REMS, and dispense rosiglitazone for enrolled patients based on an electronic or written prescription. GlaxoSmithKline will monitor and evaluate implementation of the Rosiglitazone REMS requirements.

5. GlaxoSmithKline will monitor distribution data and prescription data to ensure that only enrolled distributors are distributing, enrolled pharmacies are dispensing, and enrolled prescribers (who prescribe rosiglitazone for outpatient or long-term care use) are prescribing rosiglitazone. Additionally GlaxoSmithKline will monitor to ensure that rosiglitazone is only being dispensed to enrolled patients. Corrective action will be instituted by GlaxoSmithKline if noncompliance is found.
   a. Patients in inpatient facilities will be shipped drug per patient if the patient is enrolled in the REMS program

   b. Patients in long-term care facilities and patients prescribed rosiglitazone for outpatient use will be shipped drug per patient if the patient and the prescriber are enrolled in the REMS Program

6. GlaxoSmithKline will monitor and audit the distribution and dispensing systems to check that all processes and procedures are in place and functioning to support the requirements of the Rosiglitazone REMS.

7. GlaxoSmithKline will maintain a Program Coordinating Center with a Call Center to support patients, prescribers, pharmacies, and distributors in interfacing with the REMS. GlaxoSmithKline will ensure that all materials listed in or appended to the Rosiglitazone Medicines Access REMS Program will be available through the REMS Program website (www.Avandia.com) or by calling the Call Center at 1-800 Avandia.

8. If there are substantive changes to the Rosiglitazone REMS or REMS Program, GlaxoSmithKline will update all affected materials and notify enrolled pharmacies, prescribers, distributors, and patients of the changes, as applicable. Notification for patients will be sent to the patient's prescriber. Substantive changes are defined as:
   a. Significant changes to the operation of the Rosiglitazone REMS or REMS Program, or
   b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of rosiglitazone.

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

10. GlaxoSmithKline will develop and follow written procedures and scripts to implement the REMS.

E. Timetable for Submission of Assessments

GlaxoSmithKline will submit REMS assessments to FDA 6 months, 12 months, and annually from the date of initial approval of this REMSwith 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. GlaxoSmithKline will submit each assessment so that it will be received by the FDA on or before the due date.

GlaxoSmithKline

Avandia Rosiglitazone Medicines Access Program™

Prescriber Program Overview

The Avandia-Rosiglitazone Medicines Access Program (hereafter referred to as the Rosiglitazone Risk Evaluation and Mitigation Strategy [REMS] Program) is being required by the Food and Drug Administration (FDA) for rosiglitazone medicines [i.e., Avandia (rosiglitazone maleate), Avandamet (rosiglitazone maleate/metformin hydrochloride), and Avandaryl (rosiglitazone maleate/glimepiride) to ensure that the benefits of the drugs outweigh the potential increased risk of myocardial infarction associated with their use. This program restricts the availability of rosiglitazone medicines to healthcare providers and patients who are enrolled in the Program. As part of the Rosiglitazone REMS, prescribers are educated about this potential risk and the need to limit the use of rosiglitazone medicines to certain patients.

The Rosiglitazone REMS limits the use of rosiglitazone medicines to

- Patients already taking rosiglitazone, who have been advised by a healthcare professional of the risks and benefits of rosiglitazone, including the potential increased risk of myocardial infarction, or
- Patients not already taking rosiglitazone who are: (1) unable to achieve adequate glycemic control on other diabetes medications, and (2) have been advised of the risks and benefits of rosiglitazone, including the potential increased risk of myocardial infarction, and, (3) in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS®) for medical reasons.

Both prescribers and patients must enroll in the Rosiglitazone REMS Program in order to be able to access rosiglitazone medicines.

Steps to Prescriber Enrollment

1. Review the Prescriber Overview (included in this brochure).
2. Complete the Prescriber Enrollment Form.
3. Submit the Prescriber Enrollment Form to the Coordinating Center either online, over the phone, or by fax.

An enrollment confirmation will be sent to you by e-mail.

You may designate an office contact to assist with data entry activities and any potential communications between your office and the Coordinating Center.

You and your office contact will each receive a username and password to access the web-based system for online patient enrollment.

Once you are enrolled, you can enroll eligible patients into the Rosiglitazone REMS Program.

Steps to Enroll a Patient

1. Determine that the patient is an appropriate candidate for treatment with rosiglitazone.
2. Educate patients on the risks and benefits of taking rosiglitazone, and provide them with a Medication Guide. Encourage them to ask questions about rosiglitazone.
3. Answer the questions your patient may have about rosiglitazone and the Rosiglitazone REMS.
4. Review and complete the Patient Enrollment Form with your patient. Be sure that you both sign the form. Be sure to complete the Prescription Information section of the Patient Enrollment Form. Provide the patient with a copy of the signed Patient Enrollment Form.
5. Either fax the completed Patient Enrollment Form to the Rosiglitazone REMS Coordinating Center or log on to the online system and complete the Patient Enrollment Form. Either fax the prescription and insurance information or attach this information as prompted during online enrollment.
6. Once the Rosiglitazone REMS Program processes the Patient Enrollment Form, the prescription will be submitted to a specially certified mail order pharmacy for dispensing.
7. The patient will receive the rosiglitazone medicine by mail from the mail order pharmacy. Rosiglitazone medicines will not be available through retail pharmacies.

Avandi® rosiglitazone maleate

Avandamet® rosiglitazone maleate/metformin HCl

once daily Avandaryl® rosiglitazone maleate and glimepiride

This document is part of an FDA-approved REMS

Phone: 1-800-AVANDIA

Fax: 1-888-772-9404

www.AVANDIA.com

The Rosiglitazone REMS limits the use of rosiglitazone medicines. After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of rosiglitazone, this drug may be prescribed to:

- Patients already taking a rosiglitazone or
- Patients not already taking rosiglitazone who are unable to achieve glycemic control on other medications, and in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS) for medical reasons.

Rosiglitazone is not recommended in patients with symptomatic heart failure.

Boxed Warning

Potential Risk of Myocardial Infarction

A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with a statistically significant increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067 total patients), comparing AVANDIA to some other approved oral antidiabetic agents or placebo, showed a statistically non-significant increased risk of myocardial infarction, and a statistically non-significant decreased risk of death. There have been no clinical trials directly comparing cardiovascular risk of AVANDIA and ACTOS (pioglitazone, another thiazolidinedione), but in a separate trial, pioglitazone (when compared to placebo) did not show an increased risk of myocardial infarction or death.

For Your Patients Currently Being Treated With Rosiglitazone

You must inform each of your patients currently receiving rosiglitazone of the product's risk information, including the current state of knowledge about the potential increased risk of myocardial infarction associated with the use of rosiglitazone. Also inform patients that pioglitazone (ACTOS) has not been shown to be associated with an increased risk of myocardial infarction. You must document in the patient's medical record that the patient received the Medication Guide and acknowledged understanding of the risk information.

For Your Patients Not Currently Taking Rosiglitazone

Before starting a new patient on rosiglitazone, you must determine that they are unable to achieve glycemic control on other diabetes medications, and (in consultation with you), that they have decided not to take pioglitazone (ACTOS) for medical reasons. You must inform them of the product's risk information, including the current state of knowledge about the potential increased risk of myocardial infarction associated with the use of rosiglitazone. Also inform them that pioglitazone (ACTOS) has not been shown to be associated with an increased risk of myocardial infarction. You must document in the patient's medical record that the patient has received the Medication Guide and acknowledged understanding of the risk information.

Review the Complete Prescribing Information for Avandia®, Avandamet®, and Avandaryl®.

Additional copies of the Program materials are available through the Program website or by faxing or calling the Rosiglitazone REMS Coordinating Center. Please contact the Coordinating Center with questions regarding the Rosiglitazone REMS.

Phone: 1-800-AVANDIA (1-800-282-6342)
Fax: 1-888-772-9404
www.AVANDIA.com

Coordinating Center hours of operation: Monday through Friday from 8:00 AM to 8:00 PM ET

Avandia iglitazone Medicines Access Program™

Prescriber Enrollment Form (Please Print) *indicates required fields

This Prescriber Enrollment Form must be completed before you can prescribe rosiglitazone medicines, including:

- Avandia® (rosiglitazone maleate) Tablets,
- Avandamet® (rosiglitazone maleate and metformin hydrochloride) Tablets, and
- Avandaryl® (rosiglitazone maleate and glimepiride) Tablets.

These medicines are only available through the Rosiglitazone REMS Program.

PRESCRIBER

Prescriber Information

*First Name: _____ MI: _____ *Last Name: _____

*Credentials: ❑ MD ❑ DO ❑ NP ❑ PA ❑ Other

*Specialty: ❑ Endocrinology/Diabetology ❑ Cardiology
❑ Primary Care/Family Practice/General Practice ❑ Other _____

Name of Facility: _____

*Address 1: _____

Address 2: _____

*City: _____ *State: _____ *Zipcode: _____

*Phone Number: _____ *Fax Number: _____

*Email: _____

*National Provider Identification (NPI) Number: _____

or

*State License Number: _____ *State of Issue: _____

Office Contact Information

First Name: _____ Last Name: _____

Phone Number: _____ Fax Number: _____
(if different from above) (if different from above)

*Email (If Office Contact is provided): _____

Avandi® rosiglitazone maleate
Avandamet® rosiglitazone maleate/metformin HCl
once daily Avandaryl® rosiglitazone maleate and glimepiride
gsk GlaxoSmithKline

Reference ID: 3137934

Prescriber Agreement

By signing below, I agree to comply with the following REMS requirements:

- I have read the Rosiglitazone REMS Prescriber Overview and the Full Prescribing Information.
- I understand that rosiglitazone may be associated with an increased risk of myocardial infarction, and this is the reason that this Program is necessary.
- I understand that only patients who meet one of the following criteria are eligible to receive rosiglitazone:
  - Patients currently taking rosiglitazone who have been advised by me of the risks and benefits of rosiglitazone, including the potential increased risk of myocardial infarction, and have acknowledged that they understand the potential risk, and have agreed to enroll in the REMS Program.
  - Patients not currently taking rosiglitazone who are unable to achieve glycemic control on other medications, have acknowledged that they understand the potential increased risk of myocardial infarction associated with the use of rosiglitazone, and in consultation with me, have decided not to take the alternative medication pioglitazone (ACTOS®) for medical reasons, and have agreed to enroll in the REMS Program.
- After obtaining the patient's or caregiver's signature, I will complete and sign a Rosiglitazone REMS Patient Enrollment Form for each patient enrolled and submit it to the Rosiglitazone REMS Program.
- In signing, the Patient Enrollment Form, I document the patient is eligible to receive rosiglitazone because he/she meets the criteria in one of the two categories listed above. The Medication Guide for the prescribed rosiglitazone medicine has been provided to and reviewed with the patient or caregiver.
- The patient has acknowledged understanding about the potential increased risk of myocardial infarction associated with the use of rosiglitazone.
- I will provide a completed, signed copy of the Patient Enrollment Form to the patient, and retain a copy for my records. I will also provide a completed signed copy or verification that I have obtained the patient's signature (for online enrollment) to the Rosiglitazone REMS Program. I understand the pharmacy cannot dispense a rosiglitazone medicine without this documentation.
- I understand that if I fail to maintain compliance with the requirements of the Rosiglitazone REMS Program, I will no longer be able to participate in the Program, and therefore will not be able to prescribe rosiglitazone.
- I may provide an office contact to assist with data entry activities and any potential communications between my office and the Rosiglitazone REMS Program. My office contact and I will receive a user name and password to access the web-based system for online patient enrollment into the Rosiglitazone REMS Program.
- I understand that the Rosiglitazone REMS Program may contact me to resolve discrepancies, to obtain information about a patient, or to provide other information related to the Rosiglitazone REMS Program.

***Prescriber Signature:** _____ ***Date** (MM/DD/YY): _____

I may cancel this enrollment by notifying the Rosiglitazone REMS Program by fax at 1-888-772-9404 or by phone at 1-800-282-6342. The Rosiglitazone REMS Program may dis-enroll prescribers who are not compliant with the Program requirements.

Avandi® rosiglitazone maleate
Avandamet® rosiglitazone maleate/metformin HCl
once daily Avandaryl® rosiglitazone maleate and glimepiride
gsk GlaxoSmithKline

Reference ID: 3137934

Avandia Rosiglitazone Medicines Access Program™

Patient Enrollment Form (Please Print) *indicates required fields

***First Name:**_____ **MI:** ____ ***Last Name:** _____ ***DOB** (MM/DD/YY): _____

This Patient Enrollment Form must be completed by you and your doctor or healthcare provider before you can receive a rosiglitazone medicine. Rosiglitazone medicines are available only through the **Avandia-Rosiglitazone Medicines Access Program, hereafter called the** Rosiglitazone Risk Evaluation and Mitigation Strategy (REMS) Program. You will not be able to get your medicine at your local pharmacy. You will receive your medicine by mail.

These medicines contain rosiglitazone:

- AVANDIA® (rosiglitazone maleate)
- AVANDAMET® (rosiglitazone maleate and metformin hydrochloride)
- AVANDARYL® (rosiglitazone maleate and glimepiride)

Patient Agreement

By signing this form, I agree that:

- I have read and talked with my doctor or healthcare provider about the risk information in the Medication Guide for the rosiglitazone medicine prescribed for me.
- I understand the risk information that my doctor or healthcare provider has talked about with me, including that these medicines may increase my risk of having a heart attack. My doctor has talked to me about the risks associated with alternative medicines containing pioglitazone (ACTOS®), which has not been shown to be associated with an increased risk of having a heart attack.
- I have had enough time with my doctor or healthcare provider before signing this form to ask him or her questions and talk about any concerns I have about rosiglitazone medicines or my diabetes treatment.
- I understand that to get a rosiglitazone medicine, I have to enroll in the Rosiglitazone REMS Program.
- I understand that the Rosiglitazone REMS Program may contact me by phone, mail or email for more information about my taking part in the Rosiglitazone REMS Program.
- I give permission to my doctor, pharmacists, and any other healthcare providers (together "my Providers") participating in the Rosiglitazone REMS Program established by GlaxoSmithKline (GSK) and to the Rosiglitazone REMS Program Coordinating Center to share my personally identifiable health information, including prescription information, and my name, address, and telephone number (together my "Protected Health Information") for the purposes of enrolling me into the Rosiglitazone REMS Program, filling my prescriptions and managing the Program.
- I understand that all information collected on the enrollment form will be stored in a secure database maintained by the Coordinating Center.

After joining the program, if you do not get your first prescription within about two weeks, call your health care provider or the Rosiglitazone REMS Program at 1-800-AVANDIA (1-800-282-6342).

***Patient/Guardian Signature:**_____ ***Date** (MM/DD/YY): _____

Printed Name of Guardian:_____

Avandi® rosiglitazone maleate

Avandamet® rosiglitazone maleate/metformin HCl

once daily Avandaryl® rosiglitazone maleate and glimepiride

GlaxoSmithKline

This document is part of an FDA-approved REMS

Phone: 1-800-AVANDIA **Fax: 1-888-772-9404** **www.AVANDIA.com**

Reference ID: 3137934

Avandia iglitazone Medicines Access Program™

Patient Enrollment Form (Please Print) *indicates required fields

PATIENT

Patient Information

*First Name: _____ MI: _____ *Last Name: _____

*Date of Birth (MM/DD/YY): _____ *Gender: ❑ Female ❑ Male

*Address 1: _____

Address 2: _____

*City: _____ *State: _____ *ZIP Code: _____

*Phone: _____ Alternate Phone: _____

Email: _____

*Do you have insurance: YES ❑ NO ❑

*Is the patient: ❑ new to rosiglitazone therapy ❑ continuing rosiglitazone therapy

*Is the patient: ❑ Outpatient ❑ Long-term Care ❑ Hospitalized

FAX ALL PATIENT INSURANCE INFORMATION, INCLUDING DRUG BENEFIT CARDS (FRONT AND BACK) WITH THIS ENROLLMENT FORM TO 1 888 772 9404.

PRESCRIBER

Prescriber Information

*First Name: _____ MI: _____ *Last Name: _____

*National Provider Identification (NPI) Number: _____

or

*State License Number: _____ *State of Issue: _____

Name of Facility (if applicable): _____

*Phone Number: _____

PRESCRIPTION

Prescription Information (to be completed by your doctor or other healthcare provider):

Prescription:

❑ AVANDIA _____ (Strength (mg)) _____ (Quantity)

❑ AVANDAMET _____ (Strength (mg)) _____ (Quantity)

❑ AVANDARYL _____ (Strength (mg)) _____ (Quantity)

Provide Dosing Instructions: _____

Number of refills: _____

By signing this form, I acknowledge that I have discussed the risk information with this patient. I have documented in his/her medical record that this patient meets the eligibility criteria for enrollment into the Rosiglitazone REMS Program.

*Prescriber Signature: _____ *Date (MM/DD/YY): _____

Printed Name of Prescriber: _____

Please fax the completed form to 1-888-772-9404 and provide a copy of this form to the patient.

Avandi® rosiglitazone maleate

Avandamet® ro iglitazone maleate/metfor in HCl

once daily Avandaryl® ro iglitazone maleate and glime i ide

gsk GlaxoSmithKline

This document is part of an FDA-approved REMS.

Phone: 1-800-AVANDIA **Fax: 1-888-772-9404** **www.AVANDIA.com**

Reference ID: 3137934

Avandia Rosiglitazone Medicines Access Program™

FOR V.A. USE ONLY

V.A. Patient Enrollment Form (Please Print) *indicates required fields

***First Name:**_____ **MI:** ____ ***Last Name:** _____ ***DOB** (MM/DD/YY): _____

This Patient Enrollment Form must be completed by you and your doctor or healthcare provider before you can receive a rosiglitazone medicine. Rosiglitazone medicines are available only through the **Avandia-Rosiglitazone Medicines Access Program, hereafter called the** Rosiglitazone Risk Evaluation and Mitigation Strategy (REMS) Program. You will not be able to get your medicine at your local pharmacy. You will receive your medicine by mail.

These medicines contain rosiglitazone:

- AVANDIA® (rosiglitazone maleate)
- AVANDAMET® (rosiglitazone maleate and metformin hydrochloride)
- AVANDARYL® (rosiglitazone maleate and glimepiride)

Patient Agreement

By signing this form, I agree that:

- I have read and talked with my doctor or healthcare provider about the risk information in the Medication Guide for the rosiglitazone medicine prescribed for me.
- I understand the risk information that my doctor or healthcare provider has talked about with me, including that these medicines may increase my risk of having a heart attack. My doctor has talked to me about the risks associated with alternative medicines containing pioglitazone (ACTOS®), which has not been shown to be associated with an increased risk of having a heart attack.
- I have had enough time with my doctor or healthcare provider before signing this form to ask him or her questions and talk about any concerns I have about rosiglitazone medicines or my diabetes treatment.
- I understand that to get a rosiglitazone medicine, I have to enroll in the Rosiglitazone REMS Program.
- I understand that the Rosiglitazone REMS Program may contact me by phone, mail or email for more information about my taking part in the Rosiglitazone REMS Program.
- I give permission to my doctor, pharmacists, and any other healthcare providers (together "my Providers") participating in the Rosiglitazone REMS Program established by GlaxoSmithKline (GSK) and to the Rosiglitazone REMS Program Coordinating Center to share my personally identifiable health information, including prescription information, and my name, address, and telephone number (together my "Protected Health Information") for the purposes of enrolling me into the Rosiglitazone REMS Program, filling my prescriptions and managing the Program.
- I understand that all information collected on the enrollment form will be stored in a secure database maintained by the Coordinating Center.

After joining the program, if you do not get your first prescription within about two weeks, call your health care provider or the Rosiglitazone REMS Program at 1-800-AVANDIA (1-800-282-6342).

***Patient/Guardian Signature:**_____ ***Date** (MM/DD/YY): _____

Printed Name of Guardian:_____

Avandia® rosiglitazone maleate

Avandamet® rosiglitazone maleate/metformin HCl

once daily Avandaryl® rosiglitazone maleate and glimepiride

GlaxoSmithKline

This document is part of an FDA-approved REMS.

Phone: 1-800-AVANDIA **Fax: 1-888-772-9404** **www.AVANDIA.com**

Reference ID: 3137934

Avandia Rosiglitazone Maleate Access Program™

FOR V.A. USE ONLY

V.A. Patient Enrollment Form (Please Print) *indicates required fields

PATIENT

Patient Information

*First Name: _____ MI: _____ *Last Name: _____

*Date of Birth (MM/DD/YY): _____ *Gender: ❑ Female ❑ Male

*Address 1: _____

Address 2: _____

*City: _____ *State: _____ *ZIP Code: _____

*Phone: _____ Alternate Phone: _____

Email: _____

*Is the patient: ❑ new to rosiglitazone therapy ❑ continuing rosiglitazone therapy

*Is the patient: ❑ Outpatient ❑ Long-term Care ❑ Hospitalized

VA PATIENT – INSURANCE NOT REQUIRED

PRESCRIBER

Prescriber Information

*First Name: _____ MI: _____ *Last Name: _____

*National Provider Identification (NPI) Number: _____

or

*State License Number: _____ *State of Issue: _____

*Name of VA Facility: _____

*Phone Number: _____ *Pharmacy Secure Fax Number: _____

PRESCRIPTION

Prescription Information (to be completed by your doctor or other healthcare provider):

Prescription: ❑ AVANDIA _____ (Strength (mg)) _____ (Quantity)

❑ AVANDAMET _____ (Strength (mg)) _____ (Quantity)

❑ AVANDARYL _____ (Strength (mg)) _____ (Quantity)

Provide Dosing Instructions: _____

Number of refills: _____

SHIPPING

Shipping Information

*Ship to: ❑ Patient Home (address listed above) ❑ V.A. Pharmacy (address listed below–all fields required)

VA Facility Name: _____

Address: _____

V.A. Pharmacy Contact: _____

City: _____ State: _____ ZIP Code: _____

Phone Number: _____ Pharmacy Secure Fax Number: _____

By signing this form, I acknowledge that I have discussed the risk information with this patient. I have documented in his/her medical record that this patient meets the eligibility criteria for enrollment into the Rosiglitazone REMS Program.

***Prescriber Signature:** _____ ***Date** (MM/DD/YY): _____

Printed Name of Prescriber: _____

Please have the pharmacy fax the completed form to 1-888-772-9404 and provide a copy of this form to the patient.

Avandi® rosiglitazone maleate | Avandamet® rosiglitazone maleate/metformin HCl | once daily Avandaryl® rosiglitazone maleate and glimepiride

GlaxoSmithKline

This document is part of an FDA-approved REMS.

Phone: 1-800-AVANDIA **Fax: 1-888-772-9404** **www.AVANDIA.com**

Reference ID: 3137934

Welcome to the Avandia-Rosiglitazone Medicines Access Program

Avandia-Rosiglitazone Medicines Access Program™

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.

SAFETY INFORMATION CONTINUED BELOW

LOG IN

Prescribing Information | Medication Guide

For more information about the Avandia-Rosiglitazone Medicines Access Program, please tell us who you are:

I am a Patient

I am a Prescriber

I am a Pharmacist

Avandia® rosiglitazone maleate

Avandamet® rosiglitazone maleate/metformin HCl

once daily Avandaryl® rosiglitazone maleate and glimepiride

Complete Prescribing Information, including Boxed WARNING and Medication Guide, for AVANDIA, AVANDAMET, and AVANDARYL.

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

AVANDIA, AVANDAMET and AVANDARYL may increase your risk of a heart attack (myocardial infarction). This risk may be higher in people who are also taking insulin. **Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.**

This is not a complete description of the risks associated with rosiglitazone. Please refer to Boxed Warnings and full Prescribing Information.

600 pixel line

For more information about AVANDIA, please see Medication Guide and full Prescribing Information, including Boxed WARNING.

For more information about AVANDAMET, please see Medication Guide and full Prescribing Information, including Boxed WARNING.

For more information about AVANDARYL, please see Medication Guide and full Prescribing Information, including Boxed WARNING.

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.

Contact the Coordinating Center

gsk GlaxoSmithKline

Avandia-Rosiglitazone Medicines Access Program
Prescriber Overview

Avandia-Rosiglitazone Medicines Access Program™

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.

SAFETY INFORMATION CONTINUED BELOW

LOG IN

The Avandia-Rosiglitazone Medicines Access Program is being required by the Food and Drug Administration (FDA) for rosiglitazone medicines [i.e., AVANDIA (rosiglitazone maleate), AVANDAMET (rosiglitazone maleate/metformin hydrochloride), and AVANDARYL (rosiglitazone maleate and glimepiride) to ensure that the benefits of the drugs outweigh the potential increased risk of myocardial infarction associated with their use. This program restricts the availability of rosiglitazone medicines to healthcare providers and patients who are enrolled in the Program. As part of the Avandia-Rosiglitazone Medicines Access Program, prescribers are educated about this potential risk and the need to limit the use of rosiglitazone medicines to certain patients.

The Avandia-Rosiglitazone Medicines Access Program limits the use of rosiglitazone medicines to

- Patients already taking rosiglitazone, who have been advised by a healthcare professional of the risks and benefits of rosiglitazone, including the potential increased risk of myocardial infarction, or
- Patients not already taking rosiglitazone who are: (1) unable to achieve adequate glycemic control on other diabetes medications, and (2) have been advised of the risks and benefits of rosiglitazone, including the potential increased risk of myocardial infarction, and, (3) in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS®) for medical reasons.

Both prescribers and patients must enroll in the Avandia-Rosiglitazone Medicines Access Program in order to be able to access rosiglitazone medicines.

Enroll in the Avandia-Rosiglitazone Medicines Access Program

600 pixel line

Complete Prescribing Information, including Boxed WARNING and Medication Guide, for AVANDIA, AVANDAMET, and AVANDARYL.

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

AVANDIA, AVANDAMET and AVANDARYL may increase the risk of a myocardial infarction. This risk may be higher in people who are also taking insulin. **Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.**

This is not a complete description of the risks associated with rosiglitazone. Please refer to Boxed Warnings and full Prescribing Information.

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.

Contact the Coordinating Center

gsk GlaxoSmithKline

Avandia-Rosiglitazone Medicines Access Program
How Do I Enroll?

Avandia-Rosiglitazone Medicines Access Program™

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.

SAFETY INFORMATION CONTINUED BELOW

For Prescribers:

Only healthcare providers enrolled in the Avandia-Rosiglitazone Medicines Access Program can prescribe rosiglitazone medicines, including:

- **AVANDIA (rosiglitazone maleate) Tablets,**
- **AVANDAMET (rosiglitazone maleate and metformin hydrochloride) Tablets, and**
- **AVANDARYL (rosiglitazone maleate and glimepiride) Tablets.**

Because of a potential increased risk of myocardial infarction, these medicines are only available through the Avandia-Rosiglitazone Medicines Access Program.

Steps to Prescriber Enrollment

1. Review the Prescriber Overview.
2. Complete the Prescriber Enrollment Form.
3. Submit the Prescriber Enrollment Form to the Coordinating Center either online, over the phone, or by fax.
   - An enrollment confirmation will be sent to you by e-mail.

You may designate an office contact to assist with communications between your office and the Coordinating Center.

You and your office contact will each receive a user name and password to access the Web-based system for online patient enrollment.

Once you are enrolled, you can enroll eligible patients into the Avandia-Rosiglitazone Medicines Access Program.

Download Prescriber Overview

Download Prescriber Enrollment Form

Prescriber Enrollment Online

Enroll a Patient in the Avandia-Rosiglitazone Medicines Access Program

600 pixel line

Complete Prescribing Information, including Boxed WARNING and Medication Guide, for **AVANDIA**, **AVANDAMET**, and **AVANDARYL**.

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

AVANDIA, AVANDAMET and AVANDARYL may increase the risk of a myocardial infarction. This risk may be higher in people who are also taking insulin. **Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.**

This is not a complete description of the risks associated with rosiglitazone. Please refer to Boxed Warnings and full Prescribing Information.

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.

Contact the Coordinating Center

gsk GlaxoSmithKline

Avandia-Rosiglitazone Medicines Access Program
How Do I Enroll a Patient?

Avandia-Rosiglitazone Medicines Access Program™

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.

SAFETY INFORMATION CONTINUED BELOW

Steps to Enroll a Patient

1. Determine that the patient is an appropriate candidate for treatment with rosiglitazone.
2. Educate patients on the risks and benefits of taking rosiglitazone, and provide them with a Medication Guide. Encourage them to ask questions about rosiglitazone.
3. Answer the questions your patient may have about rosiglitazone and the Avandia-Rosiglitazone Medicines Access Program.
4. Review and complete the Patient Enrollment Form with your patient. Be sure that you both sign the form. Be sure to complete the Prescription Information section of the Patient Enrollment Form. Provide the patient with a copy of the signed Patient Enrollment Form.
5. Either fax the completed Patient Enrollment Form to the Avandia-Rosiglitazone Medicines Access Program Coordinating Center or log on to the online system and complete the Patient Enrollment Form. Either fax the prescription and insurance information or attach this information as prompted during online enrollment.
6. Once the Avandia-Rosiglitazone Medicines Access Program processes the Patient Enrollment Form, the prescription will be submitted to a specially certified mail-order pharmacy for dispensing.
7. The patient will receive the rosiglitazone medicine by mail from the mail-order pharmacy. Rosiglitazone medicines will not be available through retail pharmacies.

Download Patient Enrollment Form

English Enrollment Form

Spanish Enrollment Form

Download Veteran's Administration (VA) Patient Enrollment Form

Complete Patient Enrollment Online

600 pixel line

Complete Prescribing Information, including Boxed WARNING and Medication Guide, for AVANDIA, AVANDAMET, and AVANDARYL.

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

AVANDIA, AVANDAMET and AVANDARYL may increase the risk of a myocardial infarction. This risk may be higher in people who are also taking insulin. **Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.**

This is not a complete description of the risks associated with rosiglitazone. Please refer to Boxed Warnings and full Prescribing Information.

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.

Contact the Coordinating Center

gsk GlaxoSmithKline

Avandia-Rosiglitazone Medicines Access Program
How Do I Enroll a Patient?

Avandia-Rosiglitazone Medicines Access Program™

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.

SAFETY INFORMATION CONTINUED BELOW

Steps to Enroll a Patient

1. Determine that the patient is an appropriate candidate for treatment with rosiglitazone.
2. Educate patients on the risks and benefits of taking rosiglitazone, and provide them with a Medication Guide. Encourage them to ask questions about rosiglitazone.
3. Answer the questions your patient may have about rosiglitazone and the Avandia-Rosiglitazone Medicines Access Program.
4. Review and complete the Patient Enrollment Form with your patient. Be sure that you both sign the form. Be sure to complete the Prescription Information section of the Patient Enrollment Form. Provide the patient with a copy of the signed Patient Enrollment Form.
5. Either fax the completed Patient Enrollment Form to the Avandia-Rosiglitazone Medicines Access Program Coordinating Center or log on to the online system and complete the Patient Enrollment Form. Either fax the prescription and insurance information or attach this information as prompted during online enrollment.
6. Once the Avandia-Rosiglitazone Medicines Access Program processes the Patient Enrollment Form, the prescription will be submitted to a specially certified mail-order pharmacy for dispensing.
7. The patient will receive the rosiglitazone medicine by mail from the mail-order pharmacy. Rosiglitazone medicines will not be available through retail pharmacies.

Download Patient Enrollment Form

Download Veteran's Administration (VA) Patient Enrollment Form

English Veteran's Administration

Spanish Veteran's Administration

Complete Patient Enrollment Online

600 pixel line

Complete Prescribing Information, including Boxed WARNING and Medication Guide, for AVANDIA, AVANDAMET, and AVANDARYL.

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

AVANDIA, AVANDAMET and AVANDARYL may increase the risk of a myocardial infarction. This risk may be higher in people who are also taking insulin. **Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.**

This is not a complete description of the risks associated with rosiglitazone. Please refer to Boxed Warnings and full Prescribing Information.

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.

Contact the Coordinating Center

gsk GlaxoSmithKline

Avandia-Rosiglitazone Medicines Access Program
Information for Patients

Avandia-Rosiglitazone Medicines Access Program™

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.

SAFETY INFORMATION CONTINUED BELOW

Patient Enrollment Form

- English Enrollment Form
- Spanish Enrollment Form

Veteran's Administration (VA) Patient Enrollment Form

Medication Guide

600 pixel line

Complete Prescribing Information, including Boxed WARNING and Medication Guide, for AVANDIA, AVANDAMET, and AVANDARYL.

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

AVANDIA, AVANDAMET and AVANDARYL may increase your risk of a heart attack (myocardial infarction). This risk may be higher in people who are also taking insulin. **Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.**

This is not a complete description of the risks associated with rosiglitazone. Please refer to Boxed Warnings and full Prescribing Information.

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.

Contact the Coordinating Center

gsk GlaxoSmithKline

Avandia-Rosiglitazone Medicines Access Program
Information for Patients

Avandia-Rosiglitazone Medicines Access Program™

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.

SAFETY INFORMATION CONTINUED BELOW

Patient Enrollment Form

Veteran's Administration (VA) Patient Enrollment Form

Medication Guide

- English Medication Guide
- Spanish Medication Guide

600 pixel line

Complete Prescribing Information, including Boxed WARNING and Medication Guide, for AVANDIA, AVANDAMET, and AVANDARYL.

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

AVANDIA, AVANDAMET and AVANDARYL may increase your risk of a heart attack (myocardial infarction). This risk may be higher in people who are also taking insulin. **Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.**

This is not a complete description of the risks associated with rosiglitazone. Please refer to Boxed Warnings and full Prescribing Information.

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.

Contact the Coordinating Center

gsk GlaxoSmithKline

Avandia-Rosiglitazone Medicines Access Program
Information for Patients

Avandia-Rosiglitazone Medicines Access Program™

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.

SAFETY INFORMATION CONTINUED BELOW

Patient Enrollment Form

Veteran's Administration (VA) Patient Enrollment Form

- English Veteran's Administration
- Spanish Veteran's Administration

Medication Guide

600 pixel line

Complete Prescribing Information, including Boxed WARNING and Medication Guide, for AVANDIA, AVANDAMET, and AVANDARYL.

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

AVANDIA, AVANDAMET and AVANDARYL may increase your risk of a heart attack (myocardial infarction). This risk may be higher in people who are also taking insulin. **Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.**

This is not a complete description of the risks associated with rosiglitazone. Please refer to Boxed Warnings and full Prescribing Information.

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.

Contact the Coordinating Center

gsk GlaxoSmithKline

Avandia-Rosiglitazone Medicines Access Program
Pharmacist Overview

Avandia-Rosiglitazone Medicines Access Program™

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.

SAFETY INFORMATION CONTINUED BELOW

Under the Avandia-Rosiglitazone Medicines Access Program, there is a restricted access and dispensing system for rosiglitazone medicines.

Please refer any patients with questions about rosiglitazone medicines or enrollment in the Program to their healthcare provider.

600 pixel line

Complete Prescribing Information, including Boxed WARNING and Medication Guide, for AVANDIA, AVANDAMET, and AVANDARYL.

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

AVANDIA, AVANDAMET and AVANDARYL may increase the risk of a myocardial infarction. This risk may be higher in people who are also taking insulin. **Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.**

This is not a complete description of the risks associated with rosiglitazone. Please refer to Boxed Warnings and full Prescribing Information.

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.

Contact the Coordinating Center

gsk GlaxoSmithKline

Avandia-Rosiglitazone Medicines Access Program Coordinating Center

Avandia-Rosiglitazone Medicines Access Program™

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.

SAFETY INFORMATION CONTINUED BELOW

Please call the Coordinating Center with questions about the Avandia-Rosiglitazone Medicines Access Program.

Phone: 1-800-AVANDIA (1-800-282-6342)
Fax: 1-888-772-9404

Avandia-Rosiglitazone Medicines Access Program
PO 4649
Star City, WV 26504-4649

Hours of Operation:
Monday through Friday from 8:00 AM to 8:00 PM ET

600 pixel line

Complete Prescribing Information, including Boxed WARNING and Medication Guide, for AVANDIA, AVANDAMET, and AVANDARYL.

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

AVANDIA, AVANDAMET and AVANDARYL may increase your risk of a heart attack (myocardial infarction). This risk may be higher in people who are also taking insulin. **Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.**

This is not a complete description of the risks associated with rosiglitazone. Please refer to Boxed Warnings and full Prescribing Information.

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.

Contact the Coordinating Center

gsk GlaxoSmithKline

Welcome to the Avandia-Rosiglitazone Medicines Access Program

Avandia-Rosiglitazone Medicines Access Program™

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.

SAFETY INFORMATION CONTINUED BELOW

User Name

Password

LOG IN

Forgot Password?

Login is available only if a username and password has been received from the Avandia-Rosiglitazone Medicines Access Program.

How Does a Prescriber Enroll in the Avandia-Rosiglitazone Medicines Access Program?

Login is available for enrolled Prescribers, designated Office Contacts and designated Pharmacies only.
To learn more about the Avandia-Rosiglitazone Medicines Access Program, please click here.

To enroll in the Avandia-Rosiglitazone Medicines Access Program, you must review the Prescriber Overview.

600 pixel line

Complete Prescribing Information, including Boxed WARNING and Medication Guide, for AVANDIA, AVANDAMET, and AVANDARYL.

IMPORTANT SAFETY INFORMATION about AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) and AVANDARYL® (rosiglitazone maleate and glimepiride).

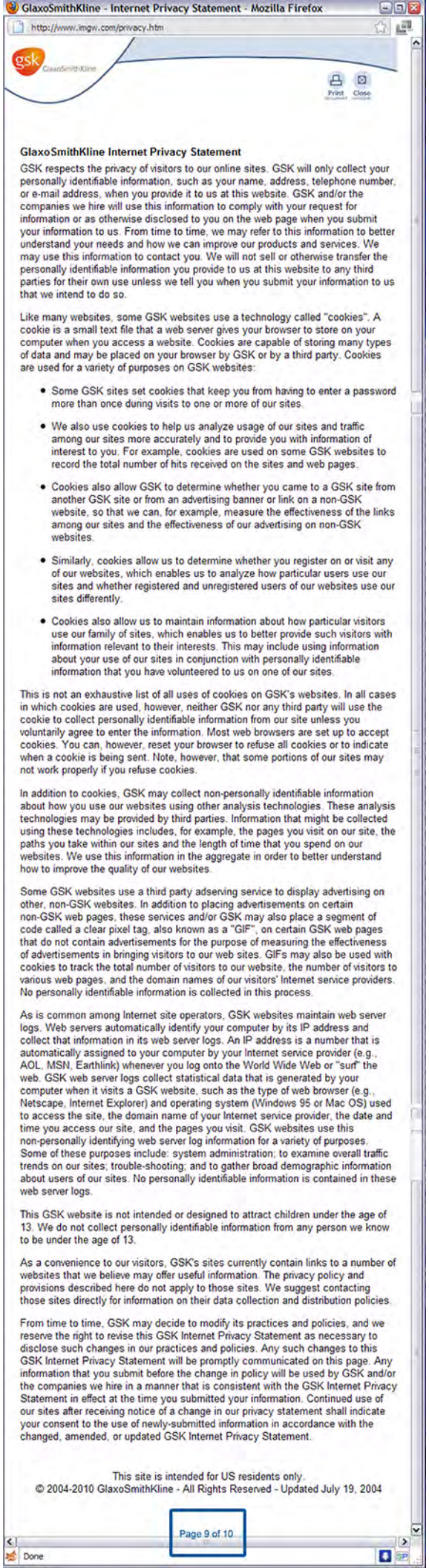
AVANDIA, AVANDAMET and AVANDARYL may increase the risk of a myocardial infarction. This risk may be higher in people who are also taking insulin. **Because of a potential increased risk of myocardial infarction, AVANDIA, AVANDAMET, and AVANDARYL are available only through the AVANDIA-Rosiglitazone Medicines Access Program.**

This is not a complete description of the risks associated with rosiglitazone. Please refer to Boxed Warnings and full Prescribing Information.

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.

Contact the Coordinating Center

gsk GlaxoSmithKline


GlaxoSmithKline - Internet Privacy Statement - Mozilla Firefox
http://www.imgw.com/privacy.htm
Print
Close

GlaxoSmithKline Internet Privacy Statement

GSK respects the privacy of visitors to our online sites. GSK will only collect your personally identifiable information, such as your name, address, telephone number, or e-mail address, when you provide it to us at this website. GSK and/or the companies we hire will use this information to comply with your request for information or as otherwise disclosed to you on the web page when you submit your information to us. From time to time, we may refer to this information to better understand your needs and how we can improve our products and services. We may use this information to contact you. We will not sell or otherwise transfer the personally identifiable information you provide to us at this website to any third parties for their own use unless we tell you when you submit your information to us that we intend to do so.

Like many websites, some GSK websites use a technology called "cookies". A cookie is a small text file that a web server gives your browser to store on your computer when you access a website. Cookies are capable of storing many types of data and may be placed on your browser by GSK or by a third party. Cookies are used for a variety of purposes on GSK websites:

- Some GSK sites set cookies that keep you from having to enter a password more than once during visits to one or more of our sites.
- We also use cookies to help us analyze usage of our sites and traffic among our sites more accurately and to provide you with information of interest to you. For example, cookies are used on some GSK websites to record the total number of hits received on the sites and web pages.
- Cookies also allow GSK to determine whether you came to a GSK site from another GSK site or from an advertising banner or link on a non-GSK website, so that we can, for example, measure the effectiveness of the links among our sites and the effectiveness of our advertising on non-GSK websites.
- Similarly, cookies allow us to determine whether you register on or visit any of our websites, which enables us to analyze how particular users use our sites and whether registered and unregistered users of our websites use our sites differently.
- Cookies also allow us to maintain information about how particular visitors use our family of sites, which enables us to better provide such visitors with information relevant to their interests. This may include using information about your use of our sites in conjunction with personally identifiable information that you have volunteered to us on one of our sites.

This is not an exhaustive list of all uses of cookies on GSK's websites. In all cases in which cookies are used, however, neither GSK nor any third party will use the cookie to collect personally identifiable information from our site unless you voluntarily agree to enter the information. Most web browsers are set up to accept cookies. You can, however, reset your browser to refuse all cookies or to indicate when a cookie is being sent. Note, however, that some portions of our sites may not work properly if you refuse cookies.

In addition to cookies, GSK may collect non-personally identifiable information about how you use our websites using other analysis technologies. These analysis technologies may be provided by third parties. Information that might be collected using these technologies includes, for example, the pages you visit on our site, the paths you take within our sites and the length of time that you spend on our websites. We use this information in the aggregate in order to better understand how to improve the quality of our websites.

Some GSK websites use a third party adserving service to display advertising on other, non-GSK websites. In addition to placing advertisements on certain non-GSK web pages, these services and/or GSK may also place a segment of code called a clear pixel tag, also known as a "GIF", on certain GSK web pages that do not contain advertisements for the purpose of measuring the effectiveness of advertisements in bringing visitors to our web sites. GIFs may also be used with cookies to track the total number of visitors to our website, the number of visitors to various web pages, and the domain names of our visitors' Internet service providers. No personally identifiable information is collected in this process.

As is common among Internet site operators, GSK websites maintain web server logs. Web servers automatically identify your computer by its IP address and collect that information in its web server logs. An IP address is a number that is automatically assigned to your computer by your Internet service provider (e.g., AOL, MSN, Earthlink) whenever you log onto the World Wide Web or "surf" the web. GSK web server logs collect statistical data that is generated by your computer when it visits a GSK website, such as the type of web browser (e.g., Netscape, Internet Explorer) and operating system (Windows 95 or Mac OS) used to access the site, the domain name of your Internet service provider, the date and time you access our site, and the pages you visit. GSK websites use this non-personally identifying web server log information for a variety of purposes. Some of these purposes include: system administration; to examine overall traffic trends on our sites; trouble-shooting; and to gather broad demographic information about users of our sites. No personally identifiable information is contained in these web server logs.

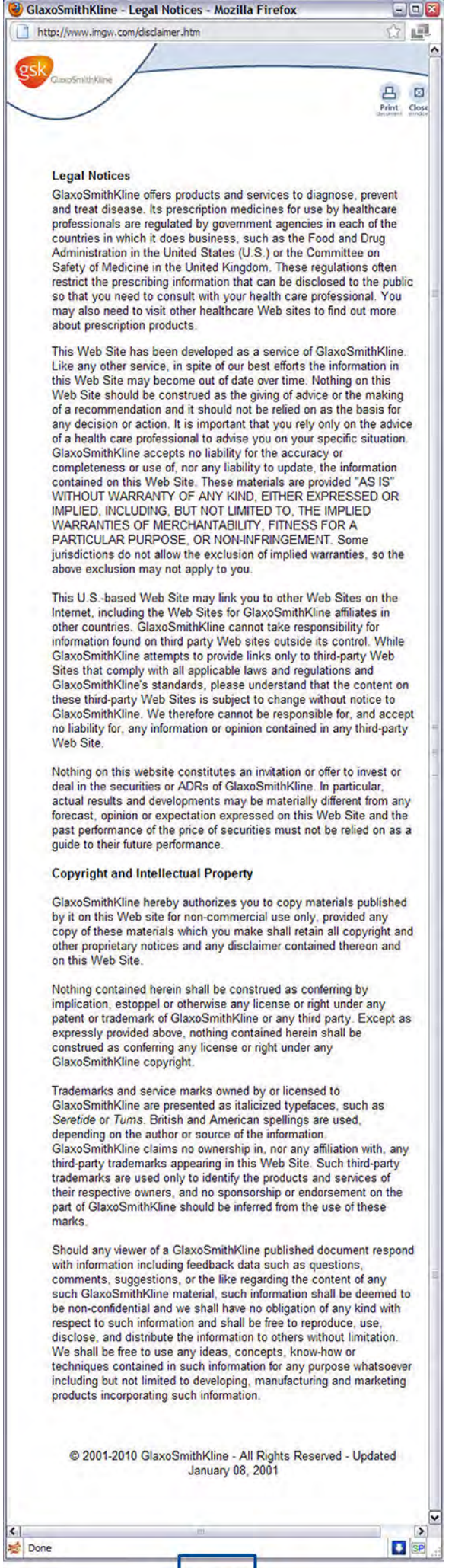
This GSK website is not intended or designed to attract children under the age of 13. We do not collect personally identifiable information from any person we know to be under the age of 13.

As a convenience to our visitors, GSK's sites currently contain links to a number of websites that we believe may offer useful information. The privacy policy and provisions described here do not apply to those sites. We suggest contacting those sites directly for information on their data collection and distribution policies.

From time to time, GSK may decide to modify its practices and policies, and we reserve the right to revise this GSK Internet Privacy Statement as necessary to disclose such changes in our practices and policies. Any such changes to this GSK Internet Privacy Statement will be promptly communicated on this page. Any information that you submit before the change in policy will be used by GSK and/or the companies we hire in a manner that is consistent with the GSK Internet Privacy Statement in effect at the time you submitted your information. Continued use of our sites after receiving notice of a change in our privacy statement shall indicate your consent to the use of newly-submitted information in accordance with the changed, amended, or updated GSK Internet Privacy Statement.

This site is intended for US residents only.

Done


GlaxoSmithKline - Legal Notices - Mozilla Firefox
http://www.imgw.com/disclaimer.htm
gsk
GlaxoSmithKline
Print
Close
Legal Notices
GlaxoSmithKline offers products and services to diagnose, prevent and treat disease. Its prescription medicines for use by healthcare professionals are regulated by government agencies in each of the countries in which it does business, such as the Food and Drug Administration in the United States (U.S.) or the Committee on Safety of Medicine in the United Kingdom. These regulations often restrict the prescribing information that can be disclosed to the public so that you need to consult with your health care professional. You may also need to visit other healthcare Web sites to find out more about prescription products.
This Web Site has been developed as a service of GlaxoSmithKline. Like any other service, in spite of our best efforts the information in this Web Site may become out of date over time. Nothing on this Web Site should be construed as the giving of advice or the making of a recommendation and it should not be relied on as the basis for any decision or action. It is important that you rely only on the advice of a health care professional to advise you on your specific situation. GlaxoSmithKline accepts no liability for the accuracy or completeness or use of, nor any liability to update, the information contained on this Web Site. These materials are provided "AS IS" WITHOUT WARRANTY OF ANY KIND, EITHER EXPRESSED OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, THE IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, OR NON-INFRINGEMENT. Some jurisdictions do not allow the exclusion of implied warranties, so the above exclusion may not apply to you.
This U.S.-based Web Site may link you to other Web Sites on the Internet, including the Web Sites for GlaxoSmithKline affiliates in other countries. GlaxoSmithKline cannot take responsibility for information found on third party Web sites outside its control. While GlaxoSmithKline attempts to provide links only to third-party Web Sites that comply with all applicable laws and regulations and GlaxoSmithKline's standards, please understand that the content on these third-party Web Sites is subject to change without notice to GlaxoSmithKline. We therefore cannot be responsible for, and accept no liability for, any information or opinion contained in any third-party Web Site.
Nothing on this website constitutes an invitation or offer to invest or deal in the securities or ADRs of GlaxoSmithKline. In particular, actual results and developments may be materially different from any forecast, opinion or expectation expressed on this Web Site and the past performance of the price of securities must not be relied on as a guide to their future performance.
Copyright and Intellectual Property
GlaxoSmithKline hereby authorizes you to copy materials published by it on this Web site for non-commercial use only, provided any copy of these materials which you make shall retain all copyright and other proprietary notices and any disclaimer contained thereon and on this Web Site.
Nothing contained herein shall be construed as conferring by implication, estoppel or otherwise any license or right under any patent or trademark of GlaxoSmithKline or any third party. Except as expressly provided above, nothing contained herein shall be construed as conferring any license or right under any GlaxoSmithKline copyright.
Trademarks and service marks owned by or licensed to GlaxoSmithKline are presented as italicized typefaces, such as Seretide or Tums. British and American spellings are used, depending on the author or source of the information. GlaxoSmithKline claims no ownership in, nor any affiliation with, any third-party trademarks appearing in this Web Site. Such third-party trademarks are used only to identify the products and services of their respective owners, and no sponsorship or endorsement on the part of GlaxoSmithKline should be inferred from the use of these marks.
Should any viewer of a GlaxoSmithKline published document respond with information including feedback data such as questions, comments, suggestions, or the like regarding the content of any such GlaxoSmithKline material, such information shall be deemed to be non-confidential and we shall have no obligation of any kind with respect to such information and shall be free to reproduce, use, disclose, and distribute the information to others without limitation. We shall be free to use any ideas, concepts, know-how or techniques contained in such information for any purpose whatsoever including but not limited to developing, manufacturing and marketing products incorporating such information.
© 2001-2010 GlaxoSmithKline - All Rights Reserved - Updated January 08, 2001
Done

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVANDIA safely and effectively. See full prescribing information for AVANDIA.

AVANDIA **(rosiglitazone maleate) Tablets**
Initial U.S. Approval: 1999

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION

See full prescribing information for complete boxed warning.

- **Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (5.1). After initiation of AVANDIA, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered.**
- **AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.1)**
- **A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with a statistically significant increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067 total patients), comparing AVANDIA to some other approved oral antidiabetic agents or placebo,showed a statistically non-significant increased risk of myocardial infarction and a statistically non-significant decreased risk of death. There have been no clinical trials directly comparing cardiovascular risk of AVANDIA and ACTOS® (pioglitazone, another thiazolidinedione), but in a separate trial, ACTOS (when compared to placebo) did not show an increased risk of myocardial infarction or death. (5.2)**
- **Because of the potential increased risk of myocardial infarction, AVANDIA is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1-800-AVANDIA or visit www.AVANDIA.com. *[See Warnings and Precautions (5.3).]***

----------RECENT MAJOR CHANGES----------

Boxed Warning	02/2011
Indications and Usage (1)	02/2011
Dosage and Administration (2)	02/2011
Warnings and Precautions, Cardiac Failure (5.1)	02/2011
Warnings and Precautions, Major Adverse Cardiovascular Events (5.2)	02/2011
Warnings and Precautions, Rosiglitazone REMS Program (5.3)	XX/2011
Warnings and Precautions, Fractures (5.8)	02/2011

----------INDICATIONS AND USAGE----------

AVANDIA is a thiazolidinedione antidiabetic agent. After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of AVANDIA, this drug is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are:

- already taking AVANDIA, or
- not already taking AVANDIA and are unable to achieve adequate glycemic control on other diabetes medications, and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS) for medical reasons. (1)

Other Important Limitations of Use:

- AVANDIA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. (1)
- Coadministration of AVANDIA and insulin is not recommended. (1, 5.1, 5.2)

---------- DOSAGE AND ADMINISTRATION----------

- Start at 4 mg daily in single or divided doses; do not exceed 8 mg daily. (2)
- Dose increases should be accompanied by careful monitoring for adverse events related to fluid retention. (2)
- Do not initiate AVANDIA if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels. (2.1)

---------- DOSAGE FORMS AND STRENGTHS----------

Pentagonal, film-coated tablets in the following strengths:

- 2 mg, 4 mg, and 8 mg (3)

----------CONTRAINDICATIONS----------

Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. (4)

----------WARNINGS AND PRECAUTIONS----------

- Fluid retention, which may exacerbate or lead to heart failure, may occur. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk of other cardiovascular effects. (5.1)
- Increased risk of myocardial infarction has been observed in a meta-analysis of 52 clinical trials (incidence rate 0.4% versus 0.3%). (5.2)
- Coadministration of AVANDIA and insulin is not recommended. (1, 5.1, 5.2)
- Dose-related edema (5.4), weight gain (5.5), and anemia (5.9) may occur.
- Macular edema has been reported. (5.7)
- Increased incidence of bone fracture. (5.8)

----------ADVERSE REACTIONS----------

Common adverse reactions (>5%) reported in clinical trials without regard to causality were upper respiratory tract infection, injury, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Inhibitors of CYP2C8 (e.g., gemfibrozil) may increase rosiglitazone levels; inducers of CYP2C8 (e.g., rifampin) may decrease rosiglitazone levels. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: XX/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*****Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION

- Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients *[see Warnings and Precautions (5.1)]*. After initiation of AVANDIA, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered.
- AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. *[See Contraindications (4) and Warnings and Precautions (5.1).]*
- A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with a statistically significant increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067 total patients), comparing AVANDIA to some other approved oral antidiabetic agents or placebo, showed a statistically non-significant increased risk of myocardial infarction, and a statistically non-significant decreased risk of death. There have been no clinical trials directly comparing cardiovascular risk of AVANDIA and ACTOS® (pioglitazone, another thiazolidinedione), but in a separate trial, pioglitazone (when compared to placebo) did not show an increased risk of myocardial infarction or death. *[See Warnings and Precautions (5.2).]*
- Because of the potential increased risk of myocardial infarction, AVANDIA is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1-800-AVANDIA or visit www.AVANDIA.com. *[See Warnings and Precautions (5.3).]*

1 INDICATIONS AND USAGE

After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of AVANDIA®, this drug is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are:

- already taking AVANDIA, or
- not already taking AVANDIA and are unable to achieve adequate glycemic control on other diabetes medications and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS®) for medical reasons.

Other Important Limitations of Use:

- Due to its mechanism of action, AVANDIA is active only in the presence of endogenous insulin. Therefore, AVANDIA should not be used in patients with type 1 diabetes mellitus or

for the treatment of diabetic ketoacidosis.

- The coadministration of AVANDIA and insulin is not recommended *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

Prior to prescribing AVANDIA, refer to *Indications and Usage (1)* for appropriate patient selection. Only prescribers enrolled in the AVANDIA-Rosiglitazone Medicines Access Program can prescribe AVANDIA *[see Warnings and Precautions (5.3)]*.

AVANDIA may be administered at a starting dose of 4 mg either as a single daily dose or in 2 divided doses. For patients who respond inadequately following 8 to 12 weeks of treatment, as determined by reduction in fasting plasma glucose (FPG), the dose may be increased to 8 mg daily. Increases in the dose of AVANDIA should be accompanied by careful monitoring for adverse events related to fluid retention *[see Boxed Warning and Warnings and Precautions (5.1)]*. AVANDIA may be taken with or without food.

The total daily dose of AVANDIA should not exceed 8 mg.

Patients receiving AVANDIA in combination with other hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

2.1 Specific Patient Populations

Renal Impairment: No dosage adjustment is necessary when AVANDIA is used as monotherapy in patients with renal impairment. Since metformin is contraindicated in such patients, concomitant administration of metformin and AVANDIA is also contraindicated in patients with renal impairment.

Hepatic Impairment: Liver enzymes should be measured prior to initiating treatment with AVANDIA. Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy). After initiation of AVANDIA, liver enzymes should be monitored periodically per the clinical judgment of the healthcare professional. *[See Warnings and Precautions (5.6) and Clinical Pharmacology (12.3).]*

Pediatric: Data are insufficient to recommend pediatric use of AVANDIA *[see Use in Specific Populations (8.4)]*.

3 DOSAGE FORMS AND STRENGTHS

Pentagonal film-coated TILTAB® tablet contains rosiglitazone as the maleate as follows:

- 2 mg - pink, debossed with SB on one side and 2 on the other
- 4 mg - orange, debossed with SB on one side and 4 on the other
- 8 mg - red-brown, debossed with SB on one side and 8 on the other

4 CONTRAINDICATIONS

Initiation of AVANDIA in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated *[see Boxed Warning]*.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Failure

AVANDIA, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered *[see Boxed Warning]*.

Patients with congestive heart failure (CHF) NYHA Class I and II treated with AVANDIA have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-controlled echocardiographic trial was conducted in 224 patients with type 2 diabetes mellitus and NYHA Class I or II CHF (ejection fraction ≤45%) on background antidiabetic and CHF therapy. An independent committee conducted a blinded evaluation of fluid-related events (including congestive heart failure) and cardiovascular hospitalizations according to predefined criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were reported by investigators. Although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed following treatment with AVANDIA compared to placebo during the 52-week trial. (See Table 1.)

Table 1. Emergent Cardiovascular Adverse Events in Patients With Congestive Heart Failure (NYHA Class I and II) Treated With AVANDIA or Placebo (in Addition to Background Antidiabetic and CHF Therapy)

Events	**AVANDIA**	**Placebo**
	N = 110 n (%)	N = 114 n (%)
Adjudicated		
Cardiovascular deaths	5 (5%)	4 (4%)
CHF worsening – with overnight hospitalization – without overnight hospitalization	7 (6%) 5 (5%) 2 (2%)	4 (4%) 4 (4%) 0 (0%)
New or worsening edema	28 (25%)	10 (9%)
New or worsening dyspnea	29 (26%)	19 (17%)
Increases in CHF medication	36 (33%)	20 (18%)
Cardiovascular hospitalization[a]	21 (19%)	15 (13%)
Investigator-reported, non-adjudicated		
Ischemic adverse events – Myocardial infarction – Angina	10 (9%) 5 (5%) 6 (5%)	5 (4%) 2 (2%) 3 (3%)

[a] Includes hospitalization for any cardiovascular reason.

Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. AVANDIA is not recommended in patients with symptomatic heart failure. *[See Boxed Warning.]*

Patients experiencing acute coronary syndromes have not been studied in controlled clinical trials. In view of the potential for development of heart failure in patients having an acute coronary event, initiation of AVANDIA is not recommended for patients experiencing an acute coronary event, and discontinuation of AVANDIA during this acute phase should be considered.

Patients with NYHA Class III and IV cardiac status (with or without CHF) have not been studied in controlled clinical trials. AVANDIA is not recommended in patients with NYHA Class III and IV cardiac status.

Congestive Heart Failure During Coadministration of AVANDIA With Insulin: In trials in which AVANDIA was added to insulin, AVANDIA increased the risk of congestive heart failure. Coadministration of AVANDIA and insulin is not recommended. *[See Indications and Usage (1) and Warnings and Precautions (5.2).]*

In 7 controlled, randomized, double-blind trials which had durations from 16 to 26 weeks

and which were included in a meta-analysis[1] *[see Warnings and Precautions (5.2)]*, patients with type 2 diabetes mellitus were randomized to coadministration of AVANDIA and insulin (N = 1,018) or insulin (N = 815). In these 7 trials, AVANDIA was added to insulin. These trials included patients with long-standing diabetes (median duration of 12 years) and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. The total number of patients with emergent congestive heart failure was 23 (2.3%) and 8 (1.0%) in the AVANDIA plus insulin and insulin groups, respectively.

Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing AVANDIA to ACTOS: Three observational studies[2-4] in elderly diabetic patients (age 65 years and older) found that AVANDIA statistically significantly increased the risk of hospitalized heart failure compared to use of ACTOS. One other observational study[5] in patients with a mean age of 54 years, which also included an analysis in a subpopulation of patients >65 years of age, found no statistically significant increase in emergency department visits or hospitalization for heart failure in patients treated with AVANDIA compared to ACTOS in the older subgroup.

5.2 Major Adverse Cardiovascular Events

Cardiovascular adverse events have been evaluated in a meta-analysis of 52 clinical trials, in long-term, prospective, randomized, controlled trials, and in observational studies.

Meta-Analysis of Major Adverse Cardiovascular Events in a Group of 52 Clinical Trials: A meta-analysis was conducted retrospectively to assess cardiovascular adverse events reported across 52 double-blind, randomized, controlled clinical trials (mean duration 6 months).[1] These trials had been conducted to assess glucose-lowering efficacy in type 2 diabetes. Prospectively planned adjudication of cardiovascular events did not occur in most of the trials. Some trials were placebo-controlled and some used active oral antidiabetic drugs as controls. Placebo-controlled trials included monotherapy trials (monotherapy with AVANDIA versus placebo monotherapy) and add-on trials (AVANDIA or placebo, added to sulfonylurea, metformin, or insulin). Active control trials included monotherapy trials (monotherapy with AVANDIA versus sulfonylurea or metformin monotherapy) and add-on trials (AVANDIA plus sulfonylurea or AVANDIA plus metformin, versus sulfonylurea plus metformin). A total of 16,995 patients were included (10,039 in treatment groups containing AVANDIA, 6,956 in comparator groups), with 5,167 patient-years of exposure to AVANDIA and 3,637 patient-years of exposure to comparator. Cardiovascular events occurred more frequently for patients who received AVANDIA than for patients who received comparators (see Table 2).

Table 2. Occurrence of Cardiovascular Events in a Meta-Analysis of 52 Clinical Trials

Event[a]	**AVANDIA (Rosiglitazone) (N = 10,039) n (%)**	**Comparator (N = 6,956) n (%)**
MACE (a composite of myocardial	70 (0.7)	39 (0.6)

infarction, cardiovascular death, or stroke)		
Myocardial Infarction	45 (0.4)	20 (0.3)
Cardiovascular Death	17 (0.2)	9 (0.1)
Stroke	18 (0.2)	16 (0.2)
All-cause Death	29 (0.3)	17 (0.2)

[a] Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial infarction would be counted in 4 event categories (myocardial infarction; myocardial infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).

In this analysis, a statistically significant increased risk of myocardial infarction with AVANDIA versus pooled comparators was observed. Analyses were performed using a composite of major adverse cardiovascular events (myocardial infarction, stroke, and cardiovascular death), referred to hereafter as MACE. AVANDIA had a statistically non-significant increased risk of MACE compared to the pooled comparators. A statistically significant increased risk of myocardial infarction and statistically non-significant increased risk of MACE with AVANDIA was observed in the placebo-controlled trials. In the active-controlled trials, there was no increased risk of myocardial infarction or MACE. (See Figure 1 and Table 3.)

Figure 1. Forest Plot of Odds Ratios (95% Confidence Intervals) for MACE and Myocardial Infarction in the Meta-Analysis of 52 Clinical Trials

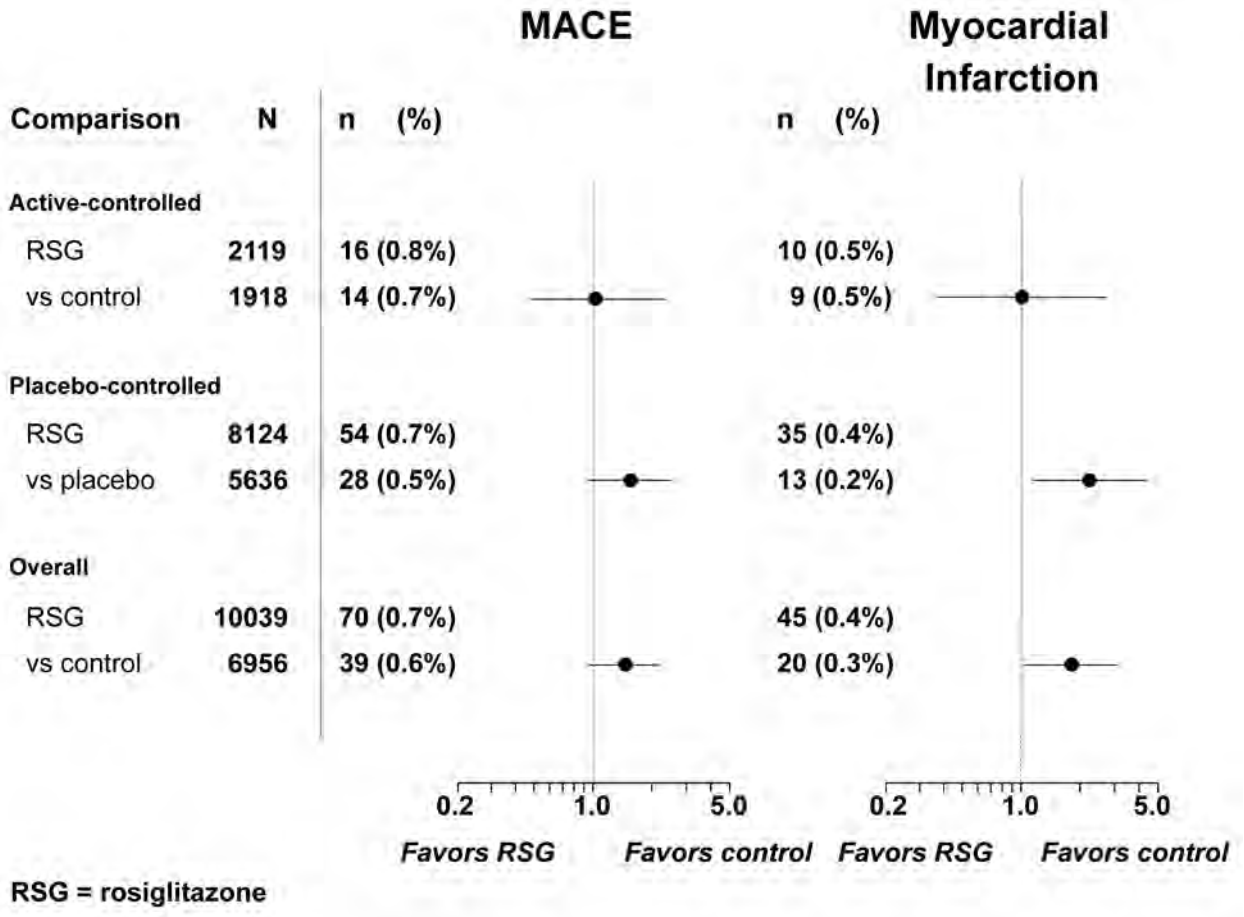


Table 3. Occurrence of MACE and Myocardial Infarction in a Meta-Analysis of 52 Clinical Trials by Trial Type

			MACE		Myocardial Infarction	
		N	n (%)	OR (95%CI)	n (%)	OR (95%CI)
Active-Controlled Trials	RSG	2,119	16 (0.8%)	1.05 (0.48, 2.34)	10 (0.5%)	1.00 (0.36, 2.82)
	Control	1,918	14 (0.7%)		9 (0.5%)	
Placebo-Controlled Trials	RSG	8,124	54 (0.7%)	1.53 (0.94, 2.54)	35 (0.4%)	2.23 (1.14, 4.64)
	Placebo	5,636	28 (0.5%)		13 (0.2%)	
Overall	RSG	10,039	70 (0.7%)	1.44 (0.95, 2.20)	45 (0.4%)	1.8 (1.03, 3.25)
	Control	6,956	39 (0.6%)		20 (0.3%)	

RSG = AVANDIA (rosiglitazone)

Of the placebo-controlled trials in the meta-analysis, 7 trials had patients randomized to AVANDIA plus insulin or insulin. There were more patients in the AVANDIA plus insulin

group compared to the insulin group with myocardial infarctions, MACE, cardiovascular deaths, and all-cause deaths (see Table 4). The total number of patients with stroke was 5 (0.5%) and 4 (0.5%) in the AVANDIA plus insulin and insulin groups, respectively. The use of AVANDIA in combination with insulin may increase the risk of myocardial infarction.

Table 4. Occurrence of Cardiovascular Events for AVANDIA in Combination With Insulin in a Meta-Analysis of 52 Clinical Trials

Event[a]	**AVANDIA (Rosiglitazone) (N=1,018) (%)**	**Insulin (N = 815) (%)**	OR (95% CI)
MACE (a composite of myocardial infarction, cardiovascular death, or stroke)	1.3	0.6	2.14 (0.70, 7.83)
Myocardial infarction	0.6	0.1	5.6 (0.67, 262.7)
Cardiovascular death	0.4	0.0	ND, (0.47, ∞)
All cause death	0.6	0.2	2.19 (0.38, 22.61)

ND = not defined

[a] Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial infarction would be counted in 4 event categories (myocardial infarction; myocardial infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).

Myocardial Infarction Events in Large, Long-Term, Prospective, Randomized, Controlled Trials of AVANDIA: Data from 3 large, long-term, prospective, randomized, controlled clinical trials of AVANDIA were assessed separately from the meta-analysis.[6-8] These 3 trials included a total of 14,067 patients (treatment groups containing AVANDIA N = 6,311; comparator groups N = 7,756), with patient-year exposure of 24,534 patient-years for AVANDIA and 28,882 patient-years for comparator. Patient populations in the trials included patients with impaired glucose tolerance, patients with type 2 diabetes who were initiating oral agent monotherapy, and patients with type 2 diabetes who had failed monotherapy and were initiating dual oral agent therapy. Duration of follow-up exceeded 3 years in each trial.

In each of these trials, there was a statistically non-significant increase in the risk of myocardial infarction for AVANDIA versus comparator medications.

In a long-term, randomized, placebo-controlled, 2x2 factorial trial intended to evaluate AVANDIA, and separately ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on progression to overt diabetes in 5,269 subjects with glucose intolerance, the incidence of myocardial infarction was higher in the subset of subjects who received AVANDIA in combination with ramipril than among subjects who received ramipril alone but not in the subset of subjects who received AVANDIA alone compared to placebo.[6] The higher incidence of myocardial infarction among subjects who received AVANDIA in combination with ramipril

was not confirmed in the two other large (total N = 8,798) long-term, randomized, active-controlled clinical trials conducted in patients with type 2 diabetes, in which 30% and 40% of patients in the two trials reported angiotensin-converting enzyme inhibitor use at baseline.[7,8]

There have been no adequately designed clinical trials directly comparing AVANDIA to ACTOS (pioglitazone) on cardiovascular risks. However, in a long-term, randomized, placebo-controlled cardiovascular outcomes trial comparing ACTOS (pioglitazone) to placebo in patients with type 2 diabetes mellitus and prior macrovascular disease, ACTOS (pioglitazone) was not associated with an increased risk of myocardial infarction or total mortality.[9]

The increased risk of myocardial infarction observed in the meta-analysis and large, long-term controlled clinical trials, and the increased risk of MACE observed in the meta-analysis described above, have not translated into a consistent finding of excess mortality from controlled clinical trials or observational studies. Clinical trials have not shown any difference between AVANDIA and comparator medications in overall mortality or CV-related mortality.

Mortality in Observational Studies of AVANDIA Compared to ACTOS: Three observational studies in elderly diabetic patients (age 65 years and older) found that AVANDIA statistically significantly increased the risk of all-cause mortality compared to use of ACTOS.[2-4] One observational study[5] in patients with a mean age of 54 years found no difference in all-cause mortality between patients treated with AVANDIA compared to ACTOS and reported similar results in the subpopulation of patients >65 years of age. One additional small, prospective, observational study[10] found no statistically significant differences for CV mortality and all-cause mortality in patients treated with AVANDIA compared to ACTOS.

5.3 Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program

Because of the potential increased risk of myocardial infarction, AVANDIA is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program *[see Indications and Usage (1)]*. Both prescribers and patients must enroll in the program to be able to prescribe or receive AVANDIA, respectively. AVANDIA will be available only from specially certified pharmacies participating in the program. As part of the program, prescribers will be educated about the potential increased risk of myocardial infarction and the need to limit the use of AVANDIA to eligible patients. Prescribers will need to discuss with patients the risks and benefits of taking AVANDIA. To enroll, call 1-800-AVANDIA or visit www.AVANDIA.com.

5.4 Edema

AVANDIA should be used with caution in patients with edema. In a clinical trial in healthy volunteers who received 8 mg of AVANDIA once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo.

Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, AVANDIA should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure *[see Boxed Warning, Warnings and Precautions (5.1), and Patient Counseling Information (17)]*.

In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with AVANDIA, and may be dose related. Patients with ongoing edema were more likely to have adverse events associated with edema if started on combination therapy with insulin and AVANDIA *[see Adverse Reactions (6.1)]*.

5.5 Weight Gain

Dose-related weight gain was seen with AVANDIA alone and in combination with other hypoglycemic agents (Table 5). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure *[see Boxed Warning]*.

Table 5. Weight Changes (kg) From Baseline at Endpoint During Clinical Trials

		Control Group		**AVANDIA 4 mg**	**AVANDIA 8 mg**
Monotherapy	**Duration**		**Median (25^{th}, 75^{th} percentile)**	**Median (25^{th}, 75^{th} percentile)**	**Median (25^{th}, 75^{th} percentile)**
	26 weeks	placebo	-0.9 (-2.8, 0.9) N = 210	1.0 (-0.9, 3.6) N = 436	3.1 (1.1, 5.8) N = 439
	52 weeks	sulfonylurea	2.0 (0, 4.0) N = 173	2.0 (-0.6, 4.0) N = 150	2.6 (0, 5.3) N = 157
Combination therapy					
Sulfonylurea	24-26 weeks	sulfonylurea	0 (-1.0, 1.3) N = 1,155	2.2 (0.5, 4.0) N = 613	3.5 (1.4, 5.9) N = 841
Metformin	26 weeks	metformin	-1.4 (-3.2, 0.2) N = 175	0.8 (-1.0, 2.6) N = 100	2.1 (0, 4.3) N = 184
Insulin	26 weeks	insulin	0.9 (-0.5, 2.7) N = 162	4.1 (1.4, 6.3) N = 164	5.4 (3.4, 7.3) N = 150
Sulfonylurea + metformin	26 weeks	sulfonylurea + metformin	0.2 (-1.2, 1.6) N = 272	2.5 (0.8, 4.6) N = 275	4.5 (2.4, 7.3) N = 276

In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed with type 2 diabetes not previously treated with antidiabetic medication *[see Clinical Studies (14.1)]*, the median weight change (25^{th}, 75^{th} percentiles) from baseline at 4 years was 3.5 kg (0.0, 8.1) for AVANDIA, 2.0 kg (-1.0, 4.8) for glyburide, and -2.4 kg (-5.4, 0.5) for metformin.

In a 24-week trial in pediatric patients aged 10 to 17 years treated with AVANDIA 4 to 8 mg daily, a median weight gain of 2.8 kg (25^{th}, 75^{th} percentiles: 0.0, 5.8) was reported.

5.6 Hepatic Effects

Liver enzymes should be measured prior to the initiation of therapy with AVANDIA in all patients and periodically thereafter per the clinical judgment of the healthcare professional. Therapy with AVANDIA should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with AVANDIA should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with AVANDIA in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X the upper limit of normal in patients on therapy with AVANDIA, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with AVANDIA should be discontinued.

If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with AVANDIA should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued. *[See Adverse Reactions (6.2, 6.3).]*

5.7 Macular Edema

Macular edema has been reported in postmarketing experience in some diabetic patients who were taking AVANDIA or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. Patients with diabetes should have regular eye exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings. *[See Adverse Reactions (6.1).]*

5.8 Fractures

In a 4- to 6-year comparative trial (ADOPT) of glycemic control with monotherapy in drug-naïve patients recently diagnosed with type 2 diabetes mellitus, an increased incidence of bone fracture was noted in female patients taking AVANDIA. Over the 4- to 6-year period, the incidence of bone fracture in females was 9.3% (60/645) for AVANDIA versus 3.5% (21/605) for glyburide and 5.1% (30/590) for metformin. This increased incidence was noted after the first year of treatment and persisted during the course of the trial. The majority of the fractures in the women who received AVANDIA occurred in the upper arm, hand, and foot. These sites of fracture are different from those usually associated with postmenopausal osteoporosis (e.g., hip or spine). Other trials suggest that this risk may also apply to men, although the risk of fracture among women appears higher than that among men. The risk of fracture should be considered in

the care of patients treated with AVANDIA, and attention given to assessing and maintaining bone health according to current standards of care.

5.9 Hematologic Effects

Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult patients treated with AVANDIA *[see Adverse Reactions (6.2)]*. The observed changes may be related to the increased plasma volume observed with treatment with AVANDIA.

5.10 Diabetes and Blood Glucose Control

Patients receiving AVANDIA in combination with other hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Periodic fasting blood glucose and HbA1c measurements should be performed to monitor therapeutic response.

5.11 Ovulation

Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDIA *[see Use in Specific Populations (8.1)]*. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical trials; therefore, the frequency of this occurrence is not known.

Although hormonal imbalance has been seen in preclinical studies *[see Nonclinical Toxicology (13.1)]*, the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with AVANDIA should be reviewed.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Adult: In clinical trials, approximately 9,900 patients with type 2 diabetes have been treated with AVANDIA.

Short-Term Trials of AVANDIA as Monotherapy and in Combination With Other Hypoglycemic Agents: The incidence and types of adverse events reported in short-term clinical trials of AVANDIA as monotherapy are shown in Table 6.

Table 6. Adverse Events (≥5% in Any Treatment Group) Reported by Patients in Short-Term[a] Double-Blind Clinical Trials With AVANDIA as Monotherapy

Preferred Term	AVANDIA Monotherapy	Placebo	Metformin	Sulfonylureas[b]
	N = 2,526	N = 601	N = 225	N = 626
	%	%	%	%
Upper respiratory tract infection	9.9	8.7	8.9	7.3
Injury	7.6	4.3	7.6	6.1
Headache	5.9	5.0	8.9	5.4
Back pain	4.0	3.8	4.0	5.0
Hyperglycemia	3.9	5.7	4.4	8.1
Fatigue	3.6	5.0	4.0	1.9
Sinusitis	3.2	4.5	5.3	3.0
Diarrhea	2.3	3.3	15.6	3.0
Hypoglycemia	0.6	0.2	1.3	5.9

[a] Short-term trials ranged from 8 weeks to 1 year.

[b] Includes patients receiving glyburide (N = 514), gliclazide (N = 91), or glipizide (N = 21).

Overall, the types of adverse reactions without regard to causality reported when AVANDIA was used in combination with a sulfonylurea or metformin were similar to those during monotherapy with AVANDIA.

Events of anemia and edema tended to be reported more frequently at higher doses, and were generally mild to moderate in severity and usually did not require discontinuation of treatment with AVANDIA.

In double-blind trials, anemia was reported in 1.9% of patients receiving AVANDIA as monotherapy compared to 0.7% on placebo, 0.6% on sulfonylureas, and 2.2% on metformin. Reports of anemia were greater in patients treated with a combination of AVANDIA and metformin (7.1%) and with a combination of AVANDIA and a sulfonylurea plus metformin (6.7%) compared to monotherapy with AVANDIA or in combination with a sulfonylurea (2.3%). Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anemia in these trials *[see Adverse Reactions (6.2)]*.

In clinical trials, edema was reported in 4.8% of patients receiving AVANDIA as monotherapy compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. The reporting rate of edema was higher for AVANDIA 8 mg in sulfonylurea combinations (12.4%) compared to other combinations, with the exception of insulin. Edema was reported in 14.7% of patients receiving AVANDIA in the insulin combination trials compared to 5.4% on insulin alone. Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with AVANDIA *[see*

Boxed Warning and Warnings and Precautions (5.1)]. The use of AVANDIA in combination with insulin may increase the risk of myocardial infarction *[see Warnings and Precautions (5.2)]*.

In controlled combination therapy trials with sulfonylureas, mild to moderate hypoglycemic symptoms, which appear to be dose related, were reported. Few patients were withdrawn for hypoglycemia (<1%) and few episodes of hypoglycemia were considered to be severe (<1%). Hypoglycemia was the most frequently reported adverse event in the fixed-dose insulin combination trials, although few patients withdrew for hypoglycemia (4 of 408 for AVANDIA plus insulin and 1 of 203 for insulin alone). Rates of hypoglycemia, confirmed by capillary blood glucose concentration ≤50 mg/dL, were 6% for insulin alone and 12% (4 mg) and 14% (8 mg) for insulin in combination with AVANDIA. *[See Warnings and Precautions (5.10).]*

Long-Term Trial of AVANDIA as Monotherapy: A 4- to 6-year trial (ADOPT) compared the use of AVANDIA (n = 1,456), glyburide (n = 1,441), and metformin (n = 1,454) as monotherapy in patients recently diagnosed with type 2 diabetes who were not previously treated with antidiabetic medication. Table 7 presents adverse reactions without regard to causality; rates are expressed per 100 patient-years (PY) exposure to account for the differences in exposure to trial medication across the 3 treatment groups.

In ADOPT, fractures were reported in a greater number of women treated with AVANDIA (9.3%, 2.7/100 patient-years) compared to glyburide (3.5%, 1.3/100 patient-years) or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who received rosiglitazone were reported in the upper arm, hand, and foot. *[See Warnings and Precautions (5.8).]* The observed incidence of fractures for male patients was similar among the 3 treatment groups.

Table 7. On-Therapy Adverse Events (≥5 Events/100 Patient-Years [PY]) in Any Treatment Group Reported in a 4- to 6-Year Clinical Trial of AVANDIA as Monotherapy (ADOPT)

	AVANDIA N = 1,456 PY = 4,954	**Glyburide** N = 1,441 PY = 4,244	**Metformin** N = 1,454 PY = 4,906
Nasopharyngitis	6.3	6.9	6.6
Back pain	5.1	4.9	5.3
Arthralgia	5.0	4.8	4.2
Hypertension	4.4	6.0	6.1
Upper respiratory tract infection	4.3	5.0	4.7
Hypoglycemia	2.9	13.0	3.4
Diarrhea	2.5	3.2	6.8

Pediatric: AVANDIA has been evaluated for safety in a single, active-controlled trial of pediatric patients with type 2 diabetes in which 99 were treated with AVANDIA and 101 were

treated with metformin. The most common adverse reactions (>10%) without regard to causality for either AVANDIA or metformin were headache (17% versus 14%), nausea (4% versus 11%), nasopharyngitis (3% versus 12%), and diarrhea (1% versus 13%). In this trial, one case of diabetic ketoacidosis was reported in the metformin group. In addition, there were 3 patients in the rosiglitazone group who had FPG of ~300 mg/dL, 2+ ketonuria, and an elevated anion gap.

6.2 Laboratory Abnormalities

Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult patients treated with AVANDIA (mean decreases in individual trials as much as 1.0 g/dL hemoglobin and as much as 3.3% hematocrit). The changes occurred primarily during the first 3 months following initiation of therapy with AVANDIA or following a dose increase in AVANDIA. The time course and magnitude of decreases were similar in patients treated with a combination of AVANDIA and other hypoglycemic agents or monotherapy with AVANDIA. Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin combination trials and may have contributed to the higher reporting rate of anemia. In a single trial in pediatric patients, decreases in hemoglobin and hematocrit (mean decreases of 0.29 g/dL and 0.95%, respectively) were reported. Small decreases in hemoglobin and hematocrit have also been reported in pediatric patients treated with AVANDIA. White blood cell counts also decreased slightly in adult patients treated with AVANDIA. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with AVANDIA.

Lipids: Changes in serum lipids have been observed following treatment with AVANDIA in adults *[see Clinical Pharmacology (12.2)]*. Small changes in serum lipid parameters were reported in children treated with AVANDIA for 24 weeks.

Serum Transaminase Levels: In pre-approval clinical trials in 4,598 patients treated with AVANDIA (3,600 patient-years of exposure) and in a long-term 4- to 6-year trial in 1,456 patients treated with AVANDIA (4,954 patient-years exposure), there was no evidence of drug-induced hepatotoxicity.

In pre-approval controlled trials, 0.2% of patients treated with AVANDIA had elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with AVANDIA were reversible. Hyperbilirubinemia was found in 0.3% of patients treated with AVANDIA compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. *[See Warnings and Precautions (5.6).]*

In the 4- to 6-year ADOPT trial, patients treated with AVANDIA (4,954 patient-years exposure), glyburide (4,244 patient-years exposure), or metformin (4,906 patient-years exposure), as monotherapy, had the same rate of ALT increase to >3X upper limit of normal (0.3 per 100 patient-years exposure).

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the events described below

have been identified during post-approval use of AVANDIA. Because these events are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or to always establish a causal relationship to drug exposure.

In patients receiving thiazolidinedione therapy, serious adverse events with or without a fatal outcome, potentially related to volume expansion (e.g., congestive heart failure, pulmonary edema, and pleural effusions) have been reported *[see Boxed Warning and Warnings and Precautions (5.1)]*.

There are postmarketing reports with AVANDIA of hepatitis, hepatic enzyme elevations to 3 or more times the upper limit of normal, and hepatic failure with and without fatal outcome, although causality has not been established.

There are postmarketing reports with AVANDIA of rash, pruritus, urticaria, angioedema, anaphylactic reaction, Stevens-Johnson syndrome, and new onset or worsening diabetic macular edema with decreased visual acuity *[see Warnings and Precautions (5.7)]*.

7 DRUG INTERACTIONS

7.1 CYP2C8 Inhibitors and Inducers

An inhibitor of CYP2C8 (e.g., gemfibrozil) may increase the AUC of rosiglitazone and an inducer of CYP2C8 (e.g., rifampin) may decrease the AUC of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response. *[See Clinical Pharmacology (12.4).]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Careful monitoring of glucose control is essential in such patients. Most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Human Data: Rosiglitazone has been reported to cross the human placenta and be detectable in fetal tissue. The clinical significance of these findings is unknown. There are no adequate and well-controlled trials in pregnant women. AVANDIA should not be used during pregnancy.

Animal Studies: There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused

placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced the number of uterine implantations and live offspring when juvenile female rats were treated at 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day (approximately 4 times human AUC at the maximum recommended daily dose). There was no effect on pre- or post-natal survival or growth.

8.2 Labor and Delivery

The effect of rosiglitazone on labor and delivery in humans is not known.

8.3 Nursing Mothers

Drug-related material was detected in milk from lactating rats. It is not known whether AVANDIA is excreted in human milk. Because many drugs are excreted in human milk, AVANDIA should not be administered to a nursing woman.

8.4 Pediatric Use

After placebo run-in including diet counseling, children with type 2 diabetes mellitus, aged 10 to 17 years and with a baseline mean body mass index (BMI) of 33 kg/m^2, were randomized to treatment with 2 mg twice daily of AVANDIA (n = 99) or 500 mg twice daily of metformin (n = 101) in a 24-week, double-blind clinical trial. As expected, FPG decreased in patients naïve to diabetes medication (n = 104) and increased in patients withdrawn from prior medication (usually metformin) (n = 90) during the run-in period. After at least 8 weeks of treatment, 49% of patients treated with AVANDIA and 55% of metformin-treated patients had their dose doubled if FPG >126 mg/dL. For the overall intent-to-treat population, at week 24, the mean change from baseline in HbA1c was -0.14% with AVANDIA and -0.49% with metformin. There was an insufficient number of patients in this trial to establish statistically whether these observed mean treatment effects were similar or different. Treatment effects differed for patients naïve to therapy with antidiabetic drugs and for patients previously treated with antidiabetic therapy (Table 8).

Table 8. Week 24 FPG and HbA1c Change From Baseline Last-Observation-Carried Forward in Children With Baseline HbA1c >6.5%

	Naïve Patients		Previously-Treated Patients	
	Metformin	**Rosiglitazone**	**Metformin**	**Rosiglitazone**
	N = 40	N = 45	N = 43	N = 32
FPG (mg/dL)				
Baseline (mean)	170	165	221	205
Change from baseline (mean)	-21	-11	-33	-5
Adjusted treatment difference[a] (rosiglitazone–metformin)[b]		8		21
(95% CI)		(-15, 30)		(-9, 51)
% of patients with ≥30 mg/dL decrease from baseline	43%	27%	44%	28%
HbA1c (%)				
Baseline (mean)	8.3	8.2	8.8	8.5
Change from baseline (mean)	-0.7	-0.5	-0.4	0.1
Adjusted treatment difference[a] (rosiglitazone–metformin)[b]		0.2		0.5
(95% CI)		(-0.6, 0.9)		(-0.2, 1.3)
% of patients with ≥0.7% decrease from baseline	63%	52%	54%	31%

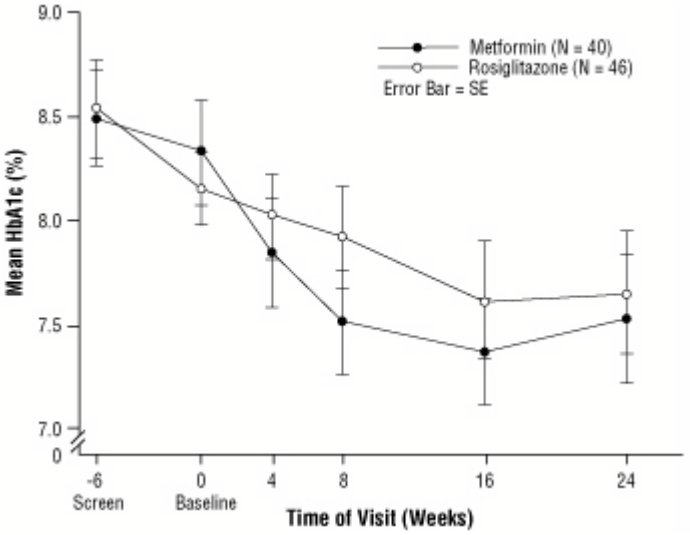
[a] Change from baseline means are least squares means adjusting for baseline HbA1c, gender, and region.

[b] Positive values for the difference favor metformin.

Treatment differences depended on baseline BMI or weight such that the effects of AVANDIA and metformin appeared more closely comparable among heavier patients. The median weight gain was 2.8 kg with rosiglitazone and 0.2 kg with metformin *[see Warnings and Precautions (5.5)]*. Fifty-four percent of patients treated with rosiglitazone and 32% of patients treated with metformin gained ≥2 kg, and 33% of patients treated with rosiglitazone and 7% of patients treated with metformin gained ≥5 kg on trial.

Adverse events observed in this trial are described in *Adverse Reactions (6.1).*

Figure 2. Mean HbA1c Over Time in a 24-Week Trial of AVANDIA and Metformin in Pediatric Patients — Drug-Naïve Subgroup



8.5 Geriatric Use

Results of the population pharmacokinetic analysis showed that age does not significantly affect the pharmacokinetics of rosiglitazone *[see Clinical Pharmacology (12.3)]*. Therefore, no dosage adjustments are required for the elderly. In controlled clinical trials, no overall differences in safety and effectiveness between older (≥65 years) and younger (<65 years) patients were observed.

10 OVERDOSAGE

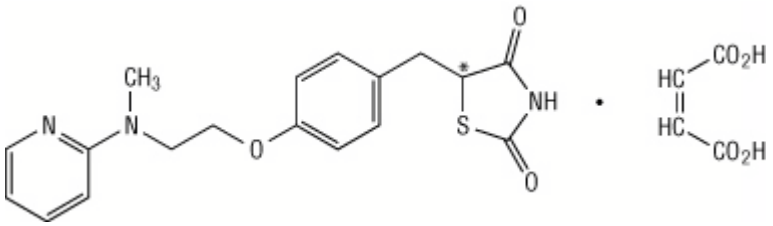
Limited data are available with regard to overdosage in humans. In clinical trials in volunteers, AVANDIA has been administered at single oral doses of up to 20 mg and was well-tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

11 DESCRIPTION

AVANDIA (rosiglitazone maleate) is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. AVANDIA improves glycemic control while reducing circulating insulin levels.

Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors.

Chemically, rosiglitazone maleate is (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (*Z*)-2-butenedioate (1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the enantiomers are functionally indistinguishable. The structural formula of rosiglitazone maleate is:



The molecular formula is $C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$. Rosiglitazone maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pKa values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

Each pentagonal film-coated TILTAB tablet contains rosiglitazone maleate equivalent to rosiglitazone, 2 mg, 4 mg, or 8 mg, for oral administration. Inactive ingredients are: Hypromellose 2910, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin, and 1 or more of the following: Synthetic red and yellow iron oxides and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPARγ-responsive genes also participate in the regulation of fatty acid metabolism.

Insulin resistance is a common feature characterizing the pathogenesis of type 2 diabetes. The antidiabetic activity of rosiglitazone has been demonstrated in animal models of type 2 diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. Rosiglitazone reduces blood glucose concentrations and reduces hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse, and fa/fa fatty Zucker rat.

In animal models, the antidiabetic activity of rosiglitazone was shown to be mediated by increased sensitivity to insulin's action in the liver, muscle, and adipose tissues. Pharmacological studies in animal models indicate that rosiglitazone inhibits hepatic gluconeogenesis. The expression of the insulin-regulated glucose transporter GLUT-4 was increased in adipose tissue. Rosiglitazone did not induce hypoglycemia in animal models of type 2 diabetes and/or impaired glucose tolerance.

12.2 Pharmacodynamics

Patients with lipid abnormalities were not excluded from clinical trials of AVANDIA. In all 26-week controlled trials, across the recommended dose range, AVANDIA as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids. These changes were statistically significantly different from placebo or glyburide controls

(Table 9).

Increases in LDL occurred primarily during the first 1 to 2 months of therapy with AVANDIA and LDL levels remained elevated above baseline throughout the trials. In contrast, HDL continued to rise over time. As a result, the LDL/HDL ratio peaked after 2 months of therapy and then appeared to decrease over time. Because of the temporal nature of lipid changes, the 52-week glyburide-controlled trial is most pertinent to assess long-term effects on lipids. At baseline, week 26, and week 52, mean LDL/HDL ratios were 3.1, 3.2, and 3.0, respectively, for AVANDIA 4 mg twice daily. The corresponding values for glyburide were 3.2, 3.1, and 2.9. The differences in change from baseline between AVANDIA and glyburide at week 52 were statistically significant.

The pattern of LDL and HDL changes following therapy with AVANDIA in combination with other hypoglycemic agents were generally similar to those seen with AVANDIA in monotherapy.

The changes in triglycerides during therapy with AVANDIA were variable and were generally not statistically different from placebo or glyburide controls.

Table 9. Summary of Mean Lipid Changes in 26-Week Placebo-Controlled and 52-Week Glyburide-Controlled Monotherapy Trials

	Placebo-Controlled Trials Week 26			**Glyburide-Controlled Trial Week 26 and Week 52**			
	Placebo	**AVANDIA**		**Glyburide Titration**		**AVANDIA 8 mg**	
		4 mg daily[a]	8 mg daily[a]	Wk 26	Wk 52	Wk 26	Wk 52
Free fatty acids							
N	207	428	436	181	168	166	145
Baseline (mean)	18.1	17.5	17.9	26.4	26.4	26.9	26.6
% Change from baseline (mean)	+0.2%	-7.8%	-14.7%	-2.4%	-4.7%	-20.8%	-21.5%
LDL							
N	190	400	374	175	160	161	133
Baseline (mean)	123.7	126.8	125.3	142.7	141.9	142.1	142.1
% Change from baseline (mean)	+4.8%	+14.1%	+18.6%	-0.9%	-0.5%	+11.9%	+12.1%
HDL							
N	208	429	436	184	170	170	145
Baseline (mean)	44.1	44.4	43.0	47.2	47.7	48.4	48.3
% Change from baseline (mean)	+8.0%	+11.4%	+14.2%	+4.3%	+8.7%	+14.0%	+18.5%

[a] Once daily and twice daily dosing groups were combined.

12.3 Pharmacokinetics

Maximum plasma concentration (C_{max}) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range (Table 10). The elimination half-life is 3 to 4 hours and is independent of dose.

Table 10. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral Doses (N = 32)

Parameter	1 mg Fasting	2 mg Fasting	8 mg Fasting	8 mg Fed
$AUC_{0\text{-}inf}$ [ng•hr/mL]	358 (112)	733 (184)	2,971 (730)	2,890 (795)
C_{max} [ng/mL]	76 (13)	156 (42)	598 (117)	432 (92)
Half-life [hr]	3.16 (0.72)	3.15 (0.39)	3.37 (0.63)	3.59 (0.70)
CL/F[a] [L/hr]	3.03 (0.87)	2.89 (0.71)	2.85 (0.69)	2.97 (0.81)

[a] CL/F = Oral clearance.

Absorption: The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing. Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), but there was an approximately 28% decrease in C_{max} and a delay in T_{max} (1.75 hours). These changes are not likely to be clinically significant; therefore, AVANDIA may be administered with or without food.

Distribution: The mean (CV%) oral volume of distribution (Vss/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

Metabolism: Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone.

In vitro data demonstrate that rosiglitazone is predominantly metabolized by Cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway.

Excretion: Following oral or intravenous administration of [^{14}C]rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [^{14}C]related material ranged from 103 to 158 hours.

Population Pharmacokinetics in Patients With Type 2 Diabetes: Population pharmacokinetic analyses from 3 large clinical trials including 642 men and 405 women with type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not

influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume of distribution (Vss/F) were shown to increase with increases in body weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted CL/F and Vss/F values varied by <1.7-fold and <2.3-fold, respectively. Additionally, rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about 15%) in female patients.

Special Populations: *Geriatric:* Results of the population pharmacokinetic analysis (n = 716 <65 years; n = 331 ≥65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone.

Gender: Results of the population pharmacokinetics analysis showed that the mean oral clearance of rosiglitazone in female patients (n = 405) was approximately 6% lower compared to male patients of the same body weight (n = 642).

As monotherapy and in combination with metformin, AVANDIA improved glycemic control in both males and females. In metformin combination trials, efficacy was demonstrated with no gender differences in glycemic response.

In monotherapy trials, a greater therapeutic response was observed in females; however, in more obese patients, gender differences were less evident. For a given body mass index (BMI), females tend to have a greater fat mass than males. Since the molecular target PPARγ is expressed in adipose tissues, this differentiating characteristic may account, at least in part, for the greater response to AVANDIA in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.

Hepatic Impairment: Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound C_{max} and $AUC_{0\text{-}inf}$ were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects.

Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal) at baseline *[see Warnings and Precautions (5.6)]*.

Pediatric: Pharmacokinetic parameters of rosiglitazone in pediatric patients were established using a population pharmacokinetic analysis with sparse data from 96 pediatric patients in a single pediatric clinical trial including 33 males and 63 females with ages ranging from 10 to 17 years (weights ranging from 35 to 178.3 kg). Population mean CL/F and V/F of rosiglitazone were 3.15 L/hr and 13.5 L, respectively. These estimates of CL/F and V/F were consistent with the typical parameter estimates from a prior adult population analysis.

Renal Impairment: There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients compared to subjects with normal renal function. No dosage adjustment is therefore required in such patients receiving AVANDIA. Since metformin is contraindicated in patients with renal impairment, coadministration of metformin with AVANDIA is contraindicated in

these patients.

Race: Results of a population pharmacokinetic analysis including subjects of Caucasian, black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of rosiglitazone.

12.4 Drug-Drug Interactions

Drugs That Inhibit, Induce, or are Metabolized by Cytochrome P450: In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. In vitro data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9. AVANDIA (4 mg twice daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinyl estradiol and norethindrone), which are predominantly metabolized by CYP3A4.

Gemfibrozil: Concomitant administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone AUC by 127%, compared to the administration of rosiglitazone (4 mg once daily) alone. Given the potential for dose-related adverse events with rosiglitazone, a decrease in the dose of rosiglitazone may be needed when gemfibrozil is introduced *[see Drug Interactions (7.1)]*.

Rifampin: Rifampin administration (600 mg once a day), an inducer of CYP2C8, for 6 days is reported to decrease rosiglitazone AUC by 66%, compared to the administration of rosiglitazone (8 mg) alone *[see Drug Interactions (7.1)]*.[11]

Glyburide: AVANDIA (2 mg twice daily) taken concomitantly with glyburide (3.75 to 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy. Repeat doses of AVANDIA (8 mg once daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and C_{max} of approximately 30%. In Japanese subjects, glyburide AUC and C_{max} slightly increased following coadministration of AVANDIA.

Glimepiride: Single oral doses of glimepiride in 14 healthy adult subjects had no clinically significant effect on the steady-state pharmacokinetics of AVANDIA. No clinically significant reductions in glimepiride AUC and C_{max} were observed after repeat doses of AVANDIA (8 mg once daily) for 8 days in healthy adult subjects.

Metformin: Concurrent administration of AVANDIA (2 mg twice daily) and metformin (500 mg twice daily) in healthy volunteers for 4 days had no effect on the steady-state pharmacokinetics of either metformin or rosiglitazone.

Acarbose: Coadministration of acarbose (100 mg three times daily) for 7 days in healthy volunteers had no clinically relevant effect on the pharmacokinetics of a single oral dose of AVANDIA.

Digoxin: Repeat oral dosing of AVANDIA (8 mg once daily) for 14 days did not alter the steady-state pharmacokinetics of digoxin (0.375 mg once daily) in healthy volunteers.

Warfarin: Repeat dosing with AVANDIA had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in type 2 diabetes mellitus patients treated with AVANDIA.

Ranitidine: Pretreatment with ranitidine (150 mg twice daily for 4 days) did not alter the pharmacokinetics of either single oral or intravenous doses of rosiglitazone in healthy volunteers. These results suggest that the absorption of oral rosiglitazone is not altered in conditions accompanied by increases in gastrointestinal pH.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: A 2-year carcinogenicity study was conducted in Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately 12 times human AUC at the maximum recommended human daily dose). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05, 0.3, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times human AUC at the maximum recommended human daily dose for male and female rats, respectively).

Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses ≥1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses ≥0.3 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic activation.

Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose). In juvenile rats dosed from 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in females (approximately 68 times human AUC at the maximum recommended human daily dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge,

lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

13.2 Animal Toxicology

Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose, respectively). Effects in juvenile rats were consistent with those seen in adults. Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

14 CLINICAL STUDIES

14.1 Monotherapy

In clinical trials, treatment with AVANDIA resulted in an improvement in glycemic control, as measured by FPG and HbA1c, with a concurrent reduction in insulin and C-peptide. Postprandial glucose and insulin were also reduced. This is consistent with the mechanism of action of AVANDIA as an insulin sensitizer.

The maximum recommended daily dose is 8 mg. Dose-ranging trials suggested that no additional benefit was obtained with a total daily dose of 12 mg.

Short-Term Clinical Trials: A total of 2,315 patients with type 2 diabetes, previously treated with diet alone or antidiabetic medication(s), were treated with AVANDIA as monotherapy in 6 double-blind trials, which included two 26-week placebo-controlled trials, one 52-week glyburide-controlled trial, and 3 placebo-controlled dose-ranging trials of 8 to 12 weeks duration. Previous antidiabetic medication(s) were withdrawn and patients entered a 2 to 4 week placebo run-in period prior to randomization.

Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes (n = 1,401) with inadequate glycemic control (mean baseline FPG approximately 228 mg/dL [101 to 425 mg/dL] and mean baseline HbA1c 8.9% [5.2% to 16.2%]), were conducted. Treatment with AVANDIA produced statistically significant improvements in FPG and HbA1c compared to baseline and relative to placebo. Data from one of these trials are summarized in Table 11.

Table 11. Glycemic Parameters in a 26-Week Placebo-Controlled Trial

	Placebo	AVANDIA 4 mg once daily	AVANDIA 2 mg twice daily	AVANDIA 8 mg once daily	AVANDIA 4 mg twice daily
	N = 173	N = 180	N = 186	N = 181	N = 187
FPG (mg/dL)					
Baseline (mean)	225	229	225	228	228
Change from baseline (mean)	8	-25	-35	-42	-55
Difference from placebo (adjusted mean)	–	-31[a]	-43[a]	-49[a]	-62[a]
% of patients with ≥30 mg/dL decrease from baseline	19%	45%	54%	58%	70%
HbA1c (%)					
Baseline (mean)	8.9	8.9	8.9	8.9	9.0
Change from baseline (mean)	0.8	0.0	-0.1	-0.3	-0.7
Difference from placebo (adjusted mean)	–	-0.8[a]	-0.9[a]	-1.1[a]	-1.5[a]
% of patients with ≥0.7% decrease from baseline	9%	28%	29%	39%	54%

[a] P <0.0001 compared to placebo.

When administered at the same total daily dose, AVANDIA was generally more effective in reducing FPG and HbA1c when administered in divided doses twice daily compared to once daily doses. However, for HbA1c, the difference between the 4 mg once daily and 2 mg twice daily doses was not statistically significant.

Long-Term Clinical Trials: Long-term maintenance of effect was evaluated in a 52-week, double-blind, glyburide-controlled trial in patients with type 2 diabetes. Patients were randomized to treatment with AVANDIA 2 mg twice daily (N = 195) or AVANDIA 4 mg twice daily (N = 189) or glyburide (N = 202) for 52 weeks. Patients receiving glyburide were given an initial dosage of either 2.5 mg/day or 5.0 mg/day. The dosage was then titrated in 2.5 mg/day increments over the next 12 weeks, to a maximum dosage of 15.0 mg/day in order to optimize glycemic control. Thereafter, the glyburide dose was kept constant.

The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a statistically significant improvement in glycemic control from baseline (Figure 3 and Figure 4). At the end of week 52, the reduction from baseline in FPG and HbA1c was -40.8 mg/dL and -0.53% with AVANDIA 4 mg twice daily; -25.4 mg/dL and -0.27% with AVANDIA 2 mg twice daily; and -30.0 mg/dL and -0.72% with glyburide. For HbA1c, the difference between AVANDIA 4 mg twice daily and glyburide was not statistically significant at week 52. The initial fall in FPG with glyburide was greater than with AVANDIA; however, this effect was less durable over time. The improvement in glycemic control seen with AVANDIA 4 mg twice daily

at week 26 was maintained through week 52 of the trial.

Figure 3. Mean FPG Over Time in a 52-Week Glyburide-Controlled Trial

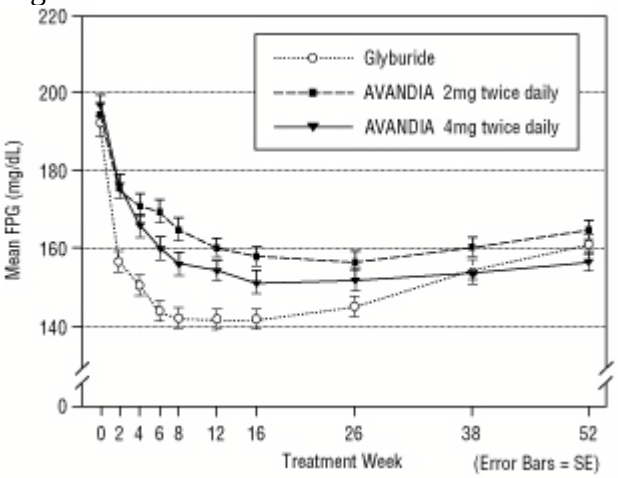
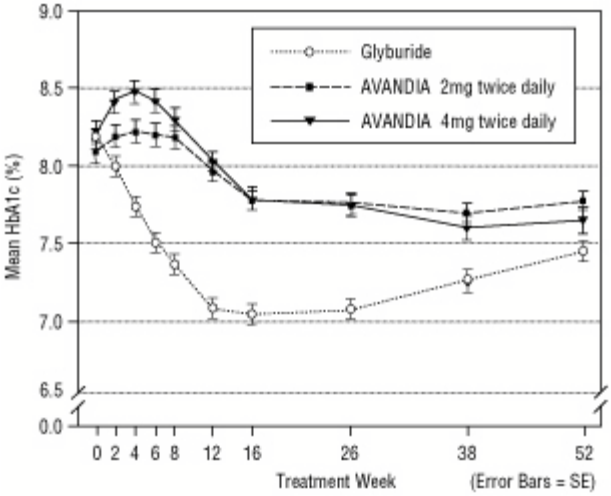


Figure 4. Mean HbA1c Over Time in a 52-Week Glyburide-Controlled Trial



Hypoglycemia was reported in 12.1% of glyburide-treated patients versus 0.5% (2 mg twice daily) and 1.6% (4 mg twice daily) of patients treated with AVANDIA. The improvements in glycemic control were associated with a mean weight gain of 1.75 kg and 2.95 kg for patients treated with 2 mg and 4 mg twice daily of AVANDIA, respectively, versus 1.9 kg in glyburide-treated patients. In patients treated with AVANDIA, C-peptide, insulin, pro-insulin, and pro-insulin split products were significantly reduced in a dose-ordered fashion, compared to an increase in the glyburide-treated patients.

A Diabetes Outcome Progression Trial (ADOPT) was a multicenter, double-blind, controlled trial (N = 4,351) conducted over 4 to 6 years to compare the safety and efficacy of AVANDIA, metformin, and glyburide monotherapy in patients recently diagnosed with type 2 diabetes mellitus (≤3 years) inadequately controlled with diet and exercise. The mean age of

patients in this trial was 57 years and the majority of patients (83%) had no known history of cardiovascular disease. The mean baseline FPG and HbA1c were 152 mg/dL and 7.4%, respectively. Patients were randomized to receive either AVANDIA 4 mg once daily, glyburide 2.5 mg once daily, or metformin 500 mg once daily, and doses were titrated to optimal glycemic control up to a maximum of 4 mg twice daily for AVANDIA, 7.5 mg twice daily for glyburide, and 1,000 mg twice daily for metformin. The primary efficacy outcome was time to consecutive FPG >180 mg/dL after at least 6 weeks of treatment at the maximum tolerated dose of study medication or time to inadequate glycemic control, as determined by an independent adjudication committee.

The cumulative incidence of the primary efficacy outcome at 5 years was 15% with AVANDIA, 21% with metformin, and 34% with glyburide (HR 0.68 [95% CI 0.55, 0.85] versus metformin, HR 0.37 [95% CI 0.30, 0.45] versus glyburide).

Cardiovascular and adverse event data (including effects on body weight and bone fracture) from ADOPT for AVANDIA, metformin, and glyburide are described in *Warnings and Precautions (5.2, 5.5, and 5.8)* and *Adverse Reactions (6.1)*, respectively. As with all medications, efficacy results must be considered together with safety information to assess the potential benefit and risk for an individual patient.

14.2 Combination With Metformin or Sulfonylurea

The addition of AVANDIA to either metformin or sulfonylurea resulted in significant reductions in hyperglycemia compared to either of these agents alone. These results are consistent with an additive effect on glycemic control when AVANDIA is used as combination therapy.

Combination With Metformin: A total of 670 patients with type 2 diabetes participated in two 26-week, randomized, double-blind, placebo/active-controlled trials designed to assess the efficacy of AVANDIA in combination with metformin. AVANDIA, administered in either once daily or twice daily dosing regimens, was added to the therapy of patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin.

In one trial, patients inadequately controlled on 2.5 grams/day of metformin (mean baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were randomized to receive 4 mg of AVANDIA once daily, 8 mg of AVANDIA once daily, or placebo in addition to metformin. A statistically significant improvement in FPG and HbA1c was observed in patients treated with the combinations of metformin and 4 mg of AVANDIA once daily and 8 mg of AVANDIA once daily, versus patients continued on metformin alone (Table 12).

Table 12. Glycemic Parameters in a 26-Week Combination Trial of AVANDIA Plus Metformin

	Metformin	**AVANDIA 4 mg once daily + metformin**	**AVANDIA 8 mg once daily + metformin**
	N = 113	N = 116	N = 110
FPG (mg/dL)			
Baseline (mean)	214	215	220
Change from baseline (mean)	6	-33	-48
Difference from metformin alone (adjusted mean)	–	-40[a]	-53[a]
% of patients with ≥30 mg/dL decrease from baseline	20%	45%	61%
HbA1c (%)			
Baseline (mean)	8.6	8.9	8.9
Change from baseline (mean)	0.5	-0.6	-0.8
Difference from metformin alone (adjusted mean)	–	-1.0[a]	-1.2[a]
% of patients with ≥0.7% decrease from baseline	11%	45%	52%

[a] *P* <0.0001 compared to metformin.

In a second 26-week trial, patients with type 2 diabetes inadequately controlled on 2.5 grams/day of metformin who were randomized to receive the combination of AVANDIA 4 mg twice daily and metformin (N = 105) showed a statistically significant improvement in glycemic control with a mean treatment effect for FPG of -56 mg/dL and a mean treatment effect for HbA1c of -0.8% over metformin alone. The combination of metformin and AVANDIA resulted in lower levels of FPG and HbA1c than either agent alone.

Patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin and who were switched to monotherapy with AVANDIA demonstrated loss of glycemic control, as evidenced by increases in FPG and HbA1c. In this group, increases in LDL and VLDL were also seen.

Combination With a Sulfonylurea: A total of 3,457 patients with type 2 diabetes participated in ten 24- to 26-week randomized, double-blind, placebo/active-controlled trials and one 2-year double-blind, active-controlled trial in elderly patients designed to assess the efficacy and safety of AVANDIA in combination with a sulfonylurea. AVANDIA 2 mg, 4 mg, or 8 mg daily was administered, either once daily (3 trials) or in divided doses twice daily (7 trials), to patients inadequately controlled on a submaximal or maximal dose of sulfonylurea.

In these trials, the combination of AVANDIA 4 mg or 8 mg daily (administered as single or twice daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c compared

to placebo plus sulfonylurea or further up-titration of the sulfonylurea. Table 13 shows pooled data for 8 trials in which AVANDIA added to sulfonylurea was compared to placebo plus sulfonylurea.

Table 13. Glycemic Parameters in 24- to 26-Week Combination Trials of AVANDIA Plus Sulfonylurea

Twice Daily Divided Dosing (5 Trials)	**Sulfonylurea**	**AVANDIA 2 mg twice daily + sulfonylurea**	**Sulfonylurea**	**AVANDIA 4 mg twice daily + sulfonylurea**
	N = 397	N = 497	N = 248	N = 346
FPG (mg/dL)				
Baseline (mean)	204	198	188	187
Change from baseline (mean)	11	-29	8	-43
Difference from sulfonylurea alone (adjusted mean)	–	-42[a]	–	-53[a]
% of patients with ≥30 mg/dL decrease from baseline	17%	49%	15%	61%
HbA1c (%)				
Baseline (mean)	9.4	9.5	9.3	9.6
Change from baseline (mean)	0.2	-1.0	0.0	-1.6
Difference from sulfonylurea alone (adjusted mean)	–	-1.1[a]	–	-1.4[a]
% of patients with ≥0.7% decrease from baseline	21%	60%	23%	75%
Once Daily Dosing (3 Trials)	**Sulfonylurea**	**AVANDIA 4 mg once daily + sulfonylurea**	**Sulfonylurea**	**AVANDIA 8 mg once daily + sulfonylurea**
	N = 172	N = 172	N = 173	N = 176
FPG (mg/dL)				
Baseline (mean)	198	206	188	192
Change from baseline (mean)	17	-25	17	-43
Difference from sulfonylurea alone (adjusted mean)	–	-47[a]	–	-66[a]
% of patients with ≥30 mg/dL decrease from baseline	17%	48%	19%	55%
HbA1c (%)				
Baseline (mean)	8.6	8.8	8.9	8.9
Change from baseline (mean)	0.4	-0.5	0.1	-1.2
Difference from sulfonylurea alone (adjusted mean)	–	-0.9[a]	–	-1.4[a]
% of patients with ≥0.7% decrease from baseline	11%	36%	20%	68%

[a] P <0.0001 compared to sulfonylurea alone.

One of the 24- to 26-week trials included patients who were inadequately controlled on maximal doses of glyburide and switched to 4 mg of AVANDIA daily as monotherapy; in this group, loss of glycemic control was demonstrated, as evidenced by increases in FPG and HbA1c.

In a 2-year double-blind trial, elderly patients (aged 59 to 89 years) on half-maximal sulfonylurea (glipizide 10 mg twice daily) were randomized to the addition of AVANDIA (n = 115, 4 mg once daily to 8 mg as needed) or to continued up-titration of glipizide (n = 110), to a maximum of 20 mg twice daily. Mean baseline FPG and HbA1c were 157 mg/dL and 7.72%, respectively, for the AVANDIA plus glipizide arm and 159 mg/dL and 7.65%, respectively, for the glipizide up-titration arm. Loss of glycemic control (FPG ≥180 mg/dL) occurred in a significantly lower proportion of patients (2%) on AVANDIA plus glipizide compared to patients in the glipizide up-titration arm (28.7%). About 78% of the patients on combination therapy completed the 2 years of therapy while only 51% completed on glipizide monotherapy. The effect of combination therapy on FPG and HbA1c was durable over the 2-year trial period, with patients achieving a mean of 132 mg/dL for FPG and a mean of 6.98% for HbA1c compared to no change on the glipizide arm.

14.3 Combination With Sulfonylurea Plus Metformin

In two 24- to 26-week, double-blind, placebo-controlled, trials designed to assess the efficacy and safety of AVANDIA in combination with sulfonylurea plus metformin, AVANDIA 4 mg or 8 mg daily, was administered in divided doses twice daily, to patients inadequately controlled on submaximal (10 mg) and maximal (20 mg) doses of glyburide and maximal dose of metformin (2 g/day). A statistically significant improvement in FPG and HbA1c was observed in patients treated with the combinations of sulfonylurea plus metformin and 4 mg of AVANDIA and 8 mg of AVANDIA versus patients continued on sulfonylurea plus metformin, as shown in Table 14.

Table 14. Glycemic Parameters in a 26-Week Combination Trial of AVANDIA Plus Sulfonylurea and Metformin

	Sulfonylurea + metformin	**AVANDIA 2 mg twice daily + sulfonylurea + metformin**	**AVANDIA 4 mg twice daily + sulfonylurea + metformin**
	N = 273	N = 276	N = 277
FPG (mg/dL)			
Baseline (mean)	189	190	192
Change from baseline (mean)	14	-19	-40
Difference from sulfonylurea plus metformin (adjusted mean)	–	-30[a]	-52[a]
% of patients with ≥30 mg/dL decrease from baseline	16%	46%	62%
HbA1c (%)			
Baseline (mean)	8.7	8.6	8.7
Change from baseline (mean)	0.2	-0.4	-0.9
Difference from sulfonylurea plus metformin (adjusted mean)	–	-0.6[a]	-1.1[a]
% of patients with ≥0.7% decrease from baseline	16%	39%	63%

[a] *P* <0.0001 compared to placebo.

15 REFERENCES

1. Food and Drug Administration Briefing Document. Joint meeting of the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees. July 13-14, 2010.
2. Winkelmayer WC, et al. Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy. *Arch Intern Med* 2008;168(21):2368-2375.
3. Juurlink DN, et al. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. *BMJ* 2009; 339.
4. Graham DJ, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly medicare patients treated with rosiglitazone or pioglitazone. *JAMA* 2010;304:411-418.
5. Wertz DA, et al. Risk of cardiovascular events and all-cause mortality in patients with Thiazolidinediones in a managed-care population. *Circ Cardiovasc Qual Outcomes* 2010;3:

538-545.
6. DREAM Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096-1105.
7. Kahn S, et al. Glycemic durability of rosiglitazone, metformin or glyburide monotherapy. *New England Journal of Medicine* 2006, 355:2427-2443.
8. Home P, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicenter, randomized, open-label trial. *Lancet* 2009, 373:2125-35.
9. Dormandy J et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (Prospective Pioglitazone Clinical Trial in Macrovascular Events): a randomized controlled trial. *Lancet* 2005, 366:1279-89.
10. Bilik D, et al. Thiazolidinediones, cardiovascular disease and cardiovascular mortality: translating research into action for diabetes (TRIAD). *Pharmocoepidemiol Drug Saf* 2010; 19: 715–721.
11. Park JY, Kim KA, Kang MH, et al. Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects. *Clin Pharmacol Ther* 2004;75:157-162.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each pentagonal film-coated TILTAB tablet contains rosiglitazone as the maleate as follows: 2 mg–pink, debossed with SB on one side and 2 on the other; 4 mg–orange, debossed with SB on one side and 4 on the other; 8 mg–red-brown, debossed with SB on one side and 8 on the other.

2 mg bottles of 60: NDC 0173-0834-18

4 mg bottles of 30: NDC 0173-0835-13

8 mg bottles of 30: NDC 0173-0836-13

Store at 25°C (77°F); excursions 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

See Medication Guide.

17.1 Patient Advice

There are multiple medications available to treat type 2 diabetes. The benefits and risks of each available diabetes medication should be taken into account when choosing a particular diabetes medication for a given patient.

Patients should be informed of the risks and benefits of AVANDIA. AVANDIA should only be taken by adults with type 2 diabetes who are already taking AVANDIA, or who are not already taking AVANDIA and are unable to achieve adequate glycemic control on other diabetes medications, and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS) for medical reasons. Inform patients that they must be enrolled in the AVANDIA-Rosiglitazone Medicines Access Program in order to receive AVANDIA.

Patients should be informed of the following:

- AVANDIA is not recommended for patients with symptomatic heart failure.
- Results of a set of clinical trials suggest that treatment with AVANDIA is associated with an increased risk for myocardial infarction (heart attack), especially in patients taking insulin. Clinical trials have not shown any difference between AVANDIA and comparator medications in overall mortality or CV-related mortality.
- AVANDIA is not recommended for patients who are taking insulin.
- Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but in maintaining the efficacy of drug therapy.
- It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. It can take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of AVANDIA.
- Blood will be drawn to check their liver function prior to the start of therapy and periodically thereafter per the clinical judgment of the healthcare professional. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician.
- Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on AVANDIA should immediately report these symptoms to their physician.
- AVANDIA can be taken with or without meals.
- When using AVANDIA in combination with other hypoglycemic agents, the risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.
- Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDIA. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical trials so the frequency of this occurrence is not known.

GlaxoSmithKline
Research Triangle Park, NC 27709

Month 2011

AVD:XXPI

MEDICATION GUIDE
AVANDIA® (ah-VAN-dee-a)
(rosiglitazone maleate) Tablets

Read this Medication Guide carefully before you start taking AVANDIA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about AVANDIA, ask your doctor or pharmacist.

What is the most important information I should know about AVANDIA?

AVANDIA is available only through the AVANDIA-Rosiglitazone Medicines Access Program. Both you and your doctor must be enrolled in the program so that you can get AVANDIA. To enroll, you must:

- talk to your doctor,
- understand the risks and benefits of AVANDIA, and
- agree to enroll in the program.

AVANDIA may cause serious side effects, including:

New or worse heart failure

- AVANDIA can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Heart failure means your heart does not pump blood well enough.
- If you have severe heart failure, you cannot start AVANDIA.
- If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, AVANDIA may not be right for you.

Call your doctor right away if you have any of the following:

- swelling or fluid retention, especially in the ankles or legs
- shortness of breath or trouble breathing, especially when you lie down
- an unusually fast increase in weight
- unusual tiredness

Myocardial Infarction ("Heart Attack")

AVANDIA may raise the risk of a heart attack. The risk of having a heart attack may be higher in people who take AVANDIA with insulin. Most people who take insulin

should not also take AVANDIA.

Symptoms of a heart attack can include the following:

- chest discomfort in the center of your chest that lasts for more than a few minutes, or that goes away or comes back
- chest discomfort that feels like uncomfortable pressure, squeezing, fullness or pain
- pain or discomfort in your arms, back, neck, jaw or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded

Call your doctor or go to the nearest hospital emergency room right away if you think you are having a heart attack.

People with diabetes have a greater risk for heart problems. It is important to work with your doctor to manage other conditions, such as high blood pressure or high cholesterol.

AVANDIA can have other serious side effects. Be sure to read the section below "What are possible side effects of AVANDIA?".

What is AVANDIA?

AVANDIA is a prescription medicine used with diet and exercise to treat certain adults with type 2 ("adult-onset" or "non-insulin dependent") diabetes mellitus ("high blood sugar") who are:

- already taking AVANDIA or
- unable to control their blood sugar on other diabetes medicines, and after talking with their doctor have decided not to take pioglitazone (ACTOS)

AVANDIA helps to control high blood sugar. AVANDIA may be used alone or with other diabetes medicines. AVANDIA can help your body respond better to insulin made in your body. AVANDIA does not cause your body to make more insulin.

AVANDIA is not for people with type 1 diabetes mellitus or to treat a condition called diabetic ketoacidosis.

It is not known if AVANDIA is safe and effective in children under 18 years old.

Who should not take AVANDIA?

Many people with heart failure should not start taking AVANDIA. See "What should

I tell my doctor before taking AVANDIA?".

What should I tell my doctor before taking AVANDIA?

Before starting AVANDIA, ask your doctor about what the choices are for diabetes medicines, and what the expected benefits and possible risks are for you in particular.

Before taking AVANDIA, tell your doctor about all your medical conditions, including if you:

- **have heart problems or heart failure.**
- **have type 1 ("juvenile") diabetes or had diabetic ketoacidosis.** These conditions should be treated with insulin.
- **have a type of diabetic eye disease called macular edema** (swelling of the back of the eye).
- **have liver problems.** Your doctor should do blood tests to check your liver before you start taking AVANDIA and during treatment as needed.
- **had liver problems while taking REZULIN® (troglitazone), another medicine for diabetes.**
- **are pregnant or plan to become pregnant.** AVANDIA should not be used during pregnancy. It is not known if AVANDIA can harm your unborn baby. You and your doctor should talk about the best way to control your diabetes during pregnancy. If you are a premenopausal woman (before the "change of life") who does not have regular monthly periods, AVANDIA may increase your chances of becoming pregnant. Talk to your doctor about birth control choices while taking AVANDIA. Tell your doctor right away if you become pregnant while taking AVANDIA.
- **are breast-feeding or planning to breast-feed.** It is not known if AVANDIA passes into breast milk. You should not use AVANDIA while breast-feeding.

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins or herbal supplements. AVANDIA and certain other medicines can affect each other and may lead to serious side effects including high or low blood sugar, or heart problems. Especially tell your doctor if you take:

- **insulin.**
- **any medicines for high blood pressure, high cholesterol or heart failure, or for prevention of heart disease or stroke.**

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist before you start a new medicine. They will tell you if it is alright to take AVANDIA with other medicines.

How should I take AVANDIA?

- Take AVANDIA exactly as prescribed. Your doctor will tell you how many tablets to take and how often. The usual daily starting dose is 4 mg a day taken one time each day or 2 mg taken two times each day. Your doctor may need to adjust your dose until your blood sugar is better controlled.
- AVANDIA may be prescribed alone or with other diabetes medicines. This will depend on how well your blood sugar is controlled.
- Take AVANDIA with or without food.
- It can take 2 weeks for AVANDIA to start lowering blood sugar. It may take 2 to 3 months to see the full effect on your blood sugar level.
- If you miss a dose of AVANDIA, take it as soon as you remember, unless it is time to take your next dose. Take your next dose at the usual time. Do not take double doses to make up for a missed dose.
- If you take too much AVANDIA, call your doctor or poison control center right away.
- Test your blood sugar regularly as your doctor tells you.
- Diet and exercise can help your body use its blood sugar better. It is important to stay on your recommended diet, lose extra weight, and get regular exercise while taking AVANDIA.
- Your doctor should do blood tests to check your liver before you start AVANDIA and during treatment as needed. Your doctor should also do regular blood sugar tests (for example, “A1C”) to monitor your response to AVANDIA.

What are possible side effects of AVANDIA?

AVANDIA may cause serious side effects including:

- **New or worse heart failure.** See “What is the most important information I should know about AVANDIA?”.
- **Heart attack.** See “What is the most important information I should know about AVANDIA?”.
- **Swelling (edema).** AVANDIA can cause swelling due to fluid retention. See “What is the most important information I should know about AVANDIA?”.
- **Weight gain.** AVANDIA can cause weight gain that may be due to fluid retention or extra body fat. Weight gain can be a serious problem for people with certain conditions including heart problems. See “What is the most important information I should know about AVANDIA?”.
- **Liver problems.** It is important for your liver to be working normally when you take AVANDIA. Your doctor should do blood tests to check your liver before you start taking AVANDIA and during treatment as needed. Call your doctor right away if you have unexplained symptoms such as:

- nausea or vomiting
- stomach pain
- unusual or unexplained tiredness
- loss of appetite
- dark urine
- yellowing of your skin or the whites of your eyes.

- **Macular edema** (a diabetic eye disease with swelling in the back of the eye). Tell your doctor right away if you have any changes in your vision. Your doctor should check your eyes regularly. Very rarely, some people have had vision changes due to swelling in the back of the eye while taking AVANDIA.
- **Fractures (broken bones),** usually in the hand, upper arm or foot. Talk to your doctor for advice on how to keep your bones healthy.
- **Low red blood cell count (anemia).**
- **Low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness or hunger may mean that your blood sugar is too low. This can happen if you skip meals, if you use another medicine that lowers blood sugar, or if you have certain medical problems. Call your doctor if low blood sugar levels are a problem for you.
- **Ovulation** (release of egg from an ovary in a woman) leading to pregnancy. Ovulation may happen in premenopausal women who do not have regular monthly periods. This can increase the chance of pregnancy. See “What should I tell my doctor before taking AVANDIA?”.

The most common side effects of AVANDIA reported in clinical trials included cold-like symptoms and headache.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AVANDIA?

- Store AVANDIA at room temperature, 59° to 86°F (15° to 30°C). Keep AVANDIA in the container it comes in.
- Safely, throw away AVANDIA that is out of date or no longer needed.
- Keep AVANDIA and all medicines out of the reach of children.

General information about AVANDIA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AVANDIA for a condition for which it was not prescribed. Do not give AVANDIA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes important information about AVANDIA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about AVANDIA that is written for healthcare professionals. You can also find out more about AVANDIA by calling 1-888-825-5249.

What are the ingredients in AVANDIA?

Active Ingredient: Rosiglitazone maleate.

Inactive Ingredients: Hypromellose 2910, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin, and 1 or more of the following: Synthetic red and yellow iron oxides and talc.

Always check to make sure that the medicine you are taking is the correct one. AVANDIA tablets are triangles with rounded corners and look like this:

2 mg – pink with “SB” on one side and “2” on the other.
4 mg – orange with “SB” on one side and “4” on the other.
8 mg – red-brown with “SB” on one side and “8” on the other.

AVANDIA is a registered trademark of GlaxoSmithKline.
The other brands listed are trademarks of their respective owners and are not trademarks of GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse GlaxoSmithKline or its products.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

GlaxoSmithKline
Research Triangle Park, NC 27709

Month 2011
AVD:XMG

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVANDAMET safely and effectively. See full prescribing information for AVANDAMET.

AVANDAMET **(rosiglitazone maleate and metformin hydrochloride) Tablets**
Initial U.S. Approval: 2002

WARNINGS

See full prescribing information for complete boxed warning.

Rosiglitazone maleate: CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION

- **Thiazolidinediones, including rosiglitazone, cause or exacerbate heart failure in some patients (5.2). After initiation of AVANDAMET, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction must be considered. (5.2)**
- **AVANDAMET is not recommended in patients with symptomatic heart failure. Initiation of AVANDAMET in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.2)**
- **A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with a statistically significant increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, showed a statistically non-significant increased risk of myocardial infarction and a statistically non-significant decreased risk of death. There have been no clinical trials directly comparing cardiovascular risk of rosiglitazone and ACTOS® (pioglitazone, another thiazolidinedione), but in a separate trial, pioglitazone (when compared to placebo) did not show an increased risk of myocardial infarction or death. (5.3)**
- **Because of the potential increased risk of myocardial infarction, AVANDAMET is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1-800-AVANDIA or visit www.AVANDIA.com. *[See Warnings and Precautions (5.4).]***

Metformin hydrochloride: LACTIC ACIDOSIS

- **Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment and acute congestive heart failure. (5.1)**
- **Symptoms include malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. (5.1)**
- **If acidosis is suspected, discontinue AVANDAMET and hospitalize the patient immediately. (5.1)**

RECENT MAJOR CHANGES

Boxed Warning	02/2011
Indications and Usage (1)	02/2011
Dosage and Administration (2)	02/2011
Warnings and Precautions, Cardiac Failure (5.2)	02/2011
Warnings and Precautions, Major Adverse Cardiovascular Events (5.3)	02/2011
Warnings and Precautions, Rosiglitazone REMS Program (5.4)	XX/2011
Warnings and Precautions, Fractures (5.9)	02/2011

INDICATIONS AND USAGE

AVANDAMET is a combination antidiabetic product containing a thiazolidinedione and a biguanide. After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of rosiglitazone, this drug is indicated as an adjunct to diet and exercise to improve glycemic control when treatment with both rosiglitazone and metformin is appropriate in adults with type 2 diabetes mellitus who either are:

- already taking rosiglitazone, or
- not already taking rosiglitazone and are unable to achieve glycemic control on other diabetes medications and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS) or pioglitazone-containing products (ACTOPLUS MET®, ACTOPLUS MET XR®, DUETACT®) for medical reasons. (1)

Other Important Limitations of Use:

- Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. (1)
- Coadministration with insulin is not recommended. (1, 5.2, 5.3)

DOSAGE AND ADMINISTRATION

- Individualize the starting dose based on the patient's current regimen. (2.1)
- Dose increases should be accompanied by careful monitoring for adverse events related to fluid retention. (2.1)
- Give in divided doses with meals with gradual dose escalation to reduce the gastrointestinal side effects. (2.2)
- Do not exceed the maximum recommended daily dose of 8 mg rosiglitazone and 2,000 mg metformin. (2.3)
- Do not initiate if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels. (2.4)

DOSAGE FORMS AND STRENGTHS

Oval, film-coated tablets containing rosiglitazone/metformin hydrochloride: 2 mg/500 mg, 4 mg/500 mg, 2 mg/1,000 mg, and 4 mg/1,000 mg (3)

CONTRAINDICATIONS

- Initiation in patients with established NYHA Class III or IV heart failure. (4)
- Use in significant renal disease or renal dysfunction. (4)
- Use in acute or chronic metabolic acidosis. (4)
- Use in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials. (4, 5.1)

WARNINGS AND PRECAUTIONS

- Fluid retention, which may exacerbate or lead to heart failure, may occur. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk of other cardiovascular effects. (5.2)
- Increased risk of myocardial infarction has been observed in a meta-analysis of 52 clinical trials of rosiglitazone (incidence rate 0.4% versus 0.3%). (5.3)
- Coadministration with insulin is not recommended. (1, 5.2, 5.3)
- Assess renal function before starting therapy and at least annually. (5.1)
- Avoid use in patients with evidence of hepatic disease. (2.4, 5.1)
- Warn patients against excessive alcohol intake. (5.1)
- Promptly evaluate patients who develop laboratory abnormalities or clinical illness for evidence of ketoacidosis or lactic acidosis. (5.1)
- Dose-related edema (5.5), weight gain (5.6), and anemia (5.10) may occur.
- Macular edema has been reported. (5.8)
- Increased incidence of bone fracture. (5.9)
- Measure hematologic parameters annually. (5.10)

ADVERSE REACTIONS

The most common adverse reactions (≥10%) include nausea/vomiting, diarrhea, headache, and dyspepsia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Inhibitors of CYP2C8 (e.g., gemfibrozil) may increase rosiglitazone levels. (7.1)
- Inducers of CYP2C8 (e.g., rifampin) may decrease rosiglitazone levels. (7.1)
- Cationic drugs eliminated by renal tubular secretion; use with caution. (7.2)

USE IN SPECIFIC POPULATIONS

- Do not use during pregnancy. No human or animal data. (8.1)
- Safety and effectiveness in children under 18 years have not been established. (8.4)
- Because reduced renal function is associated with increasing age, use with caution in elderly patients. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: XX/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNINGS

Rosiglitazone maleate: **CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION**

- Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients *[see Warnings and Precautions (5.2)]*. After initiation of AVANDAMET, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDAMET must be considered.
- AVANDAMET is not recommended in patients with symptomatic heart failure. Initiation of AVANDAMET in patients with established NYHA Class III or IV heart failure is contraindicated. *[See Contraindications (4) and Warnings and Precautions (5.2).]*
- A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, showed a statistically non-significant increased risk of myocardial infarction, and a statistically non-significant decreased risk of death. There have been no clinical trials directly comparing cardiovascular risk of rosiglitazone and ACTOS® (pioglitazone, another thiazolidinedione), but in a separate trial, pioglitazone (when compared to placebo) did not show an increased risk of myocardial infarction or death. *[See Warnings and Precautions (5.3).]*
- Because of the potential increased risk of myocardial infarction, AVANDAMET is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1-800-AVANDIA or visit www.AVANDIA.com. *[See Warnings and Precautions (5.4).]*

Metformin hydrochloride: **LACTIC ACIDOSIS**

- Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. *[See Warnings and Precautions (5.1).]*
- Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. *[See Warnings and Precautions (5.1).]*

- If acidosis is suspected, discontinue AVANDAMET and hospitalize the patient immediately *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of rosiglitazone, AVANDAMET® is indicated as an adjunct to diet and exercise to improve glycemic control when treatment with both rosiglitazone and metformin is appropriate in adults with type 2 diabetes mellitus who either are:

- already taking rosiglitazone, or
- not already taking rosiglitazone and unable to achieve glycemic control on other diabetes medications and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS®) or pioglitazone-containing products (ACTOPLUS MET®, ACTOPLUS MET XR®, DUETACT®) for medical reasons.

Other Important Limitations of Use:

- Due to its mechanism of action, rosiglitazone is active only in the presence of endogenous insulin. Therefore, AVANDAMET should not be used in patients with type 1 diabetes.
- Coadministration of AVANDAMET with insulin is not recommended *[see Warnings and Precautions (5.2, 5.3)]*.

2 DOSAGE AND ADMINISTRATION

Prior to prescribing AVANDAMET, refer to *Indications and Usage (1)* for appropriate patient selection. Only prescribers enrolled in the AVANDIA-Rosiglitazone Medicines Access Program can prescribe AVANDAMET *[see Warnings and Precautions (5.4)]*.

2.1 Starting Dose

AVANDAMET is generally given in divided doses with meals.

All patients should start the rosiglitazone component of AVANDAMET at the lowest recommended dose. Further increases in the dose of rosiglitazone should be accompanied by careful monitoring for adverse events related to fluid retention *[see **Boxed Warning** and Warnings and Precautions (5.5)]*.

If therapy with a combination tablet containing rosiglitazone and metformin is considered appropriate for a patient with type 2 diabetes mellitus, then the selection of the dose of AVANDAMET should be based on the patient's current doses of rosiglitazone and/or metformin.

To switch to AVANDAMET for patients currently treated with metformin, the usual starting dose of AVANDAMET is 4 mg rosiglitazone (total daily dose) plus the dose of metformin already being taken (see Table 1).

To switch to AVANDAMET for patients currently treated with rosiglitazone, the usual starting dose of AVANDAMET is 1,000 mg metformin (total daily dose) plus the dose of rosiglitazone already being taken (see Table 1).

When switching from combination therapy of rosiglitazone plus metformin as separate tablets, the usual starting dose of AVANDAMET is the dose of rosiglitazone and metformin already being taken.

Table 1. AVANDAMET Starting Dose for Patients Treated with Metformin and/or Rosiglitazone

PRIOR THERAPY	Usual AVANDAMET Starting Dose	
Total daily dose	**Tablet strength**	**Number of tablets**
Metformin[a]		
1,000 mg/day	2 mg/500 mg	1 tablet twice a day
2,000 mg/day	2 mg/1,000 mg	1 tablet twice a day
Rosiglitazone		
4 mg/day	2 mg/500 mg	1 tablet twice a day
8 mg/day	4 mg/500 mg	1 tablet twice a day

[a] For patients on doses of metformin between 1,000 and 2,000 mg/day, initiation of AVANDAMET requires individualization of therapy.

2.2 Dose Titration

AVANDAMET is generally given in divided doses with meals, with gradual dose escalation. This reduces gastrointestinal side effects (largely due to metformin) and permits determination of the minimum effective dose for the individual patient.

Sufficient time should be given to assess adequacy of therapeutic response. FPG should be used initially to determine the therapeutic response to AVANDAMET. If additional glycemic control is needed, the daily dose of AVANDAMET may be increased by increments of 4 mg rosiglitazone and/or 500 mg metformin.

After an increase in metformin dosage, dose titration is recommended if patients are not adequately controlled after 1 to 2 weeks. After an increase in rosiglitazone dosage, dose titration is recommended if patients are not adequately controlled after 8 to 12 weeks.

2.3 Maximum Dose

The maximum recommended total daily dose of AVANDAMET is 8 mg rosiglitazone (taken as 4 mg twice daily) and 2,000 mg metformin (taken as 1,000 mg twice daily).

2.4 Specific Patient Populations

Renal Impairment: Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of AVANDAMET. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly *[see Warnings and Precautions (5.1)]*.

Hepatic Impairment: Liver enzymes should be measured prior to initiating treatment with AVANDAMET. Therapy with AVANDAMET should not be initiated if the patient exhibits

clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy). After initiation of AVANDAMET, liver enzymes should be monitored periodically per the clinical judgment of the healthcare professional *[see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)]*.

Geriatric: The initial and maintenance dosing of AVANDAMET should be conservative in patients with advanced age, due to the potential for decreased renal function in this population.

Pediatric: Safety and effectiveness of AVANDAMET in pediatric patients have not been established. AVANDAMET and rosiglitazone are not recommended for use in pediatric patients.

Pregnancy: AVANDAMET is not recommended for use in pregnancy.

3 DOSAGE FORMS AND STRENGTHS

Each film-coated oval tablet contains rosiglitazone as the maleate and metformin hydrochloride as follows:

- 2 mg/500 mg – pale pink, debossed with gsk on one side and 2/500 on the other
- 4 mg/500 mg – orange, debossed with gsk on one side and 4/500 on the other
- 2 mg/1,000 mg – yellow, debossed with gsk on one side and 2/1000 on the other
- 4 mg/1,000 mg – pink, debossed with gsk on one side and 4/1000 on the other

4 CONTRAINDICATIONS

- Initiation in patients with established New York Heart Association (NYHA) Class III or IV heart failure *[see **Boxed Warning**]*.
- Use in patients with renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females], or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia *[see Warnings and Precautions (5.1)]*.
- Use in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
- Use in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. AVANDAMET should be temporarily discontinued in these patients. *[See Warnings and Precautions (5.1).]*

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

Incidence and Management: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with AVANDAMET; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When

metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 mcg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases/1,000 patient years of exposure, with approximately 0.015 fatal cases/1,000 patient years of exposure). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking AVANDAMET and by use of the minimum effective dose of AVANDAMET. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Treatment with AVANDAMET should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, AVANDAMET should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, AVANDAMET should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking AVANDAMET, since alcohol potentiates the effects of metformin on lactate metabolism. In addition, AVANDAMET should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. AVANDAMET should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of AVANDAMET, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking AVANDAMET do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking AVANDAMET, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery *[see Contraindications (4)]*.

Factors That May Predispose Patients to Lactic Acidosis: *Assessment of Renal Function:* Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive AVANDAMET. In patients with advanced age, AVANDAMET should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. *[See Dosage and Administration (2.4) and Use in Specific Populations (8.5).]*

Before initiation of therapy with AVANDAMET and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and AVANDAMET discontinued if evidence of renal impairment is present.

Medications That Affect Renal Function: Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion *[see Drug Interactions (7.2) and Clinical Pharmacology (12.4)]*, should be used with caution.

Hypoxic States: Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients receiving AVANDAMET, the drug should be promptly discontinued.

Radiologic Studies With Intravascular Iodinated Contrast Materials: Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin *[see Contraindications (4)]*. Therefore, in patients in whom any such study is planned, AVANDAMET should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Surgical Procedures: Use of AVANDAMET should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving AVANDAMET.

Change in Clinical Status of Patients With Previously Controlled Diabetes: A patient with type 2 diabetes previously well-controlled on AVANDAMET who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, AVANDAMET must be stopped immediately and other appropriate corrective measures initiated.

[See also Warnings and Precautions (5.7).]

5.2 Cardiac Failure

Rosiglitazone, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered *[see **Boxed Warning**]*.

Patients with congestive heart failure (CHF) NYHA Class I and II treated with rosiglitazone have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-controlled echocardiographic trial was conducted in 224 patients with type 2 diabetes mellitus and NYHA Class I or II CHF (ejection fraction ≤45%) on background antidiabetic and CHF therapy. An independent committee conducted a blinded evaluation of fluid-related events (including congestive heart failure) and cardiovascular hospitalizations according to predefined criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were reported by investigators. Although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed with rosiglitazone treatment compared to placebo during the 52-week trial. (See Table 2.)

Table 2. Emergent Cardiovascular Adverse Events in Patients With Congestive Heart Failure (NYHA Class I and II) Treated With Rosiglitazone or Placebo (in Addition to Background Antidiabetic and CHF Therapy)

Events	**Rosiglitazone**	**Placebo**
	N = 110 n (%)	N = 114 n (%)
Adjudicated		
Cardiovascular deaths	5 (5%)	4 (4%)
CHF worsening	7 (6%)	4 (4%)
– with overnight hospitalization	5 (5%)	4 (4%)
– without overnight hospitalization	2 (2%)	0 (0%)
New or worsening edema	28 (25%)	10 (9%)
New or worsening dyspnea	29 (26%)	19 (17%)
Increases in CHF medication	36 (33%)	20 (18%)
Cardiovascular hospitalization[a]	21 (19%)	15 (13%)
Investigator-reported, non-adjudicated		
Ischemic adverse events	10 (9%)	5 (4%)
– Myocardial infarction	5 (5%)	2 (2%)
– Angina	6 (5%)	3 (3%)

[a] Includes hospitalization for any cardiovascular reason.

Initiation of AVANDAMET in patients with established NYHA Class III or IV heart failure is contraindicated. AVANDAMET is not recommended in patients with symptomatic heart failure. *[See **Boxed Warning**.]*

Patients experiencing acute coronary syndromes have not been studied in controlled clinical trials. In view of the potential for development of heart failure in patients having an acute coronary event, initiation of AVANDAMET is not recommended for patients experiencing an acute coronary event, and discontinuation of AVANDAMET during this acute phase should be considered.

Patients with NYHA Class III and IV cardiac status (with or without CHF) have not been studied in controlled clinical trials. AVANDAMET is not recommended in patients with NYHA Class III and IV cardiac status.

Congestive Heart Failure During Coadministration of Rosiglitazone With Insulin: In trials in which rosiglitazone was added to insulin, rosiglitazone increased the risk of congestive heart failure. Coadministration of rosiglitazone and insulin is not recommended. *[See Indications and Usage (1) and Warnings and Precautions (5.3).]*

In 7 controlled, randomized, double-blind trials which had durations from 16 to 26 weeks and which were included in a meta-analysis[1] *[see Warnings and Precautions (5.3)]*, patients with type 2 diabetes mellitus were randomized to coadministration of rosiglitazone and insulin

(N = 1,018) or insulin (N = 815). In these 7 trials, rosiglitazone was added to insulin. These trials included patients with long-standing diabetes (median duration of 12 years) and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. The total number of patients with emergent congestive heart failure was 23 (2.3%) and 8 (1.0%) in the rosiglitazone plus insulin and insulin groups, respectively.

Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing Rosiglitazone to Pioglitazone: Three observational studies[2-4] in elderly diabetic patients (age 65 years and older) found that rosiglitazone statistically significantly increased the risk of hospitalized heart failure compared to use of pioglitazone. One other observational study[5] in patients with a mean age of 54 years, which also included an analysis in a subpopulation of patients >65 years of age, found no statistically significant increase in emergency department visits or hospitalization for heart failure in patients treated with rosiglitazone compared to pioglitazone in the older subgroup.

5.3 Major Adverse Cardiovascular Events

Cardiovascular adverse events have been evaluated in a meta-analysis of 52 clinical trials, in long-term, prospective, randomized, controlled trials, and in observational studies.

Meta-Analysis of Major Adverse Cardiovascular Events in a Group of 52 Clinical Trials: A meta-analysis was conducted retrospectively to assess cardiovascular adverse events reported across 52 double-blind, randomized, controlled clinical trials (mean duration 6 months).[1] These trials had been conducted to assess glucose-lowering efficacy in type 2 diabetes. Prospectively planned adjudication of cardiovascular events did not occur in most of the trials. Some trials were placebo-controlled and some used active oral antidiabetic drugs as controls. Placebo-controlled trials included monotherapy trials (monotherapy with rosiglitazone versus placebo monotherapy) and add-on trials (rosiglitazone or placebo, added to sulfonylurea, metformin, or insulin). Active control trials included monotherapy trials (monotherapy with rosiglitazone versus sulfonylurea or metformin monotherapy) and add-on trials (rosiglitazone plus sulfonylurea or rosiglitazone plus metformin, versus sulfonylurea plus metformin). A total of 16,995 patients were included (10,039 in treatment groups containing rosiglitazone, 6,956 in comparator groups), with 5,167 patient-years of exposure to rosiglitazone and 3,637 patient-years of exposure to comparator. Cardiovascular events occurred more frequently for patients who received rosiglitazone than for patients who received comparators (see Table 3).

Table 3. Occurrence of Cardiovascular Events in a Meta-Analysis of 52 Clinical Trials

Event[a]	Rosiglitazone (N=10,039) n (%)	Comparator (N=6,956) n (%)
MACE (a composite of myocardial infarction, cardiovascular death, or stroke)	70 (0.7)	39 (0.6)
Myocardial Infarction	45 (0.4)	20 (0.3)
Cardiovascular Death	17 (0.2)	9 (0.1)
Stroke	18 (0.2)	16 (0.2)
All-cause Death	29 (0.3)	17 (0.2)

[a] Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial infarction would be counted in 4 event categories (myocardial infarction; myocardial infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).

In this analysis, a statistically significant increased risk of myocardial infarction with rosiglitazone versus pooled comparators was observed. Analyses were performed using a composite of major adverse cardiovascular events (myocardial infarction, stroke, and cardiovascular death), referred to hereafter as MACE. Rosiglitazone had a statistically non-significant increased risk of MACE compared to the pooled comparators. A statistically significant increased risk of myocardial infarction and statistically non-significant increased risk of MACE with rosiglitazone was observed in the placebo-controlled trials. In the active-controlled trials, there was no increased risk of myocardial infarction or MACE. (See Figure 1 and Table 4.)

Figure 1. Forest Plot of Odds Ratios (95% Confidence Intervals) for MACE and Myocardial Infarction in the Meta-Analysis of 52 Clinical Trials

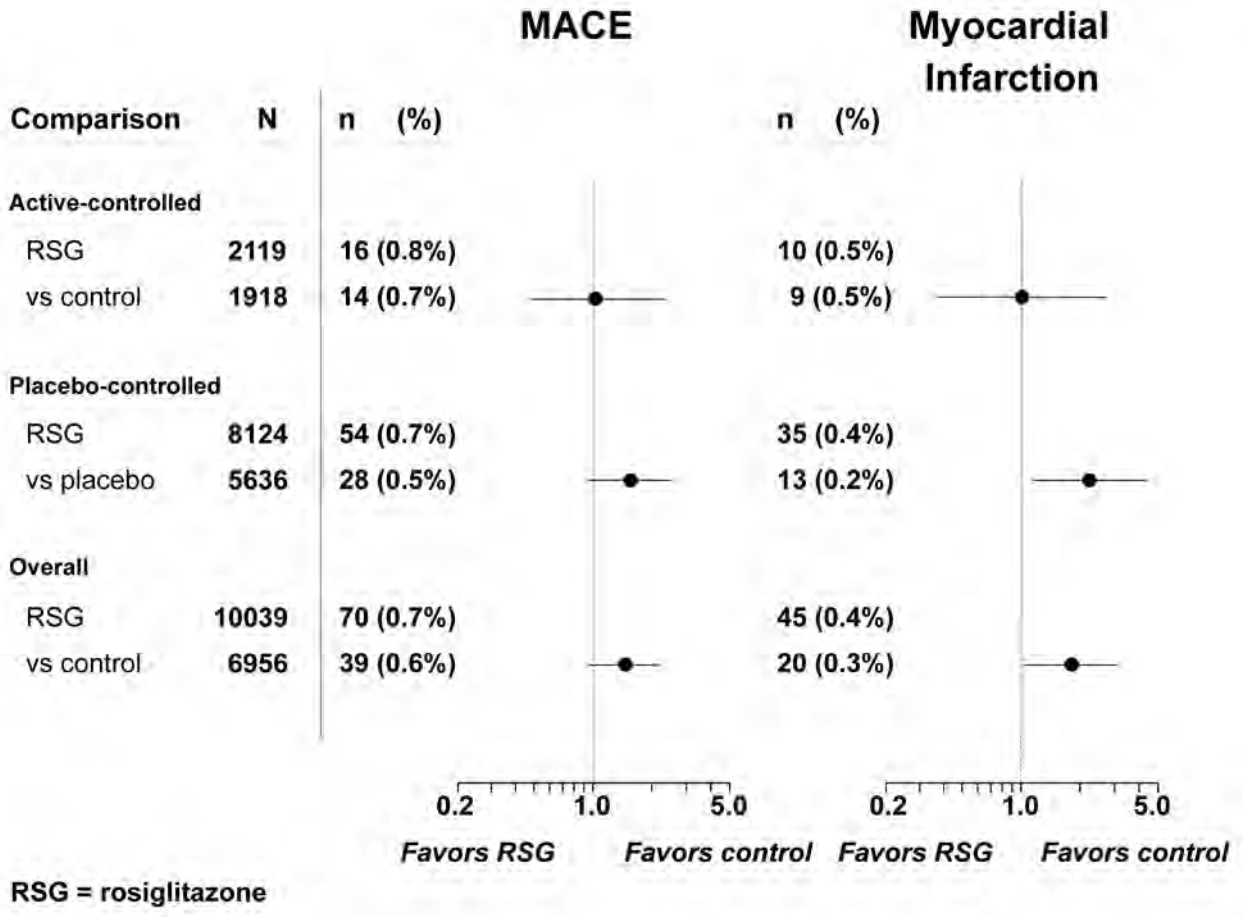


Table 4. Occurrence of MACE and Myocardial Infarction in a Meta-Analysis of 52 Clinical Trials by Trial Type

			MACE		Myocardial Infarction	
		N	n (%)	OR (95%CI)	n (%)	OR (95%CI)
Active-Controlled Trials	RSG	2,119	16 (0.8%)	1.05 (0.48, 2.34)	10 (0.5%)	1.00 (0.36, 2.82)
	Control	1,918	14 (0.7%)		9 (0.5%)	
Placebo-Controlled Trials	RSG	8,124	54 (0.7%)	1.53 (0.94, 2.54)	35 (0.4%)	2.23 (1.14, 4.64)
	Placebo	5,636	28 (0.5%)		13 (0.2%)	
Overall	RSG	10,039	70 (0.7%)	1.44 (0.95, 2.20)	45 (0.4%)	1.8 (1.03, 3.25)
	Control	6,956	39 (0.6%)		20 (0.3%)	

RSG = rosiglitazone

Of the placebo-controlled trials in the meta-analysis, 7 trials had patients randomized to rosiglitazone plus insulin or insulin. There were more patients in the rosiglitazone plus insulin

group compared to the insulin group with myocardial infarctions, MACE, cardiovascular deaths, and all-cause deaths (see Table 5). The total number of patients with stroke was 5 (0.5%) and 4 (0.5%) in the rosiglitazone plus insulin and insulin groups, respectively. The use of rosiglitazone in combination with insulin may increase the risk of myocardial infarction *[See Warnings and Precautions (5.1).]*

Table 5. Occurrence of Cardiovascular Events for Rosiglitazone in Combination With Insulin in a Meta-Analysis of 52 Clinical Trials

Event[a]	**Rosiglitazone (N=1,018) (%)**	**Insulin (N = 815) (%)**	OR (95% CI)
MACE (a composite of myocardial infarction, cardiovascular death, or stroke)	1.3	0.6	2.14 (0.70, 7.83)
Myocardial infarction	0.6	0.1	5.6 (0.67, 262.7)
Cardiovascular death	0.4	0.0	ND, (0.47, ∞)
All cause death	0.6	0.2	2.19 (0.38, 22.61)

ND = not defined

[a] Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial infarction would be counted in 4 event categories (myocardial infarction; myocardial infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).

Myocardial Infarction Events in Large, Long-Term, Prospective, Randomized, Controlled Trials of Rosiglitazone: Data from 3 large, long-term, prospective, randomized, controlled clinical trials of rosiglitazone were assessed separately from the meta-analysis.[6-8] These 3 trials included a total of 14,067 patients (treatment groups containing rosiglitazone N = 6,311; comparator groups N = 7,756), with patient-year exposure of 24,534 patient-years for rosiglitazone and 28,882 patient-years for comparator. Patient populations in the trials included patients with impaired glucose tolerance, patients with type 2 diabetes who were initiating oral agent monotherapy, and patients with type 2 diabetes who had failed monotherapy and were initiating dual oral agent therapy. Duration of follow-up exceeded 3 years in each trial.

In each of these trials, there was a statistically non-significant increase in the risk of myocardial infarction for rosiglitazone versus comparator medications.

In a long-term, randomized, placebo-controlled, 2x2 factorial trial intended to evaluate rosiglitazone, and separately ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on progression to overt diabetes in 5,269 subjects with glucose intolerance, the incidence of myocardial infarction was higher in the subset of subjects who received rosiglitazone in combination with ramipril than among subjects who received ramipril alone but not in the subset of subjects who received rosiglitazone alone compared to placebo.[6] The higher incidence of myocardial infarction among subjects who received rosiglitazone in combination with ramipril

was not confirmed in the two other large (total N = 8,798) long-term, randomized, active-controlled clinical trials conducted in patients with type 2 diabetes, in which 30% and 40% of patients in the two trials reported angiotensin-converting enzyme inhibitor use at baseline.[7,8]

There have been no adequately designed clinical trials directly comparing rosiglitazone to pioglitazone on cardiovascular risks. However, in a long-term, randomized, placebo-controlled cardiovascular outcomes trial comparing pioglitazone to placebo in patients with type 2 diabetes mellitus and prior macrovascular disease, pioglitazone was not associated with an increased risk of myocardial infarction or total mortality.[9]

The increased risk of myocardial infarction observed in the meta-analysis and large, long-term controlled clinical trials, and the increased risk of MACE observed in the meta-analysis described above, have not translated into a consistent finding of excess mortality from controlled clinical trials or observational studies. Clinical trials have not shown any difference between rosiglitazone and comparator medications in overall mortality or CV-related mortality.

Mortality in Observational Studies of Rosiglitazone Compared to Pioglitazone:

Three observational studies in elderly diabetic patients (age 65 years and older) found that rosiglitazone statistically significantly increased the risk of all-cause mortality compared to use of pioglitazone.[2-4] One observational study[5] in patients with a mean age of 54 years found no difference in all-cause mortality between patients treated with rosiglitazone compared to pioglitazone and reported similar results in the subpopulation of patients >65 years of age. One additional small, prospective, observational study[10] found no statistically significant differences for CV mortality and all-cause mortality in patients treated with rosiglitazone compared to pioglitazone.

5.4 Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program

Because of the potential increased risk of myocardial infarction, AVANDAMET is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program *[see Indications and Usage (1)]*. Both prescribers and patients must enroll in the program to be able to prescribe or receive AVANDAMET, respectively. AVANDAMET will be available only from specially certified pharmacies participating in the program. As part of the program, prescribers will be educated about the potential increased risk of myocardial infarction and the need to limit the use of AVANDAMET to eligible patients. Prescribers will need to discuss with patients the risks and benefits of taking AVANDAMET. To enroll, call 1-800-AVANDIA or visit www.AVANDIA.com.

5.5 Edema

AVANDAMET should be used with caution in patients with edema. In a clinical trial in healthy volunteers who received rosiglitazone 8 mg once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo. Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, AVANDAMET should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure *[see **Boxed Warning**, Warnings and Precautions (5.2), and Patient Counseling Information (17.1)]*.

In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with rosiglitazone, and may be dose-related. Patients with ongoing edema were more likely to have adverse events associated with edema if started on combination therapy with insulin and rosiglitazone *[see Adverse Reactions (6.1)]*. The use of AVANDAMET in combination with insulin is not recommended. *[See Warnings and Precautions (5.2, 5.3).]*

5.6 Weight Gain

Dose-related weight gain was seen with rosiglitazone alone and rosiglitazone together with other hypoglycemic agents (see Table 6). No overall change in median weight was observed with AVANDAMET in drug-naïve patients. The mechanism of weight gain with rosiglitazone is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 6. Weight Changes (kg) From Baseline at Endpoint During Clinical Trials
[Median (25^{th}, 75^{th}, Percentile)]

Monotherapy				
Duration	**Control Group**		**Rosiglitazone 4 mg**	**Rosiglitazone 8 mg**
26 weeks	Placebo	-0.9 (-2.8, 0.9) N = 210	1.0 (0.9, 3.6) N = 436	3.1 (1.1, 5.8) N = 439
52 weeks	Sulfonylurea	2.0 (0, 4.0) N = 173	2.0 (-0.6, 4.0) N = 150	2.6 (0, 5.3) N = 157
Combination Therapy				
			Rosiglitazone + Control Therapy	
Duration	**Control Group**		**Rosiglitazone 4 mg**	**Rosiglitazone 8 mg**
24-26 weeks	Sulfonylurea	0 (-1.0, 1.3) N = 1,155	2.2 (0.5, 4.0) N = 613	3.5 (1.4, 5.9) N = 841
26 weeks	Metformin	-1.4 (-3.2, 0.2) N = 175	0.8 (-1.0, 2.6) N = 100	2.1 (0, 4.3) N = 184
26 weeks	Insulin	0.9 (-0.5, 2.7) N = 162	4.1 (1.4, 6.3) N = 164	5.4 (3.4, 7.3) N = 150
AVANDAMET + Insulin				
Duration	**Control Group**		**AVANDAMET + Insulin**	
24 weeks	Insulin	2.6 kg (0.3, 4.8) N = 145	3.3 kg (1.5, 6.0) N = 147	

In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed with type 2 diabetes not previously treated with antidiabetic medication, the median weight change (25^{th}, 75^{th} percentiles) from baseline at 4 years was 3.5 kg (0.0, 8.1) for rosiglitazone, 2.0 kg (-1.0, 4.8) for glyburide, and -2.4 kg (-5.4, 0.5) for metformin.

In postmarketing experience with rosiglitazone alone or in combination with other hypoglycemic agents, there have been rare reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such

increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure *[see **Boxed Warning**]*.

5.7 Hepatic Effects

Metformin: Since impaired hepatic function has been associated with some cases of lactic acidosis, AVANDAMET should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Rosiglitazone: Liver enzymes should be measured prior to the initiation of therapy with AVANDAMET in all patients and periodically thereafter per the clinical judgment of the healthcare professional. Therapy with AVANDAMET should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with AVANDAMET should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with AVANDAMET in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X the upper limit of normal in patients on therapy with AVANDAMET, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with AVANDAMET should be discontinued.

If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with AVANDAMET should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

In addition, if the presence of hepatic disease or hepatic dysfunction of sufficient magnitude to predispose to lactic acidosis is confirmed, therapy with AVANDAMET should be discontinued.

5.8 Macular Edema

Macular edema has been reported in postmarketing experience in some diabetic patients who were taking rosiglitazone or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. Patients with diabetes should have regular eye exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings. *[See Adverse Reactions (6.3).]*

5.9 Fractures

In a 4- to 6-year comparative trial (ADOPT) of glycemic control with monotherapy in drug-naïve patients recently diagnosed with type 2 diabetes mellitus, an increased incidence of

bone fracture was noted in female patients taking rosiglitazone. Over the 4- to 6-year period, the incidence of bone fracture in females was 9.3% (60/645) for rosiglitazone versus 3.5% (21/605) for glyburide and 5.1% (30/590) for metformin. This increased incidence was noted after the first year of treatment and persisted during the course of the trial. The majority of the fractures in the women who received rosiglitazone occurred in the upper arm, hand, and foot. These sites of fracture are different from those usually associated with postmenopausal osteoporosis (e.g., hip or spine). Other trials suggest that this risk may also apply to men, although the risk of fracture among women appears higher than that among men. The risk of fracture should be considered in the care of patients treated with rosiglitazone, and attention given to assessing and maintaining bone health according to current standards of care.

5.10 Hematologic Effects

Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult patients treated with rosiglitazone *[see Adverse Reactions (6.2)]*. The observed changes may be related to the increased plasma volume observed with treatment with rosiglitazone and may be dose-related. The decrease in hemoglobin was seen more frequently in combination rosiglitazone and metformin therapy than in rosiglitazone therapy alone. Vitamin B_{12} deficiency may contribute to the observed reductions in hemoglobin *[see Warnings and Precautions (5.11)]*. Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) should be performed, at least on an annual basis.

5.11 Vitamin B_{12} Levels

In controlled clinical trials of metformin of 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at 2- to 3-year intervals may be useful. Vitamin B_{12} deficiency should be excluded if megaloblastic anemia is suspected. *[See Warnings and Precautions (5.10).]*

5.12 Diabetes and Blood Glucose Control

Periodic fasting blood glucose and HbA1c measurements should be performed to monitor therapeutic response.

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold AVANDAMET and temporarily administer insulin. AVANDAMET may be reinstituted after the acute episode is resolved.

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with hypoglycemic

agents (such as sulfonylureas or insulin) or ethanol. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking β-adrenergic blocking drugs.

Patients receiving rosiglitazone in combination with other hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

5.13 Ovulation

Therapy with rosiglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDAMET *[see Use in Specific Populations (8.1)]*. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical trials; therefore, the frequency of this occurrence is not known.

Although hormonal imbalance has been seen in preclinical studies *[see Nonclinical Toxicology (13.1)]*, the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with AVANDAMET should be reviewed.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The incidence and types of adverse events reported in controlled, 26-week clinical trials of rosiglitazone administered in combination with metformin 2,500 mg/day in comparison to adverse reactions reported in association with rosiglitazone and metformin monotherapies are shown in Table 7. Overall, the types of adverse reactions without regard to causality reported when rosiglitazone was used in combination with metformin were similar to those reported during monotherapy with rosiglitazone.

Table 7. Adverse Events (≥5% for Rosiglitazone Plus Metformin) Reported by Patients in 26-week Double-blind Clinical Trials of Rosiglitazone Added to Metformin Therapy

	Rosiglitazone + Metformin N = 338	**Rosiglitazone N = 2,526**	**Placebo N = 601**	**Metformin N = 225**
Preferred term	**%**	**%**	**%**	**%**
Upper respiratory tract infection	16.0	9.9	8.7	8.9
Diarrhea	12.7	2.3	3.3	15.6
Injury	8.0	7.6	4.3	7.6
Anemia	7.1	1.9	0.7	2.2
Headache	6.5	5.9	5.0	8.9
Sinusitis	6.2	3.2	4.5	5.3
Fatigue	5.9	3.6	5.0	4.0
Back pain	5.0	4.0	3.8	4.0
Viral infection	5.0	3.2	4.0	3.6
Arthralgia	5.0	3.0	4.0	2.2

Reports of hypoglycemia in patients treated with rosiglitazone added to maximum metformin therapy in double-blind trials were more frequent (3.0%) than in patients treated with rosiglitazone (0.6%) or metformin monotherapies (1.3%) or placebo (0.2%). Overall, anemia and edema were generally mild to moderate in severity and usually did not require discontinuation of treatment with rosiglitazone.

Edema was reported in 4.8% of patients receiving rosiglitazone compared to 1.3% on placebo, and 2.2% on metformin monotherapy and 4.4% on rosiglitazone in combination with maximum doses of metformin.

Reports of anemia (7.1%) were greater in patients treated with rosiglitazone added to metformin compared to monotherapy with rosiglitazone. Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin and rosiglitazone combination therapy clinical trials may have contributed to the higher reporting rate of anemia in these trials *[see Adverse Reactions (6.2)]*.

Combination with Insulin: The incidence of hypoglycemia (confirmed by fingerstick blood glucose concentration ≤50 mg/dL) was 14% for patients on AVANDAMET plus insulin compared to 10% for patients on insulin monotherapy.

The incidence of edema was 7% when insulin was added to AVANDAMET compared to 3% with insulin monotherapy. This trial excluded patients with pre-existing heart failure or new or worsening edema on AVANDAMET therapy. However, in 26-week double-blind, fixed-dose trials of rosiglitazone added to insulin, edema was reported with higher frequency (rosiglitazone in combination with insulin, 14.7%; insulin, 5.4%) *[see Warnings and Precautions (5.2)]*.

In trials in which rosiglitazone was added to insulin, rosiglitazone increased the risk of congestive heart failure. The use of rosiglitazone in combination with insulin may increase the risk of myocardial infarction *[see Warnings and Precautions (5.2, 5.3)]*.

In a trial in which insulin was added to AVANDAMET, no myocardial ischemia was observed in the insulin group (N = 158), and no congestive heart failure was reported in either group. There was one myocardial ischemic event and one sudden death in the group receiving AVANDAMET plus insulin (N = 161). *[See Warnings and Precautions (5.2).]*

The incidence of anemia was 2% for AVANDAMET in combination with insulin compared to 1% for insulin monotherapy.

A long-term, 4- to 6-year trial (ADOPT) compared the use of rosiglitazone (n = 1,456), glyburide (n = 1,441), and metformin (n = 1,454) as monotherapy in patients recently diagnosed with type 2 diabetes who were not previously treated with antidiabetic medication. Table 8 presents adverse reactions without regard to causality; rates are expressed per 100 patient-years (PY) exposure to account for the differences in exposure to trial medication across the 3 treatment groups.

In ADOPT, fractures were reported in a greater number of women treated with rosiglitazone (9.3%, 2.7/100 patient-years) compared to glyburide (3.5%, 1.3/100 patient-years) or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who received rosiglitazone were reported in the upper arm, hand, and foot. *[See Warnings and Precautions (5.9).]* The observed incidence of fractures for male patients was similar among the 3 treatment groups.

Table 8. On-Therapy Adverse Events (≥5 Events/100 Patient-Years [PY]) in Any Treatment Group Reported in a 4- to 6-Year Clinical Trial of Rosiglitazone as Monotherapy (ADOPT)

	Rosiglitazone N = 1,456 PY = 4,954	**Glyburide** N = 1,441 PY = 4,244	**Metformin** N = 1,454 PY = 4,906
Nasopharyngitis	6.3	6.9	6.6
Back pain	5.1	4.9	5.3
Arthralgia	5.0	4.8	4.2
Hypertension	4.4	6.0	6.1
Upper respiratory tract infection	4.3	5.0	4.7
Hypoglycemia	2.9	13.0	3.4
Diarrhea	2.5	3.2	6.8

6.2 Laboratory Abnormalities

Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult patients treated with rosiglitazone (mean decreases in individual trials as much as 1.0 gram/dL hemoglobin and as much as 3.3% hematocrit). The changes occurred primarily

during the first 3 months following initiation of rosiglitazone therapy or following an increase in rosiglitazone dose. The time course and magnitude of decreases were similar in patients treated with a combination of rosiglitazone and other hypoglycemic agents or monotherapy with rosiglitazone. Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin combination trials and may have contributed to the higher reporting rate of anemia. In a single trial in pediatric patients, decreases in hemoglobin and hematocrit (mean decreases of 0.29 g/dL and 0.95%, respectively) were reported with rosiglitazone. White blood cell counts also decreased slightly in adult patients treated with rosiglitazone. Decreases in hematologic parameters may be related to increased plasma volume observed with rosiglitazone treatment.

In controlled clinical trials of metformin of 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such a decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation.

Lipids: Changes in serum lipids have been observed following treatment with rosiglitazone in adults *[see Clinical Pharmacology (12.2)]*.

Serum Transaminase Levels: In pre-approval clinical trials in 4,598 patients treated with rosiglitazone encompassing approximately 3,600 patient years of exposure, and in a long-term 4- to 6-year trial in 1,456 patients treated with rosiglitazone (4,954 patient-years exposure), there was no evidence of drug-induced hepatotoxicity.

In pre-approval controlled trials, 0.2% of patients treated with rosiglitazone had reversible elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with rosiglitazone were reversible. Hyperbilirubinemia was found in 0.3% of patients treated with rosiglitazone compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. *[See Warnings and Precautions (5.7).]*

In the 4- to 6-year ADOPT trial, patients treated with rosiglitazone (4,954 patient-years exposure), glyburide (4,244 patient-years exposure) or metformin (4,906 patient-years exposure) as monotherapy, had the same rate of ALT increase to >3X upper limit of normal (0.3 per 100 patient-years exposure).

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the events described below have been identified during post-approval use of AVANDAMET or its individual components. Because these events are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or to always establish a causal relationship to drug exposure.

In patients receiving thiazolidinedione therapy, serious adverse events with or without a fatal outcome, potentially related to volume expansion (e.g., congestive heart failure, pulmonary

edema, and pleural effusions) have been reported *[see **Boxed Warning** and Warnings and Precautions (5.2)]*.

There are postmarketing reports with rosiglitazone of hepatitis, hepatic enzyme elevations to 3 or more times the upper limit of normal, and hepatic failure with and without fatal outcome, although causality has not been established.

There are postmarketing reports with rosiglitazone of rash, pruritus, urticaria, angioedema, anaphylactic reaction, Stevens-Johnson syndrome, and new onset or worsening diabetic macular edema with decreased visual acuity *[see Warnings and Precautions (5.8)]*.

(See also GLUCOPHAGE® prescribing information.)

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P450

An inhibitor of CYP2C8 (e.g., gemfibrozil) may increase the AUC of rosiglitazone and an inducer of CYP2C8 (e.g., rifampin) may decrease the AUC of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response. *[See Clinical Pharmacology (12.4).]*

7.2 Cationic Drugs

Although drug interactions for metformin with cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of AVANDAMET and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system. *[See Warnings and Precautions (5.1) and Clinical Pharmacology (12.4).]*

7.3 Drugs That Produce Hyperglycemia

When drugs that produce hyperglycemia which may lead to loss of glycemic control are administered to a patient receiving AVANDAMET, the patient should be closely observed to maintain adequate glycemic control. *[See Clinical Pharmacology (12.4).]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Careful monitoring of glucose control is essential in such patients. Most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible. AVANDAMET should not be used during pregnancy.

Human Data: There are no adequate and well-controlled trials with AVANDAMET or its individual components in pregnant women. Rosiglitazone has been reported to cross the human placenta and be detectable in fetal tissue. The clinical significance of these findings is unknown.

Animal Studies: No animal studies have been conducted with AVANDAMET. The following data are based on findings in studies performed with rosiglitazone or metformin individually.

Rosiglitazone: There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET. Rosiglitazone reduced the number of uterine implantations and live offspring when juvenile female rats were treated at 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day (approximately 4 times human AUC at the maximum recommended daily dose). There was no effect on pre- or post-natal survival or growth.

Metformin: Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

8.2 Labor and Delivery

The effect of AVANDAMET or its components on labor and delivery in humans is unknown.

8.3 Nursing Mothers

No studies have been conducted with AVANDAMET. In studies performed with the individual components, both rosiglitazone-related material and metformin were detectable in milk from lactating rats. It is not known whether rosiglitazone or metformin is excreted in human milk. Because many drugs are excreted in human milk, AVANDAMET should not be administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of AVANDAMET in pediatric patients have not been established. AVANDAMET and rosiglitazone are not indicated for use in pediatric patients.

8.5 Geriatric Use

Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, AVANDAMET should only be used in patients with normal renal function *[see Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*. Because reduced renal function is associated with increasing age, AVANDAMET should be used with caution in elderly patients. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of AVANDAMET *[see Dosage and Administration (2.4) and Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

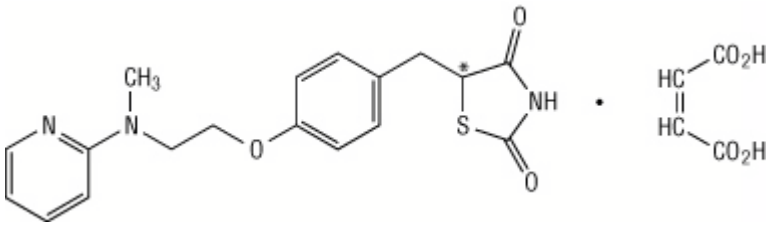
Rosiglitazone: Limited data are available with regard to overdosage in humans. In clinical trials in volunteers, rosiglitazone has been administered at single oral doses of up to 20 mg and was well tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

Metformin: Hypoglycemia has not been seen with ingestion of up to 85 grams of metformin, although lactic acidosis has occurred in such circumstances *[see Warnings and Precautions (5.1)]*. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated metformin from patients in whom metformin overdosage is suspected.

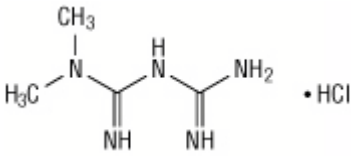
11 DESCRIPTION

AVANDAMET contains 2 oral antidiabetic drugs: rosiglitazone maleate and metformin hydrochloride.

Rosiglitazone maleate is an oral antidiabetic agent, which acts primarily by increasing insulin sensitivity. Rosiglitazone improves glycemic control while reducing circulating insulin levels. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors. Chemically, rosiglitazone maleate is (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (*Z*)-2-butenedioate (1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the enantiomers are functionally indistinguishable. The molecular formula is $C_{18}H_{19}N_3O_3S \bullet C_4H_4O_4$. Rosiglitazone maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pK_a values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range. The structural formula of rosiglitazone maleate is:



Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antidiabetic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \bullet HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula of metformin hydrochloride is:



AVANDAMET is available for oral administration as film-coated tablets containing rosiglitazone maleate and metformin hydrochloride equivalent to: 2 mg rosiglitazone with 500 mg metformin hydrochloride (2 mg/500 mg), 4 mg rosiglitazone with 500 mg metformin hydrochloride (4 mg/500 mg), 2 mg rosiglitazone with 1,000 mg metformin hydrochloride (2 mg/1,000 mg), and 4 mg rosiglitazone with 1,000 mg metformin hydrochloride (4 mg/1,000 mg). Inactive ingredients are: Hypromellose 2910, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, povidone 29-32, sodium starch glycolate, titanium dioxide, and 1 or more of the following: Red and yellow iron oxides.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

AVANDAMET: AVANDAMET combines 2 antidiabetic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: Rosiglitazone, a member of the thiazolidinedione class, and metformin, a member of the biguanide class. Thiazolidinediones are insulin sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas biguanides act primarily by decreasing endogenous hepatic glucose production.

Rosiglitazone: Rosiglitazone improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator–activated receptor-gamma (PPARγ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of

glucose production, transport, and utilization. In addition, PPARγ-responsive genes also participate in the regulation of fatty acid metabolism.

Insulin resistance is a common feature characterizing the pathogenesis of type 2 diabetes. The antidiabetic activity of rosiglitazone has been demonstrated in animal models of type 2 diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. Rosiglitazone reduces blood glucose concentrations and reduces hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse, and fa/fa fatty Zucker rat.

In animal models, the antidiabetic activity of rosiglitazone was shown to be mediated by increased sensitivity to insulin's action in the liver, muscle, and adipose tissue. Pharmacologic studies in animal models indicate that rosiglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. The expression of the insulin-regulated glucose transporter GLUT-4 was increased in adipose tissue. Rosiglitazone did not induce hypoglycemia in animal models of type 2 diabetes and/or impaired glucose tolerance.

Metformin: Metformin is an antidiabetic agent, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antidiabetic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and increases peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects except in special circumstances *[see Warnings and Precautions (5.12)]* and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

12.2 Pharmacodynamics

In all 26-week controlled trials, across the recommended dose range, rosiglitazone as monotherapy was associated with increases in total cholesterol, LDL-cholesterol and HDL-cholesterol and decreases in free fatty acids.

The lipid profiles of AVANDAMET as well as rosiglitazone and metformin monotherapies in patients who have inadequate glycemic control on diet and exercise are shown in Table 9.

Table 9. Summary of Mean[a] Lipid Changes in a 32-Week Trial of AVANDAMET in Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Diet and Exercise

	AVANDAMET N[b] = 132	**Rosiglitazone N[b] = 128**	**Metformin N[b] = 117**
Total Cholesterol (mg/dL)			
Baseline (mean)	200.4	198.4	201.6
% Change from baseline (mean)	-2.2%	5.3%	-9.0%
LDL (mg/dL)			
Baseline (mean)	113.8	114.6	116.0
% Change from baseline (mean)	-0.2%	4.5%	-10.7%
HDL (mg/dL)			
Baseline (mean)	42.6	42.8	42.9
% Change from baseline (mean)	5.8%	3.1%	0.0%
Triglycerides (mg/dL)			
Baseline (mean)	180.3	166.6	175.7
% Change from baseline (mean)	-18.7%	-4.8%	-15.4%

[a] Data presented as geometric means throughout table.

[b] N = number of subjects with a baseline and end of treatment value.

The pattern of LDL, HDL, and total cholesterol changes following therapy with rosiglitazone added to metformin was generally similar to those seen with rosiglitazone monotherapy, and a small decrease in mean triglycerides was observed with the combination therapy.

12.3 Pharmacokinetics

Absorption: *AVANDAMET:* In a bioequivalence and dose proportionality trial of AVANDAMET 4 mg/500 mg, both the rosiglitazone component and the metformin component were bioequivalent to coadministered 4 mg rosiglitazone tablet and 500 mg metformin tablet under fasted conditions (see Table 10). In this trial, dose proportionality of rosiglitazone in the combination formulations of 1 mg/500 mg and 4 mg/500 mg was demonstrated.

Table 10. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone and Metformin

		Pharmacokinetic Parameter			
Regimen	**N**	**$AUC_{0\text{-}inf}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**T_{max}[a] (h)**	**$T_{½}$ (h)**
Rosiglitazone					
A	25	1,442 (324)	242 (70)	0.95 (0.48-2.47)	4.26 (1.18)
B	25	1,398 (340)	254 (69)	0.57 (0.43-2.58)	3.95 (0.81)
C	24	349 (91)	63.0 (15.0)	0.57 (0.47-1.45)	3.87 (0.88)
Metformin					
A	25	7,116 (2,096)	1,106 (329)	2.97 (1.02-4.02)	3.46 (0.96)
B	25	7,413 (1,838)	1,135 (253)	2.50 (1.03-3.98)	3.36 (0.54)
C	24	6,945 (2,045)	1,080 (327)	2.97 (1.00-5.98)	3.35 (0.59)

[a] Median and range presented for T_{max}.

Regimen A = 4 mg/500 mg AVANDAMET; Regimen B = 4 mg rosiglitazone tablet + 500 mg metformin tablet; Regimen C = 1 mg/500 mg AVANDAMET

Administration of AVANDAMET 4 mg/500 mg with food resulted in no change in overall exposure (AUC) for either rosiglitazone or metformin. However, there were decreases in C_{max} of both components (22% for rosiglitazone and 15% for metformin, respectively) and a delay in T_{max} of both components (1.5 hours for rosiglitazone and 0.5 hours for metformin, respectively). These changes are not likely to be clinically significant. The pharmacokinetics of both the rosiglitazone component and the metformin component of AVANDAMET when taken with food were similar to the pharmacokinetics of rosiglitazone and metformin when administered concomitantly as separate tablets with food.

Absorption: *Rosiglitazone:* The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing. Maximum plasma concentration (C_{max}) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range.

Absorption: *Metformin:* The absolute bioavailability of a 500 mg metformin tablet given under fasting conditions is approximately 50% to 60%. Trials using single oral doses of metformin tablets of 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Distribution: *Rosiglitazone:* The mean (CV%) oral volume of distribution (V_{ss}/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

Distribution: *Metformin:* The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg metformin averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism and Excretion: *Rosiglitazone:* Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone. In vitro data demonstrate that rosiglitazone is predominantly metabolized by Cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway. Following oral or intravenous administration of [^{14}C]rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [^{14}C]related material ranged from 103 to 158 hours. The elimination half-life is 3 to 4 hours and is independent of dose.

Metabolism and Excretion: *Metformin:* Intravenous single-dose trials in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations: *Renal Impairment:* In subjects with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance *[see Warnings and Precautions (5.1) and GLUCOPHAGE prescribing information]*. Since metformin is contraindicated in patients with renal impairment, administration of AVANDAMET is contraindicated in these patients.

Hepatic Impairment: Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound C_{max} and $AUC_{0\text{-}inf}$ were increased 2- and 3-fold, respectively.

Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects.

Therapy with AVANDAMET should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal) at baseline *[see Warnings and Precautions (5.7)]*.

No pharmacokinetic trials of metformin have been conducted in subjects with hepatic insufficiency.

Geriatric: Results of the population pharmacokinetics analysis (N = 716 <65 years; N = 331 ≥65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone. However, limited data from controlled pharmacokinetic trials of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function *[see Use in Specific Populations (8.5) and GLUCOPHAGE prescribing information]*. Metformin treatment and therefore treatment with AVANDAMET should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced *[see Dosage and Administration (2) and Warnings and Precautions (5.1)]*.

Gender: Results of the population pharmacokinetics analysis showed that the mean oral clearance of rosiglitazone in female patients (N = 405) was approximately 6% lower compared to male patients of the same body weight (N = 642). In rosiglitazone and metformin combination trials, efficacy was demonstrated with no gender differences in glycemic response.

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender (males = 19, females = 16). Similarly, in controlled clinical trials in patients with type 2 diabetes, the antihyperglycemic effect of metformin tablets was comparable in males and females.

Race: Results of a population pharmacokinetic analysis including subjects of white, black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of rosiglitazone.

No trials of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical trials of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (N = 249), blacks (N = 51), and Hispanics (N = 24).

Pediatric: No pharmacokinetic data from trials in pediatric subjects are available for AVANDAMET.

12.4 Drug-Drug Interactions

Rosiglitazone: *Drugs That Inhibit, Induce, or are Metabolized by Cytochrome P450:* In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. In vitro data demonstrate that

rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9. *[See Drug Interactions (7.1).]*

Rosiglitazone (4 mg twice daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinyl estradiol and norethindrone), which are predominantly metabolized by CYP3A4.

Gemfibrozil: Concomitant administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone AUC by 127%, compared to the administration of rosiglitazone (4 mg once daily) alone. Given the potential for dose-related adverse events with rosiglitazone, a decrease in the dose of rosiglitazone may be needed when gemfibrozil is introduced. *[See Drug Interactions (7.1).]*

Rifampin: Rifampin administration (600 mg once a day), an inducer of CYP2C8, for 6 days is reported to decrease rosiglitazone AUC by 66%, compared to the administration of rosiglitazone (8 mg) alone.[11] *[See Drug Interactions (7.1).]*

Metformin: *Cationic Drugs:* Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction trials, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose trial. Metformin had no effect on cimetidine pharmacokinetics. *[See Warnings and Precautions (5.1) and Drug Interactions (7.2).]*

Furosemide: A single-dose, metformin-furosemide drug interaction trial in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction trial in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.

In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when coadministered in single-dose interaction trials.

Metformin is negligibly bound to plasma proteins and is therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted with AVANDAMET. The following data are based on findings in studies performed with rosiglitazone or metformin individually.

Rosiglitazone: A 2-year carcinogenicity study was conducted in Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately 12 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05, 0.3, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET for male and female rats, respectively).

Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses ≥1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses ≥0.3 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic activation.

Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET). In juvenile rats dosed from 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male reproductive performance, or on estrous cyclicity,

mating performance or pregnancy incidence in females (approximately 68 times human AUC at the maximum recommended daily dose of rosiglitazone). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

Metformin: Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2,000 mg of the metformin component of AVANDAMET based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of mutagenic potential of metformin in the following in vitro tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administrated at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose of the metformin component of AVANDAMET based on body surface area comparisons.

13.2 Animal Toxicology

Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET, respectively). Effects in juvenile rats were consistent with those seen in adults. Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

14 CLINICAL STUDIES

AVANDAMET was not studied in patients previously treated with metformin monotherapy; however, the combination of rosiglitazone and metformin was compared to rosiglitazone and metformin monotherapies in clinical trials. Bioequivalence between AVANDAMET and coadministered rosiglitazone tablets and metformin tablets has been demonstrated *[see Clinical Pharmacology (12.3)]*.

A total of 670 patients with type 2 diabetes participated in two 26-week, randomized, double-blind, placebo/active-controlled trials designed to assess the efficacy of rosiglitazone in combination with metformin. Rosiglitazone, administered in either once-daily or twice-daily

dosing regimens, was added to the therapy of patients who were inadequately controlled on 2.5 grams/day of metformin.

In one trial, patients inadequately controlled on 2.5 grams/day of metformin (mean baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were randomized to receive rosiglitazone 4 mg once daily, rosiglitazone 8 mg once daily, or placebo in addition to metformin. A statistically significant improvement in FPG and HbA1c was observed in patients treated with the combinations of metformin and rosiglitazone 4 mg once daily and rosiglitazone 8 mg once daily, versus patients continued on metformin alone (see Table 11).

Table 11. Glycemic Parameters in a 26-Week Trial of Rosiglitazone Added to Metformin Therapy

	Metformin	**Rosiglitazone 4 mg once daily + metformin**	**Rosiglitazone 8 mg once daily + metformin**
N	113	116	110
FPG (mg/dL)			
Baseline (mean)	214	215	220
Change from baseline (mean)	6	-33	-48
Difference from metformin alone (adjusted mean)		-40[a]	-53[a]
% of patients with ≥30 mg/dL decrease from baseline	20%	45%	61%
HbA1c (%)			
Baseline (mean)	8.6	8.9	8.9
Change from baseline (mean)	0.5	-0.6	-0.8
Difference from metformin alone (adjusted mean)		-1.0[a]	-1.2[a]
% of patients with HbA1c ≥0.7% decrease from baseline	11%	45%	52%

[a] P <0.0001 compared to metformin.

In a second 26-week trial, patients with type 2 diabetes inadequately controlled on 2.5 grams/day of metformin who were randomized to receive the combination of rosiglitazone 4 mg twice daily and metformin (N = 105) showed a statistically significant improvement in glycemic control with a mean treatment effect for FPG of -56 mg/dL and a mean treatment effect for HbA1c of -0.8% over metformin alone. The combination of metformin and rosiglitazone resulted in lower levels of FPG and HbA1c than either agent alone.

15 REFERENCES

1. Food and Drug Administration Briefing Document. Joint meeting of the Endocrinologic and

Metabolic Drugs and Drug Safety and Risk Management Advisory Committees. July 13-14, 2010.
2. Winkelmayer WC, et al. Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy. *Arch Intern Med* 2008;168(21):2368-2375.
3. Juurlink DN, et al. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. *BMJ* 2009; 339.
4. Graham DJ, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly medicare patients treated with rosiglitazone or pioglitazone. *JAMA* 2010;304:411-418.
5. Wertz DA, et al. Risk of cardiovascular events and all-cause mortality in patients with Thiazolidinediones in a managed-care population. *Circ Cardiovasc Qual Outcomes* 2010;3: 538-545.
6. DREAM Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096-1105.
7. Kahn S, et al. Glycemic durability of rosiglitazone, metformin or glyburide monotherapy. *New England Journal of Medicine* 2006, 355:2427-2443.
8. Home P, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicenter, randomized, open-label trial. *Lancet* 2009, 373:2125-35.
9. Dormandy J et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (Prospective Pioglitazone Clinical Trial in Macrovascular Events): a randomized controlled trial. *Lancet* 2005, 366:1279-89.
10. Bilik D, et al. Thiazolidinediones, cardiovascular disease and cardiovascular mortality: translating research into action for diabetes (TRIAD). *Pharmocoepidemiol Drug Saf* 2010; 19: 715–721.
11. Park JY, Kim KA, Kang MH, et al. Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects. *Clin Pharmacol Ther* 2004;75:157-162.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each film-coated oval tablet contains rosiglitazone as the maleate and metformin hydrochloride as follows:

2 mg/500 mg – pale pink, tablet, debossed with gsk on one side and 2/500 on the other.
4 mg/500 mg – orange, tablet, debossed with gsk on one side and 4/500 on the other.
2 mg/1,000 mg – yellow, tablet, debossed with gsk on one side and 2/1000 on the other.
4 mg/1,000 mg – pink, tablet, debossed with gsk on one side and 4/1000 on the other.

2 mg/500 mg bottles of 60: NDC 0173-0837-18
4 mg/500 mg bottles of 60: NDC 0173-0839-18

2 mg/1,000 mg bottles of 60: NDC 0173-0838-18
4 mg/1,000 mg bottles of 60: NDC 0173-0840-18

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

See Medication Guide.

17.1 Patient Advice

There are multiple medications available to treat type 2 diabetes. The benefits and risks of each available diabetes medication should be taken into account when choosing a particular diabetes medication for a given patient.

Patients should be informed of the risks and benefits of AVANDAMET. AVANDAMET should only be taken by adults with type 2 diabetes who are already taking rosiglitazone, or who are not already taking rosiglitazone and are unable to achieve adequate glycemic control on other diabetes medications, and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS) or pioglitazone-containing medications (ACTOPLUS MET, ACTOPLUS MET XR, DUETACT) for medical reasons. Inform patients that they must be enrolled in the AVANDIA-Rosiglitazone Medicines Access Program in order to receive AVANDAMET.

Patients should be informed of the following:

- The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the WARNINGS and PRECAUTIONS sections, should be explained to patients. Patients should be advised to discontinue AVANDAMET immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of AVANDAMET, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.
- Avoid excessive alcohol intake, either acute or chronic, while receiving AVANDAMET.
- AVANDAMET is not recommended for patients with symptomatic heart failure.
- Results of a set of clinical trials suggest that treatment with AVANDAMET is associated with an increased risk for myocardial infarction (heart attack), especially in patients taking insulin. Clinical trials have not shown any difference between rosiglitazone and comparator medications in overall mortality or CV-related mortality.
- AVANDAMET is not recommended for patients who are taking insulin.
- Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes but also in maintaining the efficacy of drug therapy.

- It is important to adhere to dietary instructions and to regularly have blood glucose, glycosylated hemoglobin (HbA1c), renal function, and hematologic parameters tested. It can take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of AVANDAMET.
- Blood will be drawn to check their liver function prior to the start of therapy and periodically thereafter per the clinical judgment of the healthcare professional. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician.
- Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on AVANDAMET should immediately report these symptoms to their physician.
- Therapy with AVANDAMET, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDAMET. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical trials so the frequency of this occurrence is not known.

GlaxoSmithKline
Research Triangle Park, NC 27709

Month 2011
AVM:XXPI

MEDICATION GUIDE

AVANDAMET® (ah-VAN-duh-met)

(rosiglitazone maleate and metformin hydrochloride) Tablets

Read this Medication Guide carefully before you start taking AVANDAMET and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about AVANDAMET, ask your doctor or pharmacist.

What is the most important information I should know about AVANDAMET?
AVANDAMET may cause serious side effects, including:

AVANDAMET is available only through the AVANDIA-Rosiglitazone Medicines Access Program. Both you and your doctor must be enrolled in the program so that you can get AVANDAMET. To enroll, you must:

- talk to your doctor,
- understand the risks and benefits of AVANDAMET, and
- agree to enroll in the program.

New or worse heart failure

- Rosiglitazone, one of the medicines in AVANDAMET, can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Heart failure means your heart does not pump blood well enough.
- If you have severe heart failure, you cannot start AVANDAMET.
- If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, AVANDAMET may not be right for you.

Call your doctor right away if you have any of the following:

- swelling or fluid retention, especially in the ankles or legs
- shortness of breath or trouble breathing, especially when you lie down
- an unusually fast increase in weight
- unusual tiredness

Myocardial Infarction (“Heart Attack”)

Rosiglitazone, one of the medicines in AVANDAMET, may raise the risk of heart attack. The risk of having a heart attack may be higher in people who take

AVANDAMET with insulin. Most people who take insulin should not also take AVANDAMET.

Symptoms of a heart attack can include the following:

- chest discomfort in the center of your chest that lasts for more than a few minutes, or that goes away or comes back
- chest discomfort that feels like uncomfortable pressure, squeezing, fullness or pain
- pain or discomfort in your arms, back, neck, jaw or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded

Call your doctor or go to the nearest hospital emergency room right away if you think you are having a heart attack.

People with diabetes have a greater risk for heart problems. It is important to work with your doctor to manage other conditions, such as high blood pressure or high cholesterol.

Lactic acidosis

Metformin, one of the medicines in AVANDAMET, can cause a rare but serious condition called lactic acidosis (a build-up of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Most people who have had lactic acidosis with metformin have other things that, combined with the metformin, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with AVANDAMET if you:

- have kidney problems or your kidneys are affected by certain X-ray tests that use injectable dye. People with kidney problems should not take AVANDAMET.
- have liver problems
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- have surgery
- have a heart attack, severe infection, or stroke
- are 80 years of age or older, and your kidneys are not working properly

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop your AVANDAMET for a while if you have any of these things.

Lactic acidosis can be hard to diagnose early, because the early symptoms could seem like the symptoms of many other health problems besides lactic acidosis. You should call your doctor right away if you get the following symptoms, which could be signs of lactic acidosis:

- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have stomach pains
- you have trouble breathing
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat

AVANDAMET can have other serious side effects. Be sure to read the section below "What are possible side effects of AVANDAMET?".

What is AVANDAMET?

AVANDAMET contains two prescription medicines for treating diabetes, rosiglitazone maleate (AVANDIA) and metformin hydrochloride. AVANDAMET is used, with diet and exercise, to treat certain adults with type 2 ("adult-onset" or "non-insulin dependent") diabetes ("high blood sugar") who are:

- already taking rosiglitazone or rosiglitazone-containing products
- unable to control their blood sugar on other diabetes medicines, and after talking with their doctor have decided not to take pioglitazone (ACTOS) or pioglitazone-containing products (ACTOPLUS MET, ACTOPLUS MET XR, DUETACT)

Metformin works mainly by decreasing the production of sugar by your liver. Rosiglitazone helps your body respond better to its natural insulin and does not cause your body to make more insulin. These medicines work together to help control your blood sugar. AVANDAMET may be used alone or with other diabetes medicines.

AVANDAMET is not for people with type 1 diabetes mellitus or to treat a condition called diabetic ketoacidosis.

It is not known if AVANDAMET is safe and effective in children under 18 years old.

Who should not take AVANDAMET?

Do not take AVANDAMET if you:

- have kidney problems. Before you take AVANDAMET and while you take it, your doctor should test your blood to check for signs of kidney problems.
- have a condition known as metabolic acidosis, including diabetic ketoacidosis.
- are going to have an x-ray procedure with an injection of dyes (contrast agents) in your vein with a needle. Talk to your doctor about when to stop AVANDAMET and when to start it again.

Many people with heart failure should not start taking AVANDAMET. See "What should I tell my doctor before taking AVANDAMET?".

What should I tell my doctor before taking AVANDAMET?

Before starting AVANDAMET, ask your doctor about what the choices are for diabetes medicines, and what the expected benefits and possible risks are for you in particular.

Before taking AVANDAMET, tell your doctor about all your medical conditions, including if you:

- **have heart problems or heart failure**
- **have kidney problems**
- **have type 1 ("juvenile") diabetes or had diabetic ketoacidosis.** These conditions should be treated with insulin.
- **are going to have dye injected into a vein for an X-ray, CAT scan, heart study, or other type of scanning**
- **drink a lot of alcohol** (all the time or short binge drinking).
- **develop a serious condition such as a heart attack, severe infection, or a stroke.**
- **are 80 years old or older.** People who are over 80 years old should not take AVANDAMET unless their kidney function is checked and it is normal.
- **have a type of diabetic eye disease called macular edema** (swelling of the back of the eye).
- **have liver problems.** Your doctor should do blood tests to check your liver before you start taking AVANDAMET and during treatment as needed.
- **had liver problems while taking REZULIN®** (troglitazone), another medicine for diabetes.
- **are pregnant or plan to become pregnant.** AVANDAMET should not be used during pregnancy. It is not known if AVANDAMET can harm your unborn baby. You and your doctor should talk about the best way to control your diabetes during pregnancy. If you are a premenopausal woman (before the "change of

life") who does not have regular monthly periods, AVANDAMET may increase your chances of becoming pregnant. Talk to your doctor about birth control choices while taking AVANDAMET. Tell your doctor right away if you become pregnant while taking AVANDAMET.

- **are breast-feeding or planning to breast-feed.** It is not known if AVANDAMET passes into breast milk. You should not use AVANDAMET while breast-feeding.

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins or herbal supplements. AVANDAMET and certain other medicines can affect each other and may lead to serious side effects including high or low blood sugar, or heart problems. Your doctor may need to change your dose of AVANDAMET or your other medicines. Especially tell your doctor if you take:

- **insulin.**
- **any medicines for high blood pressure, high cholesterol or heart failure, or for prevention of heart disease or stroke.**

Know the medicines you take. Keep a list of all your medicines and show it to your doctor and pharmacist before you start a new medicine. They will tell you if it is alright to take AVANDAMET with other medicines.

How should I take AVANDAMET?

- Take AVANDAMET exactly as prescribed. Your doctor may need to change your dose until your blood sugar is better controlled.
- AVANDAMET should be taken by mouth and with meals.
- AVANDAMET may be prescribed alone or with other diabetes medicines. This will depend on how well your blood sugar is controlled.
- It can take 2 weeks for AVANDAMET to start lowering your blood sugar. It may take 2 to 3 months to see the full effect on your blood sugar level.
- If you miss a dose of AVANDAMET, take it as soon as you remember, unless it is time to take your next dose. Take your next dose at the usual time. Do not take double doses to make up for a missed dose.
- If you take too much AVANDAMET, call your doctor or poison control center right away.
- Test your blood sugar regularly as your doctor tells you.
- Diet and exercise can help your body use its blood sugar better. It is important to stay on your recommended diet, lose extra weight, and get regular exercise while taking AVANDAMET.
- Your doctor should do blood tests to check your liver and kidneys before you start AVANDAMET and during treatment as needed. Your doctor should also do

regular blood sugar tests (for example, “A1C”) to monitor your response to AVANDAMET.

There may be times when you will need to stop taking AVANDAMET for a short time. Tell your doctor if you:

- are sick with severe vomiting, diarrhea or fever, or if you drink a much lower amount of liquid than normal.
- are going to have dye injected into a vein for an X-ray, CAT scan, heart study or other type of scanning.
- plan to have surgery.

What should I avoid while taking AVANDAMET?

Do not drink a lot of alcohol while taking AVANDAMET. This means you should not “binge drink”, and you should not drink a lot of alcohol on a regular basis. Drinking a lot of alcohol can increase the chance of getting lactic acidosis.

What are possible side effects of AVANDAMET?

AVANDAMET may cause serious side effects, including:

- **New or worse heart failure.** See “What is the most important information I should know about AVANDAMET?”.
- **Heart attack.** See “What is the most important information I should know about AVANDAMET?”.
- **Swelling (edema).** AVANDAMET can cause swelling due to fluid retention. See “What is the most important information I should know about AVANDAMET?”.
- **Weight gain.** Rosiglitazone, one of the medicines in AVANDAMET, can cause weight gain that may be due to fluid retention or extra body fat. Metformin, the other medicine in AVANDAMET, can cause weight loss. There is little change in weight with AVANDAMET. Weight gain can be a serious problem for people with certain conditions including heart problems. See “What is the most important information I should know about AVANDAMET?”
- **Liver problems.** It is important for your liver to be working normally when you take AVANDAMET. Your doctor should do blood tests to check your liver before you start taking AVANDAMET and during treatment as needed. Call your doctor right away if you have unexplained symptoms such as:
  - nausea or vomiting
  - stomach pain
  - unusual or unexplained tiredness
  - loss of appetite
  - dark urine
  - yellowing of your skin or the whites of your eyes.

- **Macular edema** (a diabetic eye disease with swelling in the back of the eye). Tell your doctor right away if you have any changes in your vision. Your doctor should check your eyes regularly. Very rarely, some people have had vision changes due to swelling in the back of the eye while taking rosiglitazone, one of the medicines in AVANDAMET.
- **Fractures (broken bones),** usually in the hand, upper arm or foot. Talk to your doctor for advice on how to keep your bones healthy.
- **Low red blood cell count (anemia).**
- **Low blood sugar (hypoglycemia)**. Lightheadedness, dizziness, shakiness or hunger may mean that your blood sugar is too low. This can happen if you skip meals, if you use another medicine that lowers blood sugar, or if you have certain medical problems. Call your doctor if low blood sugar levels are a problem for you.
- **Ovulation** (release of egg from an ovary in a woman) leading to pregnancy. Ovulation may happen in premenopausal women who do not have regular monthly periods. This can increase the chance of pregnancy. See “What should I tell my doctor before taking AVANDAMET?”.

Common side effects of AVANDAMET include:

- **Diarrhea, nausea, and upset stomach.** These side effects usually happen during the first few weeks of treatment. Taking AVANDAMET with food can help lessen these side effects. If you have unusual or unexpected stomach problems, talk with your doctor. Stomach problems that start up later during treatment with AVANDAMET may be a sign of something more serious and should be discussed with your doctor.
- **Cold-like symptoms**
- **Headache**
- **Joint aches**
- **Dizziness**

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AVANDAMET?

- Store AVANDAMET at room temperature, 59° to 86°F (15° to 30°C).
- Keep AVANDAMET in the container it comes in. Keep the container closed tightly.
- Safely, throw away AVANDAMET that is out of date or no longer needed.

Keep AVANDAMET and all medicines out of the reach of children.

General information about AVANDAMET

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AVANDAMET for a condition for which it was not prescribed. Do not give AVANDAMET to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes important information about AVANDAMET. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about AVANDAMET that is written for healthcare professionals. You can also find out more about AVANDAMET by calling 1-888-825-5249.

What are the ingredients in AVANDAMET?

Active Ingredients: Rosiglitazone maleate and metformin hydrochloride
Inactive Ingredients: Hypromellose 2910, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, povidone 29-32, sodium starch glycolate, titanium dioxide, and 1 or more of the following: Red and yellow iron oxides.

Always check to make sure that the medicine you are taking is the correct one. AVANDAMET tablets are oval and look like this:

- 2 mg/500 mg – pale pink, with “gsk” on one side and “2/500” on the other.
- 4 mg/500 mg – orange, with “gsk” on one side and “4/500” on the other
- 2 mg/1,000 mg – yellow, with “gsk” on one side and “2/1000” on the other
- 4 mg/1,000 mg – pink, with “gsk” on one side and “4/1000” on the other

This Medication Guide has been approved by the U.S. Food and Drug Administration.

GlaxoSmithKline
Research Triangle Park, NC 27709

Month 2011

AVM:XMG

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVANDARYL safely and effectively. See full prescribing information for AVANDARYL.

AVANDARYL **(rosiglitazone maleate and glimepiride) Tablets**
Initial U.S. Approval: 2005

WARNING: CONGESTIVE HEART FAILURE **AND MYOCARDIAL INFARCTION**

See full prescribing information for complete boxed warning.

- **Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (5.2). After initiation of AVANDARYL, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDARYL must be considered.**
- **AVANDARYL is not recommended in patients with symptomatic heart failure. Initiation of AVANDARYL in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.2)**
- **A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with a statistically significant increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, showed a statistically non-significant increased risk of myocardial infarction and a statistically non-significant decreased risk of death. There have been no clinical trials directly comparing cardiovascular risk of rosiglitazone and ACTOS® (pioglitazone, another thiazolidinedione), but in a separate trial, pioglitazone (when compared to placebo) did not show an increased risk of myocardial infarction or death. (5.3)**
- **Because of the potential increased risk of myocardial infarction, AVANDARYL is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1-800-AVANDIA or visit www.AVANDIA.com. *[See Warnings and Precautions (5.4).]***

----------RECENT MAJOR CHANGES----------

Boxed Warning	02/2011
Indications and Usage (1)	02/2011
Dosage and Administration (2)	02/2011
Warnings and Precautions, Cardiac Failure (5.2)	02/2011
Warnings and Precautions, Major Adverse Cardiovascular Events (5.3)	02/2011
Warnings and Precautions, Rosiglitazone REMS Program (5.4)	XX/2011
Warnings and Precautions, Fractures (5.10)	02/2011

----------INDICATIONS AND USAGE----------

AVANDARYL is a combination antidiabetic product containing a thiazolidinedione and a sulfonylurea. After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of rosiglitazone, this drug is indicated as an adjunct to diet and exercise to improve glycemic control when treatment with both rosiglitazone and glimepiride is appropriate in adults with type 2 diabetes who either are:

- already taking rosiglitazone, or
- not already taking rosiglitazone and unable to achieve glycemic control on other diabetes medications and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS) or pioglitazone-containing products (ACTOPLUS MET®, ACTOPLUS MET XR®, DUETACT®) for medical reasons. (1)

Other Important Limitations of Use:

- Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. (1, 4)
- Coadministration with insulin is not recommended. (1, 5.2, 5.3)

----------DOSAGE AND ADMINISTRATION----------

- Individualize the starting dose based on the patient's current regimen. (2.1)
- Dose increases should be accompanied by careful monitoring for adverse events related to fluid retention. (2.2)
- Do not exceed the maximum recommended daily dose of 8 mg rosiglitazone and 4 mg glimepiride. (2.3)
- Do not initiate if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Rounded triangular tablets containing rosiglitazone/glimepiride: 4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg, 8 mg/2 mg, and 8 mg/4 mg (3)

----------CONTRAINDICATIONS----------

- Initiation in patients with established NYHA Class III or IV heart failure. (4)

----------WARNINGS AND PRECAUTIONS----------

- One sulfonylurea has been shown to increase cardiovascular mortality; consider this risk when prescribing any sulfonylurea. (5.1)
- Fluid retention, which may exacerbate or lead to heart failure, may occur. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk of other cardiovascular effects. (5.2)
- Increased risk of myocardial infarction has been observed in a meta-analysis of 52 clinical trials of rosiglitazone (incidence rate 0.4% versus 0.3%). (5.3)
- Use with insulin is not recommended. (1, 5.2, 5.3)
- Severe hypoglycemia may occur. Use particular care in elderly or debilitated patients and those with adrenal, pituitary, renal or hepatic insufficiency. (5.5)
- Dose-related edema (5.6), weight gain (5.7), and anemia (5.11) may occur.
- Macular edema has been reported. (5.9)
- Increased incidence of bone fracture. (5.10)
- The glimepiride component may cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Consider a non-sulfonylurea alternative in these patients. (5.12)

----------ADVERSE REACTIONS----------

Common adverse reactions (≥5%) reported in clinical trials for AVANDARYL without regard to causality were headache, hypoglycemia, and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**.**

----------DRUG INTERACTIONS----------

- Inhibitors of CYP2C8 (e.g., gemfibrozil) may increase rosiglitazone levels. (7.1)
- Inducers of CYP2C8 (e.g., rifampin) may decrease rosiglitazone levels. (7.1)
- Monitor patients for loss of control with drugs that cause hyperglycemia. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Do not use during pregnancy. No human or animal data. (8.1)
- Safety and effectiveness in children under 18 years have not been established. (8.4)
- Elderly patients may be particularly susceptible to hypoglycemic effects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: XX/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION

- Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients *[see Warnings and Precautions (5.2)]*. After initiation of AVANDARYL, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDARYL must be considered.
- AVANDARYL is not recommended in patients with symptomatic heart failure. Initiation of AVANDARYL in patients with established NYHA Class III or IV heart failure is contraindicated. *[See Contraindications (4) and Warnings and Precautions (5.2).]*
- A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo,showed a statistically non-significant increased risk of myocardial infarction, and a statistically non-significant decreased risk of death. There have been no clinical trials directly comparing cardiovascular risk of rosiglitazone and ACTOS® (pioglitazone, another thiazolidinedione), but in a separate trial, pioglitazone (when compared to placebo) did not show an increased risk of myocardial infarction or death. *[See Warnings and Precautions (5.3).]*
- Because of the potential increased risk of myocardial infarction, AVANDARYL is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1-800-AVANDIA or visit www.AVANDIA.com. *[See Warnings and Precautions (5.4).]*

1 INDICATIONS AND USAGE

After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of rosiglitazone, AVANDARYL® is indicated as an adjunct to diet and exercise to improve glycemic control when treatment with both rosiglitazone and glimepiride is appropriate in adults with type 2 diabetes mellitus who either are:

- already taking rosiglitazone, or
- not already taking rosiglitazone and unable to achieve glycemic control on other diabetes medications and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS®) or pioglitazone-containing products (ACTOSPLUS MET®, ACTOPLUS MET XR®, DUETACT®) for medical reasons.

Other Important Limitations of Use:

- Due to its mechanism of action, rosiglitazone is active only in the presence of endogenous insulin. Therefore, AVANDARYL should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
- Coadministration of AVANDARYL with insulin is not recommended *[see Warnings and Precautions (5.2, 5.3)]*.

2 DOSAGE AND ADMINISTRATION

Prior to prescribing AVANDARYL, refer to *Indications and Usage (1)* for appropriate patient selection. Only prescribers enrolled in the AVANDIA-Rosiglitazone Medicines Access Program can prescribe AVANDARYL *[see Warnings and Precautions (5.4)]*.

2.1 Starting Dose

The recommended starting dose is 4 mg/1 mg administered once daily with the first meal of the day. For adults already treated with a sulfonylurea or rosiglitazone, a starting dose of 4 mg/2 mg may be considered.

All patients should start the rosiglitazone component of AVANDARYL at the lowest recommended dose. Further increases in the dose of rosiglitazone should be accompanied by careful monitoring for adverse events related to fluid retention *[see **Boxed Warning** and Warnings and Precautions (5.6)]*.

When switching from combination therapy of rosiglitazone plus glimepiride as separate tablets, the usual starting dose of AVANDARYL is the dose of rosiglitazone and glimepiride already being taken.

2.2 Dose Titration

Dose increases should be individualized according to the glycemic response of the patient. Patients who may be more sensitive to glimepiride *[see Warnings and Precautions (5.5)]*, including the elderly, debilitated, or malnourished, and those with renal, hepatic, or adrenal insufficiency, should be carefully titrated to avoid hypoglycemia. If hypoglycemia occurs during up-titration of the dose or while maintained on therapy, a dosage reduction of the glimepiride component of AVANDARYL may be considered. Increases in the dose of rosiglitazone should be accompanied by careful monitoring for adverse events related to fluid retention *[see **Boxed Warning** and Warnings and Precautions (5.6)]*.

To switch to AVANDARYL for adults currently treated with rosiglitazone, dose titration of the glimepiride component of AVANDARYL is recommended if patients are not adequately controlled after 1 to 2 weeks. The glimepiride component may be increased in no more than 2 mg increments. After an increase in the dosage of the glimepiride component, dose titration of AVANDARYL is recommended if patients are not adequately controlled after 1 to 2 weeks.

To switch to AVANDARYL for adults currently treated with sulfonylurea, it may take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of the rosiglitazone component. Therefore, dose titration of the rosiglitazone component of

AVANDARYL is recommended if patients are not adequately controlled after 8 to 12 weeks. Patients should be observed carefully (1 to 2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to AVANDARYL due to potential overlapping of drug effect. After an increase in the dosage of the rosiglitazone component, dose titration of AVANDARYL is recommended if patients are not adequately controlled after 2 to 3 months.

2.3 Maximum Dose

The maximum recommended daily dose is 8 mg rosiglitazone and 4 mg glimepiride.

2.4 Specific Patient Populations

Elderly and Malnourished Patients and Those With Renal, Hepatic, or Adrenal Insufficiency: In elderly, debilitated, or malnourished patients, or in patients with renal, hepatic, or adrenal insufficiency, the starting dose, dose increments, and maintenance dosage of AVANDARYL should be conservative to avoid hypoglycemic reactions. *[See Warnings and Precautions (5.5) and Clinical Pharmacology (12.3).]*

Hepatic Impairment: Liver enzymes should be measured prior to initiating treatment with AVANDARYL. Therapy with AVANDARYL should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy). After initiation of AVANDARYL, liver enzymes should be monitored periodically per the clinical judgment of the healthcare professional. *[See Warnings and Precautions (5.8) and Clinical Pharmacology (12.3).]*

Pregnancy and Lactation: AVANDARYL should not be used during pregnancy or in nursing mothers.

Pediatric Use: Safety and effectiveness of AVANDARYL in pediatric patients have not been established. AVANDARYL and its components, rosiglitazone and glimepiride, are not recommended for use in pediatric patients.

3 DOSAGE FORMS AND STRENGTHS

Each rounded triangular tablet contains rosiglitazone maleate and glimepiride as follows:

- 4 mg/1 mg – yellow, gsk debossed on one side and 4/1 on the other.
- 4 mg/2 mg – orange, gsk debossed on one side and 4/2 on the other.
- 4 mg/4 mg – pink, gsk debossed on one side and 4/4 on the other.
- 8 mg/2 mg – pale pink, gsk debossed on one side and 8/2 on the other.
- 8 mg/4 mg – red, gsk debossed on one side and 8/4 on the other.

4 CONTRAINDICATIONS

Initiation of AVANDARYL in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated *[see **Boxed Warning**]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Cardiovascular Mortality for Sulfonylurea Drugs

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the trial conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The trial involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes* 1970;19[Suppl. 2]:747-830). UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the trial to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP trial provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glimepiride-containing tablets and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this trial, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

5.2 Cardiac Failure With Rosiglitazone

Rosiglitazone, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered *[see **Boxed Warning**]*.

Patients with congestive heart failure (CHF) NYHA Class I and II treated with rosiglitazone have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-controlled echocardiographic trial was conducted in 224 patients with type 2 diabetes mellitus and NYHA Class I or II CHF (ejection fraction ≤45%) on background antidiabetic and CHF therapy. An independent committee conducted a blinded evaluation of fluid-related events (including congestive heart failure) and cardiovascular hospitalizations according to predefined criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were reported by investigators. Although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed with rosiglitazone treatment compared to placebo during the 52-week trial. (See Table 1.)

Table 1. Emergent Cardiovascular Adverse Events in Patients With Congestive Heart Failure (NYHA Class I and II) Treated With Rosiglitazone or Placebo (in Addition to Background Antidiabetic and CHF Therapy)

Events	**Rosiglitazone**	**Placebo**
	N = 110 n (%)	N = 114 n (%)
Adjudicated		
Cardiovascular deaths	5 (5%)	4 (4%)
CHF worsening	7 (6%)	4 (4%)
– with overnight hospitalization	5 (5%)	4 (4%)
– without overnight hospitalization	2 (2%)	0 (0%)
New or worsening edema	28 (25%)	10 (9%)
New or worsening dyspnea	29 (26%)	19 (17%)
Increases in CHF medication	36 (33%)	20 (18%)
Cardiovascular hospitalization[a]	21 (19%)	15 (13%)
Investigator-reported, non-adjudicated		
Ischemic adverse events	10 (9%)	5 (4%)
– Myocardial infarction	5 (5%)	2 (2%)
– Angina	6 (5%)	3 (3%)

[a] Includes hospitalization for any cardiovascular reason.

Initiation of AVANDARYL in patients with established NYHA Class III or IV heart failure is contraindicated. AVANDARYL is not recommended in patients with symptomatic heart failure. *[See **Boxed Warning**.]*

Patients experiencing acute coronary syndromes have not been studied in controlled clinical trials. In view of the potential for development of heart failure in patients having an acute coronary event, initiation of AVANDARYL is not recommended for patients experiencing an acute coronary event, and discontinuation of AVANDARYL during this acute phase should be considered.

Patients with NYHA Class III and IV cardiac status (with or without CHF) have not been studied in controlled clinical trials. AVANDARYL is not recommended in patients with NYHA Class III and IV cardiac status.

Congestive Heart Failure During Coadministration of Rosiglitazone With Insulin: In trials in which rosiglitazone was added to insulin, rosiglitazone increased the risk of congestive heart failure. Coadministration of rosiglitazone and insulin is not recommended. *[See Indications and Usage (1) and Warnings and Precautions (5.3).]*

In 7 controlled, randomized, double-blind trials which had durations from 16 to 26 weeks and which were included in a meta-analysis[1] *[see Warnings and Precautions (5.3)]*, patients with type 2 diabetes mellitus were randomized to coadministration of rosiglitazone and insulin

(N = 1,018) or insulin (N = 815). In these 7 trials, rosiglitazone was added to insulin. These trials included patients with long-standing diabetes (median duration of 12 years) and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. The total number of patients with emergent congestive heart failure was 23 (2.3%) and 8 (1.0%) in the rosiglitazone plus insulin and insulin groups, respectively.

Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing Rosiglitazone to Pioglitazone: Three observational studies[2-4] in elderly diabetic patients (age 65 years and older) found that rosiglitazone statistically significantly increased the risk of hospitalized heart failure compared to use of pioglitazone. One other observational study[5] in patients with a mean age of 54 years, which also included an analysis in a subpopulation of patients >65 years of age, found no statistically significant increase in emergency department visits or hospitalization for heart failure in patients treated with rosiglitazone compared to pioglitazone in the older subgroup.

5.3 Major Adverse Cardiovascular Events

Cardiovascular adverse events have been evaluated in a meta-analysis of 52 clinical trials, in long-term, prospective, randomized, controlled trials, and in observational studies.

Meta-Analysis of Major Adverse Cardiovascular Events in a Group of 52 Clinical Trials: A meta-analysis was conducted retrospectively to assess cardiovascular adverse events reported across 52 double-blind, randomized, controlled clinical trials (mean duration 6 months).[1] These trials had been conducted to assess glucose-lowering efficacy in type 2 diabetes. Prospectively planned adjudication of cardiovascular events did not occur in most of the trials. Some trials were placebo-controlled and some used active oral antidiabetic drugs as controls. Placebo-controlled trials included monotherapy trials (monotherapy with rosiglitazone versus placebo monotherapy) and add-on trials (rosiglitazone or placebo, added to sulfonylurea, metformin, or insulin). Active control trials included monotherapy trials (monotherapy with rosiglitazone versus sulfonylurea or metformin monotherapy) and add-on trials (rosiglitazone plus sulfonylurea or rosiglitazone plus metformin, versus sulfonylurea plus metformin). A total of 16,995 patients were included (10,039 in treatment groups containing rosiglitazone, 6,956 in comparator groups), with 5,167 patient-years of exposure to rosiglitazone and 3,637 patient-years of exposure to comparator. Cardiovascular events occurred more frequently for patients who received rosiglitazone than for patients who received comparators (see Table 2).

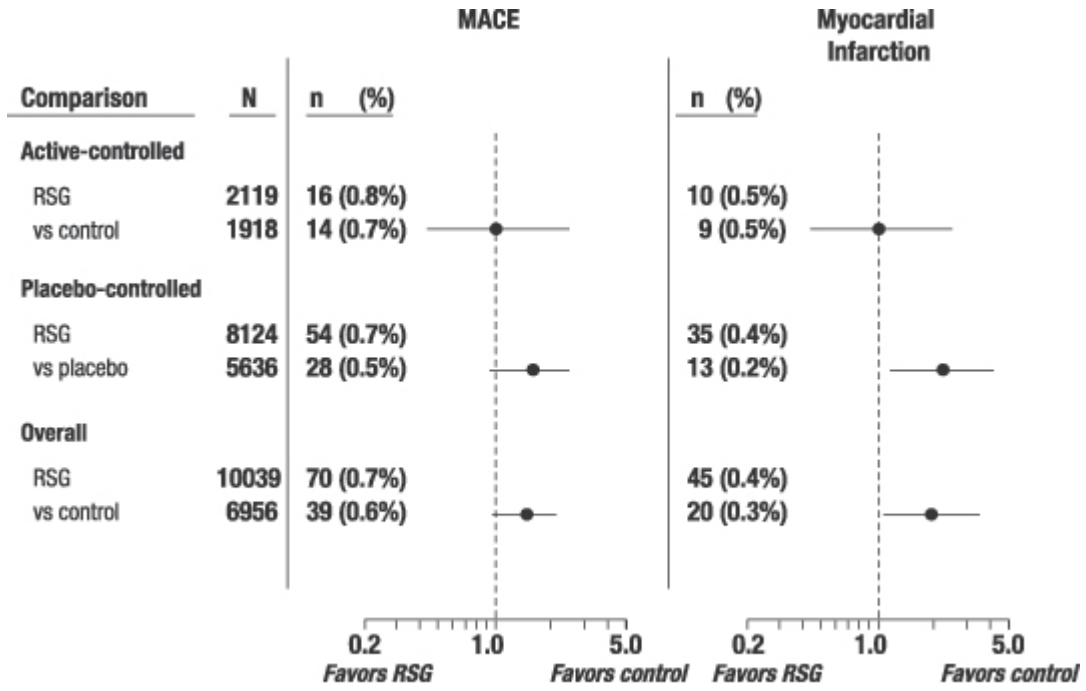
Table 2. Occurrence of Cardiovascular Events in a Meta-Analysis of 52 Clinical Trials

Event[a]	Rosiglitazone (N=10,039) n (%)	Comparator (N=6,956) n (%)
MACE (a composite of myocardial infarction, cardiovascular death, or stroke)	70 (0.7)	39 (0.6)
Myocardial Infarction	45 (0.4)	20 (0.3)
Cardiovascular Death	17 (0.2)	9 (0.1)
Stroke	18 (0.2)	16 (0.2)
All-cause Death	29 (0.3)	17 (0.2)

[a] Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial infarction would be counted in 4 event categories (myocardial infarction; myocardial infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).

In this analysis, a statistically significant increased risk of myocardial infarction with rosiglitazone versus pooled comparators was observed. Analyses were performed using a composite of major adverse cardiovascular events (myocardial infarction, stroke, and cardiovascular death), referred to hereafter as MACE. Rosiglitazone had a statistically non-significant increased risk of MACE compared to the pooled comparators. A statistically significant increased risk of myocardial infarction and statistically non-significant increased risk of MACE with rosiglitazone was observed in the placebo-controlled trials. In the active-controlled trials, there was no increased risk of myocardial infarction or MACE. (See Figure 1 and Table 3.)

Figure 1. Forest Plot of Odds Ratios (95% Confidence Intervals) for MACE and Myocardial Infarction in the Meta-Analysis of 52 Clinical Trials



RSG = rosiglitazone

Table 3. Occurrence of MACE and Myocardial Infarction in a Meta-Analysis of 52 Clinical Trials by Trial Type

			MACE		Myocardial Infarction	
		N	n (%)	OR (95%CI)	n (%)	OR (95%CI)
Active-Controlled Trials	RSG	2,119	16 (0.8%)	1.05 (0.48, 2.34)	10 (0.5%)	1.00 (0.36, 2.82)
	Control	1,918	14 (0.7%)		9 (0.5%)	
Placebo-Controlled Trials	RSG	8,124	54 (0.7%)	1.53 (0.94, 2.54)	35 (0.4%)	2.23 (1.14, 4.64)
	Placebo	5,636	28 (0.5%)		13 (0.2%)	
Overall	RSG	10,039	70 (0.7%)	1.44 (0.95, 2.20)	45 (0.4%)	1.8 (1.03, 3.25)
	Control	6,956	39 (0.6%)		20 (0.3%)	

RSG = rosiglitazone

Of the placebo-controlled trials in the meta-analysis, 7 trials had patients randomized to rosiglitazone plus insulin or insulin. There were more patients in the rosiglitazone plus insulin group compared to the insulin group with myocardial infarctions, MACE, cardiovascular deaths, and all-cause deaths (see Table 4). The total number of patients with stroke was 5 (0.5%) and 4 (0.5%) in the rosiglitazone plus insulin and insulin groups, respectively. The use of rosiglitazone

in combination with insulin may increase the risk of myocardial infarction *[See Warnings and Precautions (5.1).]*

Table 4. Occurrence of Cardiovascular Events for Rosiglitazone in Combination With Insulin in a Meta-Analysis of 52 Clinical Trials

Event[a]	**Rosiglitazone (N=1,018) (%)**	**Insulin (N = 815) (%)**	OR (95% CI)
MACE (a composite of myocardial infarction, cardiovascular death, or stroke)	1.3	0.6	2.14 (0.70, 7.83)
Myocardial infarction	0.6	0.1	5.6 (0.67, 262.7)
Cardiovascular death	0.4	0.0	ND, (0.47, ∞)
All cause death	0.6	0.2	2.19 (0.38, 22.61)

ND = not defined

[a] Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial infarction would be counted in 4 event categories (myocardial infarction; myocardial infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).

Myocardial Infarction Events in Large, Long-Term, Prospective, Randomized, Controlled Trials of Rosiglitazone: Data from 3 large, long-term, prospective, randomized, controlled clinical trials of rosiglitazone were assessed separately from the meta-analysis.[6-8] These 3 trials included a total of 14,067 patients (treatment groups containing rosiglitazone N = 6,311; comparator groups N = 7,756), with patient-year exposure of 24,534 patient-years for rosiglitazone and 28,882 patient-years for comparator. Patient populations in the trials included patients with impaired glucose tolerance, patients with type 2 diabetes who were initiating oral agent monotherapy, and patients with type 2 diabetes who had failed monotherapy and were initiating dual oral agent therapy. Duration of follow-up exceeded 3 years in each trial.

In each of these trials, there was a statistically non-significant increase in the risk of myocardial infarction for rosiglitazone versus comparator medications.

In a long-term, randomized, placebo-controlled, 2x2 factorial trial intended to evaluate rosiglitazone, and separately ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on progression to overt diabetes in 5,269 subjects with glucose intolerance, the incidence of myocardial infarction was higher in the subset of subjects who received rosiglitazone in combination with ramipril than among subjects who received ramipril alone but not in the subset of subjects who received rosiglitazone alone compared to placebo.[6] The higher incidence of myocardial infarction among subjects who received rosiglitazone in combination with ramipril was not confirmed in the two other large (total N = 8,798) long-term, randomized, active-controlled clinical trials conducted in patients with type 2 diabetes, in which 30% and 40% of patients in the two trials reported angiotensin-converting enzyme inhibitor use at baseline.[7,8]

There have been no adequately designed clinical trials directly comparing rosiglitazone to pioglitazone on cardiovascular risks. However, in a long-term, randomized, placebo-controlled cardiovascular outcomes trial comparing pioglitazone to placebo in patients with type 2 diabetes mellitus and prior macrovascular disease, pioglitazone was not associated with an increased risk of myocardial infarction or total mortality.[9]

The increased risk of myocardial infarction observed in the meta-analysis and large, long-term controlled clinical trials, and the increased risk of MACE observed in the meta-analysis described above, have not translated into a consistent finding of excess mortality from controlled clinical trials or observational studies. Clinical trials have not shown any difference between rosiglitazone and comparator medications in overall mortality or CV-related mortality.

Mortality in Observational Studies of Rosiglitazone Compared to Pioglitazone:
Three observational studies in elderly diabetic patients (age 65 years and older) found that rosiglitazone statistically significantly increased the risk of all-cause mortality compared to use of ACTOS (pioglitazone).[2-4] One observational study[5] in patients with a mean age of 54 years found no difference in all-cause mortality between patients treated with rosiglitazone compared to ACTOS (pioglitazone) and reported similar results in the subpopulation of patients >65 years of age. One additional small, prospective, observational study[10] found no statistically significant differences for CV mortality and all-cause mortality in patients treated with rosiglitazone compared to ACTOS (pioglitazone).

5.4 Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program

Because of the potential increased risk of myocardial infarction, AVANDARYL is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program *[see Indications and Usage (1)]*. Both prescribers and patients must enroll in the program to be able to prescribe or receive AVANDARYL, respectively. AVANDARYL will be available only from specially certified pharmacies participating in the program. As part of the program, prescribers will be educated about the potential increased risk of myocardial infarction and the need to limit the use of AVANDARYL to eligible patients. Prescribers will need to discuss with patients the risks and benefits of taking AVANDARYL. To enroll, call 1-800-AVANDIA or visit www.AVANDIA.com.

5.5 Hypoglycemia

AVANDARYL is a combination tablet containing rosiglitazone and glimepiride, a sulfonylurea. All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs. Debilitated or malnourished patients, and those with adrenal, pituitary, renal, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. A starting dose of 1 mg glimepiride, as contained in AVANDARYL 4 mg/1 mg, followed by appropriate dose titration is recommended in these patients. *[See Clinical Pharmacology (12.3).]* Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur

when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Patients receiving rosiglitazone in combination with a sulfonylurea may be at risk for hypoglycemia, and a reduction in the dose of the sulfonylurea may be necessary *[see Dosage and Administration (2.2)]*.

5.6 Edema

AVANDARYL should be used with caution in patients with edema. In a clinical trial in healthy volunteers who received 8 mg of rosiglitazone once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo.

Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, AVANDARYL should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure *[see **Boxed Warning**, Warnings and Precautions (5.2), and Patient Counseling Information (17.1)]*.

In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with rosiglitazone, and may be dose-related. Patients with ongoing edema were more likely to have adverse events associated with edema if started on combination therapy with insulin and rosiglitazone *[see Adverse Reactions (6.1)]*. The use of AVANDARYL in combination with insulin is not recommended *[see Warnings and Precautions (5.2, 5.3)]*.

5.7 Weight Gain

Dose-related weight gain was seen with AVANDARYL, rosiglitazone alone, and rosiglitazone together with other hypoglycemic agents (see Table 5). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 5. Weight Changes (kg) From Baseline at Endpoint During Clinical Trials
[Median (25th, 75th, Percentile)]

Monotherapy				
Duration	**Control Group**		**Rosiglitazone 4 mg**	**Rosiglitazone 8 mg**
26 weeks	Placebo	-0.9 (-2.8, 0.9) N = 210	1.0 (-0.9, 3.6) N = 436	3.1 (1.1, 5.8) N = 439
52 weeks	Sulfonylurea	2.0 (0, 4.0) N = 173	2.0 (-0.6, 4.0) N = 150	2.6 (0, 5.3) N = 157
Combination Therapy				
			Rosiglitazone + Control Therapy	
Duration	**Control Group**		**Rosiglitazone 4 mg**	**Rosiglitazone 8 mg**
24-26 weeks	Sulfonylurea	0 (-1.0, 1.3) N = 1,155	2.2 (0.5, 4.0) N = 613	3.5 (1.4, 5.9) N = 841
26 weeks	Metformin	-1.4 (-3.2, 0.2) N = 175	0.8 (-1.0, 2.6) N = 100	2.1 (0, 4.3) N = 184
26 weeks	Insulin	0.9 (-0.5, 2.7) N = 162	4.1 (1.4, 6.3) N = 164	5.4 (3.4, 7.3) N = 150

In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed with type 2 diabetes not previously treated with antidiabetic medication, the median weight change (25th, 75th percentiles) from baseline at 4 years was 3.5 kg (0.0, 8.1) for rosiglitazone, 2.0 kg (-1.0, 4.8) for glyburide, and -2.4 kg (-5.4, 0.5) for metformin.

In postmarketing experience with rosiglitazone alone or in combination with other hypoglycemic agents, there have been rare reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure *[see **Boxed Warning**]*.

5.8 Hepatic Effects

With sulfonylureas, including glimepiride, there may be an elevation of liver enzyme levels in rare cases. In isolated instances, impairment of liver function (e.g., with cholestasis and jaundice), as well as hepatitis (which may also lead to liver failure) have been reported.

Liver enzymes should be measured prior to the initiation of therapy with AVANDARYL in all patients and periodically thereafter per the clinical judgment of the healthcare professional. Therapy with AVANDARYL should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with AVANDARYL should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with AVANDARYL in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time

ALT levels increase to >3X the upper limit of normal in patients on therapy with AVANDARYL, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with AVANDARYL should be discontinued.

If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with AVANDARYL should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

5.9 Macular Edema

Macular edema has been reported in postmarketing experience in some diabetic patients who were taking rosiglitazone or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. Patients with diabetes should have regular eye exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings. *[See Adverse Reactions (6.3).]*

5.10 Fractures

In a 4- to 6-year comparative trial (ADOPT) of glycemic control with monotherapy in drug-naïve patients recently diagnosed with type 2 diabetes mellitus, an increased incidence of bone fracture was noted in female patients taking rosiglitazone. Over the 4- to 6-year period, the incidence of bone fracture in females was 9.3% (60/645) for rosiglitazone versus 3.5% (21/605) for glyburide and 5.1% (30/590) for metformin. This increased incidence was noted after the first year of treatment and persisted during the course of the trial. The majority of the fractures in the women who received rosiglitazone occurred in the upper arm, hand, and foot. These sites of fracture are different from those usually associated with postmenopausal osteoporosis (e.g., hip or spine). Other trials suggest that this risk may also apply to men, although the risk of fracture among women appears higher than that among men. The risk of fracture should be considered in the care of patients treated with rosiglitazone, and attention given to assessing and maintaining bone health according to current standards of care.

5.11 Hematologic Effects

Decreases in hemoglobin and hematocrit occurred in a dose-related fashion in adult patients treated with rosiglitazone *[see Adverse Reactions (6.2)]*. The observed changes may be related to the increased plasma volume observed with treatment with rosiglitazone.

5.12 Hemolytic Anemia

Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because glimepiride, a component of AVANDARYL, belongs to the class of sulfonylurea agents, caution should be used in patients

with G6PD deficiency and a non-sulfonylurea alternative should be considered. In post-marketing experience, hemolytic anemia has also been reported in patients receiving sulfonylureas who did not have known G6PD deficiency *[see Adverse Reactions (6.1)]*.

5.13 Diabetes and Blood Glucose Control

When a patient stabilized on any antidiabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold AVANDARYL and temporarily administer insulin. AVANDARYL may be reinstituted after the acute episode is resolved.

Periodic fasting glucose and HbA1c measurements should be performed to monitor therapeutic response.

5.14 Ovulation

Therapy with rosiglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking rosiglitazone *[see Use in Specific Populations (8.1)]*. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical trials; therefore the frequency of this occurrence is not known.

Although hormonal imbalance has been seen in preclinical studies *[see Nonclinical Toxicology (13.1)]*, the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with AVANDARYL should be reviewed.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Trials utilizing rosiglitazone in combination with a sulfonylurea provide support for the use of AVANDARYL. Adverse event data from these trials, in addition to adverse events reported with the use of rosiglitazone and glimepiride therapy, are presented below.

Rosiglitazone: The most common adverse experiences with rosiglitazone monotherapy (≥5%) were upper respiratory tract infection, injury, and headache. Overall, the types of adverse experiences reported when rosiglitazone was added to a sulfonylurea were similar to those during monotherapy with rosiglitazone. In controlled combination therapy trials with sulfonylureas, mild to moderate hypoglycemic symptoms, which appear to be dose-related, were reported. Few patients were withdrawn for hypoglycemia (<1%) and few episodes of hypoglycemia were considered to be severe (<1%).

Events of anemia and edema tended to be reported more frequently at higher doses, and were generally mild to moderate in severity and usually did not require discontinuation of treatment with rosiglitazone.

Edema was reported by 4.8% of patients receiving rosiglitazone compared to 1.3% on placebo, and 1.0% on sulfonylurea monotherapy. The reporting rate of edema was higher for rosiglitazone 8 mg added to a sulfonylurea (12.4%) compared to other combinations, with the exception of insulin. Anemia was reported by 1.9% of patients receiving rosiglitazone compared to 0.7% on placebo, 0.6% on sulfonylurea monotherapy, and 2.3% on rosiglitazone in combination with a sulfonylurea. Overall, the types of adverse experiences reported when rosiglitazone was added to a sulfonylurea were similar to those during monotherapy with rosiglitazone.

In 26-week double-blind, fixed-dose trials, edema was reported with higher frequency in the rosiglitazone plus insulin combination trials (insulin, 5.4%; and rosiglitazone in combination with insulin, 14.7%). Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with rosiglitazone *[see **Boxed Warning** and Warnings and Precautions (5.2)]*. The use of rosiglitazone in combination with insulin may increase the risk of myocardial infarction *[see Warnings and Precautions (5.3)]*.

Glimepiride: Hypoglycemia: The incidence of hypoglycemia with glimepiride, as documented by blood glucose values <60 mg/dL, ranged from 0.9% to 1.7% in 2 large, well-controlled, 1-year trials. In patients treated with glimepiride in US placebo-controlled trials (N = 746), adverse events, other than hypoglycemia, considered to be possibly or probably related to trial drug that occurred in more than 1% of patients included dizziness (1.7%), asthenia (1.6%), headache (1.5%), and nausea (1.1%).

Gastrointestinal Reactions: Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was less than 1%. In rare cases, there may be an elevation of liver enzyme levels. In isolated instances, impairment of liver function (e.g., with cholestasis and jaundice), as well as hepatitis, which may also lead to liver failure have been reported with sulfonylureas, including glimepiride.

Dermatologic Reactions: Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of glimepiride. If those hypersensitivity reactions persist or worsen, the drug should be discontinued. Porphyria cutanea tarda, photosensitivity reactions, and allergic vasculitis have been reported with sulfonylureas, including glimepiride.

Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia *[see Warnings and Precautions (5.12)]*, aplastic anemia, and pancytopenia have been reported with sulfonylureas, including glimepiride.

Metabolic Reactions: Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas, including glimepiride. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion

has been reported with certain other sulfonylureas, including glimepiride, and it has been suggested that certain sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Other Reactions: Changes in accommodation and/or blurred vision may occur with the use of glimepiride. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment. In placebo-controlled trials of glimepiride, the incidence of blurred vision was placebo, 0.7%, and glimepiride, 0.4%.

Human Ophthalmology Data: Ophthalmic examinations were carried out in more than 500 subjects during long-term trials of glimepiride using the methodology of Taylor and West and Laties et al. No significant differences were seen between glimepiride and glyburide in the number of subjects with clinically important changes in visual acuity, intraocular tension, or in any of the 5 lens-related variables examined. Ophthalmic examinations were carried out during long-term trials using the method of Chylack et al. No significant or clinically meaningful differences were seen between glimepiride and glipizide with respect to cataract progression by subjective LOCS II grading and objective image analysis systems, visual acuity, intraocular pressure, and general ophthalmic examination *[see Nonclinical Toxicology (13.2)]*.

Long-Term Trial of Rosiglitazone as Monotherapy: A 4- to 6-year trial (ADOPT) compared the use of rosiglitazone (n = 1,456), glyburide (n = 1,441), and metformin (n = 1,454) as monotherapy in patients recently diagnosed with type 2 diabetes who were not previously treated with antidiabetic medication. Table 6 presents adverse reactions without regard to causality; rates are expressed per 100 patient-years (PY) exposure to account for the differences in exposure to trial medication across the 3 treatment groups.

In ADOPT, fractures were reported in a greater number of women treated with rosiglitazone (9.3%, 2.7/100 patient-years) compared to glyburide (3.5%, 1.3/100 patient-years) or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who received rosiglitazone were reported in the upper arm, hand, and foot. *[See Warnings and Precautions (5.10).]* The observed incidence of fractures for male patients was similar among the 3 treatment groups.

Table 6. On-Therapy Adverse Events (≥5 Events/100 Patient-Years [PY]) in Any Treatment Group Reported in a 4- to 6-Year Clinical Trial of Rosiglitazone as Monotherapy (ADOPT)

	Rosiglitazone N = 1,456 PY = 4,954	**Glyburide** N = 1,441 PY = 4,244	**Metformin** N = 1,454 PY = 4,906
Nasopharyngitis	6.3	6.9	6.6
Back pain	5.1	4.9	5.3
Arthralgia	5.0	4.8	4.2
Hypertension	4.4	6.0	6.1
Upper respiratory tract infection	4.3	5.0	4.7
Hypoglycemia	2.9	13.0	3.4
Diarrhea	2.5	3.2	6.8

6.2 Laboratory Abnormalities

Rosiglitazone: *Hematologic:* Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult patients treated with rosiglitazone (mean decreases in individual trials as much as 1.0 g/dL hemoglobin and as much as 3.3% hematocrit). The changes occurred primarily during the first 3 months following initiation of therapy with rosiglitazone or following a dose increase in rosiglitazone. The time course and magnitude of decreases were similar in patients treated with a combination of rosiglitazone and other hypoglycemic agents or monotherapy with rosiglitazone. White blood cell counts also decreased slightly in adult patients treated with rosiglitazone. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with rosiglitazone.

Lipids: Changes in serum lipids have been observed following treatment with rosiglitazone in adults *[see Clinical Pharmacology (12.2)]*.

Serum Transaminase Levels: In pre-approval clinical trials in 4,598 patients treated with rosiglitazone encompassing approximately 3,600 patient-years of exposure, there was no evidence of drug-induced hepatotoxicity.

In pre-approval controlled trials, 0.2% of patients treated with rosiglitazone had reversible elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with rosiglitazone were reversible. Hyperbilirubinemia was found in 0.3% of patients treated with rosiglitazone compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. *[See Warnings and Precautions (5.8).]*

In the 4- to 6-year ADOPT trial, patients treated with rosiglitazone (4,954 patient-years exposure), glyburide (4,244 patient-years exposure) or metformin (4,906 patient-years exposure) as monotherapy had the same rate of ALT increase to >3X upper limit of normal (0.3 per 100 patient-years exposure).

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the events described below have been identified during post-approval use of AVANDARYL or its individual components. Because these events are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or to always establish a causal relationship to drug exposure.

In patients receiving thiazolidinedione therapy, serious adverse events with or without a fatal outcome, potentially related to volume expansion (e.g., congestive heart failure, pulmonary edema, and pleural effusions) have been reported *[see **Boxed Warning** and Warnings and Precautions (5.2)]*.

There are postmarketing reports with rosiglitazone of hepatitis, hepatic enzyme elevations to 3 or more times the upper limit of normal, and hepatic failure with and without fatal outcome, although causality has not been established.

There are postmarketing reports with rosiglitazone of rash, pruritus, urticaria, angioedema, anaphylactic reaction, Stevens-Johnson syndrome, and new onset or worsening diabetic macular edema with decreased visual acuity *[see Warnings and Precautions (5.9)]*.

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P450

An inhibitor of CYP2C8 (e.g., gemfibrozil) may increase the AUC of rosiglitazone and an inducer of CYP2C8 (e.g., rifampin) may decrease the AUC of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response. *[See Clinical Pharmacology (12.4).]*

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is not known. Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 2C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid. *[See Clinical Pharmacology (12.4).]*

7.2 Drugs That Produce Hyperglycemia

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid. When these drugs are administered to a patient receiving glimepiride, the patient should be closely observed for loss of control. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for hypoglycemia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Careful monitoring of glucose control is essential in such patients. Most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible. AVANDARYL should not be used during pregnancy.

Human Data: There are no adequate and well-controlled trials with AVANDARYL or its individual components in pregnant women. Rosiglitazone has been reported to cross the human placenta and be detectable in fetal tissue. The clinical significance of these findings is unknown.

Animal Studies: No animal studies have been conducted with AVANDARYL. The following data are based on findings in studies performed with rosiglitazone or glimepiride individually.

Rosiglitazone: There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced the number of uterine implantations and live offspring when juvenile female rats were treated at 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day (approximately 4 times human AUC at the maximum recommended daily dose). There was no effect on pre- or post-natal survival or growth.

Glimepiride: Glimepiride did not produce teratogenic effects in rats exposed orally up to 4,000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area). Glimepiride has been shown to be associated with intrauterine fetal death in rats when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

In some studies in rats, offspring of dams exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. Significant concentrations of glimepiride were observed in the serum and breast milk of the dams as well as in the serum of the pups. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride. Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives.

8.2 Labor and Delivery

The effect of AVANDARYL or its components on labor and delivery in humans is unknown.

8.3 Nursing Mothers

No trials have been conducted with AVANDARYL. It is not known whether rosiglitazone or glimepiride is excreted in human milk. Because many drugs are excreted in human milk, AVANDARYL should not be administered to a nursing woman.

Rosiglitazone: Drug-related material was detected in milk from lactating rats.

Glimepiride: In rat reproduction studies, significant concentrations of glimepiride were observed in the serum and breast milk of the dams, as well as in the serum of the pups. Although it is not known whether glimepiride is excreted in human milk, other sulfonylureas are excreted in human milk.

8.4 Pediatric Use

Safety and effectiveness of AVANDARYL in pediatric patients have not been established. AVANDARYL and its components, rosiglitazone and glimepiride, are not indicated for use in pediatric patients.

8.5 Geriatric Use

Rosiglitazone: Results of the population pharmacokinetic analysis showed that age does not significantly affect the pharmacokinetics of rosiglitazone *[see Clinical Pharmacology (12.3)]*. Therefore, no dosage adjustments are required for the elderly. In controlled clinical trials, no overall differences in safety and effectiveness between older (≥65 years) and younger (<65 years) patients were observed.

Glimepiride: In US clinical trials of glimepiride, 608 of 1,986 patients were 65 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Comparison of glimepiride pharmacokinetics in type 2 diabetes patients ≤65 years (N = 49) and those >65 years (N = 42) was performed in a trial using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the 2 age groups *[see Clinical Pharmacology (12.3)]*.

The drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly

patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs. In elderly, debilitated, or malnourished patients, or in patients with renal, hepatic or adrenal insufficiency, the starting dose, dose increments, and maintenance dosage should be conservative based upon blood glucose levels prior to and after initiation of treatment to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents *[see Dosage and Administration (2.4), Warnings and Precautions (5.5), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

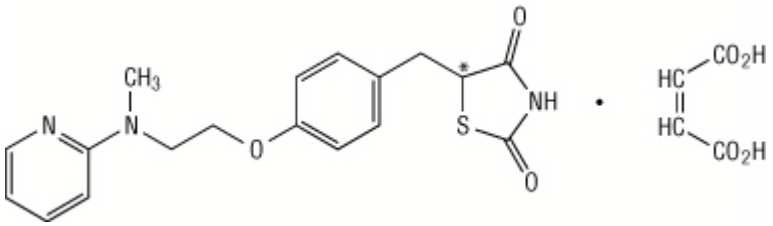
Rosiglitazone: Limited data are available with regard to overdosage in humans. In clinical trials in volunteers, rosiglitazone has been administered at single oral doses of up to 20 mg and was well tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

Glimepiride: Overdosage of sulfonylureas, including glimepiride, can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid IV injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

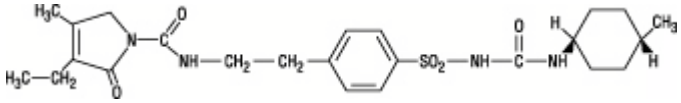
11 DESCRIPTION

AVANDARYL contains 2 oral antidiabetic drugs used in the management of type 2 diabetes: rosiglitazone maleate and glimepiride.

Rosiglitazone maleate is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors. Chemically, rosiglitazone maleate is (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (*Z*)-2-butenedioate (1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the enantiomers are functionally indistinguishable. The molecular formula is $C_{18}H_{19}N_3O_3S \bullet C_4H_4O_4$. Rosiglitazone maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pK_a values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range. The structural formula of rosiglitazone maleate is:



Glimepiride is an oral antidiabetic drug of the sulfonylurea class. Glimepiride is a white to yellowish-white, crystalline, odorless to practically odorless powder. Chemically, glimepiride is 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea with a molecular weight of 490.62. The molecular formula for glimepiride is $C_{24}H_{34}N_4O_5S$. Glimepiride is practically insoluble in water. The structural formula of glimepiride is:



AVANDARYL is available for oral administration as tablets containing rosiglitazone maleate and glimepiride, respectively, in the following strengths (expressed as rosiglitazone maleate/glimepiride): 4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg, 8 mg/2 mg, and 8 mg/4 mg. Each tablet contains the following inactive ingredients: Hypromellose 2910, lactose monohydrate, macrogol (polyethylene glycol), magnesium stearate, microcrystalline cellulose, sodium starch glycolate, titanium dioxide, and 1 or more of the following: Yellow, red, or black iron oxides.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

AVANDARYL combines 2 antidiabetic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: Rosiglitazone maleate, a member of the thiazolidinedione class, and glimepiride, a member of the sulfonylurea class. Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas sulfonylureas act primarily by stimulating release of insulin from functioning pancreatic beta cells.

Rosiglitazone: Rosiglitazone improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPARγ-responsive genes also participate in the regulation of fatty acid metabolism.

Insulin resistance is a common feature characterizing the pathogenesis of type 2 diabetes. The antidiabetic activity of rosiglitazone has been demonstrated in animal models of type 2 diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. Rosiglitazone reduces blood glucose concentrations and reduces hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse, and fa/fa fatty Zucker rat.

In animal models, the antidiabetic activity of rosiglitazone was shown to be mediated by increased sensitivity to insulin's action in the liver, muscle, and adipose tissues. Pharmacologic studies in animal models indicate that rosiglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. The expression of the insulin-regulated glucose transporter GLUT-4 was increased in adipose tissue. Rosiglitazone did not induce hypoglycemia in animal models of type 2 diabetes and/or impaired glucose tolerance.

Glimepiride: The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of sulfonylureas such as glimepiride. This is supported by both preclinical and clinical trials demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These findings are consistent with the results of a long-term, randomized, placebo-controlled trial in which glimepiride therapy improved postprandial insulin/C-peptide responses and overall glycemic control without producing clinically meaningful increases in fasting insulin/C-peptide levels. However, as with other sulfonylureas, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established.

12.2 Pharmacodynamics

The lipid profiles of rosiglitazone and glimepiride in a clinical trial of patients with inadequate glycemic control on diet and exercise were consistent with the known profile of each monotherapy. AVANDARYL was associated with increases in HDL and LDL (3% to 4% for each) and decreases in triglycerides (-4%), that were not considered to be clinically meaningful.

The pattern of LDL and HDL changes following therapy with rosiglitazone in patients previously treated with a sulfonylurea was generally similar to those seen with rosiglitazone in monotherapy. Rosiglitazone as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids. The changes in triglycerides during therapy with rosiglitazone were variable and were generally not statistically different from placebo or glyburide controls.

12.3 Pharmacokinetics

In a bioequivalence trial of AVANDARYL 4 mg/4 mg, the area under the curve (AUC) and maximum concentration (C_{max}) of rosiglitazone following a single dose of the combination tablet were bioequivalent to rosiglitazone 4 mg concomitantly administered with glimepiride 4 mg under fasted conditions. The AUC of glimepiride following a single fasted 4 mg/4 mg dose was equivalent to glimepiride concomitantly administered with rosiglitazone, while the C_{max} was 13% lower when administered as the combination tablet (see Table 7).

Table 7. Pharmacokinetic Parameters for Rosiglitazone and Glimepiride (N = 28)

	Rosiglitazone		Glimepiride	
Parameter (Units)	**Regimen A**	**Regimen B**	**Regimen A**	**Regimen B**
$AUC_{0\text{-}inf}$ (ng.hr/mL)	1,259 (833-2,060)	1,253 (756-2,758)	1,052 (643-2,117)	1,101 (648-2,555)
$AUC_{0\text{-}t}$ (ng.hr/mL)	1,231 (810-2,019)	1,224 (744-2,654)	944 (511-1,898)	1,038 (606-2,337)
C_{max} (ng/mL)	257 (157-352)	251 (77.3-434)	151 (63.2-345)	173 (70.5-329)
$T_{½}$ (hr)	3.53 (2.60-4.57)	3.54 (2.10-5.03)	7.63 (4.42-12.4)	5.08 (1.80-11.31)
T_{max} (hr)	1.00 (0.48-3.02)	0.98 (0.48-5.97)	3.02 (1.50-8.00)	2.53 (1.00-8.03)

AUC = area under the curve; C_{max} = maximum concentration; $T_{½}$ = terminal half-life; T_{max} = time of maximum concentration.

Regimen A = AVANDARYL 4 mg/4 mg tablet; Regimen B = Concomitant dosing of a rosiglitazone 4 mg tablet AND a glimepiride 4 mg tablet.

Data presented as geometric mean (range), except $T_{½}$ which is presented as arithmetic mean (range) and T_{max}, which is presented as median (range).

The rate and extent of absorption of both the rosiglitazone component and glimepiride component of AVANDARYL when taken with food were equivalent to the rate and extent of absorption of rosiglitazone and glimepiride when administered concomitantly as separate tablets with food.

Absorption: The AUC and C_{max} of glimepiride increased in a dose-proportional manner following administration of AVANDARYL 4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg. Administration of AVANDARYL in the fed state resulted in no change in the overall exposure of rosiglitazone; however, the C_{max} of rosiglitazone decreased by 32% compared to the fasted state. There was an increase in both AUC (19%) and C_{max} (55%) of glimepiride in the fed state compared to the fasted state.

Rosiglitazone: The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing. The C_{max} and AUC of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range.

Glimepiride: After oral administration, glimepiride is completely (100%) absorbed from the gastrointestinal tract. Trials with single oral doses in normal subjects and with multiple oral doses in patients with type 2 diabetes have shown significant absorption of glimepiride within 1 hour after administration and C_{max} at 2 to 3 hours.

Distribution: *Rosiglitazone:* The mean (CV%) oral volume of distribution (V_{ss}/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

Glimepiride: After intravenous (IV) dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metabolism and Excretion: *Rosiglitazone:* Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone. In vitro data demonstrate that rosiglitazone is predominantly metabolized by cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway. Following oral or IV administration of [^{14}C]rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [^{14}C]related material ranged from 103 to 158 hours. The elimination half-life is 3 to 4 hours and is independent of dose.

Glimepiride: Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about ⅓ of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1 is clinically meaningful is not clear.

When [^{14}C]glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80 to 90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent drug was recovered from urine or feces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.

Special Populations: No pharmacokinetic data are available for AVANDARYL in the following special populations. Information is provided for the individual components of AVANDARYL.

Gender: Rosiglitazone: Results of the population pharmacokinetics analysis showed that the mean oral clearance of rosiglitazone in female patients (N = 405) was approximately 6% lower compared to male patients of the same body weight (N = 642). Combination therapy with rosiglitazone and sulfonylureas improved glycemic control in both males and females with a greater therapeutic response observed in females. For a given body mass index (BMI), females tend to have a greater fat mass than males. Since the molecular target of rosiglitazone, PPARγ, is expressed in adipose tissues, this differentiating characteristic may account, at least in part, for

the greater response to rosiglitazone in combination with sulfonylureas in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.

Glimepiride: There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight.

Geriatric: Rosiglitazone: Results of the population pharmacokinetics analysis (N = 716 <65 years; N = 331 ≥65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone.

Glimepiride: Comparison of glimepiride pharmacokinetics in type 2 diabetes patients 65 years and younger with those older than 65 years was performed in a trial using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the 2 age groups. The mean AUC at steady state for the older patients was about 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was about 11% higher than that for the younger patients. *[See Use in Specific Populations (8.5).]*

Hepatic Impairment: Therapy with AVANDARYL should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal) at baseline *[see Warnings and Precautions (5.8)]*.

Rosiglitazone: Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound C_{max} and $AUC_{0\text{-}inf}$ were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects.

Glimepiride: No trials of glimepiride have been conducted in patients with hepatic insufficiency.

Race: Rosiglitazone: Results of a population pharmacokinetic analysis including subjects of white, black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of rosiglitazone.

Glimepiride: No pharmacokinetic trials to assess the effects of race have been performed, but in placebo-controlled trials of glimepiride in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (N = 536), blacks (N = 63), and Hispanics (N = 63).

Renal Impairment: Rosiglitazone: There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients compared to subjects with normal renal function.

Glimepiride: A single-dose glimepiride, open-label trial was conducted in 15 patients with renal impairment. Glimepiride (3 mg) was administered to 3 groups of patients with different levels of mean creatinine clearance (CL_{cr}); (Group I, CL_{cr} = 77.7 mL/min, N = 5), (Group II, CL_{cr} = 27.7 mL/min, N = 3), and (Group III, CL_{cr} = 9.4 mL/min, N = 7). Glimepiride was found to be well tolerated in all 3 groups. The results showed that glimepiride serum levels decreased as renal function decreased. However, M1 and M2 serum levels (mean AUC values)

increased 2.3 and 8.6 times from Group I to Group III. The apparent terminal half-life ($T_{½}$) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased (44.4%, 21.9%, and 9.3% for Groups I to III). A multiple-dose titration trial was also conducted in 16 type 2 diabetes patients with renal impairment using doses ranging from 1 to 8 mg daily for 3 months. The results were consistent with those observed after single doses. All patients with a CL_{cr} less than 22 mL/min had adequate control of their glucose levels with a dosage regimen of only 1 mg daily. The results from this trial suggest that a starting dose of 1 mg glimepiride, as contained in AVANDARYL 4 mg/1 mg, may be given to type 2 diabetes patients with kidney disease, and the dose may be titrated based on fasting glucose levels.

Pediatric: No pharmacokinetic data from trials in pediatric subjects are available for AVANDARYL.

Rosiglitazone: Pharmacokinetic parameters of rosiglitazone in pediatric patients were established using a population pharmacokinetic analysis with sparse data from 96 pediatric patients in a single pediatric clinical trial including 33 males and 63 females with ages ranging from 10 to 17 years (weights ranging from 35 to 178.3 kg). Population mean CL/F and V/F of rosiglitazone were 3.15 L/hr and 13.5 L, respectively. These estimates of CL/F and V/F were consistent with the typical parameter estimates from a prior adult population analysis.

Glimepiride: The pharmacokinetics of glimepiride (1 mg) were evaluated in a single-dose trial conducted in 30 type 2 diabetic patients (male = 7; female = 23) between ages 10 and 17 years. The mean $AUC_{0\text{-last}}$ (338.8 ± 203.1 ng.hr/mL), C_{max} (102.4 ± 47.7 ng/mL), and $T_{½}$ (3.1 ± 1.7 hours) were comparable to those previously reported in adults ($AUC_{0\text{-last}}$ 315.2 ± 95.9 ng.hr/mL, C_{max} 103.2 ± 34.3 ng/mL, and $T_{½}$ 5.3 ± 4.1 hours).

12.4 Drug-Drug Interactions

Single oral doses of glimepiride in 14 healthy adult subjects had no clinically significant effect on the steady-state pharmacokinetics of rosiglitazone. No clinically significant reductions in glimepiride AUC and C_{max} were observed after repeat doses of rosiglitazone (8 mg once daily) for 8 days in healthy adult subjects.

Rosiglitazone: *Drugs That Inhibit, Induce or are Metabolized by Cytochrome P450:* In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. In vitro data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9. *[See Drug Interactions (7.1).]*

Rosiglitazone (4 mg twice daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinyl estradiol and norethindrone), which are predominantly metabolized by CYP3A4.

Gemfibrozil: Concomitant administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone AUC by 127%, compared to the administration of rosiglitazone (4 mg once daily) alone. Given

the potential for dose-related adverse events with rosiglitazone, a decrease in the dose of rosiglitazone may be needed when gemfibrozil is introduced *[see Drug Interactions (7.1)]*.

Rifampin: Rifampin administration (600 mg once a day), an inducer of CYP2C8, for 6 days is reported to decrease rosiglitazone AUC by 66%, compared to the administration of rosiglitazone (8 mg) alone *[see Drug Interactions (7.1)]*.[11]

Glyburide: Rosiglitazone (2 mg twice daily) taken concomitantly with glyburide (3.75 to 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy. Repeat doses of rosiglitazone (8 mg once daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and C_{max} of approximately 30%. In Japanese subjects, glyburide AUC and C_{max} slightly increased following coadministration of rosiglitazone.

Digoxin: Repeat oral dosing of rosiglitazone (8 mg once daily) for 14 days did not alter the steady-state pharmacokinetics of digoxin (0.375 mg once daily) in healthy volunteers.

Warfarin: Repeat dosing with rosiglitazone had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers.

Additional pharmacokinetic trials demonstrated no clinically relevant effect of acarbose, ranitidine, or metformin on the pharmacokinetics of rosiglitazone.

Glimepiride: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs) and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. When these drugs are administered to a patient receiving glimepiride, the patient should be observed closely for hypoglycemia. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid. When these drugs are administered to a patient receiving glimepiride, the patient should be closely observed for loss of control. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for hypoglycemia.

Drugs Metabolized by Cytochrome P450: A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is not known. There is a potential interaction of glimepiride with inhibitors (e.g., fluconazole) and inducers (e.g., rifampicin) of cytochrome P450 2C9.

Aspirin: Coadministration of aspirin (1 g three times daily) and glimepiride led to a 34% decrease in the mean glimepiride AUC and, therefore, a 34% increase in the mean CL/F. The mean C_{max} had a decrease of 4%. Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported.

H_2-Receptor Antagonists: Coadministration of either cimetidine (800 mg once daily) or ranitidine (150 mg twice daily) with a single 4-mg oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride, and no differences were seen in hypoglycemic symptomatology.

Beta-Blockers: Concomitant administration of propranolol (40 mg three times daily) and glimepiride significantly increased C_{max}, AUC, and $T_{½}$ of glimepiride by 23%, 22%, and 15%, respectively, and it decreased CL/F by 18%. The recovery of M1 and M2 from urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo. Pooled data from clinical trials in patients with type 2 diabetes showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of beta-blockers. However, if beta-blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

Warfarin: Concomitant administration of glimepiride tablets (4 mg once daily) did not alter the pharmacokinetic characteristics of R- and S-warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding. Glimepiride treatment did result in a slight, but statistically significant, decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride treatment were very small (3.3% and 9.9%, respectively) and are unlikely to be clinically important.

ACE Inhibitors: The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2 mg glimepiride were unaffected by coadministration of ramipril (an ACE inhibitor) 5 mg once daily in normal subjects. No hypoglycemic symptoms were reported.

Other: Although no specific interaction trials were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of aspirin and other salicylates, H_2-receptor antagonists, ACE inhibitors, calcium-channel blockers, estrogens, fibrates, NSAIDs, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted with AVANDARYL. The following data are based on findings in studies performed with rosiglitazone or glimepiride alone.

Rosiglitazone: *Carcinogenesis:* A 2-year carcinogenicity study was conducted in Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately 12 times human AUC at the maximum recommended human daily dose). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05 mg/kg/day, 0.3 mg/kg/day, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times human AUC at the maximum recommended human daily dose for male and female rats, respectively).

Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses ≥1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses ≥0.3 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic activation.

Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose). In juvenile rats dosed from 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in females (approximately 68 times human AUC at the maximum recommended daily dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

Glimepiride: *Carcinogenesis:* Studies in rats at doses of up to 5,000 parts per million (ppm) in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation which was dose-related and is thought to be the result of chronic pancreatic stimulation. The no-effect dose for adenoma formation in mice in this study was 320 ppm in complete feed, or 46 to 54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose based on surface area.

Mutagenesis: Glimepiride was non-mutagenic in a battery of in vitro and in vivo mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, mouse micronucleus test).

Impairment of Fertility: There was no effect of glimepiride on male mouse fertility in animals exposed up to 2,500 mg/kg body weight (>1,700 times the maximum recommended

human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4,000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

13.2 Animal Toxicology and/or Pharmacology

Rosiglitazone: Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose, respectively). Effects in juvenile rats were consistent with those seen in adults. Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

Glimepiride: Reduced serum glucose values and degranulation of the pancreatic beta cells were observed in beagle dogs exposed to glimepiride 320 mg/kg/day for 12 months (approximately 1,000 times the recommended human dose based on surface area). No evidence of tumor formation was observed in any organ. One female and one male dog developed bilateral subcapsular cataracts. Non-GLP studies indicated that glimepiride was unlikely to exacerbate cataract formation. Evaluation of the co-cataractogenic potential of glimepiride in several diabetic and cataract rat models was negative and there was no adverse effect of glimepiride on bovine ocular lens metabolism in organ culture *[see Adverse Reactions (6.1)]*.

14 CLINICAL STUDIES

The safety and efficacy of rosiglitazone added to a sulfonylurea have been studied in clinical trials in patients with type 2 diabetes inadequately controlled on sulfonylureas alone. No clinical trials have been conducted with the fixed-dose combination of AVANDARYL in patients inadequately controlled on a sulfonylurea or who have initially responded to rosiglitazone alone and require additional glycemic control.

A total of 3,457 patients with type 2 diabetes participated in ten 24- to 26-week randomized, double-blind, placebo/active-controlled trials and one 2-year double-blind, active-controlled trial in elderly patients designed to assess the efficacy and safety of rosiglitazone in combination with a sulfonylurea. Rosiglitazone 2 mg, 4 mg, or 8 mg daily, was administered either once daily (3 trials) or in divided doses twice daily (7 trials), to patients inadequately controlled on a submaximal or maximal dose of sulfonylurea.

In these trials, the combination of rosiglitazone 4 mg or 8 mg daily (administered as single or twice daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c compared to placebo plus sulfonylurea or further up-titration of the sulfonylurea. Table 8 shows pooled data for 8 trials in which rosiglitazone added to sulfonylurea was compared to placebo plus sulfonylurea.

Table 8. Glycemic Parameters in 24- to 26-Week Combination Trials of Rosiglitazone Plus Sulfonylurea

Twice Daily Divided Dosing (5 Trials)	**Sulfonylurea**	**Rosiglitazone 2 mg twice daily + sulfonylurea**	**Sulfonylurea**	**Rosiglitazone 4 mg twice daily + sulfonylurea**
N	397	497	248	346
FPG (mg/dL)				
Baseline (mean)	204	198	188	187
Change from baseline (mean)	11	-29	8	-43
Difference from sulfonylurea alone (adjusted mean)	—	-42[a]	—	-53[a]
% of patients with ≥30 mg/dL decrease from baseline	17%	49%	15%	61%
HbA1c (%)				
Baseline (mean)	9.4	9.5	9.3	9.6
Change from baseline (mean)	0.2	-1.0	0.0	-1.6
Difference from sulfonylurea alone (adjusted mean)	—	-1.1[a]	—	-1.4[a]
% of patients with ≥0.7% decrease from baseline	21%	60%	23%	75%
Once Daily Dosing (3 Trials)	**Sulfonylurea**	**Rosiglitazone 4 mg once daily + sulfonylurea**	**Sulfonylurea**	**Rosiglitazone 8 mg once daily + sulfonylurea**
N	172	172	173	176
FPG (mg/dL)				
Baseline (mean)	198	206	188	192
Change from baseline (mean)	17	-25	17	-43
Difference from sulfonylurea alone (adjusted mean)	—	-47[a]	—	-66[a]
% of patients with ≥30 mg/dL decrease from baseline	17%	48%	19%	55%
HbA1c (%)				
Baseline (mean)	8.6	8.8	8.9	8.9
Change from baseline	0.4	-0.5	0.1	-1.2

(mean)				
Difference from sulfonylurea alone (adjusted mean)	-	-0.9[a]	-	-1.4[a]
% of patients with ≥0.7% decrease from baseline	11%	36%	20%	68%

[a] *P* <0.0001 compared to sulfonylurea alone.

One of the 24- to 26-week trials included patients who were inadequately controlled on maximal doses of glyburide and switched to 4 mg of rosiglitazone daily as monotherapy; in this group, loss of glycemic control was demonstrated, as evidenced by increases in FPG and HbA1c.

In a 2-year double-blind trial, elderly patients (aged 59 to 89 years) on half-maximal sulfonylurea (glipizide 10 mg twice daily) were randomized to the addition of rosiglitazone (N = 115, 4 mg once daily to 8 mg as needed) or to continued up-titration of glipizide (N = 110), to a maximum of 20 mg twice daily. Mean baseline FPG and HbA1c were 157 mg/dL and 7.72%, respectively, for the rosiglitazone plus glipizide arm and 159 mg/dL and 7.65%, respectively, for the glipizide up-titration arm. Loss of glycemic control (FPG ≥180 mg/dL) occurred in a significantly lower proportion of patients (2%) on rosiglitazone plus glipizide compared to patients in the glipizide up-titration arm (28.7%). About 78% of the patients on combination therapy completed the 2 years of therapy while only 51% completed on glipizide monotherapy. The effect of combination therapy on FPG and HbA1c was durable over the 2-year trial period, with patients achieving a mean of 132 mg/dL for FPG and a mean of 6.98% for HbA1c compared to no change on the glipizide arm.

15 REFERENCES

1. Food and Drug Administration Briefing Document. Joint meeting of the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees. July 13-14, 2010.
2. Winkelmayer WC, et al. Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy. *Arch Intern Med* 2008;168(21):2368-2375.
3. Juurlink DN, et al. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. *BMJ* 2009; 339.
4. Graham DJ, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly medicare patients treated with rosiglitazone or pioglitazone. *JAMA* 2010;304:411-418.
5. Wertz DA, et al. Risk of cardiovascular events and all-cause mortality in patients with Thiazolidinediones in a managed-care population. *Circ Cardiovasc Qual Outcomes* 2010;3: 538-545.

6. DREAM Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096-1105.
7. Kahn S, et al. Glycemic durability of rosiglitazone, metformin or glyburide monotherapy. *New England Journal of Medicine* 2006, 355:2427-2443.
8. Home P, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicenter, randomized, open-label trial. *Lancet* 2009, 373:2125-35.
9. Dormandy J et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (Prospective Pioglitazone Clinical Trial in Macrovascular Events): a randomized controlled trial. *Lancet* 2005, 366:1279-89.
10. Bilik D, et al. Thiazolidinediones, cardiovascular disease and cardiovascular mortality: translating research into action for diabetes (TRIAD). *Pharmocoepidemiol Drug Saf* 2010; 19: 715–721.
11. Park JY, Kim KA, Kang MH, et al. Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects. *Clin Pharmacol Ther* 2004;75:157-162.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each rounded triangular tablet contains rosiglitazone as the maleate and glimepiride as follows:

4 mg/1 mg – yellow, gsk debossed on one side and 4/1 on the other.
4 mg/2 mg – orange, gsk debossed on one side and 4/2 on the other.
4 mg/4 mg – pink, gsk debossed on one side and 4/4 on the other.
8 mg/2 mg – pale pink, gsk debossed on one side and 8/2 on the other.
8 mg/4 mg – red, gsk debossed on one side and 8/4 on the other.

4 mg/1 mg bottles of 30: NDC 0173-0841-13
4 mg/2 mg bottles of 30: NDC 0173-0842-13
4 mg/4 mg bottles of 30: NDC 0173-0843-13
8 mg/2 mg bottles of 30: NDC 0173-0844-13
8 mg/4 mg bottles of 30: NDC 0173-0845-13

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

See Medication Guide.

17.1 Patient Advice

There are multiple medications available to treat type 2 diabetes. The benefits and risks of each available diabetes medication should be taken into account when choosing a particular diabetes medication for a given patient.

Patient should fully understand the risks and benefits of AVANDARYL. AVANDARYL should only be taken by adults with type 2 diabetes who are already taking rosiglitazone, or who are not already taking rosiglitazone and are unable to achieve adequate glycemic control on other diabetes medications, and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS) or pioglitazone-containing medications (ACTOPLUS MET, ACTOPLUS MET XR, DUETACT) for medical reasons. Inform patients that they must be enrolled in the AVANDIA-Rosiglitazone Medicines Access Program in order to receive AVANDARYL.

Patients should be informed of the following:

- AVANDARYL is not recommended in patients with symptomatic heart failure.
- Results of a set of clinical trials suggest that treatment with AVANDARYL is associated with an increased risk for myocardial infarction (heart attack), especially in patients taking insulin. Clinical trials have not shown any difference between rosiglitazone and comparator medications in overall mortality or CV-related mortality.
- AVANDARYL is not recommended for patients who are taking insulin.
- Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but also in maintaining the efficacy of drug therapy.
- It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin (HbA1c) tested. It can take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of AVANDARYL.
- The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.
- Blood will be drawn to check their liver function prior to the start of therapy and periodically thereafter per the clinical judgment of the healthcare professional. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician.
- Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on AVANDARYL should immediately report these symptoms to their physician.
- AVANDARYL should be taken with the first meal of the day.
- Therapy with rosiglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDARYL. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical trials so the frequency of this occurrence is not known.

AVANDARYL and AVANDIA are registered trademarks of GlaxoSmithKline. ACTOS, ACTOPLUS MET, ACTOPLUS MET XR, and DUETACT are registered trademarks of Takeda Pharmaceutical Company Limited.

GlaxoSmithKline
Research Triangle Park, NC 27709

Month 2011
AVR:XXPI

MEDICATION GUIDE

AVANDARYL® (ah-VAN-duh-ril)

(rosiglitazone maleate and glimepiride) Tablets

Read this Medication Guide carefully before you start taking AVANDARYL and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about AVANDARYL, ask your doctor or pharmacist.

What is the most important information I should know about AVANDARYL?
AVANDARYL may cause serious side effects, including:

AVANDARYL is available only through the AVANDIA-Rosiglitazone Medicines Access Program. Both you and your doctor must be enrolled in the program so that you can get AVANDARYL. To enroll, you must:

- talk to your doctor,
- understand the risks and benefits of AVANDARYL, and
- agree to enroll in the program.

New or worse heart failure

- Rosiglitazone, one of the two drugs that make up AVANDARYL, can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Heart failure means your heart does not pump blood well enough.
- If you have severe heart failure, you cannot start AVANDARYL.
- If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, AVANDARYL may not be right for you.

Call your doctor right away if you have any of the following:

- swelling or fluid retention, especially in the ankles or legs
- shortness of breath or trouble breathing, especially when you lie down
- an unusually fast increase in weight
- unusual tiredness

Myocardial Infarction ("Heart Attack")

Rosiglitazone, one of the medicines in AVANDARYL, may raise the risk of heart attack. The risk of having a heart attack may be higher in people who take

AVANDARYL with insulin. Most people who take insulin should not also take AVANDARYL.

Symptoms of a heart attack can include the following:

- chest discomfort in the center of your chest that lasts for more than a few minutes, or that goes away or comes back
- chest discomfort that feels like uncomfortable pressure, squeezing, fullness or pain
- pain or discomfort in your arms, back, neck, jaw or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded

Call your doctor or go to the nearest hospital emergency room right away if you think you are having a heart attack.

People with diabetes have a greater risk for heart problems. It is important to work with your doctor to manage other conditions, such as high blood pressure or high cholesterol.

AVANDARYL can have other serious side effects. Be sure to read the section "What are possible side effects of AVANDARYL?".

What is AVANDARYL?

AVANDARYL contains 2 prescription medicines to treat diabetes, rosiglitazone maleate (AVANDIA) and glimepiride (AMARYL). AVANDARYL is used with diet and exercise to treat certain adults with type 2 ("adult-onset" or "non-insulin dependent") diabetes mellitus ("high blood sugar") who are:

- already taking rosiglitazone or rosiglitazone-containing products
- unable to control their blood sugar on other diabetes medicines, and after talking with their doctor have decided not to take pioglitazone (ACTOS) or pioglitazone-containing products (ACTOPLUS MET, ACTOPLUS MET XR, DUETACT)

Glimepiride can help your body release more of its own insulin. Rosiglitazone can help your body respond better to the insulin made in your body and does not cause your body to make more insulin. These medicines can work together to help control your blood sugar.

AVANDARYL is not for people with type 1 diabetes mellitus or to treat a condition called diabetic ketoacidosis.

It is not known if AVANDARYL is safe and effective in children under 18 years old.

Who should not take AVANDARYL?

Many people with heart failure should not start taking AVANDARYL (see "What should I tell my doctor before taking AVANDARYL?").

What should I tell my doctor before taking AVANDARYL?

Before starting AVANDARYL, ask your doctor about what the choices are for diabetes medicines and what the expected benefits and possible risks are for you in particular.

Before taking AVANDARYL, tell your doctor about all your medical conditions, including if you:

- **have heart problems or heart failure.**
- **have type 1 ("juvenile") diabetes or had diabetic ketoacidosis.** These conditions should be treated with insulin and should not be treated with AVANDARYL.
- **have a type of diabetic eye disease called macular edema** (swelling of the back of the eye).
- **have liver problems.** Your doctor should do blood tests to check your liver before you start taking AVANDARYL and during treatment as needed.
- **had liver problems while taking REZULIN® (troglitazone), another medicine for diabetes.**
- **have kidney problems.** If people with kidney problems use AVANDARYL, they may need a lower dose of the medication.
- **have glucose 6-phosphate dehydrogenase (G6PD) deficiency.** This condition runs in families. People with G6PD deficiency who take glimepiride (one of the medicines in AVANDARYL) may develop hemolytic anemia (fast breakdown of red blood cells).
- **are pregnant or plan to become pregnant.** AVANDARYL should not be used during pregnancy. It is not known if AVANDARYL can harm your unborn baby. You and your doctor should talk about the best way to control your diabetes during pregnancy. If you are a premenopausal woman (before the "change of life") who does not have regular monthly periods, AVANDARYL may increase your chances of becoming pregnant. Talk to your doctor about birth control choices while taking AVANDARYL. Tell your doctor right away if you become pregnant while taking AVANDARYL.

- **are breast-feeding or planning to breast-feed.** It is not known if AVANDARYL passes into breast milk. You should not use AVANDARYL while breast-feeding.

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins or herbal supplements. AVANDARYL and certain other medicines can affect each other and may lead to serious side effects including high or low blood sugar, or heart problems. Especially tell your doctor if you take:

- **insulin.**
- **any medicines for high blood pressure, high cholesterol or heart failure, or for prevention of heart disease or stroke.**

Know the medicines you take. Keep a list of all your medicines and show it to your doctor and pharmacist before you start a new medicine. They will tell you if it is alright to take AVANDARYL with other medicines.

How should I take AVANDARYL?

- Take AVANDARYL exactly as prescribed. Your doctor may need to change your dose until your blood sugar is better controlled.
- Take AVANDARYL by mouth one time each day with your first main meal.
- It usually takes a few days for AVANDARYL to start lowering your blood sugar. It may take 2 to 3 months to see the full effect on your blood sugar level.
- If you miss a dose of AVANDARYL, take it as soon as you remember unless it is time to take your next dose. Take your next dose at the usual time. Do not take double doses to make up for a missed dose.
- If you take too much AVANDARYL, call your doctor or poison control center right away.
- Test your blood sugar regularly as your doctor tells you.
- Your doctor should do blood tests to check your liver before you start AVANDARYL and during treatment as needed. Your doctor should also do regular blood sugar tests (for example, “A1c”) to monitor your response to AVANDARYL.
- Call your doctor if you get sick, get injured, get an infection, or have surgery. AVANDARYL may not control your blood sugar levels during these times. Your doctor may need to stop AVANDARYL for a short time and give you insulin to control your blood sugar level.
- Diet and exercise can help your body use its blood sugar better. It is important to stay on your recommended diet, lose extra weight, and get regular exercise while taking AVANDARYL.

What are possible side effects of AVANDARYL?

AVANDARYL may cause serious side effects, including:

- **New or worse heart failure.** See "What is the most important information I should know about AVANDARYL?".
- **Heart attack.** See "What is the most important information I should know about AVANDARYL?".
- **Swelling (edema).** AVANDARYL can cause swelling due to fluid retention. See "What is the most important information I should know about AVANDARYL?".
- **Low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness or hunger may mean that your blood sugar is too low. This can happen if you skip meals, drink alcohol, use another medicine that lowers blood sugar, exercise (particularly hard or long), or if you have certain medical problems. Call your doctor if low blood sugar levels are a problem for you.
- **Weight gain.** Rosiglitazone, one of the medicines in AVANDARYL, can cause weight gain that may be due to fluid retention or extra body fat. Weight gain can be a serious problem for people with certain conditions including heart problems. See "What is the most important information I should know about AVANDARYL?".
- **Liver problems.** It is important for your liver to be working normally when you take AVANDARYL. Your doctor should do blood tests to check your liver before you start taking AVANDARYL and during treatment as needed. Call your doctor right away if you have unexplained symptoms such as:
  - nausea or vomiting
  - stomach pain
  - unusual or unexplained tiredness
  - loss of appetite
  - dark urine
  - yellowing of your skin or the whites of your eyes.
- **Macular edema** (a diabetic eye disease with swelling in the back of the eye). Tell your doctor right away if you have any changes in your vision. Your doctor should check your eyes regularly. Very rarely, some people have had vision changes due to swelling in the back of the eye while taking rosiglitazone, one of the medicines in AVANDARYL.
- **Fractures (broken bones),** usually in the hand, upper arm or foot. Talk to your doctor for advice on how to keep your bones healthy.
- **Low red blood cell count (anemia).**
- **Ovulation** (release of egg from an ovary in women) leading to pregnancy**.** Ovulation may happen in premenopausal women who do not have regular monthly periods. This can increase the chance of pregnancy. See "What should I tell my doctor before taking AVANDARYL?".

The most common side effects with AVANDARYL include cold-like symptoms and headache.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AVANDARYL?

- Store AVANDARYL at room temperature, 59° to 86° F (15° to 30° C). Keep AVANDARYL in the container it comes in. Keep the container closed tightly.
- Safely, throw away AVANDARYL that is out of date or no longer needed.

Keep AVANDARYL and all medicines out of the reach of children.

General information about AVANDARYL

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AVANDARYL for a condition for which it was not prescribed. Do not give AVANDARYL to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes important information about AVANDARYL. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about AVANDARYL that is written for healthcare professionals. You can also find out more about AVANDARYL by calling 1-888-825-5249.

What are the ingredients in AVANDARYL?

Active Ingredients: Rosiglitazone maleate and glimepiride.
Inactive Ingredients: Hypromellose 2910, lactose monohydrate, macrogol (polyethylene glycol), magnesium stearate, microcrystalline cellulose, sodium starch glycolate, titanium dioxide, triacetin, and 1 or more of the following: Yellow, red, or black iron oxides.

Always check to make sure that the medicine you are taking is the correct one. AVANDARYL tablets are triangles with rounded corners and look like this:

4 mg/1 mg – yellow with “gsk” on one side and “4/1” on the other.
4 mg/2 mg – orange with “gsk” on one side and “4/2” on the other.
4 mg/4 mg – pink with “gsk” on one side and “4/4” on the other.
8 mg/2 mg – pale pink with “gsk” on one side and “8/2” on the other.
8 mg/4 mg – red with “gsk” on one side and “8/4” on the other.

AVANDARYL and AVANDIA are registered trademarks of GlaxoSmithKline.
The other brands listed are trademarks of their respective owners and are not trademarks of GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse GlaxoSmithKline or its products.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

GlaxoSmithKline
Research Triangle Park, NC 27709

Month 2011
AVR:XMG

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

/s/

AMY G EGAN
05/30/2012