

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 REMS with ETASU (May 18, 2011)]. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. GlaxoSmithKline will submit each assessment so that it will be received by the FDA on or before the due date.

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

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

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: 1-888-772-9404

Reference ID: 3137934

www.AVANDIA.com

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

*Email (If Office Contact is provided): _____



Phone: 1-800-AVANDIA

Fax: 1-888-772-9404

www.AVANDIA.com



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.



Phone: 1-800-AVANDIA

Fax: 1-888-772-9404

www.AVANDIA.com



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: _____



This document is part of an FDA-approved REMS

Phone: 1-800-AVANDIA

Fax: 1-888-772-9404

www.AVANDIA.com



Patient Enrollment Form (Please Print) *indicates required fields

PATIENT	Patient Information		
	*First Name: _____	MI: _____	*Last Name: _____
	*Date of Birth (MM/DD/YY): _____	*Gender: <input type="checkbox"/> Female <input type="checkbox"/> Male	
	*Address 1: _____		
	Address 2: _____		
	*City: _____	*State: _____	*ZIP Code: _____
	*Phone: _____		Alternate Phone: _____
Email: _____			
*Do you have insurance: YES <input type="checkbox"/> NO <input type="checkbox"/>			
*Is the patient: <input type="checkbox"/> new to rosiglitazone therapy <input type="checkbox"/> continuing rosiglitazone therapy			
*Is the patient: <input type="checkbox"/> Outpatient <input type="checkbox"/> Long-term Care <input type="checkbox"/> 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:	<input type="checkbox"/> AVANDIA _____	Strength (mg) _____ Quantity _____
		<input type="checkbox"/> AVANDAMET _____	Strength (mg) _____ Quantity _____
		<input type="checkbox"/> 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.



This document is part of an FDA-approved REMS.

Phone: 1-800-AVANDIA

Fax: 1-888-772-9404

www.AVANDIA.com



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: _____



This document is part of an FDA-approved REMS.

Phone: 1-800-AVANDIA

Fax: 1-888-772-9404

www.AVANDIA.com



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: <input type="checkbox"/> Female <input type="checkbox"/> Male	
	*Address 1: _____		
	Address 2: _____		
	*City: _____	*State: _____	*ZIP Code: _____
*Phone: _____ Alternate Phone: _____			
Email: _____			
*Is the patient: <input type="checkbox"/> new to rosiglitazone therapy <input type="checkbox"/> continuing rosiglitazone therapy			
*Is the patient: <input type="checkbox"/> Outpatient <input type="checkbox"/> Long-term Care <input type="checkbox"/> 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:	<input type="checkbox"/> AVANDIA _____	Strength (mg) _____ Quantity _____
		<input type="checkbox"/> AVANDAMET _____	Strength (mg) _____ Quantity _____
		<input type="checkbox"/> AVANDARYL _____	Strength (mg) _____ Quantity _____
	Provide Dosing Instructions: _____		
	Number of refills: _____		
SHIPPING	Shipping Information		
	*Ship to: <input type="checkbox"/> Patient Home (address listed above) <input type="checkbox"/> 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.



This document is part of an FDA-approved REMS.

Fax: 1-888-772-9404

Phone: 1-800-AVANDIA

www.AVANDIA.com

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.

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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.

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.

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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



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Avandia-Rosiglitazone Medicines Access Program Prescriber Overview

Avandia-Rosiglitazone Medicines
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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

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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.

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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.

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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



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Complete Prescribing Information, including Boxed WARNING and Medication Guide, for [AVANDIA](#), [AVANDAMET](#), and [AVANDARYL](#).

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Avandia-Rosiglitazone Medicines Access Program

How Do I Enroll a Patient?

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Access Program™

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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 Veterans Administration (VA)
Patient Enrollment Form

Complete Patient Enrollment Online

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Avandia-Rosiglitazone Medicines Access Program

How Do I Enroll a Patient?

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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.
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Download Patient Enrollment Form

Download Veteran's Administration (VA)
Patient Enrollment Form

English Veteran's Administration

Spanish Veteran's Administration

Complete Patient Enrollment Online

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Avandia-Rosiglitazone Medicines Access Program Information for Patients

Avandia-Rosiglitazone Medicines
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Avandia-Rosiglitazone Medicines Access Program Information for Patients



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Avandia-Rosiglitazone Medicines Access Program Pharmacist Overview

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

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**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.**

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Complete Prescribing Information, including Boxed WARNING and Medication Guide, for [AVANDIA](#), [AVANDAMET](#), and [AVANDARYL](#).

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Avandia-Rosiglitazone Medicines Access Program Coordinating Center

Avandia-Rosiglitazone Medicines
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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

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Complete Prescribing Information, including Boxed WARNING and Medication Guide, for [AVANDIA](#), [AVANDAMET](#), and [AVANDARYL](#).

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Welcome to the Avandia-Rosiglitazone Medicines Access Program

Avandia-Rosiglitazone Medicines
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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](#).

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Complete Prescribing Information, including Boxed WARNING and Medication Guide, for [AVANDIA](#), [AVANDAMET](#), and [AVANDARYL](#).

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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

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1 FULL PRESCRIBING INFORMATION

2 **WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION**

- 3 • Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in
4 some patients [*see Warnings and Precautions (5.1)*]. After initiation of AVANDIA, and after
5 dose increases, observe patients carefully for signs and symptoms of heart failure (including
6 excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop,
7 the heart failure should be managed according to current standards of care. Furthermore,
8 discontinuation or dose reduction of AVANDIA must be considered.
- 9 • AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of
10 AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated.
11 [*See Contraindications (4) and Warnings and Precautions (5.1)*.]
- 12 • A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of
13 which compared AVANDIA to placebo, showed AVANDIA to be associated with a
14 statistically significant increased risk of myocardial infarction. Three other trials (mean
15 duration 46 months; 14,067 total patients), comparing AVANDIA to some other approved
16 oral antidiabetic agents or placebo, showed a statistically non-significant increased risk of
17 myocardial infarction, and a statistically non-significant decreased risk of death. There have
18 been no clinical trials directly comparing cardiovascular risk of AVANDIA and ACTOS[®]
19 (pioglitazone, another thiazolidinedione), but in a separate trial, pioglitazone (when compared
20 to placebo) did not show an increased risk of myocardial infarction or death. [*See Warnings
21 and Precautions (5.2)*.]
- 22 • Because of the potential increased risk of myocardial infarction, AVANDIA is available only
23 through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines
24 Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1-
25 800-AVANDIA or visit www.AVANDIA.com. [*See Warnings and Precautions (5.3)*.]

26 **1 INDICATIONS AND USAGE**

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

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

34 **Other Important Limitations of Use:**

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

37 for the treatment of diabetic ketoacidosis.
38 • The coadministration of AVANDIA and insulin is not recommended [see Warnings and
39 Precautions (5.1)].

40 **2 DOSAGE AND ADMINISTRATION**

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

44 AVANDIA may be administered at a starting dose of 4 mg either as a single daily dose or
45 in 2 divided doses. For patients who respond inadequately following 8 to 12 weeks of treatment,
46 as determined by reduction in fasting plasma glucose (FPG), the dose may be increased to 8 mg
47 daily. Increases in the dose of AVANDIA should be accompanied by careful monitoring for
48 adverse events related to fluid retention [see *Boxed Warning and Warnings and Precautions*
49 (5.1)]. AVANDIA may be taken with or without food.

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

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

53 **2.1 Specific Patient Populations**

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

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

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

66 **3 DOSAGE FORMS AND STRENGTHS**

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

- 68 • 2 mg - pink, debossed with SB on one side and 2 on the other
- 69 • 4 mg - orange, debossed with SB on one side and 4 on the other
- 70 • 8 mg - red-brown, debossed with SB on one side and 8 on the other

71 **4 CONTRAINDICATIONS**

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

74 **5 WARNINGS AND PRECAUTIONS**

75 **5.1 Cardiac Failure**

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

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

91

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

Events	AVANDIA	Placebo
	N = 110	N = 114
	n (%)	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%)

95 ^a Includes hospitalization for any cardiovascular reason.
 96

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

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

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

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

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

112 and which were included in a meta-analysis¹ [see *Warnings and Precautions (5.2)*], patients with
 113 type 2 diabetes mellitus were randomized to coadministration of AVANDIA and insulin
 114 (N = 1,018) or insulin (N = 815). In these 7 trials, AVANDIA was added to insulin. These trials
 115 included patients with long-standing diabetes (median duration of 12 years) and a high
 116 prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy,
 117 ischemic heart disease, vascular disease, and congestive heart failure. The total number of
 118 patients with emergent congestive heart failure was 23 (2.3%) and 8 (1.0%) in the AVANDIA
 119 plus insulin and insulin groups, respectively.

120 Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing
 121 AVANDIA to ACTOS: Three observational studies²⁻⁴ in elderly diabetic patients (age 65 years
 122 and older) found that AVANDIA statistically significantly increased the risk of hospitalized
 123 heart failure compared to use of ACTOS. One other observational study⁵ in patients with a mean
 124 age of 54 years, which also included an analysis in a subpopulation of patients >65 years of age,
 125 found no statistically significant increase in emergency department visits or hospitalization for
 126 heart failure in patients treated with AVANDIA compared to ACTOS in the older subgroup.

127 **5.2 Major Adverse Cardiovascular Events**

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

130 Meta-Analysis of Major Adverse Cardiovascular Events in a Group of 52 Clinical
 131 Trials: A meta-analysis was conducted retrospectively to assess cardiovascular adverse events
 132 reported across 52 double-blind, randomized, controlled clinical trials (mean duration 6
 133 months).¹ These trials had been conducted to assess glucose-lowering efficacy in type 2 diabetes.
 134 Prospectively planned adjudication of cardiovascular events did not occur in most of the trials.
 135 Some trials were placebo-controlled and some used active oral antidiabetic drugs as controls.
 136 Placebo-controlled trials included monotherapy trials (monotherapy with AVANDIA versus
 137 placebo monotherapy) and add-on trials (AVANDIA or placebo, added to sulfonylurea,
 138 metformin, or insulin). Active control trials included monotherapy trials (monotherapy with
 139 AVANDIA versus sulfonylurea or metformin monotherapy) and add-on trials (AVANDIA plus
 140 sulfonylurea or AVANDIA plus metformin, versus sulfonylurea plus metformin). A total of
 141 16,995 patients were included (10,039 in treatment groups containing AVANDIA, 6,956 in
 142 comparator groups), with 5,167 patient-years of exposure to AVANDIA and 3,637 patient-years
 143 of exposure to comparator. Cardiovascular events occurred more frequently for patients who
 144 received AVANDIA than for patients who received comparators (see Table 2).
 145

146 **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)

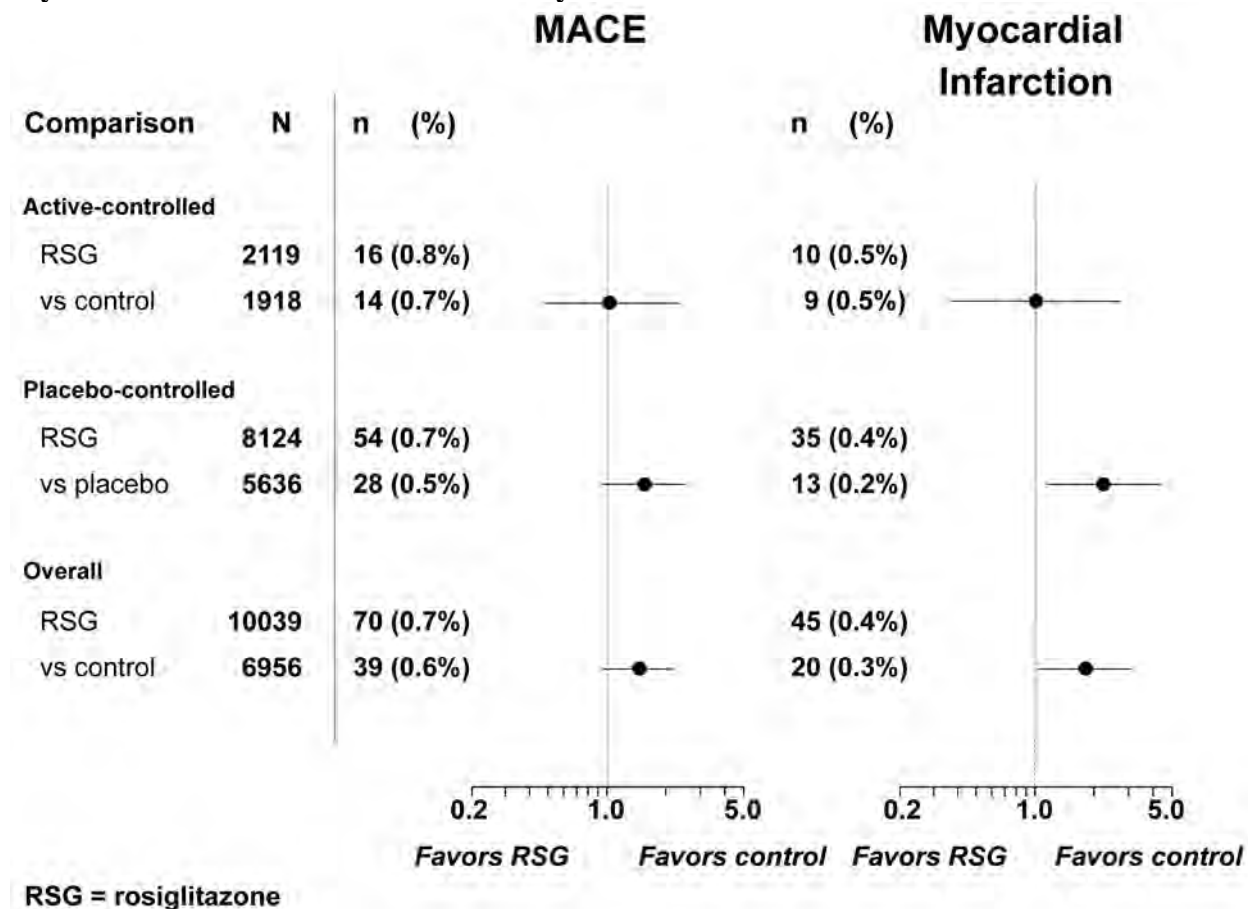
infarction, cardiovascular death, or stroke)		
Myocardial Infarction	45 (0.4)	20 (0.3)
Cardiovascular Death	17 (0.2)	9 (0.1)
Stroke	18 (0.2)	16 (0.2)
All-cause Death	29 (0.3)	17 (0.2)

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

150
151 In this analysis, a statistically significant increased risk of myocardial infarction with
152 AVANDIA versus pooled comparators was observed. Analyses were performed using a
153 composite of major adverse cardiovascular events (myocardial infarction, stroke, and
154 cardiovascular death), referred to hereafter as MACE. AVANDIA had a statistically non-
155 significant increased risk of MACE compared to the pooled comparators. A statistically
156 significant increased risk of myocardial infarction and statistically non-significant increased risk
157 of MACE with AVANDIA was observed in the placebo-controlled trials. In the active-controlled
158 trials, there was no increased risk of myocardial infarction or MACE. (See Figure 1 and Table 3.)
159

160
161

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



162
163
164
165

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

		N	MACE		Myocardial Infarction	
			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%)	

166
167
168
169

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

170 group compared to the insulin group with myocardial infarctions, MACE, cardiovascular deaths,
 171 and all-cause deaths (see Table 4). The total number of patients with stroke was 5 (0.5%) and 4
 172 (0.5%) in the AVANDIA plus insulin and insulin groups, respectively. The use of AVANDIA in
 173 combination with insulin may increase the risk of myocardial infarction.
 174

175 **Table 4. Occurrence of Cardiovascular Events for AVANDIA in Combination With Insulin**
 176 **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)

177 ND = not defined

178 ^a Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial
 179 infarction would be counted in 4 event categories (myocardial infarction; myocardial
 180 infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).
 181

182 Myocardial Infarction Events in Large, Long-Term, Prospective, Randomized,
 183 Controlled Trials of AVANDIA: Data from 3 large, long-term, prospective, randomized,
 184 controlled clinical trials of AVANDIA were assessed separately from the meta-analysis.⁶⁻⁸ These
 185 3 trials included a total of 14,067 patients (treatment groups containing AVANDIA N = 6,311;
 186 comparator groups N = 7,756), with patient-year exposure of 24,534 patient-years for
 187 AVANDIA and 28,882 patient-years for comparator. Patient populations in the trials included
 188 patients with impaired glucose tolerance, patients with type 2 diabetes who were initiating oral
 189 agent monotherapy, and patients with type 2 diabetes who had failed monotherapy and were
 190 initiating dual oral agent therapy. Duration of follow-up exceeded 3 years in each trial.

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

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

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

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

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

213 Mortality in Observational Studies of AVANDIA Compared to ACTOS: Three
214 observational studies in elderly diabetic patients (age 65 years and older) found that AVANDIA
215 statistically significantly increased the risk of all-cause mortality compared to use of ACTOS.²⁻⁴
216 One observational study⁵ in patients with a mean age of 54 years found no difference in all-cause
217 mortality between patients treated with AVANDIA compared to ACTOS and reported similar
218 results in the subpopulation of patients >65 years of age. One additional small, prospective,
219 observational study¹⁰ found no statistically significant differences for CV mortality and all-cause
220 mortality in patients treated with AVANDIA compared to ACTOS.

221 **5.3 Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program**

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

231 **5.4 Edema**

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

235 Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can
236 exacerbate or lead to congestive heart failure, AVANDIA should be used with caution in patients
237 at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure
238 [*see Boxed Warning, Warnings and Precautions (5.1), and Patient Counseling Information*
239 (17)].

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

244 5.5 Weight Gain

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

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

252

253 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

254

255 In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed
 256 with type 2 diabetes not previously treated with antidiabetic medication [see Clinical Studies
 257 (14.1)], the median weight change (25th, 75th percentiles) from baseline at 4 years was 3.5 kg
 258 (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.

259 In a 24-week trial in pediatric patients aged 10 to 17 years treated with AVANDIA 4 to
 260 8 mg daily, a median weight gain of 2.8 kg (25th, 75th percentiles: 0.0, 5.8) was reported.

261 **5.6 Hepatic Effects**

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

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

279 **5.7 Macular Edema**

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

290 **5.8 Fractures**

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

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

303 **5.9 Hematologic Effects**

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

307 **5.10 Diabetes and Blood Glucose Control**

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

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

312 **5.11 Ovulation**

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

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

322 **6 ADVERSE REACTIONS**

323 **6.1 Clinical Trial Experience**

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

326 *Short-Term Trials of AVANDIA as Monotherapy and in Combination With Other*
327 *Hypoglycemic Agents*: The incidence and types of adverse events reported in short-term
328 clinical trials of AVANDIA as monotherapy are shown in Table 6.
329

330 Table 6. Adverse Events ($\geq 5\%$ in Any Treatment Group) Reported by Patients in Short-
 331 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

332 ^a Short-term trials ranged from 8 weeks to 1 year.

333 ^b Includes patients receiving glyburide (N = 514), gliclazide (N = 91), or glipizide (N = 21).
 334

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

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

341 In double-blind trials, anemia was reported in 1.9% of patients receiving AVANDIA as
 342 monotherapy compared to 0.7% on placebo, 0.6% on sulfonylureas, and 2.2% on metformin.
 343 Reports of anemia were greater in patients treated with a combination of AVANDIA and
 344 metformin (7.1%) and with a combination of AVANDIA and a sulfonylurea plus metformin
 345 (6.7%) compared to monotherapy with AVANDIA or in combination with a sulfonylurea
 346 (2.3%). Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin
 347 combination clinical trials may have contributed to the higher reporting rate of anemia in these
 348 trials [see *Adverse Reactions* (6.2)].

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

356 *Boxed Warning and Warnings and Precautions (5.1)*]. The use of AVANDIA in combination
 357 with insulin may increase the risk of myocardial infarction [*see Warnings and Precautions*
 358 (5.2)].

359 In controlled combination therapy trials with sulfonylureas, mild to moderate
 360 hypoglycemic symptoms, which appear to be dose related, were reported. Few patients were
 361 withdrawn for hypoglycemia (<1%) and few episodes of hypoglycemia were considered to be
 362 severe (<1%). Hypoglycemia was the most frequently reported adverse event in the fixed-dose
 363 insulin combination trials, although few patients withdrew for hypoglycemia (4 of 408 for
 364 AVANDIA plus insulin and 1 of 203 for insulin alone). Rates of hypoglycemia, confirmed by
 365 capillary blood glucose concentration ≤50 mg/dL, were 6% for insulin alone and 12% (4 mg) and
 366 14% (8 mg) for insulin in combination with AVANDIA. [*See Warnings and Precautions (5.10).*]

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

373 In ADOPT, fractures were reported in a greater number of women treated with
 374 AVANDIA (9.3%, 2.7/100 patient-years) compared to glyburide (3.5%, 1.3/100 patient-years) or
 375 metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who
 376 received rosiglitazone were reported in the upper arm, hand, and foot. [*See Warnings and*
 377 *Precautions (5.8).*] The observed incidence of fractures for male patients was similar among the
 378 3 treatment groups.

379

380 Table 7. On-Therapy Adverse Events (≥5 Events/100 Patient-Years [PY]) in Any
 381 Treatment Group Reported in a 4- to 6-Year Clinical Trial of AVANDIA as Monotherapy
 382 (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

383

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

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

391 **6.2 Laboratory Abnormalities**

392 Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a dose-related
393 fashion in adult patients treated with AVANDIA (mean decreases in individual trials as much as
394 1.0 g/dL hemoglobin and as much as 3.3% hematocrit). The changes occurred primarily during
395 the first 3 months following initiation of therapy with AVANDIA or following a dose increase in
396 AVANDIA. The time course and magnitude of decreases were similar in patients treated with a
397 combination of AVANDIA and other hypoglycemic agents or monotherapy with AVANDIA.
398 Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin
399 combination trials and may have contributed to the higher reporting rate of anemia. In a single
400 trial in pediatric patients, decreases in hemoglobin and hematocrit (mean decreases of 0.29 g/dL
401 and 0.95%, respectively) were reported. Small decreases in hemoglobin and hematocrit have also
402 been reported in pediatric patients treated with AVANDIA. White blood cell counts also
403 decreased slightly in adult patients treated with AVANDIA. Decreases in hematologic
404 parameters may be related to increased plasma volume observed with treatment with
405 AVANDIA.

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

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

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

420 In the 4- to 6-year ADOPT trial, patients treated with AVANDIA (4,954 patient-years
421 exposure), glyburide (4,244 patient-years exposure), or metformin (4,906 patient-years
422 exposure), as monotherapy, had the same rate of ALT increase to >3X upper limit of normal
423 (0.3 per 100 patient-years exposure).

424 **6.3 Postmarketing Experience**

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

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

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

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

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

439 **7 DRUG INTERACTIONS**

440 **7.1 CYP2C8 Inhibitors and Inducers**

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

446 **8 USE IN SPECIFIC POPULATIONS**

447 **8.1 Pregnancy**

448 Pregnancy Category C.

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

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

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

465 placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation
466 reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible
467 after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was
468 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately
469 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced
470 the number of uterine implantations and live offspring when juvenile female rats were treated at
471 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human
472 AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day
473 (approximately 4 times human AUC at the maximum recommended daily dose). There was no
474 effect on pre- or post-natal survival or growth.

475 **8.2 Labor and Delivery**

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

477 **8.3 Nursing Mothers**

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

481 **8.4 Pediatric Use**

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

495

496 Table 8. Week 24 FPG and HbA1c Change From Baseline Last-Observation-Carried
 497 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 (95% CI)		8 (-15, 30)		21 (-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 (95% CI)		0.2 (-0.6, 0.9)		0.5 (-0.2, 1.3)
% of patients with ≥0.7% decrease from baseline	63%	52%	54%	31%

498 ^a Change from baseline means are least squares means adjusting for baseline HbA1c, gender,
 499 and region.

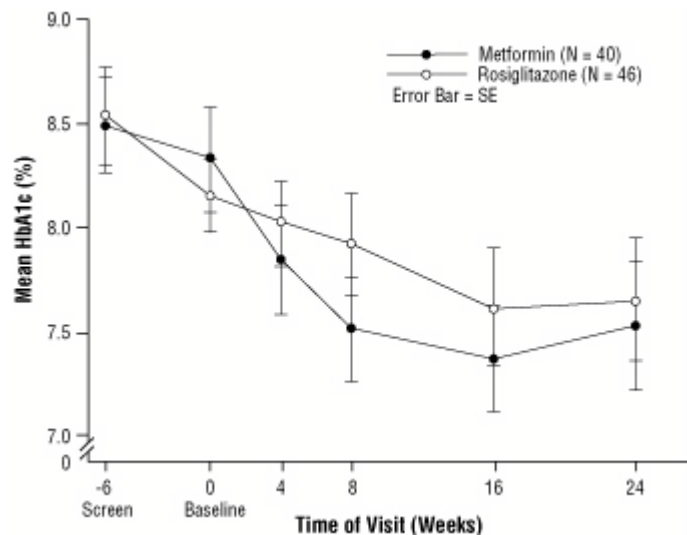
500 ^b Positive values for the difference favor metformin.

501
 502 Treatment differences depended on baseline BMI or weight such that the effects of
 503 AVANDIA and metformin appeared more closely comparable among heavier patients. The
 504 median weight gain was 2.8 kg with rosiglitazone and 0.2 kg with metformin [see *Warnings and*
 505 *Precautions (5.5)*]. Fifty-four percent of patients treated with rosiglitazone and 32% of patients
 506 treated with metformin gained ≥2 kg, and 33% of patients treated with rosiglitazone and 7% of
 507 patients treated with metformin gained ≥5 kg on trial.

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

509

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



512
513

514 8.5 Geriatric Use

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

520 10 OVERDOSAGE

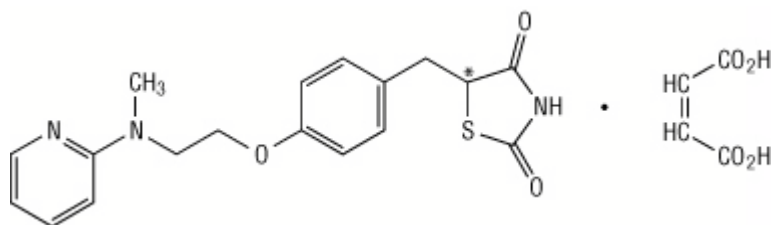
521 Limited data are available with regard to overdosage in humans. In clinical trials in
522 volunteers, AVANDIA has been administered at single oral doses of up to 20 mg and was
523 well-tolerated. In the event of an overdose, appropriate supportive treatment should be initiated
524 as dictated by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

525 11 DESCRIPTION

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

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

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



536
 537 The molecular formula is $C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$. Rosiglitazone maleate is a white to
 538 off-white solid with a melting point range of 122° to $123^\circ C$. The pKa values of rosiglitazone
 539 maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH
 540 of 2.3; solubility decreases with increasing pH in the physiological range.

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

546 12 CLINICAL PHARMACOLOGY

547 12.1 Mechanism of Action

548 Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves
 549 glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent
 550 agonist for the peroxisome proliferator-activated receptor-gamma ($PPAR\gamma$). In humans, PPAR
 551 receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle,
 552 and liver. Activation of $PPAR\gamma$ nuclear receptors regulates the transcription of insulin-responsive
 553 genes involved in the control of glucose production, transport, and utilization. In addition,
 554 $PPAR\gamma$ -responsive genes also participate in the regulation of fatty acid metabolism.

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

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

566 12.2 Pharmacodynamics

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

571 (Table 9).

572 Increases in LDL occurred primarily during the first 1 to 2 months of therapy with
573 AVANDIA and LDL levels remained elevated above baseline throughout the trials. In contrast,
574 HDL continued to rise over time. As a result, the LDL/HDL ratio peaked after 2 months of
575 therapy and then appeared to decrease over time. Because of the temporal nature of lipid
576 changes, the 52-week glyburide-controlled trial is most pertinent to assess long-term effects on
577 lipids. At baseline, week 26, and week 52, mean LDL/HDL ratios were 3.1, 3.2, and 3.0,
578 respectively, for AVANDIA 4 mg twice daily. The corresponding values for glyburide were 3.2,
579 3.1, and 2.9. The differences in change from baseline between AVANDIA and glyburide at
580 week 52 were statistically significant.

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

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

586

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

	Placebo-Controlled Trials			Glyburide-Controlled Trial			
	Week 26			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%

589 ^a Once daily and twice daily dosing groups were combined.

590

591 **12.3 Pharmacokinetics**

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

595
596 Table 10. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral
597 Doses (N = 32)

Parameter	1 mg Fasting	2 mg Fasting	8 mg Fasting	8 mg Fed
AUC _{0-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)

598 ^a CL/F = Oral clearance.

599
600 **Absorption:** The absolute bioavailability of rosiglitazone is 99%. Peak plasma
601 concentrations are observed about 1 hour after dosing. Administration of rosiglitazone with food
602 resulted in no change in overall exposure (AUC), but there was an approximately 28% decrease
603 in C_{max} and a delay in T_{max} (1.75 hours). These changes are not likely to be clinically significant;
604 therefore, AVANDIA may be administered with or without food.

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

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

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

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

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

621 influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral
622 steady-state volume of distribution (V_{ss}/F) were shown to increase with increases in body
623 weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted
624 CL/F and V_{ss}/F values varied by <1.7-fold and <2.3-fold, respectively. Additionally,
625 rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about
626 15%) in female patients.

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

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

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

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

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

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

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

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

661 these patients.

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

665 **12.4 Drug-Drug Interactions**

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

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

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

681 **Glyburide:** AVANDIA (2 mg twice daily) taken concomitantly with glyburide (3.75 to
682 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations
683 in diabetic patients stabilized on glyburide therapy. Repeat doses of AVANDIA (8 mg once
684 daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and
685 C_{max} of approximately 30%. In Japanese subjects, glyburide AUC and C_{max} slightly increased
686 following coadministration of AVANDIA.

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

691 **Metformin:** Concurrent administration of AVANDIA (2 mg twice daily) and metformin
692 (500 mg twice daily) in healthy volunteers for 4 days had no effect on the steady-state
693 pharmacokinetics of either metformin or rosiglitazone.

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

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

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

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

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

707 **13 NONCLINICAL TOXICOLOGY**

708 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

709 Carcinogenesis: A 2-year carcinogenicity study was conducted in Charles River CD-1
710 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately
711 12 times human AUC at the maximum recommended human daily dose). Sprague-Dawley rats
712 were dosed for 2 years by oral gavage at doses of 0.05, 0.3, and 2 mg/kg/day (highest dose
713 equivalent to approximately 10 and 20 times human AUC at the maximum recommended human
714 daily dose for male and female rats, respectively).

715 Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of
716 adipose hyperplasia in the mouse at doses ≥ 1.5 mg/kg/day (approximately 2 times human AUC
717 at the maximum recommended human daily dose). In rats, there was a significant increase in the
718 incidence of benign adipose tissue tumors (lipomas) at doses ≥ 0.3 mg/kg/day (approximately
719 2 times human AUC at the maximum recommended human daily dose). These proliferative
720 changes in both species are considered due to the persistent pharmacological overstimulation of
721 adipose tissue.

722 Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial
723 assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in
724 vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about
725 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic
726 activation.

727 Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats
728 given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended
729 human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility
730 (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and
731 estradiol (approximately 20 and 200 times human AUC at the maximum recommended human
732 daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times
733 human AUC at the maximum recommended human daily dose). In juvenile rats dosed from
734 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male
735 reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in
736 females (approximately 68 times human AUC at the maximum recommended human daily
737 dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human
738 AUC at the maximum recommended human daily dose, respectively) diminished the follicular
739 phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge,

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

742 **13.2 Animal Toxicology**

743 Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs
744 (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at
745 the maximum recommended human daily dose, respectively). Effects in juvenile rats were
746 consistent with those seen in adults. Morphometric measurement indicated that there was
747 hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result
748 of plasma volume expansion.

749 **14 CLINICAL STUDIES**

750 **14.1 Monotherapy**

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

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

757 Short-Term Clinical Trials: A total of 2,315 patients with type 2 diabetes, previously
758 treated with diet alone or antidiabetic medication(s), were treated with AVANDIA as
759 monotherapy in 6 double-blind trials, which included two 26-week placebo-controlled trials, one
760 52-week glyburide-controlled trial, and 3 placebo-controlled dose-ranging trials of 8 to 12 weeks
761 duration. Previous antidiabetic medication(s) were withdrawn and patients entered a 2 to 4 week
762 placebo run-in period prior to randomization.

763 Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes
764 (n = 1,401) with inadequate glycemic control (mean baseline FPG approximately 228 mg/dL
765 [101 to 425 mg/dL] and mean baseline HbA1c 8.9% [5.2% to 16.2%]), were conducted.
766 Treatment with AVANDIA produced statistically significant improvements in FPG and HbA1c
767 compared to baseline and relative to placebo. Data from one of these trials are summarized in
768 Table 11.

769

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

	Placebo	AVANDIA		AVANDIA	
		4 mg once daily	2 mg twice daily	8 mg once daily	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%

771 ^a *P* <0.0001 compared to placebo.

772
 773 When administered at the same total daily dose, AVANDIA was generally more effective
 774 in reducing FPG and HbA1c when administered in divided doses twice daily compared to once
 775 daily doses. However, for HbA1c, the difference between the 4 mg once daily and 2 mg twice
 776 daily doses was not statistically significant.

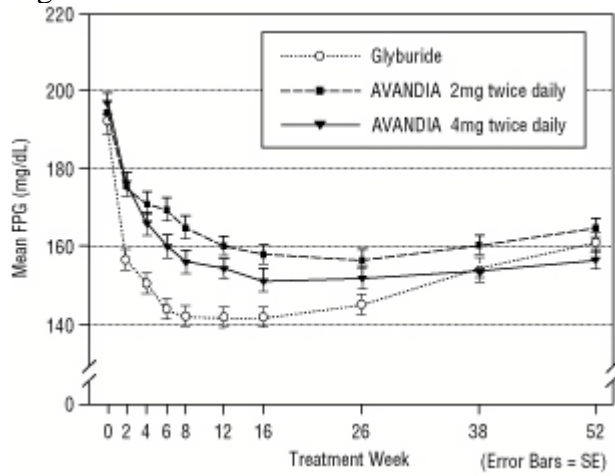
777 **Long-Term Clinical Trials:** Long-term maintenance of effect was evaluated in a
 778 52-week, double-blind, glyburide-controlled trial in patients with type 2 diabetes. Patients were
 779 randomized to treatment with AVANDIA 2 mg twice daily (N = 195) or AVANDIA 4 mg twice
 780 daily (N = 189) or glyburide (N = 202) for 52 weeks. Patients receiving glyburide were given an
 781 initial dosage of either 2.5 mg/day or 5.0 mg/day. The dosage was then titrated in 2.5 mg/day
 782 increments over the next 12 weeks, to a maximum dosage of 15.0 mg/day in order to optimize
 783 glycemic control. Thereafter, the glyburide dose was kept constant.

784 The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a
 785 statistically significant improvement in glycemic control from baseline (Figure 3 and Figure 4).
 786 At the end of week 52, the reduction from baseline in FPG and HbA1c was -40.8 mg/dL and
 787 -0.53% with AVANDIA 4 mg twice daily; -25.4 mg/dL and -0.27% with AVANDIA 2 mg twice
 788 daily; and -30.0 mg/dL and -0.72% with glyburide. For HbA1c, the difference between
 789 AVANDIA 4 mg twice daily and glyburide was not statistically significant at week 52. The
 790 initial fall in FPG with glyburide was greater than with AVANDIA; however, this effect was less
 791 durable over time. The improvement in glycemic control seen with AVANDIA 4 mg twice daily

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

793

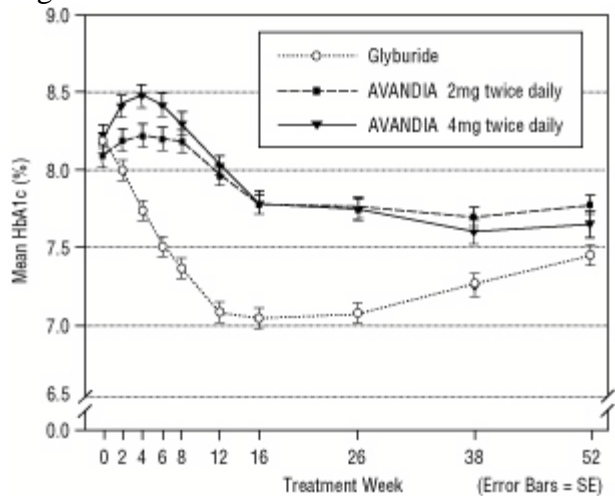
794 Figure 3. Mean FPG Over Time in a 52-Week Glyburide-Controlled Trial



795

796

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



798

799

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

807

808

809

810

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

811 patients in this trial was 57 years and the majority of patients (83%) had no known history of
812 cardiovascular disease. The mean baseline FPG and HbA1c were 152 mg/dL and 7.4%,
813 respectively. Patients were randomized to receive either AVANDIA 4 mg once daily, glyburide
814 2.5 mg once daily, or metformin 500 mg once daily, and doses were titrated to optimal glycemic
815 control up to a maximum of 4 mg twice daily for AVANDIA, 7.5 mg twice daily for glyburide,
816 and 1,000 mg twice daily for metformin. The primary efficacy outcome was time to consecutive
817 FPG >180 mg/dL after at least 6 weeks of treatment at the maximum tolerated dose of study
818 medication or time to inadequate glycemic control, as determined by an independent
819 adjudication committee.

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

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

828 **14.2 Combination With Metformin or Sulfonylurea**

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

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

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

844

845 Table 12. Glycemic Parameters in a 26-Week Combination Trial of AVANDIA Plus
 846 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%

847 ^a P <0.0001 compared to metformin.

848
 849 In a second 26-week trial, patients with type 2 diabetes inadequately controlled on
 850 2.5 grams/day of metformin who were randomized to receive the combination of AVANDIA
 851 4 mg twice daily and metformin (N = 105) showed a statistically significant improvement in
 852 glycemic control with a mean treatment effect for FPG of -56 mg/dL and a mean treatment effect
 853 for HbA1c of -0.8% over metformin alone. The combination of metformin and AVANDIA
 854 resulted in lower levels of FPG and HbA1c than either agent alone.

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

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

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

867 to placebo plus sulfonylurea or further up-titration of the sulfonylurea. Table 13 shows pooled
868 data for 8 trials in which AVANDIA added to sulfonylurea was compared to placebo plus
869 sulfonylurea.
870

871 Table 13. Glycemic Parameters in 24- to 26-Week Combination Trials of AVANDIA Plus
872 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%

873 ^a P <0.0001 compared to sulfonylurea alone.

874

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

878 In a 2-year double-blind trial, elderly patients (aged 59 to 89 years) on half-maximal
879 sulfonylurea (glipizide 10 mg twice daily) were randomized to the addition of AVANDIA
880 (n = 115, 4 mg once daily to 8 mg as needed) or to continued up-titration of glipizide (n = 110),
881 to a maximum of 20 mg twice daily. Mean baseline FPG and HbA1c were 157 mg/dL and
882 7.72%, respectively, for the AVANDIA plus glipizide arm and 159 mg/dL and 7.65%,
883 respectively, for the glipizide up-titration arm. Loss of glycemic control (FPG \geq 180 mg/dL)
884 occurred in a significantly lower proportion of patients (2%) on AVANDIA plus glipizide
885 compared to patients in the glipizide up-titration arm (28.7%). About 78% of the patients on
886 combination therapy completed the 2 years of therapy while only 51% completed on glipizide
887 monotherapy. The effect of combination therapy on FPG and HbA1c was durable over the 2-year
888 trial period, with patients achieving a mean of 132 mg/dL for FPG and a mean of 6.98% for
889 HbA1c compared to no change on the glipizide arm.

890 **14.3 Combination With Sulfonylurea Plus Metformin**

891 In two 24- to 26-week, double-blind, placebo-controlled, trials designed to assess the
892 efficacy and safety of AVANDIA in combination with sulfonylurea plus metformin, AVANDIA
893 4 mg or 8 mg daily, was administered in divided doses twice daily, to patients inadequately
894 controlled on submaximal (10 mg) and maximal (20 mg) doses of glyburide and maximal dose
895 of metformin (2 g/day). A statistically significant improvement in FPG and HbA1c was observed
896 in patients treated with the combinations of sulfonylurea plus metformin and 4 mg of AVANDIA
897 and 8 mg of AVANDIA versus patients continued on sulfonylurea plus metformin, as shown in
898 Table 14.

899

900 Table 14. Glycemic Parameters in a 26-Week Combination Trial of AVANDIA Plus
 901 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%

902 ^a P <0.0001 compared to placebo.
 903

904 **15 REFERENCES**

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935 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

940 2 mg bottles of 60: NDC 0173-0834-18

941 4 mg bottles of 30: NDC 0173-0835-13

942 8 mg bottles of 30: NDC 0173-0836-13

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

945 **17 PATIENT COUNSELING INFORMATION**

946 See Medication Guide.

947 **17.1 Patient Advice**

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

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

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

987
988 AVANDIA and TILTAB are registered trademarks of GlaxoSmithKline. ACTOS is a registered
989 trademark of Takeda Pharmaceutical Company Limited.

990



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992 GlaxoSmithKline
993 Research Triangle Park, NC 27709
994

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997 Month 2011

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

1003 Read this Medication Guide carefully before you start taking AVANDIA and each
1004 time you get a refill. There may be new information. This information does not take
1005 the place of talking with your doctor about your medical condition or your
1006 treatment. If you have any questions about AVANDIA, ask your doctor or
1007 pharmacist.

1008
1009 **What is the most important information I should know about AVANDIA?**

1010
1011 AVANDIA is available only through the AVANDIA-Rosiglitazone Medicines Access
1012 Program. Both you and your doctor must be enrolled in the program so that you
1013 can get AVANDIA. To enroll, you must:

- 1014 • talk to your doctor,
1015 • understand the risks and benefits of AVANDIA, and
1016 • agree to enroll in the program.

1017
1018 **AVANDIA may cause serious side effects, including:**

1019
1020 **New or worse heart failure**

- 1021 • AVANDIA can cause your body to keep extra fluid (fluid retention), which leads
1022 to swelling (edema) and weight gain. Extra body fluid can make some heart
1023 problems worse or lead to heart failure. Heart failure means your heart does not
1024 pump blood well enough.
1025 • If you have severe heart failure, you cannot start AVANDIA.
1026 • If you have heart failure with symptoms (such as shortness of breath or
1027 swelling), even if these symptoms are not severe, AVANDIA may not be right for
1028 you.

1029
1030 Call your doctor right away if you have any of the following:

- 1031 • swelling or fluid retention, especially in the ankles or legs
1032 • shortness of breath or trouble breathing, especially when you lie down
1033 • an unusually fast increase in weight
1034 • unusual tiredness

1035
1036 **Myocardial Infarction (“Heart Attack”)**

1037 AVANDIA may raise the risk of a heart attack. The risk of having a heart attack may
1038 be higher in people who take AVANDIA with insulin. Most people who take insulin

1039 should not also take AVANDIA.

1040 **Symptoms of a heart attack can include the following:**

- 1041 • chest discomfort in the center of your chest that lasts for more than a few
- 1042 minutes, or that goes away or comes back
- 1043 • chest discomfort that feels like uncomfortable pressure, squeezing, fullness or
- 1044 pain
- 1045 • pain or discomfort in your arms, back, neck, jaw or stomach
- 1046 • shortness of breath with or without chest discomfort
- 1047 • breaking out in a cold sweat
- 1048 • nausea or vomiting
- 1049 • feeling lightheaded

1050 **Call your doctor or go to the nearest hospital emergency room right away if**

1051 **you think you are having a heart attack.**

1052

1053 People with diabetes have a greater risk for heart problems. It is important to work

1054 with your doctor to manage other conditions, such as high blood pressure or high

1055 cholesterol.

1056

1057 AVANDIA can have other serious side effects. Be sure to read the section below

1058 “What are possible side effects of AVANDIA?”.

1059

1060 **What is AVANDIA?**

1061 AVANDIA is a prescription medicine used with diet and exercise to treat certain

1062 adults with type 2 (“adult-onset” or “non-insulin dependent”) diabetes mellitus

1063 (“high blood sugar”) who are:

- 1064 • already taking AVANDIA or
- 1065 • unable to control their blood sugar on other diabetes medicines, and after
- 1066 talking with their doctor have decided not to take pioglitazone (ACTOS)

1067

1068 AVANDIA helps to control high blood sugar. AVANDIA may be used alone or with

1069 other diabetes medicines. AVANDIA can help your body respond better to insulin

1070 made in your body. AVANDIA does not cause your body to make more insulin.

1071

1072 AVANDIA is not for people with type 1 diabetes mellitus or to treat a condition

1073 called diabetic ketoacidosis.

1074

1075 It is not known if AVANDIA is safe and effective in children under 18 years old.

1076

1077 **Who should not take AVANDIA?**

1078 Many people with heart failure should not start taking AVANDIA. See “What should

1079 I tell my doctor before taking AVANDIA?”.

1080

1081 **What should I tell my doctor before taking AVANDIA?**

1082 Before starting AVANDIA, ask your doctor about what the choices are for diabetes
1083 medicines, and what the expected benefits and possible risks are for you in
1084 particular.

1085

1086 Before taking AVANDIA, tell your doctor about all your medical conditions, including
1087 if you:

- 1088 • **have heart problems or heart failure.**
- 1089 • **have type 1 (“juvenile”) diabetes or had diabetic ketoacidosis.** These
1090 conditions should be treated with insulin.
- 1091 • **have a type of diabetic eye disease called macular edema** (swelling of the
1092 back of the eye).
- 1093 • **have liver problems.** Your doctor should do blood tests to check your liver
1094 before you start taking AVANDIA and during treatment as needed.
- 1095 • **had liver problems while taking REZULIN® (troglitazone), another**
1096 **medicine for diabetes.**
- 1097 • **are pregnant or plan to become pregnant.** AVANDIA should not be used
1098 during pregnancy. It is not known if AVANDIA can harm your unborn baby. You
1099 and your doctor should talk about the best way to control your diabetes during
1100 pregnancy. If you are a premenopausal woman (before the “change of life”) who
1101 does not have regular monthly periods, AVANDIA may increase your chances of
1102 becoming pregnant. Talk to your doctor about birth control choices while taking
1103 AVANDIA. Tell your doctor right away if you become pregnant while taking
1104 AVANDIA.
- 1105 • **are breast-feeding or planning to breast-feed.** It is not known if AVANDIA
1106 passes into breast milk. You should not use AVANDIA while breast-feeding.

1107

1108 Tell your doctor about all the medicines you take including prescription and non-
1109 prescription medicines, vitamins or herbal supplements. AVANDIA and certain other
1110 medicines can affect each other and may lead to serious side effects including high
1111 or low blood sugar, or heart problems. Especially tell your doctor if you take:

- 1112 • **insulin.**
- 1113 • **any medicines for high blood pressure, high cholesterol or heart failure,**
1114 **or for prevention of heart disease or stroke.**

1115

1116 Know the medicines you take. Keep a list of your medicines and show it to your
1117 doctor and pharmacist before you start a new medicine. They will tell you if it is
1118 alright to take AVANDIA with other medicines.

1119

1120 **How should I take AVANDIA?**

- 1121 • Take AVANDIA exactly as prescribed. Your doctor will tell you how many tablets
- 1122 to take and how often. The usual daily starting dose is 4 mg a day taken one
- 1123 time each day or 2 mg taken two times each day. Your doctor may need to
- 1124 adjust your dose until your blood sugar is better controlled.
- 1125 • AVANDIA may be prescribed alone or with other diabetes medicines. This will
- 1126 depend on how well your blood sugar is controlled.
- 1127 • Take AVANDIA with or without food.
- 1128 • It can take 2 weeks for AVANDIA to start lowering blood sugar. It may take 2 to
- 1129 3 months to see the full effect on your blood sugar level.
- 1130 • If you miss a dose of AVANDIA, take it as soon as you remember, unless it is
- 1131 time to take your next dose. Take your next dose at the usual time. Do not take
- 1132 double doses to make up for a missed dose.
- 1133 • If you take too much AVANDIA, call your doctor or poison control center right
- 1134 away.
- 1135 • Test your blood sugar regularly as your doctor tells you.
- 1136 • Diet and exercise can help your body use its blood sugar better. It is important
- 1137 to stay on your recommended diet, lose extra weight, and get regular exercise
- 1138 while taking AVANDIA.
- 1139 • Your doctor should do blood tests to check your liver before you start AVANDIA
- 1140 and during treatment as needed. Your doctor should also do regular blood sugar
- 1141 tests (for example, "A1C") to monitor your response to AVANDIA.

1142

1143 **What are possible side effects of AVANDIA?**

1144 **AVANDIA may cause serious side effects including:**

- 1145 • **New or worse heart failure.** See "What is the most important information I
- 1146 should know about AVANDIA?".
- 1147 • **Heart attack.** See "What is the most important information I should know
- 1148 about AVANDIA?".
- 1149 • **Swelling (edema).** AVANDIA can cause swelling due to fluid retention. See
- 1150 "What is the most important information I should know about AVANDIA?".
- 1151 • **Weight gain.** AVANDIA can cause weight gain that may be due to fluid
- 1152 retention or extra body fat. Weight gain can be a serious problem for people
- 1153 with certain conditions including heart problems. See "What is the most
- 1154 important information I should know about AVANDIA?".
- 1155 • **Liver problems.** It is important for your liver to be working normally when you
- 1156 take AVANDIA. Your doctor should do blood tests to check your liver before you
- 1157 start taking AVANDIA and during treatment as needed. Call your doctor right
- 1158 away if you have unexplained symptoms such as:

- 1159 • nausea or vomiting
- 1160 • stomach pain
- 1161 • unusual or unexplained tiredness
- 1162 • loss of appetite
- 1163 • dark urine
- 1164 • yellowing of your skin or the whites of your eyes.
- 1165 • **Macular edema** (a diabetic eye disease with swelling in the back of the eye).
1166 Tell your doctor right away if you have any changes in your vision. Your doctor
1167 should check your eyes regularly. Very rarely, some people have had vision
1168 changes due to swelling in the back of the eye while taking AVANDIA.
- 1169 • **Fractures (broken bones)**, usually in the hand, upper arm or foot. Talk to
1170 your doctor for advice on how to keep your bones healthy.
- 1171 • **Low red blood cell count (anemia)**.
- 1172 • **Low blood sugar (hypoglycemia)**. Lightheadedness, dizziness, shakiness or
1173 hunger may mean that your blood sugar is too low. This can happen if you skip
1174 meals, if you use another medicine that lowers blood sugar, or if you have
1175 certain medical problems. Call your doctor if low blood sugar levels are a
1176 problem for you.
- 1177 • **Ovulation** (release of egg from an ovary in a woman) leading to pregnancy.
1178 Ovulation may happen in premenopausal women who do not have regular
1179 monthly periods. This can increase the chance of pregnancy. See “What should I
1180 tell my doctor before taking AVANDIA?”.

1181
1182 The most common side effects of AVANDIA reported in clinical trials included cold-
1183 like symptoms and headache.

1184
1185 Call your doctor for medical advice about side effects. You may report side effects
1186 to FDA at 1-800-FDA-1088.

1187 1188 **How should I store AVANDIA?**

- 1189 • Store AVANDIA at room temperature, 59° to 86°F (15° to 30°C). Keep AVANDIA
1190 in the container it comes in.
- 1191 • Safely, throw away AVANDIA that is out of date or no longer needed.
- 1192 • Keep AVANDIA and all medicines out of the reach of children.

1193 1194 **General information about AVANDIA**

1195 Medicines are sometimes prescribed for purposes other than those listed in a
1196 Medication Guide. Do not use AVANDIA for a condition for which it was not
1197 prescribed. Do not give AVANDIA to other people, even if they have the same
1198 symptoms you have. It may harm them.

1199
1200 This Medication Guide summarizes important information about AVANDIA. If you
1201 would like more information, talk with your doctor. You can ask your doctor or
1202 pharmacist for information about AVANDIA that is written for healthcare
1203 professionals. You can also find out more about AVANDIA by calling 1-888-825-
1204 5249.

1205
1206 **What are the ingredients in AVANDIA?**

1207 Active Ingredient: Rosiglitazone maleate.
1208 Inactive Ingredients: Hypromellose 2910, lactose monohydrate, magnesium
1209 stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch
1210 glycolate, titanium dioxide, triacetin, and 1 or more of the following: Synthetic red
1211 and yellow iron oxides and talc.

1212
1213 Always check to make sure that the medicine you are taking is the correct one.
1214 AVANDIA tablets are triangles with rounded corners and look like this:

- 1215 2 mg – pink with "SB" on one side and "2" on the other.
- 1216 4 mg – orange with "SB" on one side and "4" on the other.
- 1217 8 mg – red-brown with "SB" on one side and "8" on the other.

1218
1219 AVANDIA is a registered trademark of GlaxoSmithKline.
1220 The other brands listed are trademarks of their respective owners and are not
1221 trademarks of GlaxoSmithKline. The makers of these brands are not affiliated with
1222 and do not endorse GlaxoSmithKline or its products.

1223
1224 **This Medication Guide has been approved by the U.S. Food and Drug**
1225 **Administration.**



1227
1228 GlaxoSmithKline
1229 Research Triangle Park, NC 27709
1230
1231 ©2011, GlaxoSmithKline. All rights reserved.
1232
1233 Month 2011
1234 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

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1 FULL PRESCRIBING INFORMATION

2 **WARNINGS**

3 ***Rosiglitazone maleate*: CONGESTIVE HEART FAILURE AND MYOCARDIAL** 4 **INFARCTION**

- 5 • Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in
6 some patients [see *Warnings and Precautions (5.2)*]. After initiation of AVANDAMET, and
7 after dose increases, observe patients carefully for signs and symptoms of heart failure
8 (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and
9 symptoms develop, the heart failure should be managed according to current standards of
10 care. Furthermore, discontinuation or dose reduction of AVANDAMET must be considered.
- 11 • AVANDAMET is not recommended in patients with symptomatic heart failure. Initiation of
12 AVANDAMET in patients with established NYHA Class III or IV heart failure is
13 contraindicated. [See *Contraindications (4) and Warnings and Precautions (5.2)*.]
- 14 • A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of
15 which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an
16 increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067
17 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or
18 placebo, showed a statistically non-significant increased risk of myocardial infarction, and a
19 statistically non-significant decreased risk of death. There have been no clinical trials directly
20 comparing cardiovascular risk of rosiglitazone and ACTOS[®] (pioglitazone, another
21 thiazolidinedione), but in a separate trial, pioglitazone (when compared to placebo) did not
22 show an increased risk of myocardial infarction or death. [See *Warnings and Precautions*
23 *(5.3)*.]
- 24 • Because of the potential increased risk of myocardial infarction, AVANDAMET is available
25 only through a restricted distribution program called the AVANDIA-Rosiglitazone
26 Medicines Access Program. Both prescribers and patients need to enroll in the program. To
27 enroll, call 1-800-AVANDIA or visit www.AVANDIA.com. [See *Warnings and Precautions*
28 *(5.4)*.]

29 ***Metformin hydrochloride*: LACTIC ACIDOSIS**

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

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

39 1 INDICATIONS AND USAGE

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

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

49 Other Important Limitations of Use:

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

54 2 DOSAGE AND ADMINISTRATION

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

58 2.1 Starting Dose

59 AVANDAMET is generally given in divided doses with meals.

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

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

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

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

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

77
 78 Table 1. AVANDAMET Starting Dose for Patients Treated with Metformin and/or
 79 Rosiglitazone

PRIOR THERAPY	Usual AVANDAMET Starting 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

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

82
 83 **2.2 Dose Titration**

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

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

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

94 **2.3 Maximum Dose**

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

97 **2.4 Specific Patient Populations**

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

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

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

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

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

113 Pregnancy: AVANDAMET is not recommended for use in pregnancy.

114 **3 DOSAGE FORMS AND STRENGTHS**

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

- 117 • 2 mg/500 mg – pale pink, debossed with gsk on one side and 2/500 on the other
- 118 • 4 mg/500 mg – orange, debossed with gsk on one side and 4/500 on the other
- 119 • 2 mg/1,000 mg – yellow, debossed with gsk on one side and 2/1000 on the other
- 120 • 4 mg/1,000 mg – pink, debossed with gsk on one side and 4/1000 on the other

121 **4 CONTRAINDICATIONS**

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

134 **5 WARNINGS AND PRECAUTIONS**

135 **5.1 Lactic Acidosis**

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

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

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

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

178 Levels of fasting venous plasma lactate above the upper limit of normal but less than
179 5 mmol/L in patients taking AVANDAMET do not necessarily indicate impending lactic
180 acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or
181 obesity, vigorous physical activity or technical problems in sample handling.

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

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

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

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

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

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

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

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

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

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

232 [*See also Warnings and Precautions (5.7).*]

233 **5.2 Cardiac Failure**

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

240 Patients with congestive heart failure (CHF) NYHA Class I and II treated with
241 rosiglitazone have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-
242 controlled echocardiographic trial was conducted in 224 patients with type 2 diabetes mellitus
243 and NYHA Class I or II CHF (ejection fraction $\leq 45\%$) on background antidiabetic and CHF
244 therapy. An independent committee conducted a blinded evaluation of fluid-related events
245 (including congestive heart failure) and cardiovascular hospitalizations according to predefined
246 criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were
247 reported by investigators. Although no treatment difference in change from baseline of ejection
248 fractions was observed, more cardiovascular adverse events were observed with rosiglitazone
249 treatment compared to placebo during the 52-week trial. (See Table 2.)
250

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

Events	Rosiglitazone	Placebo
	N = 110	N = 114
	n (%)	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%)

254 ^a Includes hospitalization for any cardiovascular reason.
 255

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

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

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

267 **Congestive Heart Failure During Coadministration of Rosiglitazone With Insulin:**

268 In trials in which rosiglitazone was added to insulin, rosiglitazone increased the risk of
 269 congestive heart failure. Coadministration of rosiglitazone and insulin is not recommended. [See
 270 *Indications and Usage (1) and Warnings and Precautions (5.3)*.]

271 In 7 controlled, randomized, double-blind trials which had durations from 16 to 26 weeks
 272 and which were included in a meta-analysis¹ [see *Warnings and Precautions (5.3)*], patients with
 273 type 2 diabetes mellitus were randomized to coadministration of rosiglitazone and insulin

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

280 Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing
281 Rosiglitazone to Pioglitazone: Three observational studies²⁻⁴ in elderly diabetic patients (age
282 65 years and older) found that rosiglitazone statistically significantly increased the risk of
283 hospitalized heart failure compared to use of pioglitazone. One other observational study⁵ in
284 patients with a mean age of 54 years, which also included an analysis in a subpopulation of
285 patients >65 years of age, found no statistically significant increase in emergency department
286 visits or hospitalization for heart failure in patients treated with rosiglitazone compared to
287 pioglitazone in the older subgroup.

288 **5.3 Major Adverse Cardiovascular Events**

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

291 Meta-Analysis of Major Adverse Cardiovascular Events in a Group of 52 Clinical
292 Trials: A meta-analysis was conducted retrospectively to assess cardiovascular adverse events
293 reported across 52 double-blind, randomized, controlled clinical trials (mean duration 6
294 months).¹ These trials had been conducted to assess glucose-lowering efficacy in type 2 diabetes.
295 Prospectively planned adjudication of cardiovascular events did not occur in most of the trials.
296 Some trials were placebo-controlled and some used active oral antidiabetic drugs as controls.
297 Placebo-controlled trials included monotherapy trials (monotherapy with rosiglitazone versus
298 placebo monotherapy) and add-on trials (rosiglitazone or placebo, added to sulfonylurea,
299 metformin, or insulin). Active control trials included monotherapy trials (monotherapy with
300 rosiglitazone versus sulfonylurea or metformin monotherapy) and add-on trials (rosiglitazone
301 plus sulfonylurea or rosiglitazone plus metformin, versus sulfonylurea plus metformin). A total
302 of 16,995 patients were included (10,039 in treatment groups containing rosiglitazone, 6,956 in
303 comparator groups), with 5,167 patient-years of exposure to rosiglitazone and 3,637 patient-
304 years of exposure to comparator. Cardiovascular events occurred more frequently for patients
305 who received rosiglitazone than for patients who received comparators (see Table 3).
306

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

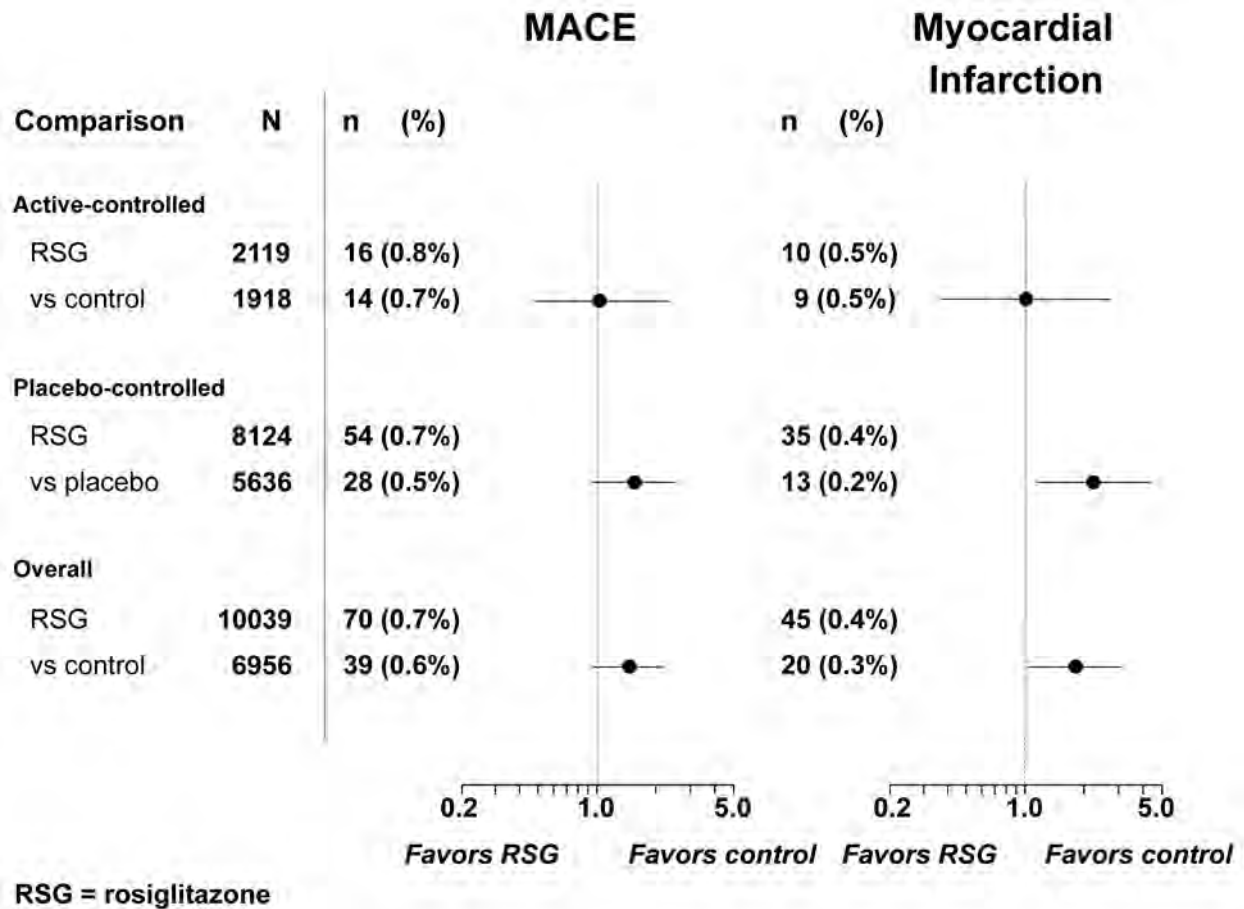
Event ^a	Rosiglitazone (N=10,039) n (%)	Comparator (N=6,956) n (%)
MACE (a composite of myocardial infarction, cardiovascular death, or stroke)	70 (0.7)	39 (0.6)
Myocardial Infarction	45 (0.4)	20 (0.3)
Cardiovascular Death	17 (0.2)	9 (0.1)
Stroke	18 (0.2)	16 (0.2)
All-cause Death	29 (0.3)	17 (0.2)

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

311
 312 In this analysis, a statistically significant increased risk of myocardial infarction with
 313 rosiglitazone versus pooled comparators was observed. Analyses were performed using a
 314 composite of major adverse cardiovascular events (myocardial infarction, stroke, and
 315 cardiovascular death), referred to hereafter as MACE. Rosiglitazone had a statistically non-
 316 significant increased risk of MACE compared to the pooled comparators. A statistically
 317 significant increased risk of myocardial infarction and statistically non-significant increased risk
 318 of MACE with rosiglitazone was observed in the placebo-controlled trials. In the active-
 319 controlled trials, there was no increased risk of myocardial infarction or MACE. (See Figure 1
 320 and Table 4.)
 321

322
323

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



324
325
326
327

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

		N	MACE		Myocardial Infarction	
			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%)	

328
329
330
331

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

332 group compared to the insulin group with myocardial infarctions, MACE, cardiovascular deaths,
 333 and all-cause deaths (see Table 5). The total number of patients with stroke was 5 (0.5%) and 4
 334 (0.5%) in the rosiglitazone plus insulin and insulin groups, respectively. The use of rosiglitazone
 335 in combination with insulin may increase the risk of myocardial infarction [See Warnings and
 336 Precautions (5.1).]
 337

338 **Table 5. Occurrence of Cardiovascular Events for Rosiglitazone in Combination With**
 339 **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)

340 ND = not defined

341 ^a Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial
 342 infarction would be counted in 4 event categories (myocardial infarction; myocardial
 343 infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).
 344

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

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

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

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

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

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

376 Mortality in Observational Studies of Rosiglitazone Compared to Pioglitazone:

377 Three observational studies in elderly diabetic patients (age 65 years and older) found that
378 rosiglitazone statistically significantly increased the risk of all-cause mortality compared to use
379 of pioglitazone.²⁻⁴ One observational study⁵ in patients with a mean age of 54 years found no
380 difference in all-cause mortality between patients treated with rosiglitazone compared to
381 pioglitazone and reported similar results in the subpopulation of patients >65 years of age. One
382 additional small, prospective, observational study¹⁰ found no statistically significant differences
383 for CV mortality and all-cause mortality in patients treated with rosiglitazone compared to
384 pioglitazone.

385 **5.4 Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program**

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

395 **5.5 Edema**

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

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

408 5.6 Weight Gain

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

413

414 Table 6. 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
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	

415 In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed
 416 with type 2 diabetes not previously treated with antidiabetic medication, the median weight
 417 change (25th, 75th percentiles) from baseline at 4 years was 3.5 kg (0.0, 8.1) for rosiglitazone,
 418 2.0 kg (-1.0, 4.8) for glyburide, and -2.4 kg (-5.4, 0.5) for metformin.

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

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

425 **5.7 Hepatic Effects**

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

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

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

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

449 **5.8 Macular Edema**

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

460 **5.9 Fractures**

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

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

473 **5.10 Hematologic Effects**

474 Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult
475 patients treated with rosiglitazone [*see Adverse Reactions (6.2)*]. The observed changes may be
476 related to the increased plasma volume observed with treatment with rosiglitazone and may be
477 dose-related. The decrease in hemoglobin was seen more frequently in combination rosiglitazone
478 and metformin therapy than in rosiglitazone therapy alone. Vitamin B₁₂ deficiency may
479 contribute to the observed reductions in hemoglobin [*see Warnings and Precautions (5.11)*].
480 Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red
481 blood cell indices) should be performed, at least on an annual basis.

482 **5.11 Vitamin B₁₂ Levels**

483 In controlled clinical trials of metformin of 29 weeks' duration, a decrease to subnormal
484 levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, was
485 observed in approximately 7% of patients. Such decrease, possibly due to interference with B₁₂
486 absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia
487 and appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂
488 supplementation. Certain individuals (those with inadequate vitamin B₁₂ or calcium intake or
489 absorption) appear to be predisposed to developing subnormal vitamin B₁₂ levels. In these
490 patients, routine serum vitamin B₁₂ measurements at 2- to 3-year intervals may be useful.
491 Vitamin B₁₂ deficiency should be excluded if megaloblastic anemia is suspected. [*See Warnings
492 and Precautions (5.10).*]

493 **5.12 Diabetes and Blood Glucose Control**

494 Periodic fasting blood glucose and HbA_{1c} measurements should be performed to monitor
495 therapeutic response.

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

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

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

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

509 **5.13 Ovulation**

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

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

519 **6 ADVERSE REACTIONS**

520 **6.1 Clinical Trial Experience**

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

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

530

531 Table 7. Adverse Events ($\geq 5\%$ for Rosiglitazone Plus Metformin) Reported by Patients in
 532 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

533
 534 Reports of hypoglycemia in patients treated with rosiglitazone added to maximum
 535 metformin therapy in double-blind trials were more frequent (3.0%) than in patients treated with
 536 rosiglitazone (0.6%) or metformin monotherapies (1.3%) or placebo (0.2%). Overall, anemia and
 537 edema were generally mild to moderate in severity and usually did not require discontinuation of
 538 treatment with rosiglitazone.

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

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

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

550 The incidence of edema was 7% when insulin was added to AVANDAMET compared to
 551 3% with insulin monotherapy. This trial excluded patients with pre-existing heart failure or new
 552 or worsening edema on AVANDAMET therapy. However, in 26-week double-blind, fixed-dose
 553 trials of rosiglitazone added to insulin, edema was reported with higher frequency (rosiglitazone
 554 in combination with insulin, 14.7%; insulin, 5.4%) [see *Warnings and Precautions* (5.2)].

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

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

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

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

570 In ADOPT, fractures were reported in a greater number of women treated with
 571 rosiglitazone (9.3%, 2.7/100 patient-years) compared to glyburide (3.5%, 1.3/100 patient-years)
 572 or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who
 573 received rosiglitazone were reported in the upper arm, hand, and foot. [See Warnings and
 574 Precautions (5.9).] The observed incidence of fractures for male patients was similar among the
 575 3 treatment groups.

576

577 **Table 8. On-Therapy Adverse Events (≥5 Events/100 Patient-Years [PY]) in Any**
 578 **Treatment Group Reported in a 4- to 6-Year Clinical Trial of Rosiglitazone as**
 579 **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

580

581 **6.2 Laboratory Abnormalities**

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

585 during the first 3 months following initiation of rosiglitazone therapy or following an increase in
586 rosiglitazone dose. The time course and magnitude of decreases were similar in patients treated
587 with a combination of rosiglitazone and other hypoglycemic agents or monotherapy with
588 rosiglitazone. Pre-treatment levels of hemoglobin and hematocrit were lower in patients in
589 metformin combination trials and may have contributed to the higher reporting rate of anemia. In
590 a single trial in pediatric patients, decreases in hemoglobin and hematocrit (mean decreases of
591 0.29 g/dL and 0.95%, respectively) were reported with rosiglitazone. White blood cell counts
592 also decreased slightly in adult patients treated with rosiglitazone. Decreases in hematologic
593 parameters may be related to increased plasma volume observed with rosiglitazone treatment.

594 In controlled clinical trials of metformin of 29 weeks' duration, a decrease to subnormal
595 levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, was
596 observed in approximately 7% of patients. Such a decrease, possibly due to interference with B₁₂
597 absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia
598 and appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂
599 supplementation.

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

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

606 In pre-approval controlled trials, 0.2% of patients treated with rosiglitazone had
607 reversible elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and
608 0.5% on active comparators. The ALT elevations in patients treated with rosiglitazone were
609 reversible. Hyperbilirubinemia was found in 0.3% of patients treated with rosiglitazone
610 compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In
611 pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic
612 failure. [*See Warnings and Precautions (5.7)*].

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

617 **6.3 Postmarketing Experience**

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

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

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

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

630 There are postmarketing reports with rosiglitazone of rash, pruritus, urticaria,
631 angioedema, anaphylactic reaction, Stevens-Johnson syndrome, and new onset or worsening
632 diabetic macular edema with decreased visual acuity [*see Warnings and Precautions (5.8)*].
633 (*See also GLUCOPHAGE[®] prescribing information.*)

634 **7 DRUG INTERACTIONS**

635 **7.1 Drugs Metabolized by Cytochrome P450**

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

641 **7.2 Cationic Drugs**

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

648 **7.3 Drugs That Produce Hyperglycemia**

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

652 **8 USE IN SPECIFIC POPULATIONS**

653 **8.1 Pregnancy**

654 Pregnancy Category C.

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

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

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

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

686 *Metformin:* Metformin was not teratogenic in rats and rabbits at doses up to
687 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended
688 human daily dose of 2,000 mg based on body surface area comparisons for rats and rabbits,
689 respectively. Determination of fetal concentrations demonstrated a partial placental barrier to
690 metformin.

691 **8.2 Labor and Delivery**

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

694 **8.3 Nursing Mothers**

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

700 **8.4 Pediatric Use**

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

703 **8.5 Geriatric Use**

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

713 **10 OVERDOSAGE**

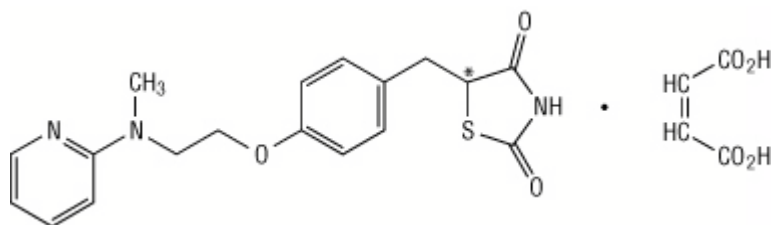
714 **Rosiglitazone:** Limited data are available with regard to overdosage in humans. In
715 clinical trials in volunteers, rosiglitazone has been administered at single oral doses of up to
716 20 mg and was well tolerated. In the event of an overdose, appropriate supportive treatment
717 should be initiated as dictated by the patient's clinical status.

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

723 **11 DESCRIPTION**

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

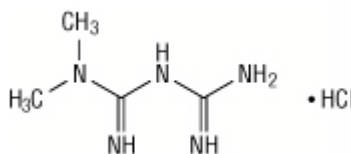
726 Rosiglitazone maleate is an oral antidiabetic agent, which acts primarily by increasing
727 insulin sensitivity. Rosiglitazone improves glycemic control while reducing circulating insulin
728 levels. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the
729 biguanides, or the alpha-glucosidase inhibitors. Chemically, rosiglitazone maleate is (±)-5-[[4-[2-
730 (methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (Z)-2-butenedioate
731 (1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral
732 center and is present as a racemate. Due to rapid interconversion, the enantiomers are
733 functionally indistinguishable. The molecular formula is C₁₈H₁₉N₃O₃S•C₄H₄O₄. Rosiglitazone
734 maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pK_a values
735 of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous
736 solution with pH of 2.3; solubility decreases with increasing pH in the physiological range. The
737 structural formula of rosiglitazone maleate is:



738

739 Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is
 740 not chemically or pharmacologically related to any other classes of oral antidiabetic agents.

741 Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula
 742 of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in
 743 water and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is
 744 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural
 745 formula of metformin hydrochloride is:



746

747 AVANDAMET is available for oral administration as film-coated tablets containing
 748 rosiglitazone maleate and metformin hydrochloride equivalent to: 2 mg rosiglitazone with
 749 500 mg metformin hydrochloride (2 mg/500 mg), 4 mg rosiglitazone with 500 mg metformin
 750 hydrochloride (4 mg/500 mg), 2 mg rosiglitazone with 1,000 mg metformin hydrochloride
 751 (2 mg/1,000 mg), and 4 mg rosiglitazone with 1,000 mg metformin hydrochloride
 752 (4 mg/1,000 mg). Inactive ingredients are: Hypromellose 2910, lactose monohydrate, magnesium
 753 stearate, microcrystalline cellulose, polyethylene glycol 400, povidone 29-32, sodium starch
 754 glycolate, titanium dioxide, and 1 or more of the following: Red and yellow iron oxides.

755 12 CLINICAL PHARMACOLOGY

756 12.1 Mechanism of Action

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

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

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

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

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

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

790 **12.2 Pharmacodynamics**

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

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

797

798 Table 9. Summary of Mean^a Lipid Changes in a 32-Week Trial of AVANDAMET in
 799 Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Diet
 800 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%

801 ^a Data presented as geometric means throughout table.

802 ^b N = number of subjects with a baseline and end of treatment value.

803

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

808 **12.3 Pharmacokinetics**

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

814

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

Regimen	N	Pharmacokinetic Parameter			
		AUC _{0-inf} (ng.h/mL)	C _{max} (ng/mL)	T _{max} ^a (h)	T _{1/2} (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)

816 ^a Median and range presented for T_{max}.817 Regimen A = 4 mg/500 mg AVANDAMET; Regimen B = 4 mg rosiglitazone tablet + 500 mg
818 metformin tablet; Regimen C = 1 mg/500 mg AVANDAMET819
820 Administration of AVANDAMET 4 mg/500 mg with food resulted in no change in
821 overall exposure (AUC) for either rosiglitazone or metformin. However, there were decreases in
822 C_{max} of both components (22% for rosiglitazone and 15% for metformin, respectively) and a
823 delay in T_{max} of both components (1.5 hours for rosiglitazone and 0.5 hours for metformin,
824 respectively). These changes are not likely to be clinically significant. The pharmacokinetics of
825 both the rosiglitazone component and the metformin component of AVANDAMET when taken
826 with food were similar to the pharmacokinetics of rosiglitazone and metformin when
827 administered concomitantly as separate tablets with food.828 **Absorption: Rosiglitazone:** The absolute bioavailability of rosiglitazone is 99%. Peak
829 plasma concentrations are observed about 1 hour after dosing. Maximum plasma concentration
830 (C_{max}) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional
831 manner over the therapeutic dose range.832 **Absorption: Metformin:** The absolute bioavailability of a 500 mg metformin tablet given
833 under fasting conditions is approximately 50% to 60%. Trials using single oral doses of
834 metformin tablets of 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack
835 of dose proportionality with increasing doses, which is due to decreased absorption rather than
836 an alteration in elimination.

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

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

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

858 Metabolism and Excretion: Metformin: Intravenous single-dose trials in normal
859 subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo
860 hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal
861 clearance is approximately 3.5 times greater than creatinine clearance which indicates that
862 tubular secretion is the major route of metformin elimination. Following oral administration,
863 approximately 90% of the absorbed drug is eliminated via the renal route within the first
864 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the
865 elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a
866 compartment of distribution.

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

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

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

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

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

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

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

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

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

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

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

911 **12.4 Drug-Drug Interactions**

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

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

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

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

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

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

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

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

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

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

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

960 **13 NONCLINICAL TOXICOLOGY**

961 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

964 Rosiglitazone: A 2-year carcinogenicity study was conducted in Charles River CD-1
965 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately
966 12 times human AUC at the maximum recommended human daily dose of the rosiglitazone
967 component of AVANDAMET). Sprague-Dawley rats were dosed for 2 years by oral gavage at
968 doses of 0.05, 0.3, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times
969 human AUC at the maximum recommended human daily dose of the rosiglitazone component of
970 AVANDAMET for male and female rats, respectively).

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

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

984 Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day
985 (approximately 116 times human AUC at the maximum recommended human daily dose of the
986 rosiglitazone component of AVANDAMET). Rosiglitazone altered estrous cyclicity
987 (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower
988 plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the
989 maximum recommended human daily dose of the rosiglitazone component of AVANDAMET,
990 respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC
991 at the maximum recommended human daily dose of the rosiglitazone component of
992 AVANDAMET). In juvenile rats dosed from 27 days of age through to sexual maturity (at up to
993 40 mg/kg/day), there was no effect on male reproductive performance, or on estrous cyclicity,

994 mating performance or pregnancy incidence in females (approximately 68 times human AUC at
995 the maximum recommended daily dose of rosiglitazone). In monkeys, rosiglitazone (0.6 and
996 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended
997 human daily dose of the rosiglitazone component of AVANDAMET, respectively) diminished
998 the follicular phase rise in serum estradiol with consequential reduction in the luteinizing
999 hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for
1000 these effects appears to be direct inhibition of ovarian steroidogenesis.

1001 **Metformin:** Long-term carcinogenicity studies have been performed in rats (dosing
1002 duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including
1003 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately 4 times
1004 the maximum recommended human daily dose of 2,000 mg of the metformin component of
1005 AVANDAMET based on body surface area comparisons. No evidence of carcinogenicity with
1006 metformin was found in either male or female mice. Similarly, there was no tumorigenic
1007 potential observed with metformin in male rats. There was, however, an increased incidence of
1008 benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

1009 There was no evidence of mutagenic potential of metformin in the following in vitro
1010 tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal
1011 aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also
1012 negative.

1013 Fertility of male or female rats was unaffected by metformin when administered at doses
1014 as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human
1015 daily dose of the metformin component of AVANDAMET based on body surface area
1016 comparisons.

1017 **13.2 Animal Toxicology**

1018 Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs
1019 (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at
1020 the maximum recommended human daily dose of the rosiglitazone component of
1021 AVANDAMET, respectively). Effects in juvenile rats were consistent with those seen in adults.
1022 Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues,
1023 which may be due to increased heart work as a result of plasma volume expansion.

1024 **14 CLINICAL STUDIES**

1025 AVANDAMET was not studied in patients previously treated with metformin
1026 monotherapy; however, the combination of rosiglitazone and metformin was compared to
1027 rosiglitazone and metformin monotherapies in clinical trials. Bioequivalence between
1028 AVANDAMET and coadministered rosiglitazone tablets and metformin tablets has been
1029 demonstrated [*see Clinical Pharmacology (12.3)*].

1030 A total of 670 patients with type 2 diabetes participated in two 26-week, randomized,
1031 double-blind, placebo/active-controlled trials designed to assess the efficacy of rosiglitazone in
1032 combination with metformin. Rosiglitazone, administered in either once-daily or twice-daily

1033 dosing regimens, was added to the therapy of patients who were inadequately controlled on
 1034 2.5 grams/day of metformin.

1035 In one trial, patients inadequately controlled on 2.5 grams/day of metformin (mean
 1036 baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were randomized to receive
 1037 rosiglitazone 4 mg once daily, rosiglitazone 8 mg once daily, or placebo in addition to
 1038 metformin. A statistically significant improvement in FPG and HbA1c was observed in patients
 1039 treated with the combinations of metformin and rosiglitazone 4 mg once daily and rosiglitazone
 1040 8 mg once daily, versus patients continued on metformin alone (see Table 11).
 1041

1042 Table 11. Glycemic Parameters in a 26-Week Trial of Rosiglitazone Added to Metformin
 1043 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 $\geq 0.7\%$ decrease from baseline	11%	45%	52%

1044 ^a *P* <0.0001 compared to metformin.
 1045

1046 In a second 26-week trial, patients with type 2 diabetes inadequately controlled on
 1047 2.5 grams/day of metformin who were randomized to receive the combination of rosiglitazone
 1048 4 mg twice daily and metformin (N = 105) showed a statistically significant improvement in
 1049 glycemic control with a mean treatment effect for FPG of -56 mg/dL and a mean treatment effect
 1050 for HbA1c of -0.8% over metformin alone. The combination of metformin and rosiglitazone
 1051 resulted in lower levels of FPG and HbA1c than either agent alone.

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1083 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1084 Each film-coated oval tablet contains rosiglitazone as the maleate and metformin
 1085 hydrochloride as follows:

- 1086 2 mg/500 mg – pale pink, tablet, debossed with gsk on one side and 2/500 on the other.
- 1087 4 mg/500 mg – orange, tablet, debossed with gsk on one side and 4/500 on the other.
- 1088 2 mg/1,000 mg – yellow, tablet, debossed with gsk on one side and 2/1000 on the other.
- 1089 4 mg/1,000 mg – pink, tablet, debossed with gsk on one side and 4/1000 on the other.

- 1091 2 mg/500 mg bottles of 60: NDC 0173-0837-18
- 1092 4 mg/500 mg bottles of 60: NDC 0173-0839-18

1093 2 mg/1,000 mg bottles of 60: NDC 0173-0838-18

1094 4 mg/1,000 mg bottles of 60: NDC 0173-0840-18

1095

1096 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Dispense in a
1097 tight, light-resistant container.

1098 **17 PATIENT COUNSELING INFORMATION**

1099 See Medication Guide.

1100 **17.1 Patient Advice**

1101 There are multiple medications available to treat type 2 diabetes. The benefits and risks
1102 of each available diabetes medication should be taken into account when choosing a particular
1103 diabetes medication for a given patient.

1104 Patients should be informed of the risks and benefits of AVANDAMET. AVANDAMET
1105 should only be taken by adults with type 2 diabetes who are already taking rosiglitazone, or who
1106 are not already taking rosiglitazone and are unable to achieve adequate glycemic control on other
1107 diabetes medications, and, in consultation with their healthcare provider, have decided not to
1108 take pioglitazone (ACTOS) or pioglitazone-containing medications (ACTOPLUS MET,
1109 ACTOPLUS MET XR, DUETACT) for medical reasons. Inform patients that they must be
1110 enrolled in the AVANDIA-Rosiglitazone Medicines Access Program in order to receive
1111 AVANDAMET.

1112 Patients should be informed of the following:

- 1113 • The risks of lactic acidosis, its symptoms, and conditions that predispose to its development,
1114 as noted in the WARNINGS and PRECAUTIONS sections, should be explained to patients.
1115 Patients should be advised to discontinue AVANDAMET immediately and to promptly
1116 notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual
1117 somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose
1118 level of AVANDAMET, gastrointestinal symptoms, which are common during initiation of
1119 metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal
1120 symptoms could be due to lactic acidosis or other serious disease.
- 1121 • Avoid excessive alcohol intake, either acute or chronic, while receiving AVANDAMET.
- 1122 • AVANDAMET is not recommended for patients with symptomatic heart failure.
- 1123 • Results of a set of clinical trials suggest that treatment with AVANDAMET is associated
1124 with an increased risk for myocardial infarction (heart attack), especially in patients taking
1125 insulin. Clinical trials have not shown any difference between rosiglitazone and comparator
1126 medications in overall mortality or CV-related mortality.
- 1127 • AVANDAMET is not recommended for patients who are taking insulin.
- 1128 • Management of type 2 diabetes should include diet control. Caloric restriction, weight loss,
1129 and exercise are essential for the proper treatment of the diabetic patient because they help
1130 improve insulin sensitivity. This is important not only in the primary treatment of type 2
1131 diabetes but also in maintaining the efficacy of drug therapy.

- 1132 • It is important to adhere to dietary instructions and to regularly have blood glucose,
1133 glycosylated hemoglobin (HbA1c), renal function, and hematologic parameters tested. It can
1134 take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of
1135 AVANDAMET.
- 1136 • Blood will be drawn to check their liver function prior to the start of therapy and periodically
1137 thereafter per the clinical judgment of the healthcare professional. Patients with unexplained
1138 symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should
1139 immediately report these symptoms to their physician.
- 1140 • Patients who experience an unusually rapid increase in weight or edema or who develop
1141 shortness of breath or other symptoms of heart failure while on AVANDAMET should
1142 immediately report these symptoms to their physician.
- 1143 • Therapy with AVANDAMET, like other thiazolidinediones, may result in ovulation in some
1144 premenopausal anovulatory women. As a result, these patients may be at an increased risk for
1145 pregnancy while taking AVANDAMET. Thus, adequate contraception in premenopausal
1146 women should be recommended. This possible effect has not been specifically investigated
1147 in clinical trials so the frequency of this occurrence is not known.

1148
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1163 **MEDICATION GUIDE**
1164 **AVANDAMET® (ah-VAN-duh-met)**

1165 **(rosiglitazone maleate and metformin hydrochloride) Tablets**
1166

1167 Read this Medication Guide carefully before you start taking AVANDAMET and each
1168 time you get a refill. There may be new information. This information does not take
1169 the place of talking with your doctor about your medical condition or your
1170 treatment. If you have any questions about AVANDAMET, ask your doctor or
1171 pharmacist.

1172
1173 **What is the most important information I should know about AVANDAMET?**
1174 **AVANDAMET may cause serious side effects, including:**

1175
1176 AVANDAMET is available only through the AVANDIA-Rosiglitazone Medicines Access
1177 Program. Both you and your doctor must be enrolled in the program so that you
1178 can get AVANDAMET. To enroll, you must:

- 1179 • talk to your doctor,
 - 1180 • understand the risks and benefits of AVANDAMET, and
 - 1181 • agree to enroll in the program.
- 1182

1183 **New or worse heart failure**

- 1184 • Rosiglitazone, one of the medicines in AVANDAMET, can cause your body to
1185 keep extra fluid (fluid retention), which leads to swelling (edema) and weight
1186 gain. Extra body fluid can make some heart problems worse or lead to heart
1187 failure. Heart failure means your heart does not pump blood well enough.
 - 1188 • If you have severe heart failure, you cannot start AVANDAMET.
 - 1189 • If you have heart failure with symptoms (such as shortness of breath or
1190 swelling), even if these symptoms are not severe, AVANDAMET may not be right
1191 for you.
- 1192

1193 Call your doctor right away if you have any of the following:

- 1194 • swelling or fluid retention, especially in the ankles or legs
 - 1195 • shortness of breath or trouble breathing, especially when you lie down
 - 1196 • an unusually fast increase in weight
 - 1197 • unusual tiredness
- 1198

1199 **Myocardial Infarction (“Heart Attack”)**

1200 Rosiglitazone, one of the medicines in AVANDAMET, may raise the risk of heart
1201 attack. The risk of having a heart attack may be higher in people who take

1202 AVANDAMET with insulin. Most people who take insulin should not also take
1203 AVANDAMET.
1204

1205 **Symptoms of a heart attack can include the following:**

- 1206 • chest discomfort in the center of your chest that lasts for more than a few
1207 minutes, or that goes away or comes back
- 1208 • chest discomfort that feels like uncomfortable pressure, squeezing, fullness or
1209 pain
- 1210 • pain or discomfort in your arms, back, neck, jaw or stomach
- 1211 • shortness of breath with or without chest discomfort
- 1212 • breaking out in a cold sweat
- 1213 • nausea or vomiting
- 1214 • feeling lightheaded

1215 **Call your doctor or go to the nearest hospital emergency room right away if**
1216 **you think you are having a heart attack.**

1217
1218 People with diabetes have a greater risk for heart problems. It is important to work
1219 with your doctor to manage other conditions, such as high blood pressure or high
1220 cholesterol.

1221
1222 **Lactic acidosis**

1223 Metformin, one of the medicines in AVANDAMET, can cause a rare but serious
1224 condition called lactic acidosis (a build-up of an acid in the blood) that can cause
1225 death. Lactic acidosis is a medical emergency and must be treated in the hospital.

1226
1227 Most people who have had lactic acidosis with metformin have other things that,
1228 combined with the metformin, led to the lactic acidosis. Tell your doctor if you have
1229 any of the following, because you have a higher chance for getting lactic acidosis
1230 with AVANDAMET if you:

- 1231 • have kidney problems or your kidneys are affected by certain X-ray tests that
1232 use injectable dye. People with kidney problems should not take AVANDAMET.
- 1233 • have liver problems
- 1234 • drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking
- 1235 • get dehydrated (lose a large amount of body fluids). This can happen if you are
1236 sick with a fever, vomiting or diarrhea. Dehydration can also happen when you
1237 sweat a lot with activity or exercise and do not drink enough fluids.
- 1238 • have surgery
- 1239 • have a heart attack, severe infection, or stroke
- 1240 • are 80 years of age or older, and your kidneys are not working properly

1241

1242 The best way to keep from having a problem with lactic acidosis from metformin is
1243 to tell your doctor if you have any of the problems in the list above. Your doctor
1244 may decide to stop your AVANDAMET for a while if you have any of these things.

1245

1246 Lactic acidosis can be hard to diagnose early, because the early symptoms could
1247 seem like the symptoms of many other health problems besides lactic acidosis. You
1248 should call your doctor right away if you get the following symptoms, which could
1249 be signs of lactic acidosis:

- 1250 • you feel very weak or tired
- 1251 • you have unusual (not normal) muscle pain
- 1252 • you have stomach pains
- 1253 • you have trouble breathing
- 1254 • you feel dizzy or lightheaded
- 1255 • you have a slow or irregular heartbeat

1256

1257 AVANDAMET can have other serious side effects. Be sure to read the section below
1258 “What are possible side effects of AVANDAMET?”.

1259

1260 **What is AVANDAMET?**

1261 AVANDAMET contains two prescription medicines for treating diabetes, rosiglitazone
1262 maleate (AVANDIA) and metformin hydrochloride. AVANDAMET is used, with diet
1263 and exercise, to treat certain adults with type 2 (“adult-onset” or “non-insulin
1264 dependent”) diabetes (“high blood sugar”) who are:

- 1265 • already taking rosiglitazone or rosiglitazone-containing products
- 1266 • unable to control their blood sugar on other diabetes medicines, and after
1267 talking with their doctor have decided not to take pioglitazone (ACTOS) or
1268 pioglitazone-containing products (ACTOPLUS MET, ACTOPLUS MET XR,
1269 DUETACT)

1270

1271 Metformin works mainly by decreasing the production of sugar by your liver.
1272 Rosiglitazone helps your body respond better to its natural insulin and does not
1273 cause your body to make more insulin. These medicines work together to help
1274 control your blood sugar. AVANDAMET may be used alone or with other diabetes
1275 medicines.

1276

1277 AVANDAMET is not for people with type 1 diabetes mellitus or to treat a condition
1278 called diabetic ketoacidosis.

1279

1280 It is not known if AVANDAMET is safe and effective in children under 18 years old.

1281

1282 **Who should not take AVANDAMET?**

1283 Do not take AVANDAMET if you:

- 1284 • have kidney problems. Before you take AVANDAMET and while you take it, your
1285 doctor should test your blood to check for signs of kidney problems.
- 1286 • have a condition known as metabolic acidosis, including diabetic ketoacidosis.
- 1287 • are going to have an x-ray procedure with an injection of dyes (contrast agents)
1288 in your vein with a needle. Talk to your doctor about when to stop AVANDAMET
1289 and when to start it again.

1290

1291 Many people with heart failure should not start taking AVANDAMET. See “What
1292 should I tell my doctor before taking AVANDAMET?”.

1293

1294 **What should I tell my doctor before taking AVANDAMET?**

1295 Before starting AVANDAMET, ask your doctor about what the choices are for
1296 diabetes medicines, and what the expected benefits and possible risks are for you
1297 in particular.

1298

1299 Before taking AVANDAMET, tell your doctor about all your medical conditions,
1300 including if you:

- 1301 • **have heart problems or heart failure**
- 1302 • **have kidney problems**
- 1303 • **have type 1 (“juvenile”) diabetes or had diabetic ketoacidosis.** These
1304 conditions should be treated with insulin.
- 1305 • **are going to have dye injected into a vein for an X-ray, CAT scan, heart**
1306 **study, or other type of scanning**
- 1307 • **drink a lot of alcohol** (all the time or short binge drinking).
- 1308 • **develop a serious condition such as a heart attack, severe infection, or a**
1309 **stroke.**
- 1310 • **are 80 years old or older.** People who are over 80 years old should not take
1311 AVANDAMET unless their kidney function is checked and it is normal.
- 1312 • **have a type of diabetic eye disease called macular edema** (swelling of the
1313 back of the eye).
- 1314 • **have liver problems.** Your doctor should do blood tests to check your liver
1315 before you start taking AVANDAMET and during treatment as needed.
- 1316 • **had liver problems while taking REZULIN[®]** (troglitazone), another medicine
1317 for diabetes.
- 1318 • **are pregnant or plan to become pregnant.** AVANDAMET should not be used
1319 during pregnancy. It is not known if AVANDAMET can harm your unborn baby.
1320 You and your doctor should talk about the best way to control your diabetes
1321 during pregnancy. If you are a premenopausal woman (before the “change of

1322 life”) who does not have regular monthly periods, AVANDAMET may increase
1323 your chances of becoming pregnant. Talk to your doctor about birth control
1324 choices while taking AVANDAMET. Tell your doctor right away if you become
1325 pregnant while taking AVANDAMET.

1326 • **are breast-feeding or planning to breast-feed.** It is not known if
1327 AVANDAMET passes into breast milk. You should not use AVANDAMET while
1328 breast-feeding.

1329
1330 Tell your doctor about all the medicines you take including prescription and non-
1331 prescription medicines, vitamins or herbal supplements. AVANDAMET and certain
1332 other medicines can affect each other and may lead to serious side effects including
1333 high or low blood sugar, or heart problems. Your doctor may need to change your
1334 dose of AVANDAMET or your other medicines. Especially tell your doctor if you take:

1335 • **insulin.**
1336 • **any medicines for high blood pressure, high cholesterol or heart failure,**
1337 **or for prevention of heart disease or stroke.**

1338
1339 Know the medicines you take. Keep a list of all your medicines and show it to your
1340 doctor and pharmacist before you start a new medicine. They will tell you if it is
1341 alright to take AVANDAMET with other medicines.

1342

1343 **How should I take AVANDAMET?**

1344 • Take AVANDAMET exactly as prescribed. Your doctor may need to change your
1345 dose until your blood sugar is better controlled.
1346 • AVANDAMET should be taken by mouth and with meals.
1347 • AVANDAMET may be prescribed alone or with other diabetes medicines. This will
1348 depend on how well your blood sugar is controlled.
1349 • It can take 2 weeks for AVANDAMET to start lowering your blood sugar. It may
1350 take 2 to 3 months to see the full effect on your blood sugar level.
1351 • If you miss a dose of AVANDAMET, take it as soon as you remember, unless it is
1352 time to take your next dose. Take your next dose at the usual time. Do not take
1353 double doses to make up for a missed dose.
1354 • If you take too much AVANDAMET, call your doctor or poison control center right
1355 away.
1356 • Test your blood sugar regularly as your doctor tells you.
1357 • Diet and exercise can help your body use its blood sugar better. It is important
1358 to stay on your recommended diet, lose extra weight, and get regular exercise
1359 while taking AVANDAMET.
1360 • Your doctor should do blood tests to check your liver and kidneys before you
1361 start AVANDAMET and during treatment as needed. Your doctor should also do

1362 regular blood sugar tests (for example, "A1C") to monitor your response to
1363 AVANDAMET.

1364

1365 There may be times when you will need to stop taking AVANDAMET for a short
1366 time. Tell your doctor if you:

- 1367 • are sick with severe vomiting, diarrhea or fever, or if you drink a much lower
1368 amount of liquid than normal.
- 1369 • are going to have dye injected into a vein for an X-ray, CAT scan, heart study or
1370 other type of scanning.
- 1371 • plan to have surgery.

1372

1373 **What should I avoid while taking AVANDAMET?**

1374 Do not drink a lot of alcohol while taking AVANDAMET. This means you should not
1375 "binge drink", and you should not drink a lot of alcohol on a regular basis. Drinking
1376 a lot of alcohol can increase the chance of getting lactic acidosis.

1377

1378 **What are possible side effects of AVANDAMET?**

1379 **AVANDAMET may cause serious side effects, including:**

- 1380 • **New or worse heart failure.** See "What is the most important information I
1381 should know about AVANDAMET?".
- 1382 • **Heart attack.** See "What is the most important information I should know
1383 about AVANDAMET?".
- 1384 • **Swelling (edema).** AVANDAMET can cause swelling due to fluid retention. See
1385 "What is the most important information I should know about AVANDAMET?".
- 1386 • **Weight gain.** Rosiglitazone, one of the medicines in AVANDAMET, can cause
1387 weight gain that may be due to fluid retention or extra body fat. Metformin, the
1388 other medicine in AVANDAMET, can cause weight loss. There is little change in
1389 weight with AVANDAMET. Weight gain can be a serious problem for people with
1390 certain conditions including heart problems. See "What is the most important
1391 information I should know about AVANDAMET?".
- 1392 • **Liver problems.** It is important for your liver to be working normally when you
1393 take AVANDAMET. Your doctor should do blood tests to check your liver before
1394 you start taking AVANDAMET and during treatment as needed. Call your doctor
1395 right away if you have unexplained symptoms such as:
 - 1396 • nausea or vomiting
 - 1397 • stomach pain
 - 1398 • unusual or unexplained tiredness
 - 1399 • loss of appetite
 - 1400 • dark urine
 - 1401 • yellowing of your skin or the whites of your eyes.

- 1402 • **Macular edema** (a diabetic eye disease with swelling in the back of the eye).
1403 Tell your doctor right away if you have any changes in your vision. Your doctor
1404 should check your eyes regularly. Very rarely, some people have had vision
1405 changes due to swelling in the back of the eye while taking rosiglitazone, one of
1406 the medicines in AVANDAMET.
- 1407 • **Fractures (broken bones)**, usually in the hand, upper arm or foot. Talk to
1408 your doctor for advice on how to keep your bones healthy.
- 1409 • **Low red blood cell count (anemia)**.
- 1410 • **Low blood sugar (hypoglycemia)**. Lightheadedness, dizziness, shakiness or
1411 hunger may mean that your blood sugar is too low. This can happen if you skip
1412 meals, if you use another medicine that lowers blood sugar, or if you have
1413 certain medical problems. Call your doctor if low blood sugar levels are a
1414 problem for you.
- 1415 • **Ovulation** (release of egg from an ovary in a woman) leading to pregnancy.
1416 Ovulation may happen in premenopausal women who do not have regular
1417 monthly periods. This can increase the chance of pregnancy. See “What should I
1418 tell my doctor before taking AVANDAMET?”.

1419

1420 **Common side effects of AVANDAMET include:**

- 1421 • **Diarrhea, nausea, and upset stomach.** These side effects usually happen
1422 during the first few weeks of treatment. Taking AVANDAMET with food can help
1423 lessen these side effects. If you have unusual or unexpected stomach problems,
1424 talk with your doctor. Stomach problems that start up later during treatment
1425 with AVANDAMET may be a sign of something more serious and should be
1426 discussed with your doctor.
- 1427 • **Cold-like symptoms**
- 1428 • **Headache**
- 1429 • **Joint aches**
- 1430 • **Dizziness**

1431

1432 Call your doctor for medical advice about side effects. You may report side effects
1433 to FDA at 1-800-FDA-1088.

1434

1435 **How should I store AVANDAMET?**

- 1436 • Store AVANDAMET at room temperature, 59° to 86°F (15° to 30°C).
1437 • Keep AVANDAMET in the container it comes in. Keep the container closed
1438 tightly.
1439 • Safely, throw away AVANDAMET that is out of date or no longer needed.

1440

1441 Keep AVANDAMET and all medicines out of the reach of children.

1442

1443 **General information about AVANDAMET**

1444 Medicines are sometimes prescribed for purposes other than those listed in a
1445 Medication Guide. Do not use AVANDAMET for a condition for which it was not
1446 prescribed. Do not give AVANDAMET to other people, even if they have the same
1447 symptoms you have. It may harm them.

1448

1449 This Medication Guide summarizes important information about AVANDAMET. If you
1450 would like more information, talk with your doctor. You can ask your doctor or
1451 pharmacist for information about AVANDAMET that is written for healthcare
1452 professionals. You can also find out more about AVANDAMET by calling 1-888-825-
1453 5249.

1454

1455 **What are the ingredients in AVANDAMET?**

1456 Active Ingredients: Rosiglitazone maleate and metformin hydrochloride

1457 Inactive Ingredients: Hypromellose 2910, lactose monohydrate, magnesium
1458 stearate, microcrystalline cellulose, polyethylene glycol 400, povidone 29-32,
1459 sodium starch glycolate, titanium dioxide, and 1 or more of the following: Red and
1460 yellow iron oxides.

1461

1462 Always check to make sure that the medicine you are taking is the correct one.
1463 AVANDAMET tablets are oval and look like this:

- 1464 • 2 mg/500 mg – pale pink, with “gsk” on one side and “2/500” on the other.
- 1465 • 4 mg/500 mg – orange, with “gsk” on one side and “4/500” on the other
- 1466 • 2 mg/1,000 mg – yellow, with “gsk” on one side and “2/1000” on the other
- 1467 • 4 mg/1,000 mg – pink, with “gsk” on one side and “4/1000” on the other

1468

1469 AVANDAMET and AVANDIA are registered trademarks of GlaxoSmithKline.

1470 The other brands listed are trademarks of their respective owners and are not
1471 trademarks of GlaxoSmithKline. The makers of these brands are not affiliated with
1472 and do not endorse GlaxoSmithKline or its products.

1473

1474 **This Medication Guide has been approved by the U.S. Food and Drug
1475 Administration.**

1476



1477

1478 GlaxoSmithKline

1479 Research Triangle Park, NC 27709

1480

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1482

1483 Month 2011

1484 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

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1 FULL PRESCRIBING INFORMATION

2 **WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION**

- 3 ● Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in
4 some patients [see *Warnings and Precautions (5.2)*]. After initiation of AVANDARYL, and
5 after dose increases, observe patients carefully for signs and symptoms of heart failure
6 (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms
7 develop, the heart failure should be managed according to current standards of care.
8 Furthermore, discontinuation or dose reduction of AVANDARYL must be considered.
- 9 ● AVANDARYL is not recommended in patients with symptomatic heart failure. Initiation of
10 AVANDARYL in patients with established NYHA Class III or IV heart failure is
11 contraindicated. [See *Contraindications (4) and Warnings and Precautions (5.2)*.]
- 12 ● A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of
13 which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an
14 increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067
15 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or
16 placebo, showed a statistically non-significant increased risk of myocardial infarction, and a
17 statistically non-significant decreased risk of death. There have been no clinical trials directly
18 comparing cardiovascular risk of rosiglitazone and ACTOS[®] (pioglitazone, another
19 thiazolidinedione), but in a separate trial, pioglitazone (when compared to placebo) did not
20 show an increased risk of myocardial infarction or death. [See *Warnings and Precautions*
21 *(5.3)*.]
- 22 ● Because of the potential increased risk of myocardial infarction, AVANDARYL is available
23 only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines
24 Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1-
25 800-AVANDIA or visit www.AVANDIA.com. [See *Warnings and Precautions (5.4)*.]

26 **1 INDICATIONS AND USAGE**

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

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

36 **Other Important Limitations of Use:**

- 37 • Due to its mechanism of action, rosiglitazone is active only in the presence of endogenous
38 insulin. Therefore, AVANDARYL should not be used in patients with type 1 diabetes or for
39 the treatment of diabetic ketoacidosis.
40 • Coadministration of AVANDARYL with insulin is not recommended [see *Warnings and*
41 *Precautions (5.2, 5.3)*].

42 **2 DOSAGE AND ADMINISTRATION**

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

46 **2.1 Starting Dose**

47 The recommended starting dose is 4 mg/1 mg administered once daily with the first meal
48 of the day. For adults already treated with a sulfonylurea or rosiglitazone, a starting dose of
49 4 mg/2 mg may be considered.

50 All patients should start the rosiglitazone component of AVANDARYL at the lowest
51 recommended dose. Further increases in the dose of rosiglitazone should be accompanied by
52 careful monitoring for adverse events related to fluid retention [see **Boxed Warning and**
53 *Warnings and Precautions (5.6)*].

54 When switching from combination therapy of rosiglitazone plus glimepiride as separate
55 tablets, the usual starting dose of AVANDARYL is the dose of rosiglitazone and glimepiride
56 already being taken.

57 **2.2 Dose Titration**

58 Dose increases should be individualized according to the glycemic response of the
59 patient. Patients who may be more sensitive to glimepiride [see *Warnings and Precautions*
60 *(5.5)*], including the elderly, debilitated, or malnourished, and those with renal, hepatic, or
61 adrenal insufficiency, should be carefully titrated to avoid hypoglycemia. If hypoglycemia
62 occurs during up-titration of the dose or while maintained on therapy, a dosage reduction of the
63 glimepiride component of AVANDARYL may be considered. Increases in the dose of
64 rosiglitazone should be accompanied by careful monitoring for adverse events related to fluid
65 retention [see **Boxed Warning and Warnings and Precautions (5.6)].**

66 **To switch to AVANDARYL for adults currently treated with rosiglitazone,** dose
67 titration of the glimepiride component of AVANDARYL is recommended if patients are not
68 adequately controlled after 1 to 2 weeks. The glimepiride component may be increased in no
69 more than 2 mg increments. After an increase in the dosage of the glimepiride component, dose
70 titration of AVANDARYL is recommended if patients are not adequately controlled after 1 to 2
71 weeks.

72 **To switch to AVANDARYL for adults currently treated with sulfonylurea,** it may
73 take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of the
74 rosiglitazone component. Therefore, dose titration of the rosiglitazone component of

75 AVANDARYL is recommended if patients are not adequately controlled after 8 to 12 weeks.
76 Patients should be observed carefully (1 to 2 weeks) for hypoglycemia when being transferred
77 from longer half-life sulfonylureas (e.g., chlorpropamide) to AVANDARYL due to potential
78 overlapping of drug effect. After an increase in the dosage of the rosiglitazone component, dose
79 titration of AVANDARYL is recommended if patients are not adequately controlled after 2 to 3
80 months.

81 **2.3 Maximum Dose**

82 The maximum recommended daily dose is 8 mg rosiglitazone and 4 mg glimepiride.

83 **2.4 Specific Patient Populations**

84 Elderly and Malnourished Patients and Those With Renal, Hepatic, or Adrenal
85 Insufficiency: In elderly, debilitated, or malnourished patients, or in patients with renal, hepatic,
86 or adrenal insufficiency, the starting dose, dose increments, and maintenance dosage of
87 AVANDARYL should be conservative to avoid hypoglycemic reactions. [See *Warnings and*
88 *Precautions (5.5) and Clinical Pharmacology (12.3).*]

89 Hepatic Impairment: Liver enzymes should be measured prior to initiating treatment
90 with AVANDARYL. Therapy with AVANDARYL should not be initiated if the patient exhibits
91 clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X
92 upper limit of normal at start of therapy). After initiation of AVANDARYL, liver enzymes
93 should be monitored periodically per the clinical judgment of the healthcare professional. [See
94 *Warnings and Precautions (5.8) and Clinical Pharmacology (12.3).*]

95 Pregnancy and Lactation: AVANDARYL should not be used during pregnancy or in
96 nursing mothers.

97 Pediatric Use: Safety and effectiveness of AVANDARYL in pediatric patients have not
98 been established. AVANDARYL and its components, rosiglitazone and glimepiride, are not
99 recommended for use in pediatric patients.

100 **3 DOSAGE FORMS AND STRENGTHS**

101 Each rounded triangular tablet contains rosiglitazone maleate and glimepiride as follows:

- 102 • 4 mg/1 mg – yellow, gsk debossed on one side and 4/1 on the other.
- 103 • 4 mg/2 mg – orange, gsk debossed on one side and 4/2 on the other.
- 104 • 4 mg/4 mg – pink, gsk debossed on one side and 4/4 on the other.
- 105 • 8 mg/2 mg – pale pink, gsk debossed on one side and 8/2 on the other.
- 106 • 8 mg/4 mg – red, gsk debossed on one side and 8/4 on the other.

107 **4 CONTRAINDICATIONS**

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

110 **5 WARNINGS AND PRECAUTIONS**

111 **5.1 Increased Risk of Cardiovascular Mortality for Sulfonylurea Drugs**

112 The administration of oral hypoglycemic drugs has been reported to be associated
113 with increased cardiovascular mortality as compared to treatment with diet alone or diet
114 plus insulin. This warning is based on the trial conducted by the University Group Diabetes
115 Program (UGDP), a long-term, prospective clinical trial designed to evaluate the
116 effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in
117 patients with non-insulin-dependent diabetes. The trial involved 823 patients who were
118 randomly assigned to one of four treatment groups (*Diabetes* 1970;19[Suppl. 2]:747-830).
119 UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of
120 tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately
121 2½ times that of patients treated with diet alone. A significant increase in total mortality
122 was not observed, but the use of tolbutamide was discontinued based on the increase in
123 cardiovascular mortality, thus limiting the opportunity for the trial to show an increase in
124 overall mortality. Despite controversy regarding the interpretation of these results, the
125 findings of the UGDP trial provide an adequate basis for this warning. The patient should
126 be informed of the potential risks and advantages of glimepiride-containing tablets and of
127 alternative modes of therapy.

128 Although only one drug in the sulfonylurea class (tolbutamide) was included in this
129 trial, it is prudent from a safety standpoint to consider that this warning may also apply to
130 other oral hypoglycemic drugs in this class, in view of their close similarities in mode of
131 action and chemical structure.

132 **5.2 Cardiac Failure With Rosiglitazone**

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

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

149

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

Events	Rosiglitazone	Placebo
	N = 110	N = 114
	n (%)	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%)

153 ^a Includes hospitalization for any cardiovascular reason.
 154

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

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

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

166 **Congestive Heart Failure During Coadministration of Rosiglitazone With Insulin:**

167 In trials in which rosiglitazone was added to insulin, rosiglitazone increased the risk of
 168 congestive heart failure. Coadministration of rosiglitazone and insulin is not recommended. [See
 169 *Indications and Usage (1) and Warnings and Precautions (5.3)*.]

170 In 7 controlled, randomized, double-blind trials which had durations from 16 to 26 weeks
 171 and which were included in a meta-analysis¹ [see *Warnings and Precautions (5.3)*], patients with
 172 type 2 diabetes mellitus were randomized to coadministration of rosiglitazone and insulin

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

179 Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing
180 Rosiglitazone to Pioglitazone: Three observational studies²⁻⁴ in elderly diabetic patients (age
181 65 years and older) found that rosiglitazone statistically significantly increased the risk of
182 hospitalized heart failure compared to use of pioglitazone. One other observational study⁵ in
183 patients with a mean age of 54 years, which also included an analysis in a subpopulation of
184 patients >65 years of age, found no statistically significant increase in emergency department
185 visits or hospitalization for heart failure in patients treated with rosiglitazone compared to
186 pioglitazone in the older subgroup.

187 **5.3 Major Adverse Cardiovascular Events**

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

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

205

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

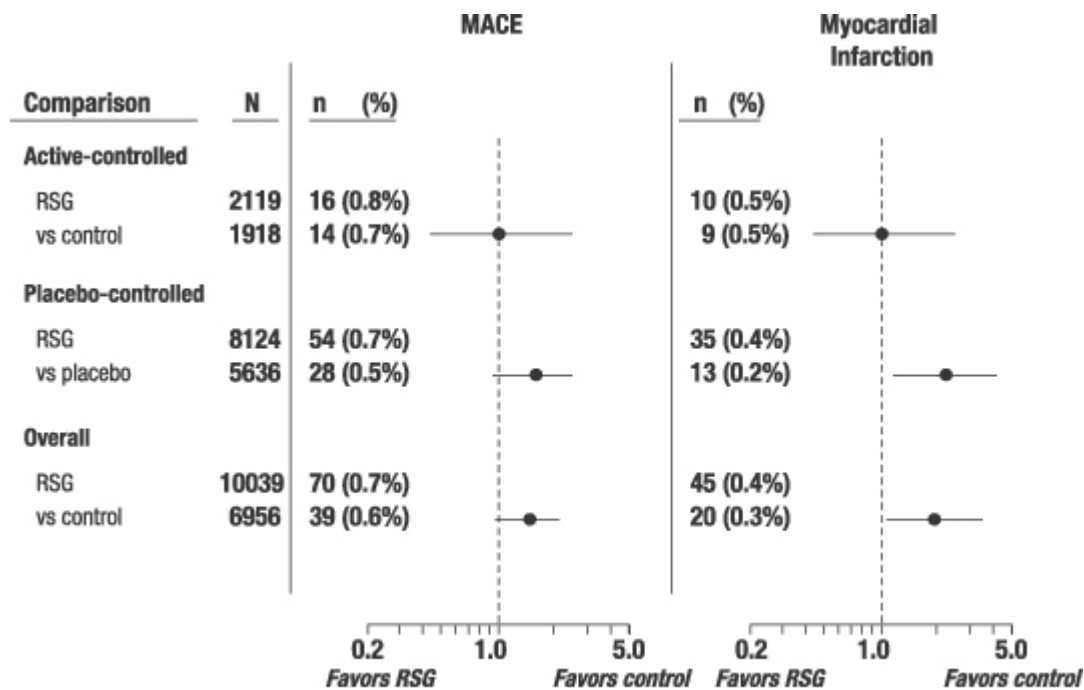
Event ^a	Rosiglitazone (N=10,039) n (%)	Comparator (N=6,956) n (%)
MACE (a composite of myocardial infarction, cardiovascular death, or stroke)	70 (0.7)	39 (0.6)
Myocardial Infarction	45 (0.4)	20 (0.3)
Cardiovascular Death	17 (0.2)	9 (0.1)
Stroke	18 (0.2)	16 (0.2)
All-cause Death	29 (0.3)	17 (0.2)

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

210
 211 In this analysis, a statistically significant increased risk of myocardial infarction with
 212 rosiglitazone versus pooled comparators was observed. Analyses were performed using a
 213 composite of major adverse cardiovascular events (myocardial infarction, stroke, and
 214 cardiovascular death), referred to hereafter as MACE. Rosiglitazone had a statistically non-
 215 significant increased risk of MACE compared to the pooled comparators. A statistically
 216 significant increased risk of myocardial infarction and statistically non-significant increased risk
 217 of MACE with rosiglitazone was observed in the placebo-controlled trials. In the active-
 218 controlled trials, there was no increased risk of myocardial infarction or MACE. (See Figure 1
 219 and Table 3.)
 220

221
222
223

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



224
225

RSG = rosiglitazone

226
227

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%)	

228
229

RSG = rosiglitazone

230
231
232
233
234

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

235 in combination with insulin may increase the risk of myocardial infarction [See Warnings and
236 Precautions (5.1).]
237

238 **Table 4. Occurrence of Cardiovascular Events for Rosiglitazone in Combination With**
239 **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)

240 ND = not defined

241 ^a Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial
242 infarction would be counted in 4 event categories (myocardial infarction; myocardial
243 infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).
244

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

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

256 In a long-term, randomized, placebo-controlled, 2x2 factorial trial intended to evaluate
257 rosiglitazone, and separately ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on
258 progression to overt diabetes in 5,269 subjects with glucose intolerance, the incidence of
259 myocardial infarction was higher in the subset of subjects who received rosiglitazone in
260 combination with ramipril than among subjects who received ramipril alone but not in the subset
261 of subjects who received rosiglitazone alone compared to placebo.⁶ The higher incidence of
262 myocardial infarction among subjects who received rosiglitazone in combination with ramipril
263 was not confirmed in the two other large (total N = 8,798) long-term, randomized, active-
264 controlled clinical trials conducted in patients with type 2 diabetes, in which 30% and 40% of
265 patients in the two trials reported angiotensin-converting enzyme inhibitor use at baseline.^{7,8}

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

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

276 Mortality in Observational Studies of Rosiglitazone Compared to Pioglitazone:

277 Three observational studies in elderly diabetic patients (age 65 years and older) found that
278 rosiglitazone statistically significantly increased the risk of all-cause mortality compared to use
279 of ACTOS (pioglitazone).²⁻⁴ One observational study⁵ in patients with a mean age of 54 years
280 found no difference in all-cause mortality between patients treated with rosiglitazone compared
281 to ACTOS (pioglitazone) and reported similar results in the subpopulation of patients >65 years
282 of age. One additional small, prospective, observational study¹⁰ found no statistically significant
283 differences for CV mortality and all-cause mortality in patients treated with rosiglitazone
284 compared to ACTOS (pioglitazone).

285 **5.4 Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program**

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

295 **5.5 Hypoglycemia**

296 AVANDARYL is a combination tablet containing rosiglitazone and glimepiride, a
297 sulfonylurea. All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper
298 patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Elderly
299 patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs.
300 Debilitated or malnourished patients, and those with adrenal, pituitary, renal, or hepatic
301 insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs.
302 A starting dose of 1 mg glimepiride, as contained in AVANDARYL 4 mg/1 mg, followed by
303 appropriate dose titration is recommended in these patients. [See *Clinical Pharmacology (12.3)*.]
304 Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-
305 adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur

306 when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or
307 when more than one glucose-lowering drug is used.

308 Patients receiving rosiglitazone in combination with a sulfonylurea may be at risk for
309 hypoglycemia, and a reduction in the dose of the sulfonylurea may be necessary [*see Dosage and*
310 *Administration (2.2)*].

311 **5.6 Edema**

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

315 Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can
316 exacerbate or lead to congestive heart failure, AVANDARYL should be used with caution in
317 patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart
318 failure [*see **Boxed Warning**, Warnings and Precautions (5.2), and Patient Counseling*
319 *Information (17.1)*].

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

325 **5.7 Weight Gain**

326 Dose-related weight gain was seen with AVANDARYL, rosiglitazone alone, and
327 rosiglitazone together with other hypoglycemic agents (see Table 5). The mechanism of weight
328 gain is unclear but probably involves a combination of fluid retention and fat accumulation.

329

330 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

331
 332 In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed
 333 with type 2 diabetes not previously treated with antidiabetic medication, the median weight
 334 change (25th, 75th percentiles) from baseline at 4 years was 3.5 kg (0.0, 8.1) for rosiglitazone,
 335 2.0 kg (-1.0, 4.8) for glyburide, and -2.4 kg (-5.4, 0.5) for metformin.

336 In postmarketing experience with rosiglitazone alone or in combination with other
 337 hypoglycemic agents, there have been rare reports of unusually rapid increases in weight and
 338 increases in excess of that generally observed in clinical trials. Patients who experience such
 339 increases should be assessed for fluid accumulation and volume-related events such as excessive
 340 edema and congestive heart failure [see **Boxed Warning**].

341 **5.8 Hepatic Effects**

342 With sulfonylureas, including glimepiride, there may be an elevation of liver enzyme
 343 levels in rare cases. In isolated instances, impairment of liver function (e.g., with cholestasis and
 344 jaundice), as well as hepatitis (which may also lead to liver failure) have been reported.

345 Liver enzymes should be measured prior to the initiation of therapy with AVANDARYL
 346 in all patients and periodically thereafter per the clinical judgment of the healthcare professional.
 347 Therapy with AVANDARYL should not be initiated in patients with increased baseline liver
 348 enzyme levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes
 349 (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with AVANDARYL
 350 should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or
 351 continuation of, therapy with AVANDARYL in patients with mild liver enzyme elevations
 352 should proceed with caution and include close clinical follow-up, including more frequent liver
 353 enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time

354 ALT levels increase to >3X the upper limit of normal in patients on therapy with
355 AVANDARYL, liver enzyme levels should be rechecked as soon as possible. If ALT levels
356 remain >3X the upper limit of normal, therapy with AVANDARYL should be discontinued.

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

362 **5.9 Macular Edema**

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

373 **5.10 Fractures**

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

386 **5.11 Hematologic Effects**

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

390 **5.12 Hemolytic Anemia**

391 Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with
392 sulfonylurea agents can lead to hemolytic anemia. Because glimepiride, a component of
393 AVANDARYL, belongs to the class of sulfonylurea agents, caution should be used in patients

394 with G6PD deficiency and a non-sulfonylurea alternative should be considered. In post-
395 marketing experience, hemolytic anemia has also been reported in patients receiving
396 sulfonylureas who did not have known G6PD deficiency [see *Adverse Reactions (6.1)*].

397 **5.13 Diabetes and Blood Glucose Control**

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

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

404 **5.14 Ovulation**

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

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

414 **6 ADVERSE REACTIONS**

415 **6.1 Clinical Trial Experience**

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

419 Trials utilizing rosiglitazone in combination with a sulfonylurea provide support for the
420 use of AVANDARYL. Adverse event data from these trials, in addition to adverse events
421 reported with the use of rosiglitazone and glimepiride therapy, are presented below.

422 *Rosiglitazone*: The most common adverse experiences with rosiglitazone monotherapy
423 ($\geq 5\%$) were upper respiratory tract infection, injury, and headache. Overall, the types of adverse
424 experiences reported when rosiglitazone was added to a sulfonylurea were similar to those
425 during monotherapy with rosiglitazone. In controlled combination therapy trials with
426 sulfonylureas, mild to moderate hypoglycemic symptoms, which appear to be dose-related, were
427 reported. Few patients were withdrawn for hypoglycemia ($< 1\%$) and few episodes of
428 hypoglycemia were considered to be severe ($< 1\%$).

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

432 Edema was reported by 4.8% of patients receiving rosiglitazone compared to 1.3% on
433 placebo, and 1.0% on sulfonylurea monotherapy. The reporting rate of edema was higher for
434 rosiglitazone 8 mg added to a sulfonylurea (12.4%) compared to other combinations, with the
435 exception of insulin. Anemia was reported by 1.9% of patients receiving rosiglitazone compared
436 to 0.7% on placebo, 0.6% on sulfonylurea monotherapy, and 2.3% on rosiglitazone in
437 combination with a sulfonylurea. Overall, the types of adverse experiences reported when
438 rosiglitazone was added to a sulfonylurea were similar to those during monotherapy with
439 rosiglitazone.

440 In 26-week double-blind, fixed-dose trials, edema was reported with higher frequency in
441 the rosiglitazone plus insulin combination trials (insulin, 5.4%; and rosiglitazone in combination
442 with insulin, 14.7%). Reports of new onset or exacerbation of congestive heart failure occurred
443 at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with
444 rosiglitazone [see **Boxed Warning and Warnings and Precautions (5.2)**]. The use of
445 rosiglitazone in combination with insulin may increase the risk of myocardial infarction [see
446 **Warnings and Precautions (5.3)**].

447 **Glimepiride: Hypoglycemia:** The incidence of hypoglycemia with glimepiride, as
448 documented by blood glucose values <60 mg/dL, ranged from 0.9% to 1.7% in 2 large, well-
449 controlled, 1-year trials. In patients treated with glimepiride in US placebo-controlled trials
450 (N = 746), adverse events, other than hypoglycemia, considered to be possibly or probably
451 related to trial drug that occurred in more than 1% of patients included dizziness (1.7%), asthenia
452 (1.6%), headache (1.5%), and nausea (1.1%).

453 **Gastrointestinal Reactions:** Vomiting, gastrointestinal pain, and diarrhea have been
454 reported, but the incidence in placebo-controlled trials was less than 1%. In rare cases, there may
455 be an elevation of liver enzyme levels. In isolated instances, impairment of liver function (e.g.,
456 with cholestasis and jaundice), as well as hepatitis, which may also lead to liver failure have been
457 reported with sulfonylureas, including glimepiride.

458 **Dermatologic Reactions:** Allergic skin reactions, e.g., pruritus, erythema, urticaria,
459 and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These
460 may be transient and may disappear despite continued use of glimepiride. If those
461 hypersensitivity reactions persist or worsen, the drug should be discontinued. Porphyria cutanea
462 tarda, photosensitivity reactions, and allergic vasculitis have been reported with sulfonylureas,
463 including glimepiride.

464 **Hematologic Reactions:** Leukopenia, agranulocytosis, thrombocytopenia, hemolytic
465 anemia [see **Warnings and Precautions (5.12)**], aplastic anemia, and pancytopenia have been
466 reported with sulfonylureas, including glimepiride.

467 **Metabolic Reactions:** Hepatic porphyria reactions and disulfiram-like reactions have
468 been reported with sulfonylureas, including glimepiride. Cases of hyponatremia have been
469 reported with glimepiride and all other sulfonylureas, most often in patients who are on other
470 medications or have medical conditions known to cause hyponatremia or increase release of
471 antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion

472 has been reported with certain other sulfonylureas, including glimepiride, and it has been
473 suggested that certain sulfonylureas may augment the peripheral (antidiuretic) action of ADH
474 and/or increase release of ADH.

475 *Other Reactions:* Changes in accommodation and/or blurred vision may occur with
476 the use of glimepiride. This is thought to be due to changes in blood glucose, and may be more
477 pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients,
478 and may actually be reduced by treatment. In placebo-controlled trials of glimepiride, the
479 incidence of blurred vision was placebo, 0.7%, and glimepiride, 0.4%.

480 *Human Ophthalmology Data:* Ophthalmic examinations were carried out in more
481 than 500 subjects during long-term trials of glimepiride using the methodology of Taylor and
482 West and Laties et al. No significant differences were seen between glimepiride and glyburide in
483 the number of subjects with clinically important changes in visual acuity, intraocular tension, or
484 in any of the 5 lens-related variables examined. Ophthalmic examinations were carried out
485 during long-term trials using the method of Chylack et al. No significant or clinically meaningful
486 differences were seen between glimepiride and glipizide with respect to cataract progression by
487 subjective LOCS II grading and objective image analysis systems, visual acuity, intraocular
488 pressure, and general ophthalmic examination [see *Nonclinical Toxicology (13.2)*].

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

495 In ADOPT, fractures were reported in a greater number of women treated with
496 rosiglitazone (9.3%, 2.7/100 patient-years) compared to glyburide (3.5%, 1.3/100 patient-years)
497 or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who
498 received rosiglitazone were reported in the upper arm, hand, and foot. [See *Warnings and*
499 *Precautions (5.10)*.] The observed incidence of fractures for male patients was similar among the
500 3 treatment groups.

501

502 **Table 6. On-Therapy Adverse Events (≥5 Events/100 Patient-Years [PY]) in Any**
 503 **Treatment Group Reported in a 4- to 6-Year Clinical Trial of Rosiglitazone as**
 504 **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

505

506 **6.2 Laboratory Abnormalities**

507 Rosiglitazone: Hematologic: Decreases in mean hemoglobin and hematocrit occurred
 508 in a dose-related fashion in adult patients treated with rosiglitazone (mean decreases in
 509 individual trials as much as 1.0 g/dL hemoglobin and as much as 3.3% hematocrit). The changes
 510 occurred primarily during the first 3 months following initiation of therapy with rosiglitazone or
 511 following a dose increase in rosiglitazone. The time course and magnitude of decreases were
 512 similar in patients treated with a combination of rosiglitazone and other hypoglycemic agents or
 513 monotherapy with rosiglitazone. White blood cell counts also decreased slightly in adult patients
 514 treated with rosiglitazone. Decreases in hematologic parameters may be related to increased
 515 plasma volume observed with treatment with rosiglitazone.

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

518 Serum Transaminase Levels: In pre-approval clinical trials in 4,598 patients treated
 519 with rosiglitazone encompassing approximately 3,600 patient-years of exposure, there was no
 520 evidence of drug-induced hepatotoxicity.

521 In pre-approval controlled trials, 0.2% of patients treated with rosiglitazone had
 522 reversible elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and
 523 0.5% on active comparators. The ALT elevations in patients treated with rosiglitazone were
 524 reversible. Hyperbilirubinemia was found in 0.3% of patients treated with rosiglitazone
 525 compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In
 526 pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic
 527 failure. [See *Warnings and Precautions (5.8)*.]

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

532 **6.3 Postmarketing Experience**

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

538 In patients receiving thiazolidinedione therapy, serious adverse events with or without a
539 fatal outcome, potentially related to volume expansion (e.g., congestive heart failure, pulmonary
540 edema, and pleural effusions) have been reported [*see **Boxed Warning and Warnings and***
541 *Precautions (5.2)*].

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

545 There are postmarketing reports with rosiglitazone of rash, pruritus, urticaria,
546 angioedema, anaphylactic reaction, Stevens-Johnson syndrome, and new onset or worsening
547 diabetic macular edema with decreased visual acuity [*see **Warnings and Precautions (5.9)***].

548 **7 DRUG INTERACTIONS**

549 **7.1 Drugs Metabolized by Cytochrome P450**

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

555 A potential interaction between oral miconazole and oral hypoglycemic agents leading to
556 severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical,
557 or vaginal preparations of miconazole is not known. Potential interactions of glimepiride with
558 other drugs metabolized by cytochrome P450 2C9 also include phenytoin, diclofenac, ibuprofen,
559 naproxen, and mefenamic acid. [*See **Clinical Pharmacology (12.4)***].

560 **7.2 Drugs That Produce Hyperglycemia**

561 Certain drugs tend to produce hyperglycemia and may lead to loss of control. These
562 drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products,
563 estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid.
564 When these drugs are administered to a patient receiving glimepiride, the patient should be
565 closely observed for loss of control. When these drugs are withdrawn from a patient receiving
566 glimepiride, the patient should be observed closely for hypoglycemia.

567 **8 USE IN SPECIFIC POPULATIONS**

568 **8.1 Pregnancy**

569 Pregnancy Category C.

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

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

582 Animal Studies: No animal studies have been conducted with AVANDARYL. The
583 following data are based on findings in studies performed with rosiglitazone or glimepiride
584 individually.

585 *Rosiglitazone:* There was no effect on implantation or the embryo with rosiglitazone
586 treatment during early pregnancy in rats, but treatment during mid-late gestation was associated
587 with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed
588 at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human
589 AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused
590 placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation
591 reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible
592 after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was
593 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately
594 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced
595 the number of uterine implantations and live offspring when juvenile female rats were treated at
596 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human
597 AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day
598 (approximately 4 times human AUC at the maximum recommended daily dose). There was no
599 effect on pre- or post-natal survival or growth.

600 *Glimepiride:* Glimepiride did not produce teratogenic effects in rats exposed orally up to
601 4,000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose
602 based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately
603 60 times the maximum recommended human dose based on surface area). Glimepiride has been
604 shown to be associated with intrauterine fetal death in rats when given in doses as low as
605 50 times the human dose based on surface area and in rabbits when given in doses as low as
606 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses
607 inducing maternal hypoglycemia, has been similarly noted with other sulfonyleureas, and is
608 believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

609 In some studies in rats, offspring of dams exposed to high levels of glimepiride during
610 pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and
611 bending of the humerus during the postnatal period. Significant concentrations of glimepiride
612 were observed in the serum and breast milk of the dams as well as in the serum of the pups.
613 These skeletal deformations were determined to be the result of nursing from mothers exposed to
614 glimepiride. Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to
615 mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported
616 more frequently with the use of agents with prolonged half-lives.

617 **8.2 Labor and Delivery**

618 The effect of AVANDARYL or its components on labor and delivery in humans is
619 unknown.

620 **8.3 Nursing Mothers**

621 No trials have been conducted with AVANDARYL. It is not known whether
622 rosiglitazone or glimepiride is excreted in human milk. Because many drugs are excreted in
623 human milk, AVANDARYL should not be administered to a nursing woman.

624 Rosiglitazone: Drug-related material was detected in milk from lactating rats.

625 Glimepiride: In rat reproduction studies, significant concentrations of glimepiride were
626 observed in the serum and breast milk of the dams, as well as in the serum of the pups. Although
627 it is not known whether glimepiride is excreted in human milk, other sulfonylureas are excreted
628 in human milk.

629 **8.4 Pediatric Use**

630 Safety and effectiveness of AVANDARYL in pediatric patients have not been
631 established. AVANDARYL and its components, rosiglitazone and glimepiride, are not indicated
632 for use in pediatric patients.

633 **8.5 Geriatric Use**

634 Rosiglitazone: Results of the population pharmacokinetic analysis showed that age does
635 not significantly affect the pharmacokinetics of rosiglitazone [*see Clinical Pharmacology*
636 (12.3)]. Therefore, no dosage adjustments are required for the elderly. In controlled clinical
637 trials, no overall differences in safety and effectiveness between older (≥ 65 years) and younger
638 (< 65 years) patients were observed.

639 Glimepiride: In US clinical trials of glimepiride, 608 of 1,986 patients were 65 and older.
640 No overall differences in safety or effectiveness were observed between these subjects and
641 younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

642 Comparison of glimepiride pharmacokinetics in type 2 diabetes patients ≤ 65 years
643 (N = 49) and those > 65 years (N = 42) was performed in a trial using a dosing regimen of 6 mg
644 daily. There were no significant differences in glimepiride pharmacokinetics between the 2 age
645 groups [*see Clinical Pharmacology* (12.3)].

646 The drug is known to be substantially excreted by the kidney, and the risk of toxic
647 reactions to this drug may be greater in patients with impaired renal function. Because elderly

648 patients are more likely to have decreased renal function, care should be taken in dose selection,
649 and it may be useful to monitor renal function.

650 Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering
651 drugs. In elderly, debilitated, or malnourished patients, or in patients with renal, hepatic or
652 adrenal insufficiency, the starting dose, dose increments, and maintenance dosage should be
653 conservative based upon blood glucose levels prior to and after initiation of treatment to avoid
654 hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly and in people
655 who are taking beta-adrenergic blocking drugs or other sympatholytic agents [see *Dosage and*
656 *Administration (2.4), Warnings and Precautions (5.5), and Clinical Pharmacology (12.3)*].

657 **10 OVERDOSAGE**

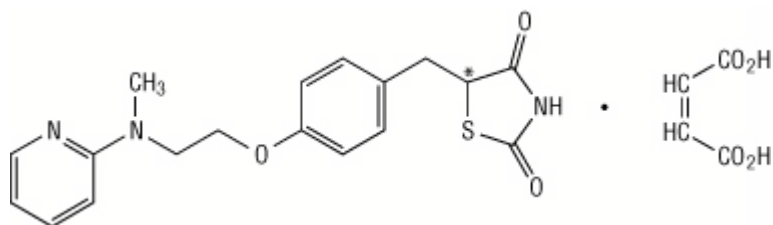
658 **Rosiglitazone:** Limited data are available with regard to overdosage in humans. In
659 clinical trials in volunteers, rosiglitazone has been administered at single oral doses of up to
660 20 mg and was well tolerated. In the event of an overdose, appropriate supportive treatment
661 should be initiated as dictated by the patient's clinical status.

662 **Glimepiride:** Overdosage of sulfonylureas, including glimepiride, can produce
663 hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic
664 findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or
665 meal patterns. Close monitoring should continue until the physician is assured that the patient is
666 out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological
667 impairment occur infrequently, but constitute medical emergencies requiring immediate
668 hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a
669 rapid IV injection of concentrated (50%) glucose solution. This should be followed by a
670 continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood
671 glucose level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to
672 48 hours, because hypoglycemia may recur after apparent clinical recovery.

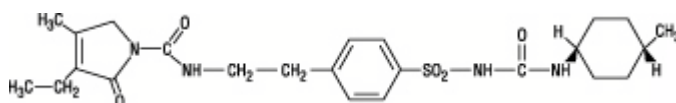
673 **11 DESCRIPTION**

674 AVANDARYL contains 2 oral antidiabetic drugs used in the management of type 2
675 diabetes: rosiglitazone maleate and glimepiride.

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



687
 688 Glimepiride is an oral antidiabetic drug of the sulfonylurea class. Glimepiride is a white
 689 to yellowish-white, crystalline, odorless to practically odorless powder. Chemically, glimepiride
 690 is 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-
 691 4-methylcyclohexyl)urea with a molecular weight of 490.62. The molecular formula for
 692 glimepiride is $C_{24}H_{34}N_4O_5S$. Glimepiride is practically insoluble in water. The structural formula
 693 of glimepiride is:



694
 695 AVANDARYL is available for oral administration as tablets containing rosiglitazone
 696 maleate and glimepiride, respectively, in the following strengths (expressed as rosiglitazone
 697 maleate/glimepiride): 4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg, 8 mg/2 mg, and 8 mg/4 mg. Each
 698 tablet contains the following inactive ingredients: Hypromellose 2910, lactose monohydrate,
 699 macrogol (polyethylene glycol), magnesium stearate, microcrystalline cellulose, sodium starch
 700 glycolate, titanium dioxide, and 1 or more of the following: Yellow, red, or black iron oxides.

701 12 CLINICAL PHARMACOLOGY

702 12.1 Mechanism of Action

703 AVANDARYL combines 2 antidiabetic agents with different mechanisms of action to
 704 improve glycemic control in patients with type 2 diabetes: Rosiglitazone maleate, a member of
 705 the thiazolidinedione class, and glimepiride, a member of the sulfonylurea class.
 706 Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral
 707 glucose utilization, whereas sulfonylureas act primarily by stimulating release of insulin from
 708 functioning pancreatic beta cells.

709 **Rosiglitazone:** Rosiglitazone improves glycemic control by improving insulin
 710 sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome
 711 proliferator-activated receptor-gamma ($PPAR\gamma$). In humans, $PPAR\gamma$ receptors are found in key
 712 target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of
 713 $PPAR\gamma$ nuclear receptors regulates the transcription of insulin-responsive genes involved in the
 714 control of glucose production, transport, and utilization. In addition, $PPAR\gamma$ -responsive genes
 715 also participate in the regulation of fatty acid metabolism.

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

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

727 **Glimepiride:** The primary mechanism of action of glimepiride in lowering blood glucose
728 appears to be dependent on stimulating the release of insulin from functioning pancreatic beta
729 cells. In addition, extrapancreatic effects may also play a role in the activity of sulfonylureas
730 such as glimepiride. This is supported by both preclinical and clinical trials demonstrating that
731 glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These
732 findings are consistent with the results of a long-term, randomized, placebo-controlled trial in
733 which glimepiride therapy improved postprandial insulin/C-peptide responses and overall
734 glycemic control without producing clinically meaningful increases in fasting insulin/C-peptide
735 levels. However, as with other sulfonylureas, the mechanism by which glimepiride lowers blood
736 glucose during long-term administration has not been clearly established.

737 **12.2 Pharmacodynamics**

738 The lipid profiles of rosiglitazone and glimepiride in a clinical trial of patients with
739 inadequate glycemic control on diet and exercise were consistent with the known profile of each
740 monotherapy. AVANDARYL was associated with increases in HDL and LDL (3% to 4% for
741 each) and decreases in triglycerides (-4%), that were not considered to be clinically meaningful.

742 The pattern of LDL and HDL changes following therapy with rosiglitazone in patients
743 previously treated with a sulfonylurea was generally similar to those seen with rosiglitazone in
744 monotherapy. Rosiglitazone as monotherapy was associated with increases in total cholesterol,
745 LDL, and HDL and decreases in free fatty acids. The changes in triglycerides during therapy
746 with rosiglitazone were variable and were generally not statistically different from placebo or
747 glyburide controls.

748 **12.3 Pharmacokinetics**

749 In a bioequivalence trial of AVANDARYL 4 mg/4 mg, the area under the curve (AUC)
750 and maximum concentration (C_{max}) of rosiglitazone following a single dose of the combination
751 tablet were bioequivalent to rosiglitazone 4 mg concomitantly administered with glimepiride
752 4 mg under fasted conditions. The AUC of glimepiride following a single fasted 4 mg/4 mg dose
753 was equivalent to glimepiride concomitantly administered with rosiglitazone, while the C_{max} was
754 13% lower when administered as the combination tablet (see Table 7).

755

756 Table 7. Pharmacokinetic Parameters for Rosiglitazone and Glimepiride (N = 28)

Parameter (Units)	Rosiglitazone		Glimepiride	
	Regimen A	Regimen B	Regimen A	Regimen B
AUC _{0-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-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 _{1/2} (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)

757 AUC = area under the curve; C_{max} = maximum concentration; T_{1/2} = terminal half-life;758 T_{max} = time of maximum concentration.759 Regimen A = AVANDARYL 4 mg/4 mg tablet; Regimen B = Concomitant dosing of a
760 rosiglitazone 4 mg tablet AND a glimepiride 4 mg tablet.761 Data presented as geometric mean (range), except T_{1/2} which is presented as arithmetic mean
762 (range) and T_{max}, which is presented as median (range).

763

764 The rate and extent of absorption of both the rosiglitazone component and glimepiride
765 component of AVANDARYL when taken with food were equivalent to the rate and extent of
766 absorption of rosiglitazone and glimepiride when administered concomitantly as separate tablets
767 with food.768 **Absorption:** The AUC and C_{max} of glimepiride increased in a dose-proportional manner
769 following administration of AVANDARYL 4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg.770 Administration of AVANDARYL in the fed state resulted in no change in the overall exposure
771 of rosiglitazone; however, the C_{max} of rosiglitazone decreased by 32% compared to the fasted
772 state. There was an increase in both AUC (19%) and C_{max} (55%) of glimepiride in the fed state
773 compared to the fasted state.774 **Rosiglitazone:** The absolute bioavailability of rosiglitazone is 99%. Peak plasma
775 concentrations are observed about 1 hour after dosing. The C_{max} and AUC of rosiglitazone
776 increase in a dose-proportional manner over the therapeutic dose range.777 **Glimepiride:** After oral administration, glimepiride is completely (100%) absorbed from
778 the gastrointestinal tract. Trials with single oral doses in normal subjects and with multiple oral
779 doses in patients with type 2 diabetes have shown significant absorption of glimepiride within
780 1 hour after administration and C_{max} at 2 to 3 hours.

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

784 Glimepiride: After intravenous (IV) dosing in normal subjects, the volume of distribution
785 (V_d) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein
786 binding was greater than 99.5%.

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

798 Glimepiride: Glimepiride is completely metabolized by oxidative biotransformation after
799 either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative
800 (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 has been shown to be involved in
801 the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several
802 cytosolic enzymes. M1, but not M2, possesses about $\frac{1}{3}$ of the pharmacological activity as
803 compared to its parent in an animal model; however, whether the glucose-lowering effect of M1
804 is clinically meaningful is not clear.

805 When [14 C]glimepiride was given orally, approximately 60% of the total radioactivity
806 was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80 to 90% of
807 that recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces
808 and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent
809 drug was recovered from urine or feces. After IV dosing in patients, no significant biliary
810 excretion of glimepiride or its M1 metabolite has been observed.

811 Special Populations: No pharmacokinetic data are available for AVANDARYL in the
812 following special populations. Information is provided for the individual components of
813 AVANDARYL.

814 Gender: Rosiglitazone: Results of the population pharmacokinetics analysis showed
815 that the mean oral clearance of rosiglitazone in female patients (N = 405) was approximately 6%
816 lower compared to male patients of the same body weight (N = 642). Combination therapy with
817 rosiglitazone and sulfonylureas improved glycemic control in both males and females with a
818 greater therapeutic response observed in females. For a given body mass index (BMI), females
819 tend to have a greater fat mass than males. Since the molecular target of rosiglitazone, PPAR γ , is
820 expressed in adipose tissues, this differentiating characteristic may account, at least in part, for

821 the greater response to rosiglitazone in combination with sulfonylureas in females. Since therapy
822 should be individualized, no dose adjustments are necessary based on gender alone.

823 *Glimepiride:* There were no differences between males and females in the
824 pharmacokinetics of glimepiride when adjustment was made for differences in body weight.

825 *Geriatric: Rosiglitazone:* Results of the population pharmacokinetics analysis (N = 716
826 <65 years; N = 331 ≥65 years) showed that age does not significantly affect the
827 pharmacokinetics of rosiglitazone.

828 *Glimepiride:* Comparison of glimepiride pharmacokinetics in type 2 diabetes patients
829 65 years and younger with those older than 65 years was performed in a trial using a dosing
830 regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics
831 between the 2 age groups. The mean AUC at steady state for the older patients was about 13%
832 lower than that for the younger patients; the mean weight-adjusted clearance for the older
833 patients was about 11% higher than that for the younger patients. [See Use in Specific
834 Populations (8.5).]

835 *Hepatic Impairment:* Therapy with AVANDARYL should not be initiated if the patient
836 exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT
837 >2.5X upper limit of normal) at baseline [see Warnings and Precautions (5.8)].

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

843 *Glimepiride:* No trials of glimepiride have been conducted in patients with hepatic
844 insufficiency.

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

848 *Glimepiride:* No pharmacokinetic trials to assess the effects of race have been
849 performed, but in placebo-controlled trials of glimepiride in patients with type 2 diabetes, the
850 antihyperglycemic effect was comparable in whites (N = 536), blacks (N = 63), and Hispanics
851 (N = 63).

852 *Renal Impairment: Rosiglitazone:* There are no clinically relevant differences in the
853 pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in
854 hemodialysis-dependent patients compared to subjects with normal renal function.

855 *Glimepiride:* A single-dose glimepiride, open-label trial was conducted in 15 patients
856 with renal impairment. Glimepiride (3 mg) was administered to 3 groups of patients with
857 different levels of mean creatinine clearance (CL_{cr}); (Group I, $CL_{cr} = 77.7$ mL/min, N = 5),
858 (Group II, $CL_{cr} = 27.7$ mL/min, N = 3), and (Group III, $CL_{cr} = 9.4$ mL/min, N = 7). Glimepiride
859 was found to be well tolerated in all 3 groups. The results showed that glimepiride serum levels
860 decreased as renal function decreased. However, M1 and M2 serum levels (mean AUC values)

861 increased 2.3 and 8.6 times from Group I to Group III. The apparent terminal half-life ($T_{1/2}$) for
862 glimepiride did not change, while the half-lives for M1 and M2 increased as renal function
863 decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased
864 (44.4%, 21.9%, and 9.3% for Groups I to III). A multiple-dose titration trial was also conducted
865 in 16 type 2 diabetes patients with renal impairment using doses ranging from 1 to 8 mg daily for
866 3 months. The results were consistent with those observed after single doses. All patients with a
867 CL_{cr} less than 22 mL/min had adequate control of their glucose levels with a dosage regimen of
868 only 1 mg daily. The results from this trial suggest that a starting dose of 1 mg glimepiride, as
869 contained in AVANDARYL 4 mg/1 mg, may be given to type 2 diabetes patients with kidney
870 disease, and the dose may be titrated based on fasting glucose levels.

871 *Pediatric:* No pharmacokinetic data from trials in pediatric subjects are available for
872 AVANDARYL.

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

879 *Glimepiride:* The pharmacokinetics of glimepiride (1 mg) were evaluated in a single-
880 dose trial conducted in 30 type 2 diabetic patients (male = 7; female = 23) between ages 10 and
881 17 years. The mean AUC_{0-last} (338.8 ± 203.1 ng.hr/mL), C_{max} (102.4 ± 47.7 ng/mL), and $T_{1/2}$
882 (3.1 ± 1.7 hours) were comparable to those previously reported in adults (AUC_{0-last}
883 315.2 ± 95.9 ng.hr/mL, C_{max} 103.2 ± 34.3 ng/mL, and $T_{1/2}$ 5.3 ± 4.1 hours).

884 **12.4 Drug-Drug Interactions**

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

889 Rosiglitazone: Drugs That Inhibit, Induce or are Metabolized by Cytochrome
890 *P450:* In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the
891 major P450 enzymes at clinically relevant concentrations. In vitro data demonstrate that
892 rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9. [See *Drug*
893 *Interactions (7.1).*]

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

897 *Gemfibrozil:* Concomitant administration of gemfibrozil (600 mg twice daily), an
898 inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone
899 AUC by 127%, compared to the administration of rosiglitazone (4 mg once daily) alone. Given

900 the potential for dose-related adverse events with rosiglitazone, a decrease in the dose of
901 rosiglitazone may be needed when gemfibrozil is introduced [see Drug Interactions (7.1)].

902 **Rifampin:** Rifampin administration (600 mg once a day), an inducer of CYP2C8, for
903 6 days is reported to decrease rosiglitazone AUC by 66%, compared to the administration of
904 rosiglitazone (8 mg) alone [see Drug Interactions (7.1)].¹¹

905 **Glyburide:** Rosiglitazone (2 mg twice daily) taken concomitantly with glyburide (3.75 to
906 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations
907 in diabetic patients stabilized on glyburide therapy. Repeat doses of rosiglitazone (8 mg once
908 daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and
909 C_{max} of approximately 30%. In Japanese subjects, glyburide AUC and C_{max} slightly increased
910 following coadministration of rosiglitazone.

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

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

915 Additional pharmacokinetic trials demonstrated no clinically relevant effect of acarbose,
916 ranitidine, or metformin on the pharmacokinetics of rosiglitazone.

917 **Glimepiride:** The hypoglycemic action of sulfonylureas may be potentiated by certain
918 drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs) and other drugs that are highly
919 protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid,
920 monoamine oxidase inhibitors, and beta-adrenergic blocking agents. When these drugs are
921 administered to a patient receiving glimepiride, the patient should be observed closely for
922 hypoglycemia. When these drugs are withdrawn from a patient receiving glimepiride, the patient
923 should be observed closely for loss of glycemic control.

924 Certain drugs tend to produce hyperglycemia and may lead to loss of control. These
925 drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products,
926 estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid.
927 When these drugs are administered to a patient receiving glimepiride, the patient should be
928 closely observed for loss of control. When these drugs are withdrawn from a patient receiving
929 glimepiride, the patient should be observed closely for hypoglycemia.

930 **Drugs Metabolized by Cytochrome P450:** A potential interaction between oral
931 miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported.
932 Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is
933 not known. There is a potential interaction of glimepiride with inhibitors (e.g., fluconazole) and
934 inducers (e.g., rifampicin) of cytochrome P450 2C9.

935 **Aspirin:** Coadministration of aspirin (1 g three times daily) and glimepiride led to a 34%
936 decrease in the mean glimepiride AUC and, therefore, a 34% increase in the mean CL/F. The
937 mean C_{max} had a decrease of 4%. Blood glucose and serum C-peptide concentrations were
938 unaffected and no hypoglycemic symptoms were reported.

939 *H₂-Receptor Antagonists:* Coadministration of either cimetidine (800 mg once daily) or
940 ranitidine (150 mg twice daily) with a single 4-mg oral dose of glimepiride did not significantly
941 alter the absorption and disposition of glimepiride, and no differences were seen in
942 hypoglycemic symptomatology.

943 *Beta-Blockers:* Concomitant administration of propranolol (40 mg three times daily) and
944 glimepiride significantly increased C_{max}, AUC, and T_{1/2} of glimepiride by 23%, 22%, and 15%,
945 respectively, and it decreased CL/F by 18%. The recovery of M1 and M2 from urine, however,
946 did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal
947 subjects receiving propranolol and placebo. Pooled data from clinical trials in patients with
948 type 2 diabetes showed no evidence of clinically significant adverse interactions with
949 uncontrolled concurrent administration of beta-blockers. However, if beta-blockers are used,
950 caution should be exercised and patients should be warned about the potential for hypoglycemia.

951 *Warfarin:* Concomitant administration of glimepiride tablets (4 mg once daily) did not
952 alter the pharmacokinetic characteristics of R- and S-warfarin enantiomers following
953 administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were
954 observed in warfarin plasma protein binding. Glimepiride treatment did result in a slight, but
955 statistically significant, decrease in the pharmacodynamic response to warfarin. The reductions
956 in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride
957 treatment were very small (3.3% and 9.9%, respectively) and are unlikely to be clinically
958 important.

959 *ACE Inhibitors:* The responses of serum glucose, insulin, C-peptide, and plasma
960 glucagon to 2 mg glimepiride were unaffected by coadministration of ramipril (an ACE
961 inhibitor) 5 mg once daily in normal subjects. No hypoglycemic symptoms were reported.

962 *Other:* Although no specific interaction trials were performed, pooled data from clinical
963 trials showed no evidence of clinically significant adverse interactions with uncontrolled
964 concurrent administration of aspirin and other salicylates, H₂-receptor antagonists, ACE
965 inhibitors, calcium-channel blockers, estrogens, fibrates, NSAIDs, HMG CoA reductase
966 inhibitors, sulfonamides, or thyroid hormone.

967 **13 NONCLINICAL TOXICOLOGY**

968 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

969 No animal studies have been conducted with AVANDARYL. The following data are
970 based on findings in studies performed with rosiglitazone or glimepiride alone.

971 Rosiglitazone: *Carcinogenesis:* A 2-year carcinogenicity study was conducted in
972 Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose
973 equivalent to approximately 12 times human AUC at the maximum recommended human daily
974 dose). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05 mg/kg/day,
975 0.3 mg/kg/day, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times
976 human AUC at the maximum recommended human daily dose for male and female rats,
977 respectively).

978 Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of
979 adipose hyperplasia in the mouse at doses ≥ 1.5 mg/kg/day (approximately 2 times human AUC
980 at the maximum recommended human daily dose). In rats, there was a significant increase in the
981 incidence of benign adipose tissue tumors (lipomas) at doses ≥ 0.3 mg/kg/day (approximately
982 2 times human AUC at the maximum recommended human daily dose). These proliferative
983 changes in both species are considered due to the persistent pharmacological overstimulation of
984 adipose tissue.

985 **Mutagenesis:** Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial
986 assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in
987 vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about
988 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic
989 activation.

990 **Impairment of Fertility:** Rosiglitazone had no effects on mating or fertility of male rats
991 given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended
992 human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility
993 (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and
994 estradiol (approximately 20 and 200 times human AUC at the maximum recommended human
995 daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times
996 human AUC at the maximum recommended human daily dose). In juvenile rats dosed from
997 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male
998 reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in
999 females (approximately 68 times human AUC at the maximum recommended daily dose). In
1000 monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at
1001 the maximum recommended human daily dose, respectively) diminished the follicular phase rise
1002 in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal
1003 phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct
1004 inhibition of ovarian steroidogenesis.

1005 **Glimepiride: Carcinogenesis:** Studies in rats at doses of up to 5,000 parts per million
1006 (ppm) in complete feed (approximately 340 times the maximum recommended human dose,
1007 based on surface area) for 30 months showed no evidence of carcinogenesis. In mice,
1008 administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma
1009 formation which was dose-related and is thought to be the result of chronic pancreatic
1010 stimulation. The no-effect dose for adenoma formation in mice in this study was 320 ppm in
1011 complete feed, or 46 to 54 mg/kg body weight/day. This is about 35 times the maximum human
1012 recommended dose based on surface area.

1013 **Mutagenesis:** Glimepiride was non-mutagenic in a battery of in vitro and in vivo
1014 mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled
1015 DNA synthesis, mouse micronucleus test).

1016 **Impairment of Fertility:** There was no effect of glimepiride on male mouse fertility in
1017 animals exposed up to 2,500 mg/kg body weight ($>1,700$ times the maximum recommended

1018 human dose based on surface area). Glimepiride had no effect on the fertility of male and female
1019 rats administered up to 4,000 mg/kg body weight (approximately 4,000 times the maximum
1020 recommended human dose based on surface area).

1021 **13.2 Animal Toxicology and/or Pharmacology**

1022 Rosiglitazone: Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day),
1023 and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human
1024 AUC at the maximum recommended human daily dose, respectively). Effects in juvenile rats
1025 were consistent with those seen in adults. Morphometric measurement indicated that there was
1026 hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result
1027 of plasma volume expansion.

1028 Glimepiride: Reduced serum glucose values and degranulation of the pancreatic beta
1029 cells were observed in beagle dogs exposed to glimepiride 320 mg/kg/day for 12 months
1030 (approximately 1,000 times the recommended human dose based on surface area). No evidence
1031 of tumor formation was observed in any organ. One female and one male dog developed bilateral
1032 subcapsular cataracts. Non-GLP studies indicated that glimepiride was unlikely to exacerbate
1033 cataract formation. Evaluation of the co-cataractogenic potential of glimepiride in several
1034 diabetic and cataract rat models was negative and there was no adverse effect of glimepiride on
1035 bovine ocular lens metabolism in organ culture [*see Adverse Reactions (6.1)*].

1036 **14 CLINICAL STUDIES**

1037 The safety and efficacy of rosiglitazone added to a sulfonylurea have been studied in
1038 clinical trials in patients with type 2 diabetes inadequately controlled on sulfonylureas alone. No
1039 clinical trials have been conducted with the fixed-dose combination of AVANDARYL in
1040 patients inadequately controlled on a sulfonylurea or who have initially responded to
1041 rosiglitazone alone and require additional glycemic control.

1042 A total of 3,457 patients with type 2 diabetes participated in ten 24- to 26-week
1043 randomized, double-blind, placebo/active-controlled trials and one 2-year double-blind, active-
1044 controlled trial in elderly patients designed to assess the efficacy and safety of rosiglitazone in
1045 combination with a sulfonylurea. Rosiglitazone 2 mg, 4 mg, or 8 mg daily, was administered
1046 either once daily (3 trials) or in divided doses twice daily (7 trials), to patients inadequately
1047 controlled on a submaximal or maximal dose of sulfonylurea.

1048 In these trials, the combination of rosiglitazone 4 mg or 8 mg daily (administered as
1049 single or twice daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c
1050 compared to placebo plus sulfonylurea or further up-titration of the sulfonylurea. Table 8 shows
1051 pooled data for 8 trials in which rosiglitazone added to sulfonylurea was compared to placebo
1052 plus sulfonylurea.

1053

1054 Table 8. Glycemic Parameters in 24- to 26-Week Combination Trials of Rosiglitazone Plus
 1055 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%

1056 ^a P <0.0001 compared to sulfonylurea alone.

1057

1058 One of the 24- to 26-week trials included patients who were inadequately controlled on
1059 maximal doses of glyburide and switched to 4 mg of rosiglitazone daily as monotherapy; in this
1060 group, loss of glycemic control was demonstrated, as evidenced by increases in FPG and HbA1c.

1061 In a 2-year double-blind trial, elderly patients (aged 59 to 89 years) on half-maximal
1062 sulfonylurea (glipizide 10 mg twice daily) were randomized to the addition of rosiglitazone
1063 (N = 115, 4 mg once daily to 8 mg as needed) or to continued up-titration of glipizide (N = 110),
1064 to a maximum of 20 mg twice daily. Mean baseline FPG and HbA1c were 157 mg/dL and
1065 7.72%, respectively, for the rosiglitazone plus glipizide arm and 159 mg/dL and 7.65%,
1066 respectively, for the glipizide up-titration arm. Loss of glycemic control (FPG ≥180 mg/dL)
1067 occurred in a significantly lower proportion of patients (2%) on rosiglitazone plus glipizide
1068 compared to patients in the glipizide up-titration arm (28.7%). About 78% of the patients on
1069 combination therapy completed the 2 years of therapy while only 51% completed on glipizide
1070 monotherapy. The effect of combination therapy on FPG and HbA1c was durable over the 2-year
1071 trial period, with patients achieving a mean of 132 mg/dL for FPG and a mean of 6.98% for
1072 HbA1c compared to no change on the glipizide arm.

1073

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1105 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1106 Each rounded triangular tablet contains rosiglitazone as the maleate and glimepiride as
1107 follows:

1108 4 mg/1 mg – yellow, gsk debossed on one side and 4/1 on the other.

1109 4 mg/2 mg – orange, gsk debossed on one side and 4/2 on the other.

1110 4 mg/4 mg – pink, gsk debossed on one side and 4/4 on the other.

1111 8 mg/2 mg – pale pink, gsk debossed on one side and 8/2 on the other.

1112 8 mg/4 mg – red, gsk debossed on one side and 8/4 on the other.

1113

1114 4 mg/1 mg bottles of 30: NDC 0173-0841-13

1115 4 mg/2 mg bottles of 30: NDC 0173-0842-13

1116 4 mg/4 mg bottles of 30: NDC 0173-0843-13

1117 8 mg/2 mg bottles of 30: NDC 0173-0844-13

1118 8 mg/4 mg bottles of 30: NDC 0173-0845-13

1119

1120 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Dispense in a
1121 tight, light-resistant container.

1122 **17 PATIENT COUNSELING INFORMATION**

1123 See Medication Guide.

1124 **17.1 Patient Advice**

1125 There are multiple medications available to treat type 2 diabetes. The benefits and risks
1126 of each available diabetes medication should be taken into account when choosing a particular
1127 diabetes medication for a given patient.

1128 Patient should fully understand the risks and benefits of AVANDARYL. AVANDARYL
1129 should only be taken by adults with type 2 diabetes who are already taking rosiglitazone, or who
1130 are not already taking rosiglitazone and are unable to achieve adequate glycemic control on other
1131 diabetes medications, and, in consultation with their healthcare provider, have decided not to
1132 take pioglitazone (ACTOS) or pioglitazone-containing medications (ACTOPLUS MET,
1133 ACTOPLUS MET XR, DUETACT) for medical reasons. Inform patients that they must be
1134 enrolled in the AVANDIA-Rosiglitazone Medicines Access Program in order to receive
1135 AVANDARYL.

1136 Patients should be informed of the following:

- 1137 • AVANDARYL is not recommended in patients with symptomatic heart failure.
- 1138 • Results of a set of clinical trials suggest that treatment with AVANDARYL is associated
1139 with an increased risk for myocardial infarction (heart attack), especially in patients taking
1140 insulin. Clinical trials have not shown any difference between rosiglitazone and comparator
1141 medications in overall mortality or CV-related mortality.
- 1142 • AVANDARYL is not recommended for patients who are taking insulin.
- 1143 • Management of type 2 diabetes should include diet control. Caloric restriction, weight loss,
1144 and exercise are essential for the proper treatment of the diabetic patient because they help
1145 improve insulin sensitivity. This is important not only in the primary treatment of type 2
1146 diabetes, but also in maintaining the efficacy of drug therapy.
- 1147 • It is important to adhere to dietary instructions and to regularly have blood glucose and
1148 glycosylated hemoglobin (HbA1c) tested. It can take 2 weeks to see a reduction in blood
1149 glucose and 2 to 3 months to see the full effect of AVANDARYL.
- 1150 • The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its
1151 development should be explained to patients and their family members.
- 1152 • Blood will be drawn to check their liver function prior to the start of therapy and periodically
1153 thereafter per the clinical judgment of the healthcare professional. Patients with unexplained
1154 symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should
1155 immediately report these symptoms to their physician.
- 1156 • Patients who experience an unusually rapid increase in weight or edema or who develop
1157 shortness of breath or other symptoms of heart failure while on AVANDARYL should
1158 immediately report these symptoms to their physician.
- 1159 • AVANDARYL should be taken with the first meal of the day.
- 1160 • Therapy with rosiglitazone, like other thiazolidinediones, may result in ovulation in some
1161 premenopausal anovulatory women. As a result, these patients may be at an increased risk for
1162 pregnancy while taking AVANDARYL. Thus, adequate contraception in premenopausal
1163 women should be recommended. This possible effect has not been specifically investigated
1164 in clinical trials so the frequency of this occurrence is not known.
- 1165

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1169



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1176 Month 2011
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1178 **MEDICATION GUIDE**
1179 **AVANDARYL® (ah-VAN-duh-riil)**
1180 **(rosiglitazone maleate and glimepiride) Tablets**
1181

1182 Read this Medication Guide carefully before you start taking AVANDARYL and each
1183 time you get a refill. There may be new information. This information does not take
1184 the place of talking with your doctor about your medical condition or your
1185 treatment. If you have any questions about AVANDARYL, ask your doctor or
1186 pharmacist.

1187
1188 **What is the most important information I should know about AVANDARYL?**
1189 **AVANDARYL may cause serious side effects, including:**

1190
1191 AVANDARYL is available only through the AVANDIA-Rosiglitazone Medicines Access
1192 Program. Both you and your doctor must be enrolled in the program so that you
1193 can get AVANDARYL. To enroll, you must:

- 1194 • talk to your doctor,
- 1195 • understand the risks and benefits of AVANDARYL, and
- 1196 • agree to enroll in the program.

1197
1198 **New or worse heart failure**

- 1199 • Rosiglitazone, one of the two drugs that make up AVANDARYL, can cause your
1200 body to keep extra fluid (fluid retention), which leads to swelling (edema) and
1201 weight gain. Extra body fluid can make some heart problems worse or lead to
1202 heart failure. Heart failure means your heart does not pump blood well enough.
- 1203 • If you have severe heart failure, you cannot start AVANDARYL.
- 1204 • If you have heart failure with symptoms (such as shortness of breath or
1205 swelling), even if these symptoms are not severe, AVANDARYL may not be right
1206 for you.

1207
1208 Call your doctor right away if you have any of the following:

- 1209 • swelling or fluid retention, especially in the ankles or legs
- 1210 • shortness of breath or trouble breathing, especially when you lie down
- 1211 • an unusually fast increase in weight
- 1212 • unusual tiredness

1213
1214 **Myocardial Infarction (“Heart Attack”)**

1215 Rosiglitazone, one of the medicines in AVANDARYL, may raise the risk of heart
1216 attack. The risk of having a heart attack may be higher in people who take

1217 AVANDARYL with insulin. Most people who take insulin should not also take
1218 AVANDARYL.

1219 **Symptoms of a heart attack can include the following:**

- 1220 • chest discomfort in the center of your chest that lasts for more than a few
1221 minutes, or that goes away or comes back
- 1222 • chest discomfort that feels like uncomfortable pressure, squeezing, fullness or
1223 pain
- 1224 • pain or discomfort in your arms, back, neck, jaw or stomach
- 1225 • shortness of breath with or without chest discomfort
- 1226 • breaking out in a cold sweat
- 1227 • nausea or vomiting
- 1228 • feeling lightheaded

1229 **Call your doctor or go to the nearest hospital emergency room right away if**
1230 **you think you are having a heart attack.**

1231

1232 People with diabetes have a greater risk for heart problems. It is important to work
1233 with your doctor to manage other conditions, such as high blood pressure or high
1234 cholesterol.

1235

1236 AVANDARYL can have other serious side effects. Be sure to read the section “What
1237 are possible side effects of AVANDARYL?”.

1238

1239 **What is AVANDARYL?**

1240 AVANDARYL contains 2 prescription medicines to treat diabetes, rosiglitazone
1241 maleate (AVANDIA) and glimepiride (AMARYL). AVANDARYL is used with diet and
1242 exercise to treat certain adults with type 2 (“adult-onset” or “non-insulin
1243 dependent”) diabetes mellitus (“high blood sugar”) who are:

- 1244 • already taking rosiglitazone or rosiglitazone-containing products
- 1245 • unable to control their blood sugar on other diabetes medicines, and after
1246 talking with their doctor have decided not to take pioglitazone (ACTOS) or
1247 pioglitazone-containing products (ACTOPLUS MET, ACTOPLUS MET XR,
1248 DUETACT)

1249

1250 Glimepiride can help your body release more of its own insulin. Rosiglitazone can
1251 help your body respond better to the insulin made in your body and does not cause
1252 your body to make more insulin. These medicines can work together to help control
1253 your blood sugar.

1254

1255 AVANDARYL is not for people with type 1 diabetes mellitus or to treat a condition
1256 called diabetic ketoacidosis.

1257

1258 It is not known if AVANDARYL is safe and effective in children under 18 years old.

1259

1260 **Who should not take AVANDARYL?**

1261 Many people with heart failure should not start taking AVANDARYL (see “What
1262 should I tell my doctor before taking AVANDARYL?”).

1263

1264 **What should I tell my doctor before taking AVANDARYL?**

1265 Before starting AVANDARYL, ask your doctor about what the choices are for
1266 diabetes medicines and what the expected benefits and possible risks are for you in
1267 particular.

1268

1269 Before taking AVANDARYL, tell your doctor about all your medical conditions,
1270 including if you:

- 1271 • **have heart problems or heart failure.**
- 1272 • **have type 1 (“juvenile”) diabetes or had diabetic ketoacidosis.** These
1273 conditions should be treated with insulin and should not be treated with
1274 AVANDARYL.
- 1275 • **have a type of diabetic eye disease called macular edema** (swelling of the
1276 back of the eye).
- 1277 • **have liver problems.** Your doctor should do blood tests to check your liver
1278 before you start taking AVANDARYL and during treatment as needed.
- 1279 • **had liver problems while taking REZULIN[®] (troglitazone), another
1280 medicine for diabetes.**
- 1281 • **have kidney problems.** If people with kidney problems use AVANDARYL, they
1282 may need a lower dose of the medication.
- 1283 • **have glucose 6-phosphate dehydrogenase (G6PD) deficiency.** This
1284 condition runs in families. People with G6PD deficiency who take glimepiride
1285 (one of the medicines in AVANDARYL) may develop hemolytic anemia (fast
1286 breakdown of red blood cells).
- 1287 • **are pregnant or plan to become pregnant.** AVANDARYL should not be used
1288 during pregnancy. It is not known if AVANDARYL can harm your unborn baby.
1289 You and your doctor should talk about the best way to control your diabetes
1290 during pregnancy. If you are a premenopausal woman (before the “change of
1291 life”) who does not have regular monthly periods, AVANDARYL may increase
1292 your chances of becoming pregnant. Talk to your doctor about birth control
1293 choices while taking AVANDARYL. Tell your doctor right away if you become
1294 pregnant while taking AVANDARYL.

1295 • **are breast-feeding or planning to breast-feed.** It is not known if
1296 AVANDARYL passes into breast milk. You should not use AVANDARYL while
1297 breast-feeding.

1298
1299 Tell your doctor about all the medicines you take including prescription and non-
1300 prescription medicines, vitamins or herbal supplements. AVANDARYL and certain
1301 other medicines can affect each other and may lead to serious side effects including
1302 high or low blood sugar, or heart problems. Especially tell your doctor if you take:

- 1303 • **insulin.**
- 1304 • **any medicines for high blood pressure, high cholesterol or heart failure,**
1305 **or for prevention of heart disease or stroke.**

1306
1307 Know the medicines you take. Keep a list of all your medicines and show it to your
1308 doctor and pharmacist before you start a new medicine. They will tell you if it is
1309 alright to take AVANDARYL with other medicines.

1310

1311 **How should I take AVANDARYL?**

- 1312 • Take AVANDARYL exactly as prescribed. Your doctor may need to change your
1313 dose until your blood sugar is better controlled.
- 1314 • Take AVANDARYL by mouth one time each day with your first main meal.
- 1315 • It usually takes a few days for AVANDARYL to start lowering your blood sugar. It
1316 may take 2 to 3 months to see the full effect on your blood sugar level.
- 1317 • If you miss a dose of AVANDARYL, take it as soon as you remember unless it is
1318 time to take your next dose. Take your next dose at the usual time. Do not take
1319 double doses to make up for a missed dose.
- 1320 • If you take too much AVANDARYL, call your doctor or poison control center right
1321 away.
- 1322 • Test your blood sugar regularly as your doctor tells you.
- 1323 • Your doctor should do blood tests to check your liver before you start
1324 AVANDARYL and during treatment as needed. Your doctor should also do regular
1325 blood sugar tests (for example, "A1c") to monitor your response to AVANDARYL.
- 1326 • Call your doctor if you get sick, get injured, get an infection, or have surgery.
1327 AVANDARYL may not control your blood sugar levels during these times. Your
1328 doctor may need to stop AVANDARYL for a short time and give you insulin to
1329 control your blood sugar level.
- 1330 • Diet and exercise can help your body use its blood sugar better. It is important
1331 to stay on your recommended diet, lose extra weight, and get regular exercise
1332 while taking AVANDARYL.

1333

- 1334 **What are possible side effects of AVANDARYL?**
- 1335 **AVANDARYL may cause serious side effects, including:**
- 1336 • **New or worse heart failure.** See “What is the most important information I
1337 should know about AVANDARYL?”.
 - 1338 • **Heart attack.** See “What is the most important information I should know
1339 about AVANDARYL?”.
 - 1340 • **Swelling (edema).** AVANDARYL can cause swelling due to fluid retention. See
1341 “What is the most important information I should know about AVANDARYL?”.
 - 1342 • **Low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness or
1343 hunger may mean that your blood sugar is too low. This can happen if you skip
1344 meals, drink alcohol, use another medicine that lowers blood sugar, exercise
1345 (particularly hard or long), or if you have certain medical problems. Call your
1346 doctor if low blood sugar levels are a problem for you.
 - 1347 • **Weight gain.** Rosiglitazone, one of the medicines in AVANDARYL, can cause
1348 weight gain that may be due to fluid retention or extra body fat. Weight gain can
1349 be a serious problem for people with certain conditions including heart problems.
1350 See “What is the most important information I should know about
1351 AVANDARYL?”.
 - 1352 • **Liver problems.** It is important for your liver to be working normally when you
1353 take AVANDARYL. Your doctor should do blood tests to check your liver before
1354 you start taking AVANDARYL and during treatment as needed. Call your doctor
1355 right away if you have unexplained symptoms such as:
 - 1356 • nausea or vomiting
 - 1357 • stomach pain
 - 1358 • unusual or unexplained tiredness
 - 1359 • loss of appetite
 - 1360 • dark urine
 - 1361 • yellowing of your skin or the whites of your eyes.
 - 1362 • **Macular edema** (a diabetic eye disease with swelling in the back of the eye).
1363 Tell your doctor right away if you have any changes in your vision. Your doctor
1364 should check your eyes regularly. Very rarely, some people have had vision
1365 changes due to swelling in the back of the eye while taking rosiglitazone, one of
1366 the medicines in AVANDARYL.
 - 1367 • **Fractures (broken bones)**, usually in the hand, upper arm or foot. Talk to
1368 your doctor for advice on how to keep your bones healthy.
 - 1369 • **Low red blood cell count (anemia).**
 - 1370 • **Ovulation** (release of egg from an ovary in women) leading to pregnancy.
1371 Ovulation may happen in premenopausal women who do not have regular
1372 monthly periods. This can increase the chance of pregnancy. See “What should I
1373 tell my doctor before taking AVANDARYL?”.

1374

1375 The most common side effects with AVANDARYL include cold-like symptoms and
1376 headache.

1377

1378 Call your doctor for medical advice about side effects. You may report side effects
1379 to FDA at 1-800-FDA-1088.

1380

1381 **How should I store AVANDARYL?**

1382 • Store AVANDARYL at room temperature, 59° to 86° F (15° to 30° C). Keep
1383 AVANDARYL in the container it comes in. Keep the container closed tightly.

1384 • Safely, throw away AVANDARYL that is out of date or no longer needed.

1385

1386 Keep AVANDARYL and all medicines out of the reach of children.

1387

1388 **General information about AVANDARYL**

1389 Medicines are sometimes prescribed for purposes other than those listed in a
1390 Medication Guide. Do not use AVANDARYL for a condition for which it was not
1391 prescribed. Do not give AVANDARYL to other people, even if they have the same
1392 symptoms you have. It may harm them.

1393

1394 This Medication Guide summarizes important information about AVANDARYL. If you
1395 would like more information, talk with your doctor. You can ask your doctor or
1396 pharmacist for information about AVANDARYL that is written for healthcare
1397 professionals. You can also find out more about AVANDARYL by calling 1-888-825-
1398 5249.

1399

1400 **What are the ingredients in AVANDARYL?**

1401 Active Ingredients: Rosiglitazone maleate and glimepiride.

1402 Inactive Ingredients: Hypromellose 2910, lactose monohydrate, macrogol
1403 (polyethylene glycol), magnesium stearate, microcrystalline cellulose, sodium
1404 starch glycolate, titanium dioxide, triacetin, and 1 or more of the following: Yellow,
1405 red, or black iron oxides.

1406

1407 Always check to make sure that the medicine you are taking is the correct one.

1408 AVANDARYL tablets are triangles with rounded corners and look like this:

1409 4 mg/1 mg – yellow with “gsk” on one side and “4/1” on the other.

1410 4 mg/2 mg – orange with “gsk” on one side and “4/2” on the other.

1411 4 mg/4 mg – pink with “gsk” on one side and “4/4” on the other.

1412 8 mg/2 mg – pale pink with “gsk” on one side and “8/2” on the other.

1413 8 mg/4 mg – red with “gsk” on one side and “8/4” on the other.

1414
1415 AVANDARYL and AVANDIA are registered trademarks of GlaxoSmithKline.
1416 The other brands listed are trademarks of their respective owners and are not
1417 trademarks of GlaxoSmithKline. The makers of these brands are not affiliated with
1418 and do not endorse GlaxoSmithKline or its products.

1419
1420 **This Medication Guide has been approved by the U.S. Food and Drug**
1421 **Administration.**

1422



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1424 GlaxoSmithKline
1425 Research Triangle Park, NC 27709
1426
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1428
1429 Month 2011
1430 AVR: XMG

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/s/

AMY G EGAN
05/30/2012