CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021071/S-048

Trade Name:	**AVANDIA**
Generic Name:	**rosiglitazone maleate**
Sponsor:	**SmithKline Beecham (Cork) Ltd, Ireland d/b/a GlaxoSmithKline**
Approval Date:	May 7, 2014
Indications:	AVANDIA is a thiazolidinedione antidiabetic agent indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021071/S-048

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021071/S-048

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021071/S-047
NDA 021071/S-048
NDA 021071/S-049

SUPPLEMENT APPROVALS
REMOVE REMS ELEMENT

SmithKline Beecham (Cork) Ltd, Ireland d/b/a GlaxoSmithKline
Attention: Margaret Kreider, Ph.D.
Senior Director, Regulatory Affairs
2301 Renaissance Blvd.
Mail Code RN 0420
King of Prussia, PA 19406-2772

Dear Dr. Kreider:

Please refer to the following Supplemental New Drug Applications (sNDAs), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA):

NDA Number	Supplement Number	Product Name	Date of Submission	Date of Receipt
021071	047	Avandia (rosiglitazone maleate) tablets	July 1, 2013	July 1, 2013
	048		January 20, 2014	January 22, 2014
	049		January 22, 2014	January 22, 2014

We acknowledge receipt of your amendments dated August 23, 2013 (S-047), September 30, 2013 (S-047), December 20, 2013 (S-047), February 12, 2014 (S-047), March 4, 2014 (S-049), March 31, 2014 (S-049), April 14, 2014 (S-049) and April 29, 2014 (S-049), and your risk evaluation and mitigation strategy (REMS) assessments dated July 1, 2013 and January 22, 2014. We also acknowledge receipt of your email dated April 11, 2014, which included the final, agreed-upon labeling. The submission dated April 29, 2014 contained the final risk evaluation and mitigation strategy (REMS) documents.

The "Prior Approval" supplemental new drug application S-047 proposes to add a contraindication for use in patients with a history of hypersensitivity reaction to rosiglitazone or any of the inactive ingredients.

We also refer to our letter dated November 25, 2013, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for rosiglitazone products. This information pertains to the readjudicated results of the

Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial.

The "Prior Approval" supplemental new drug applications S-048 and S-049 provide for revisions to the labeling for Avandia (rosiglitazone maleate), and propose modifications to the approved Rosiglitazone REMS Program, consistent with our November 25, 2013, Safety Labeling Change Notification and REMS Modification Notification letter.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions indicated in the enclosed labeling.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to, except with the revisions indicated, the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Avandia was originally approved on May 18, 2011, and the most recent REMS modification was approved on September 16, 2013. The single, shared system REMS program for rosiglitazone-containing medicines, the Rosiglitazone REMS Program was approved on January 25, 2013, and the most recent REMS modification was approved on September 16, 2013. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of the changes outlined in the November 25, 2013 letter, including removal of the Medication Guide as an element of the REMS and modification of the elements to assure safe use.

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Avandia outweigh the risks. We remind you that the Medication Guide will continue to be part of the approved labeling for Avandia in accordance with 21 CFR 208.

We have also determined that elements to assure safe use that require that healthcare providers who prescribe rosiglitazone for outpatient or long-term care use are specially certified, that rosiglitazone be dispensed only by specially certified pharmacies, and that rosiglitazone be dispensed only to patients with evidence or other documentation of safe use conditions are no longer necessary to ensure the benefits of the drug outweigh the risks.

Your proposed modified REMS, submitted on April 29, 2014, and appended to this letter, is approved.

The modified REMS consists of elements to assure safe use to provide training on the current state of knowledge concerning the cardiovascular risk of rosiglitazone-containing medicines to health care providers who are likely to prescribe rosiglitazone-containing medicines and a timetable for submission of assessments of the REMS.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

The timetable for submission of assessments of the REMS will remain the same as that approved on May 18, 2011.

At least 24 hours prior to issuing the Dear Healthcare Provider letter(s) that are required as part of the REMS, please submit an electronic copy of the letter to this NDA, and to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

The revised REMS assessment plan should include, but is not limited to, the following:

- Total number of letters sent to prescribers
- Total number of letters returned, i.e. not received by prescribers
- Total number of letters sent to Professional Society Leaders
    - Results of follow-up with Professional Society leaders regarding the disposition of the letters
        - the number and names of Professional Societies that acknowledged receipt of letter
        - the number and names of Professional Societies that conveyed the information from the letter to members
        - the number and names of Professional Societies that did not convey the information from the letter to members
            - reasons the information was not conveyed to members

- Number of emails sent to prescribers previously enrolled in the Rosiglitazone REMS Program
    - Number of these prescribers for which returned receipt (opened email notification) is not received
- Number of visits to access the training materials by self-identified prescribers for the reporting period.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved

strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021071 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 021071 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021071
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021071
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

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

/s/

JEAN-MARC P GUETTIER
05/07/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021071/S-048

LABELING

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

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)**

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

Boxed Warning, AVANDIA-Rosiglitazone Medicines Access Program removal	05/2014
Indications and Usage, patient population restrictions removal (1)	05/2014
Contraindications (4)	05/2014
Warnings and Precautions, Cardiac Failure (5.1)	05/2014
Warnings and Precautions, Major Adverse Cardiovascular Events (5.2)	05/2014
Warnings and Precautions, Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program removal (formerly 5.3)	05/2014

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

AVANDIA is a thiazolidinedione antidiabetic agent indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

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 in patients with established NYHA Class III or IV heart failure. (4)
- Hypersensitivity to rosiglitazone or any of the product's ingredients. (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)
- Meta-analysis of 52 mostly short-term trials suggested a potential risk of ischemic cardiovascular (CV) events relative to placebo, not confirmed in a long-term CV outcome trial versus metformin or sulfonylurea. (5.2)
- Dose-related edema (5.3), weight gain (5.4), and anemia (5.8) may occur.
- Macular edema has been reported. (5.6)
- Increased incidence of bone fracture. (5.7)

---------- 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)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: No adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- Nursing Mothers: Discontinue drug or nursing (8.3)
- Safety and effectiveness in children younger than 18 years have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: CONGESTIVE HEART FAILURE

- **Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients *[see Warnings and Precautions (5.1)]*. After initiation of AVANDIA, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered.**
- **AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. *[See Contraindications (4), Warnings and Precautions (5.1).]***

1 INDICATIONS AND USAGE

AVANDIA® is a thiazolidinedione antidiabetic agent indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Important Limitations of Use:

- Due to its mechanism of action, AVANDIA is active only in the presence of endogenous insulin. Therefore, AVANDIA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- The coadministration of AVANDIA and insulin is not recommended *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

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

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

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

2.1 Specific Patient Populations

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

patients with renal impairment.

Hepatic Impairment: Liver enzymes should be measured prior to initiating treatment with AVANDIA. Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy). After initiation of AVANDIA, liver enzymes should be monitored periodically per the clinical judgment of the healthcare professional. *[See Warnings and Precautions (5.5), Clinical Pharmacology (12.3).]*

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

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

- Initiation of AVANDIA in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated *[see Boxed Warning]*.
- Use in patients with a history of a hypersensitivity reaction to rosiglitazone or any of the product's ingredients.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Failure

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

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

Table 1. Emergent Cardiovascular Adverse Events in Patients With Congestive Heart

Failure (NYHA Class I and II) Treated With AVANDIA or Placebo (in Addition to Background Antidiabetic and CHF Therapy)

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

[a] Includes hospitalization for any cardiovascular reason.

In a long-term, cardiovascular outcome trial (RECORD) in patients with type 2 diabetes *[see Adverse Reactions (6.1)]*, the incidence of heart failure was higher in patients treated with AVANDIA [2.7% (61/2,220) compared with active control 1.3% (29/2,227), HR 2.10 (95% CI: 1.35, 3.27)].

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

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

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

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

In 7 controlled, randomized, double-blind trials which had durations from 16 to 26 weeks and which were included in a meta-analysis *[see Warnings and Precautions (5.2)]*, patients with

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

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

5.2 Major Adverse Cardiovascular Events

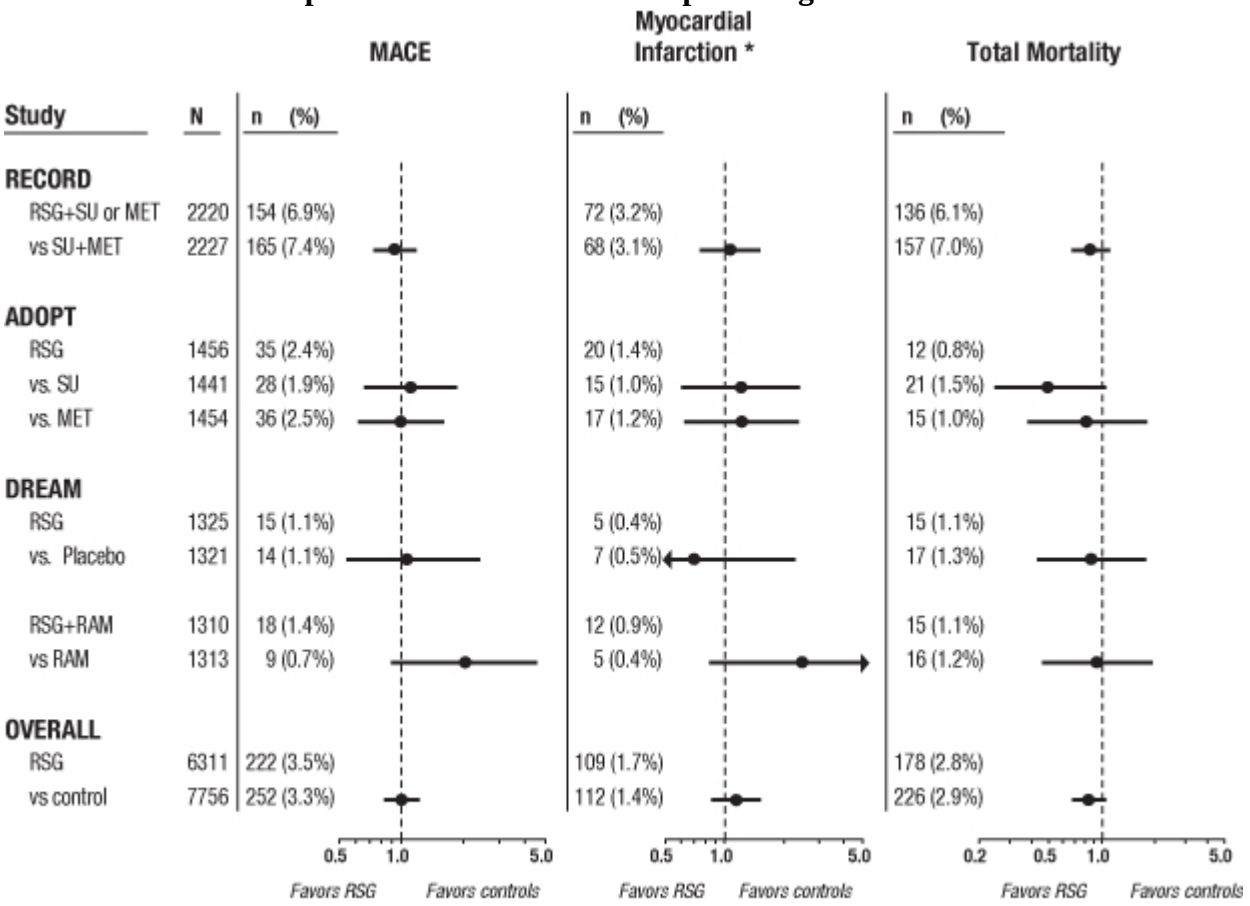
Data from long-term, prospective, randomized, controlled clinical trials of AVANDIA versus metformin or sulfonylureas, particularly a cardiovascular outcome trial (RECORD), observed no difference in overall mortality or in major adverse cardiovascular events (MACE) and its components. A meta-analysis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

Cardiovascular Events in Large, Long-term, Prospective, Randomized, Controlled Trials of AVANDIA: RECORD, a prospectively designed cardiovascular outcome trial (mean follow-up 5.5 years; 4,447 patients), compared the addition of AVANDIA to metformin or a sulfonylurea (N = 2,220) with a control group of metformin plus sulfonylurea (N = 2,227) in patients with type 2 diabetes *[see Adverse Reactions (6.1)]*. Non-inferiority was demonstrated for the primary endpoint, cardiovascular hospitalization or cardiovascular death, for AVANDIA compared with control [HR 0.99 (95% CI: 0.85, 1.16)] demonstrating no overall increased risk in cardiovascular morbidity or mortality. The hazard ratios for total mortality and MACE were consistent with the primary endpoint and the 95% CI similarly excluded a 20% increase in risk for AVANDIA. The hazard ratios for the components of MACE were 0.72 (95% CI: 0.49, 1.06) for stroke, 1.14 (95% CI: 0.80, 1.63) for myocardial infarction, and 0.84 (95% CI: 0.59, 1.18) for cardiovascular death.

The results of RECORD are consistent with the findings of 2 earlier long-term, prospective, randomized, controlled clinical trials (each trial >3 years' duration; total of 9,620 patients) (see Figure 1). In patients with impaired glucose tolerance (DREAM trial), although the incidence of cardiovascular events was higher among subjects who were randomized to AVANDIA in combination with ramipril than among subjects randomized to ramipril alone, no statistically significant differences were observed for MACE and its components between AVANDIA and placebo. In type 2 diabetes patients who were initiating oral agent monotherapy

(ADOPT trial), no statistically significant differences were observed for MACE and its components between AVANDIA and metformin or a sulfonylurea.

Figure 1. Hazard Ratios for the Risk of MACE, Myocardial Infarction, and Total Mortality With AVANDIA Compared With a Control Group in Long-term Trials



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

Cardiovascular Events in a Group of 52 Clinical Trials: In a meta-analysis of 52 double-blind, randomized, controlled clinical trials designed to assess glucose-lowering efficacy in type 2 diabetes (mean duration 6 months), a statistically significant increased risk of myocardial infarction with AVANDIA versus pooled comparators was observed [0.4% versus 0.3%; OR 1.8, (95% CI: 1.03, 3.25)]. A statistically non-significant increased risk of MACE was observed with AVANDIA versus pooled comparators (OR 1.44, 95% CI: 0.95, 2.20). In the placebo-controlled trials, a statistically significant increased risk of myocardial infarction [0.4% versus 0.2%, OR 2.23 (95% CI: 1.14, 4.64)] and statistically non-significant increased risk of MACE [0.7% versus 0.5%, OR 1.53 (95% CI: 0.94, 2.54)] with AVANDIA were ~~was~~ observed. In the active-controlled trials, there was no increased risk of myocardial infarction or MACE.

Mortality in Observational Studies of AVANDIA Compared to Pioglitazone: Three

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

5.3 Edema

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

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

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

5.4 Weight Gain

Dose-related weight gain was seen with AVANDIA alone and in combination with other hypoglycemic agents (Table 2). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

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

Table 2. Weight Changes (kg) From Baseline at Endpoint During Clinical Trials

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

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

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

5.5 Hepatic Effects

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

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

5.6 Macular Edema

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

5.7 Fractures

Long-term trials (ADOPT and RECORD) show an increased incidence of bone fracture in patients, particularly female patients, taking AVANDIA *[see Adverse Reactions (6.1)]*. This increased incidence was noted after the first year of treatment and persisted during the course of the trial. The majority of the fractures in the women who received AVANDIA occurred in the upper arm, hand, and foot. These sites of fracture are different from those usually associated with postmenopausal osteoporosis (e.g., hip or spine). Other trials suggest that this risk may also apply to men, although the risk of fracture among women appears higher than that among men. The risk of fracture should be considered in the care of patients treated with AVANDIA, and attention given to assessing and maintaining bone health according to current standards of care.

5.8 Hematologic Effects

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

5.9 Diabetes and Blood Glucose Control

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

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

5.10 Ovulation

Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDIA *[see Use in Specific Populations (8.1)]*. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not

been specifically investigated in clinical trials; therefore, the frequency of this occurrence is not known.

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

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail elsewhere in the labeling:

- Cardiac Failure *[see Warnings and Precautions (5.1)]*
- Major Adverse Cardiovascular Events *[see Warnings and Precautions (5.2)]*
- Edema *[see Warnings and Precautions (5.3)]*
- Weight Gain *[see Warnings and Precautions (5.4)]*
- Hepatic Effects *[see Warnings and Precautions (5.5)]*
- Macular Edema *[see Warnings and Precautions (5.6)]*
- Fractures *[see Warnings and Precautions (5.7)]*
- Hematologic Effects *[see Warnings and Precautions (5.8)]*
- Ovulation *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trial Experience

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

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

Short-term Trials of AVANDIA as Monotherapy and in Combination With Other Hypoglycemic Agents: The incidence and types of adverse events reported in short-term clinical trials of AVANDIA as monotherapy are shown in Table 3.

Table 3. Adverse Events (≥5% in any Treatment Group) Reported by Patients in Short-term[a] Double-blind Clinical Trials With AVANDIA as Monotherapy

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

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

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

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

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

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

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

AVANDIA *[see Boxed Warning, Warnings and Precautions (5.1)]*.

In controlled combination therapy trials with sulfonylureas, mild to moderate hypoglycemic symptoms, which appear to be dose related, were reported. Few patients were withdrawn for hypoglycemia (<1%) and few episodes of hypoglycemia were considered to be severe (<1%). Hypoglycemia was the most frequently reported adverse event in the fixed-dose insulin combination trials, although few patients withdrew for hypoglycemia (4 of 408 for AVANDIA plus insulin and 1 of 203 for insulin alone). Rates of hypoglycemia, confirmed by capillary blood glucose concentration ≤50 mg/dL, were 6% for insulin alone and 12% (4 mg) and 14% (8 mg) for insulin in combination with AVANDIA. *[See Warnings and Precautions (5.9).]*

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

In ADOPT, fractures were reported in a greater number of women treated with AVANDIA (9.3%, 2.7/100 patient-years) compared with glyburide (3.5%, 1.3/100 patient-years) or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who received rosiglitazone were reported in the upper arm, hand, and foot. *[See Warnings and Precautions (5.7).]* The observed incidence of fractures for male patients was similar among the 3 treatment groups.

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

Preferred Term	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

Long-term Trial of AVANDIA as Combination Therapy (RECORD): RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) was a multicenter, randomized, open-label, non-inferiority trial in subjects with type 2 diabetes inadequately controlled on maximum doses of metformin or sulfonylurea (glyburide, gliclazide, or glimepiride) to compare the time to reach the combined cardiovascular endpoint of

cardiovascular death or cardiovascular hospitalization between patients randomized to the addition of AVANDIA versus metformin or sulfonylurea. The trial included patients who have failed metformin or sulfonylurea monotherapy; those who failed metformin (n = 2,222) were randomized to receive either AVANDIA as add-on therapy (n = 1,117) or add-on sulfonylurea (n = 1,105), and those who failed sulfonylurea (n = 2,225) were randomized to receive either AVANDIA as add-on therapy (n = 1,103) or add-on metformin (n = 1,122). Patients were treated to target HbA1c ≤7% throughout the trial.

The mean age of patients in this trial was 58 years, 52% were male, and the mean duration of follow-up was 5.5 years. AVANDIA demonstrated non-inferiority to active control for the primary endpoint of cardiovascular hospitalization or cardiovascular death (HR 0.99, 95% CI: 0.85-1.16). There were no significant differences between groups for secondary endpoints with the exception of congestive heart failure (see Table 5). The incidence of congestive heart failure was significantly greater among patients randomized to AVANDIA.

Table 5. Cardiovascular (CV) Outcomes for the RECORD Trial

Primary Endpoint	**AVANDIA N = 2,220**	**Active Control N = 2,227**	**Hazard Ratio**	**95% CI**
CV death or CV hospitalization	321	323	0.99	0.85-1.16
Secondary Endpoint				
All-cause death	136	157	0.86	0.68-1.08
CV death	60	71	0.84	0.59-1.18
Myocardial infarction	64	56	1.14	0.80-1.63
Stroke	46	63	0.72	0.49-1.06
CV death, myocardial infarction, or stroke	154	165	0.93	0.74-1.15
Heart failure	61	29	2.10	1.35-3.27

There was an increased incidence of bone fracture for subjects randomized to AVANDIA in addition to metformin or sulfonylurea compared with those randomized to metformin plus sulfonylurea (8.3% versus 5.3%) *[see Warnings and Precautions (5.7)]*. The majority of fractures were reported in the upper limbs and distal lower limbs. The risk of fracture appeared to be higher in females relative to control (11.5% versus 6.3%), than in males relative to control (5.3% versus 4.3%). Additional data are necessary to determine whether there is an increased risk of fracture in males after a longer period of follow-up.

Pediatric: AVANDIA has been evaluated for safety in a single, active-controlled trial of pediatric patients with type 2 diabetes in which 99 were treated with AVANDIA and 101 were treated with metformin. The most common adverse reactions (>10%) without regard to causality for either AVANDIA or metformin were headache (17% versus 14%), nausea (4% versus 11%), nasopharyngitis (3% versus 12%), and diarrhea (1% versus 13%). In this trial, one case of diabetic ketoacidosis was reported in the metformin group. In addition, there were 3 patients in the rosiglitazone group who had FPG of approximately 300 mg/dL, 2+ ketonuria, and an

elevated anion gap.

6.2 Laboratory Abnormalities

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

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

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

In pre-approval controlled trials, 0.2% of patients treated with AVANDIA had elevations in ALT >3X the upper limit of normal compared with 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with AVANDIA were reversible. Hyperbilirubinemia was found in 0.3% of patients treated with AVANDIA compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. *[See Warnings and Precautions (5.5).]*

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

In the RECORD trial, patients randomized to AVANDIA in addition to metformin or sulfonylurea (10,849 patient-years exposure) and to metformin plus sulfonylurea (10,209 patient-years exposure) had a rate of ALT increase to ≥3X upper limit of normal of approximately 0.2 and 0.3 per 100 patient-years exposure, respectively.

6.3 Postmarketing Experience

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

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

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

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

There are postmarketing reports with AVANDIA of rash, pruritus, urticaria, angioedema, anaphylactic reaction, Stevens-Johnson syndrome *[see Contraindications (4)]*, and new onset or worsening diabetic macular edema with decreased visual acuity *[see Warnings and Precautions (5.6)]*.

7 DRUG INTERACTIONS

7.1 CYP2C8 Inhibitors and Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

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

Human Data: Rosiglitazone has been reported to cross the human placenta and be detectable in fetal tissue. The clinical significance of these findings is unknown. There are no adequate and well-controlled trials in pregnant women. AVANDIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

Drug-related material was detected in milk from lactating rats. It is not known whether AVANDIA is excreted in human milk. Because many drugs are excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue AVANDIA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

After placebo run-in including diet counseling, children with type 2 diabetes mellitus, aged 10 to 17 years and with a baseline mean body mass index (BMI) of 33 kg/m^2, were randomized to treatment with 2 mg twice daily of AVANDIA (n = 99) or 500 mg twice daily of metformin (n = 101) in a 24-week, double-blind clinical trial. As expected, FPG decreased in patients naïve to diabetes medication (n = 104) and increased in patients withdrawn from prior medication (usually metformin) (n = 90) during the run-in period. After at least 8 weeks of treatment, 49% of patients treated with AVANDIA and 55% of metformin-treated patients had their dose doubled if FPG >126 mg/dL. For the overall intent-to-treat population, at Week 24, the mean change from baseline in HbA1c was -0.14% with AVANDIA and -0.49% with metformin. There was an insufficient number of patients in this trial to establish statistically whether these observed mean treatment effects were similar or different. Treatment effects differed for patients naïve to therapy with antidiabetic drugs and for patients previously treated with antidiabetic therapy (Table 6).

Table 6. Week 24 FPG and HbA1c Change From Baseline Last-observation—carried Forward in Children With Baseline HbA1c >6.5%

Parameter	Naïve Patients		Previously-treated Patients	
	Metformin N = 40	Rosiglitazone N = 45	Metformin N = 43	Rosiglitazone 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%

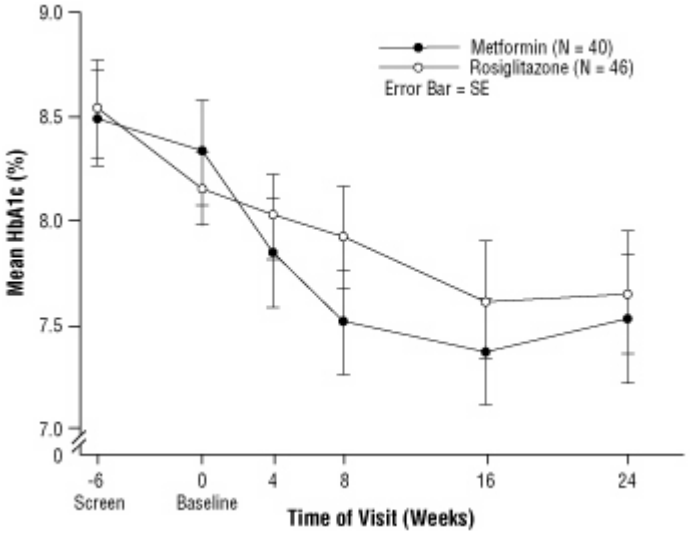
[a] Change from baseline means are least squares means adjusting for baseline HbA1c, gender, and region.

[b] Positive values for the difference favor metformin.

Treatment differences depended on baseline BMI or weight such that the effects of AVANDIA and metformin appeared more closely comparable among heavier patients. The median weight gain was 2.8 kg with rosiglitazone and 0.2 kg with metformin *[see Warnings and Precautions (5.4)]*. Fifty-four percent of patients treated with rosiglitazone and 32% of patients treated with metformin gained ≥2 kg, and 33% of patients treated with rosiglitazone and 7% of patients treated with metformin gained ≥5 kg on trial.

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

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



8.5 Geriatric Use

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

10 OVERDOSAGE

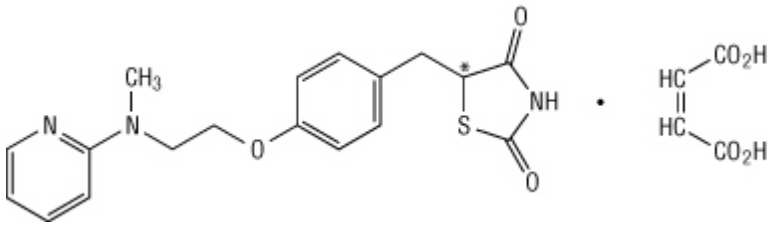
Limited data are available with regard to overdosage in humans. In clinical trials in volunteers, AVANDIA has been administered at single oral doses of up to 20 mg and was well tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical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

11 DESCRIPTION

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

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

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



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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

12.2 Pharmacodynamics

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

(Table 7).

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

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

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

Table 7. Summary of Mean Lipid Changes in 26-Week, Placebo-controlled and 52-Week, Glyburide-controlled Monotherapy Trials

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

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

12.3 Pharmacokinetics

Maximum plasma concentration (C_{max}) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range (Table 8). The elimination half-life is 3 to 4 hours and is independent of dose.

Table 8. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral Doses (N = 32)

Parameter	1 mg Fasting	2 mg Fasting	8 mg Fasting	8 mg Fed
$AUC_{0\text{-}inf}$ (ng.h/mL)	358 (112)	733 (184)	2,971 (730)	2,890 (795)
C_{max} (ng/mL)	76 (13)	156 (42)	598 (117)	432 (92)
$T_{½}$ (h)	3.16 (0.72)	3.15 (0.39)	3.37 (0.63)	3.59 (0.70)
CL/F (L/h)	3.03 (0.87)	2.89 (0.71)	2.85 (0.69)	2.97 (0.81)

AUC = area under the curve; C_{max} = maximum concentration; $T_{½}$ = terminal half-life; CL/F = Oral clearance.

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

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

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

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

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

Population Pharmacokinetics in Patients With Type 2 Diabetes: Population pharmacokinetic analyses from 3 large clinical trials including 642 men and 405 women with

type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume of distribution (Vss/F) were shown to increase with increases in body weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted CL/F and Vss/F values varied by <1.7-fold and <2.3-fold, respectively. Additionally, rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about 15%) in female patients.

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

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

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

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

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

Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal) at baseline *[see Warnings and Precautions (5.5)]*.

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

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

contraindicated in patients with renal impairment, coadministration of metformin with AVANDIA is contraindicated in these patients.

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

12.4 Drug-drug Interactions

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

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

Rifampin: Rifampin administration (600 mg once a day), an inducer of CYP2C8, for 6 days is reported to decrease rosiglitazone AUC by 66%, compared with the administration of rosiglitazone (8 mg) alone *[see Drug Interactions (7.1)]*.[1]

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

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

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

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

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

Warfarin: Repeat dosing with AVANDIA had no clinically relevant effect on the steady-

state pharmacokinetics of warfarin enantiomers.

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

13.2 Animal Toxicology

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

14 CLINICAL STUDIES

14.1 Monotherapy

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

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

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

Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes (n = 1,401) with inadequate glycemic control [mean baseline FPG approximately 228 mg/dL (101 to 425 mg/dL) and mean baseline HbA1c 8.9% (5.2% to 16.2%)], were conducted. Treatment with AVANDIA produced statistically significant improvements in FPG and HbA1c compared with baseline and relative to placebo. Data from one of these trials are summarized in Table 9.

Table 9. Glycemic Parameters in a 26-Week, Placebo-controlled Trial

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

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

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

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

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

durable over time. The improvement in glycemic control seen with AVANDIA 4 mg twice daily at Week 26 was maintained through Week 52 of the trial.

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

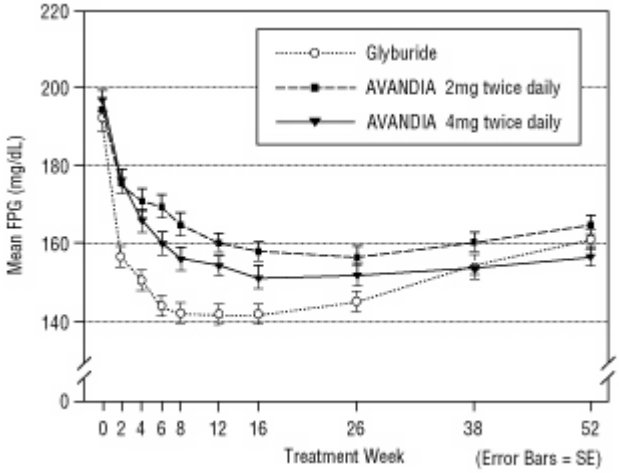
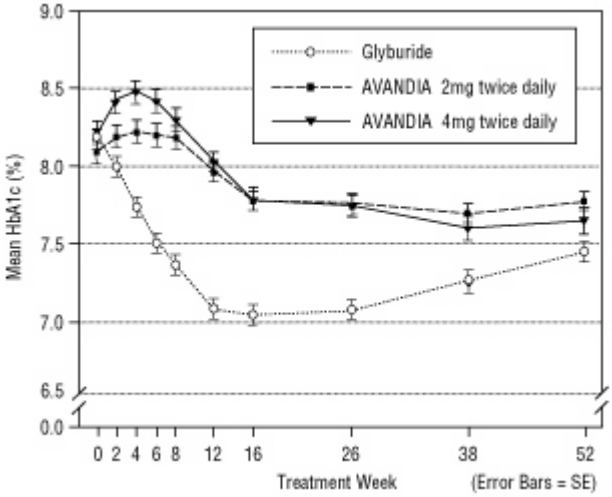


Figure 4. Mean HbA1c Over Time in a 52-Week, Glyburide-controlled Trial



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

A Diabetes Outcome Progression Trial (ADOPT) was a multicenter, double-blind, controlled trial (N = 4,351) conducted over 4 to 6 years to compare the safety and efficacy of AVANDIA, metformin, and glyburide monotherapy in patients recently diagnosed with type 2

diabetes mellitus (≤3 years) inadequately controlled with diet and exercise. The mean age of patients in this trial was 57 years and the majority of patients (83%) had no known history of cardiovascular disease. The mean baseline FPG and HbA1c were 152 mg/dL and 7.4%, respectively. Patients were randomized to receive either AVANDIA 4 mg once daily, glyburide 2.5 mg once daily, or metformin 500 mg once daily, and doses were titrated to optimal glycemic control up to a maximum of 4 mg twice daily for AVANDIA, 7.5 mg twice daily for glyburide, and 1,000 mg twice daily for metformin. The primary efficacy outcome was time to consecutive FPG >180 mg/dL after at least 6 weeks of treatment at the maximum tolerated dose of study medication or time to inadequate glycemic control, as determined by an independent adjudication committee.

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

Cardiovascular and adverse event data (including effects on body weight and bone fracture) from ADOPT for AVANDIA, metformin, and glyburide are described in *Warnings and Precautions (5.2, 5.4, and 5.7)* and *Adverse Reactions (6.1)*, respectively. As with all medications, efficacy results must be considered together with safety information to assess the potential benefit and risk for an individual patient.

14.2 Combination With Metformin or Sulfonylurea

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

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

In one trial, patients inadequately controlled on 2.5 grams/day of metformin (mean baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were randomized to receive 4 mg of AVANDIA once daily, 8 mg of AVANDIA once daily, or placebo in addition to metformin. A statistically significant improvement in FPG and HbA1c was observed in patients treated with the combinations of metformin and 4 mg of AVANDIA once daily and 8 mg of AVANDIA once daily, versus patients continued on metformin alone (Table 10).

Table 10. Glycemic Parameters in a 26-Week Combination Trial of AVANDIA Plus Metformin

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

[a] P <0.0001 compared with metformin.

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

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

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

In these trials, the combination of AVANDIA 4 mg or 8 mg daily (administered as

single-or twice-daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c compared with placebo plus sulfonylurea or further up-titration of the sulfonylurea. Table 11 shows pooled data for 8 trials in which AVANDIA added to sulfonylurea was compared with placebo plus sulfonylurea.

Table 11. Glycemic Parameters in 24- to 26-Week Combination Trials of AVANDIA Plus Sulfonylurea

Twice-Daily Divided Dosing (5 Trials)	Sulfonylurea N = 397	AVANDIA 2 mg Twice Daily + Sulfonylurea N = 497	Sulfonylurea N = 248	AVANDIA 4 mg Twice Daily + Sulfonylurea 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 N = 172**	**AVANDIA 4 mg Once Daily + Sulfonylurea N = 172**	**Sulfonylurea N = 173**	**AVANDIA 8 mg Once Daily + Sulfonylurea N = 176**
FPG (mg/dL)				
Baseline (mean)	198	206	188	192
Change from baseline (mean)	17	-25	17	-43
Difference from sulfonylurea alone (adjusted mean)	–	-47[a]	–	-66[a]
% of patients with ≥30 mg/dL decrease from baseline	17%	48%	19%	55%
HbA1c (%)				
Baseline (mean)	8.6	8.8	8.9	8.9
Change from baseline (mean)	0.4	-0.5	0.1	-1.2
Difference from sulfonylurea alone (adjusted mean)	–	-0.9[a]	–	-1.4[a]
% of patients with ≥0.7% decrease from baseline	11%	36%	20%	68%

[a] P <0.0001 compared with sulfonylurea alone.

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

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

14.3 Combination With Sulfonylurea Plus Metformin

In two 24- to 26-week, double-blind, placebo-controlled trials designed to assess the efficacy and safety of AVANDIA in combination with sulfonylurea plus metformin, AVANDIA 4 mg or 8 mg daily, was administered in divided doses twice daily, to patients inadequately controlled on submaximal (10 mg) and maximal (20 mg) doses of glyburide and maximal dose of metformin (2 g/day). A statistically significant improvement in FPG and HbA1c was observed in patients treated with the combinations of sulfonylurea plus metformin and 4 mg of AVANDIA and 8 mg of AVANDIA versus patients continued on sulfonylurea plus metformin, as shown in Table 12.

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

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

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

15 REFERENCES

1. Park JY, Kim KA, Kang MH, et al. Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects. *Clin Pharmacol Ther* 2004;75:157-162.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

2 mg bottles of 60: NDC 0173-0861-18

4 mg bottles of 30: NDC 0173-0863-13

8 mg bottles of 30: NDC 0173-0864-13

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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

Patients should be informed of the following:

- AVANDIA is not recommended for patients with symptomatic heart failure.
- A meta-analysis of mostly short-term trials suggested an increased risk for myocardial infarction with AVANDIA compared with placebo. Data from long-term clinical trials of AVANDIA versus other antidiabetes agents (metformin or sulfonylureas), including a cardiovascular outcome trial (RECORD), observed no difference in overall mortality or in major adverse cardiovascular events (MACE) and its components.
- AVANDIA is not recommended for patients who are taking insulin.
- Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but in maintaining the efficacy of drug therapy.
- It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. It can take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of AVANDIA.
- Blood will be drawn to check their liver function prior to the start of therapy and periodically thereafter per the clinical judgment of the healthcare professional. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician.
- Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on AVANDIA should immediately report these symptoms to their physician.
- AVANDIA can be taken with or without meals.
- When using AVANDIA in combination with other hypoglycemic agents, the risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.
- Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDIA. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical trials so the frequency of this occurrence is not known.

AVANDIA and TILTAB are registered trademarks of the GSK group of companies.

GlaxoSmithKline
Research Triangle Park, NC 27709

AVD:XXPI

MEDICATION GUIDE

AVANDIA® (ah-VAN-dee-a)

(rosiglitazone maleate) tablets

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

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

AVANDIA may cause serious side effects, including:

New or worse heart failure

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

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

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

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

What is AVANDIA?

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

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

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

called diabetic ketoacidosis.

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

Who should not take AVANDIA?

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

Do not take AVANDIA if you are allergic to rosiglitazone or any of the ingredients in AVANDIA. See the end of this leaflet for a complete list of ingredients in AVANDIA.

Symptoms of a severe allergic reaction with AVANDIA may include:

- swelling of your face, lips, tongue, or throat
- problems with breathing or swallowing
- skin rash or itching
- raised red areas on your skin (hives)
- blisters on your skin or in your mouth, nose, or eyes
- peeling of your skin
- fainting or feeling dizzy
- very rapid heartbeat

What should I tell my doctor before taking AVANDIA?

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

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

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

about birth control choices while taking AVANDIA. Tell your doctor right away if you become pregnant while taking AVANDIA.

- **are breastfeeding or planning to breastfeed.** It is not known if AVANDIA passes into breast milk. You and your doctor should decide if you will take AVANDIA or breastfeed. You should not do both.

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

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

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

How should I take AVANDIA?

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

What are possible side effects of AVANDIA?

AVANDIA may cause serious side effects including:

- **New or worse heart failure.** See "What is the most important information I should know about AVANDIA?"
- **Heart attack.** AVANDIA may increase the risk of a heart attack. Talk to your doctor about what this means to you.

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

  Call your doctor or go to the nearest hospital emergency room right away if you think you are having a heart attack.
- **Swelling (edema).** AVANDIA can cause swelling due to fluid retention. See "What is the most important information I should know about AVANDIA?"
- **Weight gain.** AVANDIA can cause weight gain that may be due to fluid retention or extra body fat. Weight gain can be a serious problem for people with certain conditions including heart problems. See "What is the most important information I should know about AVANDIA?"
- **Liver problems.** It is important for your liver to be working normally when you take AVANDIA. Your doctor should do blood tests to check your liver before you start taking AVANDIA and during treatment as needed. Call your doctor right away if you have unexplained symptoms such as:
  - nausea or vomiting
  - stomach pain
  - unusual or unexplained tiredness
  - loss of appetite
  - dark urine
  - yellowing of your skin or the whites of your eyes.
- **Macular edema** (a diabetic eye disease with swelling in the back of the eye). Tell your doctor right away if you have any changes in your vision. Your doctor should check your eyes regularly. Very rarely, some people have had vision changes due to swelling in the back of the eye while taking AVANDIA.
- **Fractures (broken bones),** usually in the hand, upper arm, or foot. Talk to your doctor for advice on how to keep your bones healthy.

- **Low red blood cell count (anemia).**
- **Low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness, or hunger may mean that your blood sugar is too low. This can happen if you skip meals, if you use another medicine that lowers blood sugar, or if you have certain medical problems. Call your doctor if low blood sugar levels are a problem for you.
- **Ovulation** (release of egg from an ovary in a woman) leading to pregnancy. Ovulation may happen in premenopausal women who do not have regular monthly periods. This can increase the chance of pregnancy. See "What should I tell my doctor before taking AVANDIA?"

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

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

How should I store AVANDIA?

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

General information about AVANDIA

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

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

What are the ingredients in AVANDIA?

Active Ingredient: rosiglitazone maleate.

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

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

AVANDIA tablets are triangles with rounded corners and look like this:

2 mg – pink with “GSK” on one side and “2” on the other.

4 mg – orange with “GSK” on one side and “4” on the other.

8 mg – red-brown with “GSK” on one side and “8” on the other.

AVANDIA is a registered trademark of the GSK group of companies.

REZULIN is a trademark of its respective owner and is not a trademark of the GSK group of companies. The maker of this brand is not affiliated with and does not endorse the GSK group of companies or its products.

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

GlaxoSmithKline

Research Triangle Park, NC 27709

May 2014

AVD:XMG

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021071/S-048

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)

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

Memorandum

Date: February 13, 2014

To: Raymond Chiang, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Kendra Y. Jones, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 021071/S48 & S49, 021410/S37 & S38, 021700/S19 & 20 OPDP labeling comments for AVANDIA® (rosiglitazone maleate) Tablets, AVANDAMET® (rosiglitazone maleate and metformin hydrochloride) Tablets, and AVANDARYL® (rosiglitazone maleate and glimepiride) Tablets

---

OPDP has reviewed the proposed draft prescribing information (PI) and medication guides for AVANDIA® (rosiglitazone maleate) Tablets (Avandia), AVANDAMET® (rosiglitazone maleate and metformin hydrochloride) Tablets (Avandamet), and AVANDARYL® (rosiglitazone maleate and glimepiride) Tablets (Avandaryl) submitted for consult on January 31, 2014.

OPDP's review is based on versions of the PIs located in the eRoom entitled, "21071 - S48 rosi draft-proposed label submitted.doc," (Avandia) "21410 - S37 Avandamet draft-proposed label.doc," (Avandamet) and "21700 - S19 Avandaryl draft-proposed label submitted.doc" (Avandaryl) last modified February 12, 2014. In addition, OPDP's review of the medication guides are based on the versions provided in DMPP's February 13, 2014, review. OPDP's review focuses specifically on the *changes* to the PIs and medication guides based on these supplements only.

Comments regarding changes to the proposed REMS materials will be provided under separate cover.

OPDP has no comments on the proposed PIs and medication guides at this time.

Thank you for the opportunity to comment on the proposed draft PIs and medication guides. If you have any questions, please contact Kendra Jones at 301.796.3917 or Kendra.jones@fda.hhs.gov.

151 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

KENDRA Y JONES
02/13/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	February 13, 2014
To:	Jean-Marc Guettier, M.D. Acting Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Focused Review of Patient Labeling: Medication Guide (MG)
Drug Names (established names):	AVANDIA (rosiglitazone maleate) AVANDAMET (rosiglitazone maleate, metformin hydrochloride AVANDARYL (rosiglitazone maleate, glimepiride)
Dosage Form and Route:	Tablet
Application Type/Number:	NDA 021071/S-048 and S049 NDA 021410/S-037 and S038 NDA 021700/S-019 and S020
Applicant:	GlaskoSmithKline

1 INTRODUCTION

On December 20, 2013, GlaskoSmithKline submitted for the Agency's review a REMS Modification to amend the pending applications. The purpose was to remove the glimepiride conforming language from the Avandaryl Prescribing information and Medication Guide as requested by the Agency on December 13, 2013, for AVANDIA (rosiglitazone maleate), AVANDAMET (rosiglitazone maleate and metformin hydrochloride), and AVANDARYL (rosiglitazone maleate and glimpiride) Tablets. These drugs with diet and exercise are indicated to treat certain adults with type 2 diabetes mellitus. In addition, safety labeling changes were made which included the following:

- renaming the REMS program to the Rosiglitazone REMS Program
- adding hypersensitivity as a contraindication
- modifying the REMS website address to www. rosiglitazonerems.com and the REMS telephone number from 1-800-Avandia to 1-800-282-6342 for consistency with the REMS document
- modifying the "GlaxoSmithKline" group of companies
- modifying the symptoms of an allergic reaction
- updates to Sections 8.1 (Pregnancy) and 8.3 (Nursing Mothers) of the Prescribing Information

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on January 30, 2014, for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG), for AVANDIA (rosiglitazone maleate), AVANDAMET (rosiglitazone maleate and metformin hydrochloride), and AVANDARYL (rosiglitazone maleate and glimpiride).

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DMEP under separate cover.

2 MATERIAL REVIEWED

- Draft AVANDIA (rosiglitazone maleate), MG received on December 20, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on February 7, 2014.
- Draft AVANDAMET (rosiglitazone maleate and metformin hydrochloride), MG received on December 20, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on February 7, 2014.
- AVANDARYL (rosiglitazone maleate and glimpiride) MG received on December 20, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on February 7, 2014.

- Draft AVANDIA (rosiglitazone maleate), Prescribing Information (PI) received on December 20, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on February 7, 2014.
- Draft AVANDAMET (rosiglitazone maleate and metformin hydrochloride), Prescribing Information (PI) received on December 20, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on January 17, 2014.
- Draft AVANDARYL (rosiglitazone maleate and glimpiride) Prescribing Information (PI) received on December 20, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on January 17, 2014.
- Completed rosiglitazone maleate (AVANDIA), rosiglitazone maleate and metformin (AVANDAMET), and rosiglitazone maleate and glimepride (AVANDARYL) MG reviews provided to DMEP on January 27, 2014.

3 REVIEW METHODS

In our focused review of the Medication Guides we have:

- simplified wording and clarified concepts where possible
- ensured that the Medication Guides are consistent with the Prescribing Information (PI)

4 CONCLUSIONS

The Medication Guides are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Consult DMPP during the next review cycle for a comprehensive review of the Patient Labeling to bring it up to current Patient Labeling standards.
- Our focused reviews of the Medication Guides are appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the Medication Guides.

Please let us know if you have any questions.

40 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

SHARON W WILLIAMS
02/13/2014

MELISSA I HULETT
02/13/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021071/S-048

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021071/S-048
NDA 021410/S-037
NDA 021700/S-019

LABELING DISCUSSION EXTENSION

SmithKline Beecham (Cork) Ltd d/b/a GlaxoSmithKline
Attention: Margaret Kreider, Ph.D.
Senior Director, Regulatory Affairs
2301 Renaissance Blvd.; Mail Code RN 0420
King of Prussia, PA 19406-2772

Dear Dr. Kreider:

Please refer to your Supplemental New Drug Applications (sNDAs) dated January 20, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Avandia (rosiglitazone maleate) tablets, Avandamet (rosiglitazone maleate and metformin hydrochloride) tablets, and Avandaryl (rosiglitazone maleate and glimepiride) tablets.

On November 25, 2013, we sent a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Avandia, Avandamet and Avandaryl to address the risk of ischemic cardiovascular events as assessed by the readjudicated results of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, based on new safety information about this risk identified since the product was approved. You were directed to submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On January 22, 2014, we received your prior approval supplements dated January 20, 2014, containing your proposed safety related labeling changes, including changes to the Medication Guide. Section 505(o) requires FDA to promptly review these supplements and if we disagree with the proposed changes, to initiate discussions with you on the content of the changes. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

We refer to our letter dated February 20, 2014, informing you that we determined that a 30-day extension of the discussion period was warranted to allow us to complete our review and reach agreement on the content of the labeling.

This letter is to inform you that we have determined that a second 30-day extension of the discussion period is warranted to allow us to complete our review and reach agreement on the

content of the labeling. Therefore, the discussion period for this supplement ends on April 22, 2014.

If you have any questions, call Raymond Chiang, Regulatory Project Manager, at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Jennifer R. Pippins, M.D., M.P.H.
Deputy Director for Safety (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

JENNIFER R PIPPINS
03/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021071/S-048
NDA 021410/S-037
NDA 021700/S-019

LABELING DISCUSSION EXTENSION

SmithKline Beecham (Cork) Ltd d/b/a GlaxoSmithKline
Attention: Margaret Kreider, Ph.D.
Senior Director, Regulatory Affairs
2301 Renaissance Blvd.; Mail Code RN 0420
King of Prussia, PA 19406-2772

Dear Dr. Kreider:

Please refer to your Supplemental New Drug Applications (sNDAs) dated January 20, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Avandia (rosiglitazone maleate) tablets, Avandamet (rosiglitazone maleate and metformin hydrochloride) tablets, and Avandaryl (rosiglitazone maleate and glimepiride) tablets.

On November 25, 2013, we sent a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Avandia, Avandamet and Avandaryl to address the risk of ischemic cardiovascular events as assessed by the readjudicated results of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, based on new safety information about this risk identified since the product was approved. You were directed to submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On January 22, 2014, we received your prior approval supplements dated January 20, 2014, containing your proposed safety related labeling changes, including changes to the Medication Guide. Section 505(o) requires FDA to promptly review these supplements and if we disagree with the proposed changes, to initiate discussions with you on the content of the changes. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

This letter is to inform you that we have determined that a 30-day extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for these supplements ends on March 23, 2014.

If you have any questions, call Raymond Chiang, Regulatory Project Manager, at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Suchitra Balakrishnan, M.D., Ph.D.
Deputy Director for Safety (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

SUCHITRA M BALAKRISHNAN
02/20/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:

CDER-OPDP-RPM

FROM: Raymond Chiang
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Raymond.chiang@fda.hhs.gov
(301) 796-1940

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
January 30, 2014		NDA 21071/S48 and 49 NDA 21410/S37 and 38 NDA 21700/19 and 20	(PLEASE CHECK OFF BELOW)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Avandia, Avandamet and Avandaryl	High	TDM	February 15, 2014 (depending on when we provide you the substantially complete label)

NAME OF FIRM:

GSK

PDUFA Date: PDUFA Date: February 21, 2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☒ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☒ SAFETY SUPPLEMENT
☒ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

For OSE USE ONLY
☒ REMS

EDR link to submission:

EDR Location: \\CDSESUB1\evsprod\NDA021071\021071.enx
EDR Location: \\CDSESUB1\evsprod\NDA021410\021410.enx
EDR Location: \\CDSESUB1\evsprod\NDA021700\021700.enx

eRoom link to all the documents
http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_40ce7

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

These supplements are in response to our Safety Labeling Change and REMS Modification notification letter issued on 11/25/2013, for Avandia, Avandamet and Avandaryl. Please review the revised labeling once the labels are substantially complete. The documents have been placed in the eRoom for review.

http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_40ce7

SIGNATURE OF REQUESTER
Raymond Chiang

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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

/s/

RAYMOND S CHIANG
01/31/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: Raymond Chiang
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Raymond.chiang@fda.hhs.gov
(301) 796-1940

REQUEST DATE:
January 30, 2014

NDA/BLA NO.:
NDA 21071/S48 and 49
NDA 21410/S37 and 38
NDA 21700/19 and 20

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

NAME OF DRUG:
Rosiglitazone-containing products (Avandia, Avandamet and Avandaryl)

PRIORITY CONSIDERATION:
High

CLASSIFICATION OF DRUG:
TDM

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)
February 15, 2014 (depending on when we provide you the substantially complete label)

SPONSOR:
GSK

PDUFA Date: February 21, 2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PATIENT PACKAGE INSERT (PPI)
☒ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ EFFICACY SUPPLEMENT
☒ SAFETY SUPPLEMENT
☒ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

EDR link to submission:
EDR Location: \\CDSESUB1\evsprod\NDA021071\021071.enx
EDR Location: \\CDSESUB1\evsprod\NDA021410\021410.enx
EDR Location: \\CDSESUB1\evsprod\NDA021700\021700.enx

eRoom link to all the documents
http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_40ce7

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

These supplements are in response to our Safety Labeling Change and REMS Modification notification letter issued on 11/25/2013, for Avandia, Avandamet and Avandaryl. Please review the revised labeling once the labels are substantially complete. The documents have been placed in the eRoom for review.

http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_40ce7

SIGNATURE OF REQUESTER
Raymond Chiang

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL (BLAs Only) ☐ DARRTS

Version: 12/9/2011

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

/s/

RAYMOND S CHIANG
01/31/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE

FROM: Raymond Chiang
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Raymond.chiang@fda.hhs.gov
(301) 796-1940

DATE	IND NO.	NDA NO	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 30, 2014		NDA 21071/S48 and 49 NDA 21410/S37 and 38 NDA 21700/19 and 20	Submitted revised rosiglitazone-containing product labels, REMS, and REMS supporting document in response to our Safety Labeling Changes letter	January 17, 2014 and January 20, 2014 (received January 22, 2014)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Avandia, Avandamet and Avandaryl	HIgh	TDM	**February 4, 2014**

NAME OF FIRM: GSK

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

These supplements are in response to our Safety Labeling Change and REMS Modification notification letter issued on 11/25/2013, for Avandia, Avandamet and Avandaryl. Please review the revised labeling (DEPI) and REMS (DRISK). The documents have been placed in the eRoom for review. Please provide any necessary revisions/comments. Since the Safety Labeling Change supplements are on a 30-day clock (due February 21, 2014), we are asking for you to put in your revisions by **February 4, 2014.**

http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_40ce7

SIGNATURE OF REQUESTER Raymond Chiang	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

RAYMOND S CHIANG
01/31/2014