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*APPLICATION NUMBER:*

**21-700**

**MEDICAL REVIEW**

## CLINICAL REVIEW

<b>Application Type</b>	NDA
<b>Submission Number</b>	NDA 21-700 second cycle
<b>Submission Code</b>	
<b>Letter Date</b>	9/23/05
<b>Filing Date</b>	
<b>PDUFA Goal Date</b>	11/26/05
<b>Reviewer Name</b>	Joanna K. Zawadzki M.D.
<b>Review Completion Date</b>	11/14/05
<b>Established Name</b>	rosiglitazone maleate <i>Avandia</i> ®(GlaxoSmithKline) and glimepiride] <i>Amaryl</i> ®(Hoechst AG) fixed dose combination tablets
<b>(Proposed) Trade Name</b>	<i>Avandaryl</i> <sup>TM</sup> Tablets
<b>Therapeutic Class</b>	Hypoglycemic Agent (3031400)
<b>Applicant</b>	GlaxoSmithKline
<b>Priority Designation</b>	S
<b>Formulation</b>	Combination tablets containing fixed dose of rosiglitazone and variable doses of glimepiride; three dose formulations: rosiglitazone maleate/glimepiride 4 mg/1mg; 4 mg/2 mg; 4 mg/4 mg
<b>Dosing Regimen</b>	once daily with first main meal
<b>Indication</b>	Treatment of Type 2 Diabetes Mellitus
<b>Intended Population</b>	Patients with Type 2 Diabetes Mellitus treated with rosiglitazone maleate and sulfonylurea combination therapy or poorly controlled on one of these agents alone; This combination therapy is not intended for patients who are not treated with rosiglitazone or a sulfonylurea.
<b>Relevant NDA(s)</b>	NDA 21-071 (rosiglitazone maleate [BRL-049653-C] <i>Avandia</i> ®,GlaxoSmithKline) approved 5/25/99; NDA 20-496 (glimepiride [HOE 490] <i>Amaryl</i> ®,Hoechst AG) approved 11/30/95
<b>Relevant IND(s)</b>	IND 66,162
<b>Medical Team Leader and Division Director</b>	David G. Orloff, M.D.
<b>Statistical Reviewer</b>	Joy Mele, M.S.
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<b>Project Manager</b>	Lina AlJuburi, Pharm.D.

## **EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

Approval, with labeling revisions, clear designation of proprietary name and dosage strengths of the component drugs, and educational program for clinicians to minimize confusion of *Avandaryl*<sup>TM</sup> with *Avandia*<sup>®</sup>, *Avandamet*<sup>®</sup>, or *Amaryl*<sup>®</sup>.

*Avandaryl*<sup>TM</sup> is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of rosiglitazone and sulfonylurea or who are not adequately controlled on sulfonylurea therapy alone or for those patients who have initially responded to rosiglitazone alone and require additional glycemic control.

*Note: The phrase or for those patients who have initially responded to rosiglitazone alone and require additional glycemic control was proposed by the sponsor, after the example of approved labelling for ACTOPLUS-Met. In those clinical studies, pioglitazone was added to metformin. FDA concurred for consistency across drug products.*

### **1.2 Recommendation on Postmarketing Actions**

Risk management, as proposed by GlaxoSmithKline, will include education programs for clinicians to minimize confusion of *Avandaryl*<sup>TM</sup> with *Avandia*<sup>®</sup>, *Avandamet*<sup>®</sup>, or *Amaryl*<sup>®</sup>. The usual postmarketing pharmacovigilance, including reporting of any drug substitution errors, is recommended.

### **1.3 Required Phase 4 Commitments**

There are no required Phase 4 commitments.

### **1.4 Summary of Clinical Findings**

Rosiglitazone maleate [subsequently referred to as rosiglitazone] and glimepiride are two oral antidiabetic drugs that are each approved for the treatment of Type 2 diabetes mellitus. In addition, combination of rosiglitazone and sulfonylurea therapy was approved for the treatment of patients who are inadequately treated with diet, exercise, and sulfonylurea monotherapy (NDA 21-071 SE001). The current NDA (NDA 21-700) presents the clinical program for the development of *Avandaryl*<sup>TM</sup>, rosiglitazone maleate and glimepiride fixed dose combination tablets for the second-line therapy of patients with Type 2 diabetes mellitus, who have been inadequately treated with diet, exercise, and sulfonylurea, or who are currently treated with combination rosiglitazone and sulfonylurea. Approval of this fixed dose combination product is based on the demonstration of bioequivalence of the fixed dose combination product to concomitantly administered rosiglitazone maleate and glimepiride. The results for the fixed dose

combination product are bridged to the three double blind, controlled clinical studies previously submitted for the approved concomitantly administered rosiglitazone and sulfonylurea combination and to the additional two clinical studies in this submission. The three proposed dose formulations of *Avandaryl*<sup>TM</sup> are rosiglitazone maleate/glimepiride 4 mg/1mg; 4 mg/2 mg; and 4 mg/4 mg.

The NDA was initially submitted on 10/31/03. Please refer to the clinical and statistical reviews dated 8/12/04. An approvable letter was issued on 8/31/04 because of manufacturing problems. The choice of the proprietary name and the labeling, both prescribing information (PI) and patient prescribing information (PPI) were not fully completed at the time of the approvable letter and are discussed below. On 9/23/05, the sponsor submitted a complete response to the approvable letter, which addressed the chemistry issues.

## 1.5 Overall Assessment

The fixed dose combination drug product *Avandaryl*<sup>TM</sup> (rosiglitazone and glimepiride) can be approved, with the postmarketing risk assessment proposed by the sponsor.

## 2.0 Proprietary Name

In the first review cycle, the proposed proprietary name *Avandaryl*<sup>TM</sup> (rosiglitazone maleate, glimepiride) was found unacceptable by the Division of Medication Errors and Technical Support (DMETS) and the Division of Metabolism and Endocrinology Products (DMEDP) because of its similarity ('sound-alike' and/or 'look-alike') with the approved drug products *Amaryl*® (glimepiride), *Avandia*® (rosiglitazone), and *Avandamet*® (rosiglitazone and metformin). See DMETS review dated 7/1/04, DMEDP review dated 8/17/04, and letter to the sponsor dated 8/25/04. FDA raised concern about the possible prescribing errors, risk to patient safety, and risk of lack of efficacy that might result from the confusion of some of these names. The major safety risk includes sulfonylurea-induced hypoglycemia if *Avandaryl*<sup>TM</sup> is prescribed instead of *Avandia*® and *Avandamet*®, both of which are associated with a smaller risk of hypoglycemia. Conversely, if the proprietary name is distinct from *Avandia*® and *Avandamet*®, a theoretical risk of "double-dosing" is greater, and the risk of thiazolidinedione-associated fluid excess and congestive heart failure are dose-related.

In the 9/15/04 response, the sponsor noted that the risk of confusion between *Avandaryl*<sup>TM</sup> and *Avandia*® was minimal in their tests (1% in the verbalized tests; no confusion noted in the handwriting tests) and *Avandamet*® was not tested. The sponsor noted the beneficial effect of the name similarities, as it would be less likely that patients would be 'double-dosed' –e.g., prescribed both *Avandaryl*<sup>TM</sup> and *Avandia*® or *Amaryl*®. The sponsor proposed a communication and education plan for caregivers and patients at the time of the *Avandaryl*<sup>TM</sup> launch to minimize this risk.

Since patients receiving any of these drugs - *Avandaryl*<sup>TM</sup>, *Avandia*®, *Avandamet*® or *Amaryl*® - have Type 2 diabetes mellitus and are hyperglycemic, the risk of hypoglycemia is less . In addition, the proprietary names of all these drugs have to be accompanied by dosage strengths, which differ for the four drug products, and that should further reduce the risk of mistaking one proprietary name for another. (See Table below).

**Table: Comparison of Oral Hypoglycemic Drugs with Similar Proprietary Names**

<b>Proprietary Name</b>	<b>Generic Names</b>	<b>Dosage Strengths and Administration</b>
<i>Avandia</i> ®	rosiglitazone	2, 4, 8 mg; given qd or bid; maximum daily dose 8 mg
<i>Avandamet</i> ®	rosiglitazone + metformin	rosiglitazone/metformin 1 mg/500 mg, 2 mg/500 mg, 2mg/1000 mg; 4 mg/500mg, 4mg/1000 mg qd or bid; maximum daily dose 8 mg/2000 mg
<i>Amaryl</i> ®	glimepiride	1, 2, 4 mg qd maximum daily dose 8 mg
<i>Avandaryl</i> <sup>TM</sup>	rosiglitazone + glimepiride	rosiglitazone / glimepiride 4 mg/1mg; 4 mg/2 mg; 4 mg/4 mg; given once daily

### 3.0 Labeling

FDA revisions of the prescribing information (PI) and patient prescribing information (PPI) were forwarded to the sponsor in the first review cycle. GlaxoSmithKline responded on 9/16/2004. The annotated line-by-line PI includes responses to the sponsor's suggestions and comments. The key areas for further discussion include the **indication** and the use of rosiglitazone, rather than thiazolidinedione, as all the studies were rosiglitazone, and the presentation of data from both arms of Study 235 in the **Clinical Studies** section. The discrepancy between some of the sponsor's numbers and those from the FDA review is highlighted.

The sponsor's changes to the PPI were again reviewed in the Office of Drug Safety and additional comments are included.

The submission of the proposed labeling for *Avandaryl*<sup>TM</sup> preceded the approval of several labeling supplements for *Avandia*®. In the final labeling discussions, the sponsor proposed modifying the *Avandaryl*<sup>TM</sup> label to be consistent with the currently approved *Avandia*® label. This proposal concurred with the style of the originally proposed labeling for *Avandaryl*<sup>TM</sup>, which was a composite of the *Avandia*® and *Amaryl*® prescribing information. FDA concurred. Since there are many changes in this label, it is also appended. (There were other labeling versions during the discussion, but the 11/18/05 is the final or near-final version.)



In the final discussion regarding the PPI, it was agreed to omit the reference to the UGDP warning, as this reference was not included in the PPI for another combination product with a sulfonylurea (e.g., Metaglip = metformin + glipizide)

#### APPENDIX

- 1) Line-by-Line Labeling (PI) (FDA comments 11/10/05)
- 2) Line-by-Line Labeling (PI) (GSK comments 11/18/05)
- 3) Line-by-Line Labeling (PPI) (FDA comments 11/10/05)
- 4) Line-by-Line Labeling (PPI) (GSK comments 11/18/05)

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       Trade Secret / Confidential

✓ Draft Labeling

       Deliberative Process

**MEMORANDUM**  
SERVICES

DEPARTMENT OF HEALTH AND HUMAN  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND

RESEARCH

**DATE:** November 4, 2004

**TO:** David Orloff, M.D., Director  
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**VIA:** Lina AlJuburi, Regulatory Health  
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**THROUGH:** Gerald Dal Pan, M.D., M.H.S., Director  
Division of Surveillance, Research, and Communication  
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**SUBJECT:** DSRCS Review of the Patient Labeling for  
Avandaryl (rosiglitazone maleate and glimepiride) Tablets,  
NDA 21-700

**Background and Summary**

Please refer to the DSRCS PPI review dated May 27, 2004. The sponsor sent in revised labeling for Avandaryl (rosiglitazone maleate and glimepiride) Tablets, NDA 21-700 on October 8, 2004, in response to FDA comments. We have simplified the wording, made it consistent with the PI, and removed other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

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       Trade Secret / Confidential

✓ Draft Labeling

       Deliberative Process

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/s/

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## CLINICAL REVIEW

<b>Application Type</b>	NDA (new drug application)
<b>Submission Number</b>	<b>NDA 21-700</b>
<b>Submission Code</b>	N-000
<b>Letter Date</b>	10/31/03
<b>Filing Date</b>	12/30/03
<b>PDUFA Goal Date</b>	8/31/04
<b>Reviewer Name</b>	Joanna K. Zawadzki M.D.
<b>Review Completion Date</b>	8/12/04
<b>Established Name</b>	rosiglitazone maleate, <i>Avandia</i> ®(GlaxoSmithKline) and glimepiride, <i>Amaryl</i> ®(Hoechst AG) fixed dose combination tablets
<b>(Proposed) Trade Name</b>	<i>Avandaryl</i> <sup>TM</sup> Tablets
<b>Therapeutic Class</b>	Hypoglycemic Agent (3031450)
<b>Applicant</b>	SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline
<b>Priority Designation</b>	S
<b>Formulation</b>	Combination tablets containing fixed dose of rosiglitazone and variable doses of glimepiride; three dose formulations: rosiglitazone maleate/glimepiride 4 mg/1mg; 4 mg/2 mg; 4 mg/4 mg
<b>Dosing Regimen</b>	once daily with first meal
<b>Indication</b>	Treatment of Type 2 Diabetes Mellitus
<b>Intended Population</b>	Patients with Type 2 Diabetes Mellitus treated with rosiglitazone maleate and sulfonylurea combination therapy or poorly controlled on sulfonylurea therapy alone; This fixed dose combination therapy is not intended for patients who are new to pharmacologic therapy for Type 2 diabetes mellitus.
<b>Relevant NDA(s)</b>	<b>NDA 21-071</b> (rosiglitazone maleate [BRL-049653-C] <i>Avandia</i> ®,GlaxoSmithKline) approved 5/25/99; <b>NDA supplement 21-071 SE001</b> for combination rosiglitazone and sulfonylurea therapy; approved 4/00 <b>NDA 20-496</b> (glimepiride [HOE 490] <i>Amaryl</i> ®, Hoechst AG) approved 11/30/95
<b>Relevant IND(s)</b>	<b>IND 66,162</b>

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Clinical Reviewer  
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Rosiglitazone maleate / glimepiride

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The electronic submissions to NDA 21-700 include the original submission and 11 amendments. These submissions are listed in the table below, with the initial submission at the bottom of the table. The modifying type amendment abbreviations include the following: BC = chemistry amendment, BL = labeling amendment, BZ=multidisciplinary amendment; C=general correspondence; and PU=pediatric followup document.

Letter date	Doc Type	Seq Number	Mod Type	Comments
6-AUG-2004	N	000	BC	Response to FDA regarding BA/BE, CMC
16-JUL-2004	N	000	BZ	Response to FDA regarding CMC and Labeling
24-JUN-2004	N	000	BC	Response to FDA regarding BA/BE, CMC
8-JUN-2004	N	000	BL	Revised proposed package insert: change in liver enzyme monitoring
21-MAY-2004	N	000	PU	Additional information regarding rational for request for deferral of pediatric studies
20-MAY-2004	N	000	BL	Revised proposed container and carton labels for <i>Avandaryl</i> tablets
13-MAY-2004	N	000	BC	
31-MAR-2004	N	000	BC	
15-MAR-2004	N	000	BL	Final proposed container and carton labels for <i>Avandaryl</i> tablets
8-MAR-2004	N	000	C	Response to FDA's financial disclosure information request
29-JAN-2004	N	000	BC	
31-OCT-2003	N	000		

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**Please Note:**

- Tables, unless otherwise stated, are from the sponsor's submission.
- The table numbers reflect the order in this review.

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## Abbreviations

<u>Abbreviation</u>	<u>Unabridged Terms</u>
ADA	American Diabetes Association
AE	Adverse Experience/Event
ALT	Alanine Aminotransferase (SGPT)
AST	Aspartate Aminotransferase (SGOT)
AUC	Area Under the Plasma Concentration Curve (i.e., extent of exposure)
AUC(O-∞)	Area Under the Plasma Concentration Curve from Time 0 to Infinite Time
AUC(0-t)	Area Under the Plasma Concentration Curve from Time 0 to Last Measurable Concentration
bid	Twice daily
BMI	Body Mass Index [weight (kg)/square of height (m <sup>2</sup> )]
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CI	Confidence Interval
C <sub>max</sub>	Observed Maximum Plasma Concentration (i.e., rate)
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRT	Case Report Data Tabulations
CT	Clinical Trial
dL	Deciliter
DM	Diabetes Mellitus
EMA	European Association for the Evaluation of Medicinal Products
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
FU	followup
GCP	Good Clinical Practice
GLB	Glibenclamide/Glyburide
GLIC	Gliclazide
GLIM	Glimepiride
GLIP	Glipizide
hr/hrs	Hour/Hours
Hb	Hemoglobin
HbA <sub>1c</sub>	Glycosylated hemoglobin A1c
Hct	Hematocrit
HDL	High Density Lipoprotein
IDDM	Insulin Dependent Diabetes Mellitus (Type 1 Diabetes Mellitus)
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Units
L	Liter
LDL	Low Density Lipoprotein
MET	Metformin

mg	Milligrams
MI	Myocardial Infarction
mm	Minute
mL	Milliliter
mmol	Millimole
mol	Mole
NDA	New Drug Application
NIDDM	Non-insulin Dependent Diabetes Mellitus (Type 2 Diabetes Mellitus)
od	Once daily
OLE	Open Label Extension
Pbo	Placebo
PDUFA	Prescription Drug User Fee Act of 1992
pmol	Picomole
PPAR	Peroxisomal Proliferator Activated Receptor
qd	abbreviation for Latin <i>qua'que di'e</i> , every day
®	registered trademark
RBC	Red Blood Cell
RSG	Rosiglitazone
SAE	Serious Adverse Experience/Event
SB	SmithKline Beecham
SBCL	SmithKline Beecham Clinical Laboratories
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SEM	Standard Error of the Mean
SGOT	Serum Glutamic Oxaloacetic Transaminase (See AST)
SGPT	Serum Glutamic Pyruvic Transaminase (See ALT)
SI	International System of Units
SU	Sulfonylurea
T 1/2	Half-life
tdd	Total Daily Dose
TG	Triglyceride
™	trademark
Tmax	Time of Observed Maximum Concentration
TZD	Thiazolidinedione
u	Micro
UGDP	University Group Diabetes Program
UK	United Kingdom
UKPDS	United Kingdom
ULN	Upper Limit Normal
ULRR	Upper Limit of the Reference Range
umol	micromole
URI/URTI	Upper Respiratory Tract Infection
USA	United States of America
UTI	Urinary Tract Infection
VLDL	Very Low Density Lipoprotein
WBC	White Blood Cell

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NDA 21-700  
Rosiglitazone maleate / glimepiride

WHO

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## 1 EXECUTIVE SUMMARY

### Recommendation on Regulatory Action

This reviewer recommends approval of *Avandaryl*<sup>TM</sup> (rosiglitazone maleate and glimepiride fixed dose combination product) for the following indication, with the revised labeling and change of the proposed proprietary or trade name from *Avandaryl*<sup>TM</sup>:

*Avandaryl*<sup>TM</sup> is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of rosiglitazone and sulfonylurea in doses comparable to or less than the rosiglitazone and glimepiride doses in *Avandaryl*<sup>TM</sup> or who are not adequately controlled on sulfonylurea therapy alone.

This reviewer agrees with the Division of Medication Errors and Technical Support (DMETS) consult, which does not recommend the use of the *Avandaryl* trade name or proprietary name. According to their review, the *Avandaryl* name may potentially be confused with the following trade names: *Avandia* (rosiglitazone maleate), *Amaryl* (glimepiride), *Avandamet* (rosiglitazone maleate and metformin), and *Vanceril* (beclomethasone dipropionate inhalation aerosol). Confusion with the first three trade names may pose the greatest safety issues. The DMETS consult should be forwarded to the sponsor.

### Recommendation on Postmarketing Actions

#### 1.1.1 Risk Management Activity

Other than the adverse events previously associated with rosiglitazone and sulfonylurea therapy, no specific risk has been identified with the fixed dose combination tablet of rosiglitazone maleate and glimepiride that requires additional risk management activity.

#### 1.1.2 Required Phase 4 Commitments

There is no required Phase 4 commitment.

#### 1.1.3 Other Phase 4 Requests

There are no other Phase 4 requests.

## Summary of Clinical Findings

### 1.1.4 Brief Overview of Clinical Program

Rosiglitazone maleate [subsequently referred to as rosiglitazone] and glimepiride are two oral antidiabetic drugs that are each approved for the treatment of Type 2 diabetes mellitus. In addition, combination of rosiglitazone and sulfonylurea therapy was approved for the treatment of patients who are inadequately treated with diet, exercise, and sulfonylurea monotherapy (NDA 21-071 SE001). The current NDA (NDA 21-700) presents the clinical program for the development of *Avandaryl*<sup>TM</sup>, rosiglitazone maleate and glimepiride fixed dose combination tablets for the second-line therapy of patients with Type 2 diabetes mellitus, who have been inadequately treated with diet, exercise, and sulfonylurea, or who are currently treated with combination rosiglitazone and sulfonylurea. The three proposed dose formulations of *Avandaryl*<sup>TM</sup> are rosiglitazone maleate/glimepiride 4 mg/1mg; 4 mg/2 mg; and 4 mg/4 mg.

At the pre-NDA meeting, the sponsor and FDA agreed that approval of this fixed dose combination product would be based on the demonstration of bioequivalence of the fixed dose combination product to concomitantly administered rosiglitazone maleate and glimepiride. The results for the fixed dose combination product would be bridged to the double blind, controlled clinical studies previously submitted for the approved concomitantly administered rosiglitazone and sulfonylurea combination and to the additional clinical studies in this submission. The sponsor submits these data in support of the following proposed indication:



The NDA 21-700 submission comprises four pharmacokinetic studies: dose proportionality study, bioequivalence study, food study, and drug interaction study. Two pivotal clinical studies, Studies 234 and 135, are also submitted. Study 234 is a 26-week, double-blind, controlled 3-arm clinical trial in which two doses of rosiglitazone (4 mg and 8 mg) added to glimepiride (3 mg) are compared to glimepiride (3 mg) alone. This is the only pivotal clinical study in which concomitantly administered rosiglitazone and glimepiride are studied, though the glimepiride dose of 3 mg is not one of the proposed doses in the fixed combination drug product, and it is lower than the proposed maximum dose of glimepiride (4 mg). The primary endpoint in Study 234 is change in glycosylated hemoglobin A1c (HbA1c) from baseline.

Study 135 is a two year double-blind controlled clinical trial in which rosiglitazone added to glipizide therapy is compared to glipizide therapy alone. The primary endpoint is the time to failure of therapy, defined as a fasting plasma glucose  $\geq$  180 mg/dl, despite titration to maximal rosiglitazone therapy (8 mg) and glipizide therapy (20 mg bid). Data from the third submitted clinical study (Study 4034, Aventis) in which glimepiride is added to rosiglitazone therapy, has not been extensively reviewed as only 41 patients of a planned 200 patient population were enrolled.

The sponsor cross-references three double-blind, active-controlled clinical studies from the approved NDA 21-071 SE001 supplement for combination rosiglitazone and sulfonylurea therapy. In two of these studies (Studies 015 and 096), rosiglitazone was added to sulfonylureas and compared to the sulfonylurea group and in the third study (Study 079) concomitant administration of rosiglitazone and glyburide was compared to administration of each component. Glimepiride was not studied in the cross-referenced studies.

All of the five pivotal clinical studies, including the two clinical studies in this submission and the three clinical studies that are cross-referenced, evaluated the combination rosiglitazone and sulfonylurea therapy as a second line therapy; i.e., all the patients were previously treated with oral antidiabetic drugs. A first-line indication in patients naïve to pharmacologic therapy for Type 2 diabetes mellitus was not evaluated in these studies. The proposed fixed dose combination drug product rosiglitazone and glimepiride was not evaluated in the clinical studies. The two clinical studies in this submission confirm the data of the three cross-referenced clinical studies, that formed the basis of the second-line indication of combination rosiglitazone and sulfonylurea therapy for the treatment of Type 2 diabetes mellitus. The main emphasis of this clinical review is to evaluate how the pharmacokinetic and clinical data support the proposed indication and labeling for *Avandaryl*<sup>TM</sup>, rosiglitazone maleate and glimepiride fixed dose combination tablets for the second-line therapy of patients with Type 2 diabetes mellitus, who have been inadequately treated with diet, exercise, and sulfonylurea, or who are currently treated with concomitantly administered rosiglitazone and a sulfonylurea.

### 1.1.5 Efficacy

The pharmacokinetic data indicate that the fixed dose combination product rosiglitazone and glimepiride is similar to concomitantly administered rosiglitazone and glimepiride. The five controlled clinical studies (two from this submission and three from the prior submission) all indicate that treatment with rosiglitazone (4 mg) added to a sulfonylurea therapy results in better glycemic control than treatment with the sulfonylurea alone. From baseline glycosylated hemoglobin A1c (HbA1c) values of 8 – 9% and baseline fasting plasma glucose (FPG) values of 200 – 220 mg/dl, there was a decrease in HbA1c and FPG, in the range of 0.3 to 0.9% and 25-38 mg/dl, respectively, in the four 26-week studies.

The two-year study also showed a similar change in HbA1c and FPG, though those patients were less hyperglycemic at baseline. This study also showed that the combination rosiglitazone and sulfonylurea therapy is more durable. The primary endpoint in this study was defined as the mean time to the final action point (FAP), FPG  $\geq$  180 mg/dl, or mean time to treatment failure, when patients could be withdrawn from the study or treated with insulin. The mean duration of exposure to medication differed between the two treatment groups (644 days in the rosiglitazone and glipizide group versus 560 days in the glipizide group), as only 2 patients (2%) in the rosiglitazone and glipizide group achieved the FAP, or failed therapy, while 27 (28.7%) patients in the glipizide group achieved the FAP ( $p < 0.0001$ ).

See table below, summarizing the efficacy data for the clinical studies.

Table. Summary of Efficacy Data

	Sample Size	HbA1c Mean (%)		FPG Mean (mg/dL)	
		Baseline	Change	Baseline	Change
<i>Study Reports Submitted in NDA 21-700</i>					
Study 234					
Avandia 4 mg OD+Glimepiride	56	8.2	<b>-0.63*</b>	189	<b>-26</b>
Glimepiride	57	7.9	-0.08	176	+2
Study 135 (2-year study)					
Avandia 4 mg OD+Glipizide	115	7.6	<b>-0.65*</b>	149	<b>-25*</b>
Glipizide	110	7.4	+0.13	149	+14
<i>Study Reports Submitted in NDA 21-071 SE1-001 (approved 4/00)</i>					
Study 096					
Avandia 4 mg OD+Glyburide	116	9.1	<b>-0.3*</b>	214	<b>-25*</b>
Glyburide	115	8.9	+0.6	209	+23
Study 015					
Avandia 2 mg BID+SU	183	9.2	<b>-0.9*</b>	205	<b>-38*</b>
Sulfonylurea (SU)	192	9.2	+0.2	207	+6
Study 079					
Avandia 2 mg BID+Glyburide	98	9.2	<b>-0.5*</b>	222	<b>-34*</b>
Glyburide	99	9.2	+0.9	220	+24
<i>Source:</i> This table is adapted from the FDA Statistical Labeling Review. Please see also Section 6.1.4 Efficacy Findings, of this review for further discussion of these data.					

The observation that the efficacy data for the different sulfonylureas in these clinical trials is similar is consistent with the observation of noninferiority in active-controlled one-year monotherapy trials of glimepiride and glyburide and glipizide in the original glimepiride NDA (NDA 20-496) and in published literature. (Clark CM Jr., Helmy AW. *Drugs Today*. 1998, 34:401-8.) In a 12-month double-blind study in 577 patients with Type 2 diabetes mellitus comparing glimepiride and glyburide therapy, which was included in the NDA and also published, baseline and endpoint HbA1c values were similar for the two groups. The mean baseline HbA1c was 8.5% in the two groups and the endpoint HbA1c was 8.2%. (Dills DG et al, *Horm. Metab. Res.* 1996, 28: 426-429.)

The clinical studies support the second line indication of concomitantly administered rosiglitazone and sulfonylurea treatment of patients with Type 2 diabetes mellitus, who are inadequately treated with sulfonylurea treatment alone. Since the pharmacokinetic data indicate that that the fixed dose combination product rosiglitazone and glimepiride is similar to concomitantly administered rosiglitazone and glimepiride, the clinical studies then also support the second line indication of fixed dose combination rosiglitazone and sulfonylurea treatment of patients with Type 2 diabetes mellitus, who are inadequately treated with sulfonylurea treatment alone.

### 1.1.6 Safety

The safety data base comprised 1689 patients randomized in the clinical studies: 587 (35%) were randomized to sulfonylurea monotherapy, 119 (7%) were randomized to rosiglitazone monotherapy, and 983 (58%) were randomized to rosiglitazone and sulfonylurea combination

therapy. There were more withdrawals due to lack of efficacy in the sulfonylurea monotherapy (14%) and rosiglitazone monotherapy (18%) than in the combination therapy groups (5%). The withdrawal rate secondary to adverse events was similar in the sulfonylurea monotherapy (7%) and combination rosiglitazone and sulfonylurea therapy (5%) and higher in the rosiglitazone monotherapy (20%).

There were a total of 14 reported deaths associated with the following adverse events in these combination therapy studies : cardiovascular (10), cancer (2), subarachnoid hemorrhage (1), and cerebrovascular accident (1). The monotherapy and combination therapy treatment groups did not differ significantly in the number or reported etiologies of the deaths. The total number of deaths in the database submitted in NDA 20-496 for glimepiride monotherapy approval was similar for glimepiride and glyburide, and the etiology of most of the deaths was also thought to be cardiovascular.

“Serious” hypoglycemia, hypoglycemia requiring the assistance of another person, was reported in one patient treated with sulfonylurea monotherapy (Study 079) and two patients treated with combination rosiglitazone and sulfonylurea therapy (Studies 135 and 079). “Nonserious”, or milder, hypoglycemia tended to be more common with combination therapy (rates ranging from 2% to 32%), , than with sulfonylurea monotherapy (rates ranging from 0 to 27%) in the five pivotal clinical studies. This finding was consistent with the lower HbA1c in the combination therapy group.

Based on the data from the 120-day safety update for Studies 096, 015, and 079 (NDA supplement 21-071 SE001 for the combination rosiglitazone and sulfonylurea therapy indication), comparison of the rosiglitazone and sulfonylurea combination and sulfonylurea monotherapy treatment groups revealed that the rates of the adverse events fluid retention (4% vs. 1%, in the 2 groups, respectively), weight gain (1.5% vs. 0.6%), and anemia (2% vs 0.6%) were more common in the combination therapy groups. The reported rates for congestive heart failure and pulmonary edema were similar in the two groups in the clinical trials. New cases of congestive heart failure and exacerbations of existing congestive heart failure have been reported in postmarketing data in association with rosiglitazone monotherapy and combination therapy.

Troglitazone, the first approved thiazolidinedione, was withdrawn because of hepatic toxicity. To evaluate the risk of hepatic injury in association with rosiglitazone, another thiazolidinedione, rates of liver abnormalities (defined as ALT level > 3 x ULRR, or upper limit of the reference range) were reviewed in the rosiglitazone clinical program (both double blind and open label studies) through January 2004. Rates of liver abnormalities (ALT level > 3 x ULRR) in rosiglitazone monotherapy, (0.2 per 100 years of patient exposure) and combination rosiglitazone and sulfonylurea therapy (0.3 per 100 years of patient exposure) were lower than rates of liver abnormalities (ALT level > 3 x ULRR) in sulfonylurea monotherapy (0.5 per 100 years of patient exposure), suggesting that rosiglitazone *per se* is not associated with hepatic injury. (NDA 21071 SLR009, reviewed per Dr. Misbin 5/04) The safety data in Studies 234 and 135 in this submission were consistent with the previously reported safety data for rosiglitazone and sulfonylurea combination therapy.

See Section 7, Integrated Review of Safety – Postmarketing Experience, for a listing of the 25 most common postmarketing adverse events reported for rosiglitazone and glimepiride.

### 1.1.7 Dosing Regimen and Administration

The recommended dosing regimen comprises a starting once daily dose of one of two fixed oral dose combinations, rosiglitazone (4 mg) and glimepiride (1 mg) or rosiglitazone (4 mg) and glimepiride (2 mg), to be given with the first meal. The lower starting dose with glimepiride 1 mg is recommended for individuals who are particularly at risk for hypoglycemia, including those who are elderly or have hepatic or renal insufficiency. The recommended maximum once daily dose of the fixed dose combination tablet is rosiglitazone (4 mg) with glimepiride (4 mg). The drug should be taken with food, as food increases the bioavailability of the glimepiride component. Of note, each of the components of the fixed dose combination, rosiglitazone and glimepiride, are indicated in doses up to 8 mg as monotherapy for the treatment of type 2 diabetes mellitus. Rosiglitazone is approved as 2 mg, 4 mg, and 8 mg doses for monotherapy, but only the rosiglitazone 4 mg dose was approved for combination rosiglitazone and sulfonylurea treatment. The glimepiride monotherapy starting dose is 1 or 2 mg. The usual recommended dose is 4 mg and the maximal recommended dose is 8 mg.

### 1.1.8 Drug-Drug Interactions

Drug-drug interactions have not been evaluated for *Avandaryl*<sup>TM</sup> (rosiglitazone maleate and glimepiride fixed dose combination product).

As described in the clinical pharmacology review, no interaction of glimepiride upon rosiglitazone was noted at steady state (i.e., day 8), but a drug-drug interaction was noted when rosiglitazone was added to glimepiride on day 1, with 20% decreases in glimepiride AUC and  $C_{max}$  and 33% increase in  $T_{max}$  and 32% decrease in  $T_{1/2}$ . It is not known if these changes would persist at steady state.

The drug-drug interactions in the proposed Prescribing Information summarize drug-drug interactions noted with either rosiglitazone or glimepiride. Some examples from the Prescribing Information are cited below.

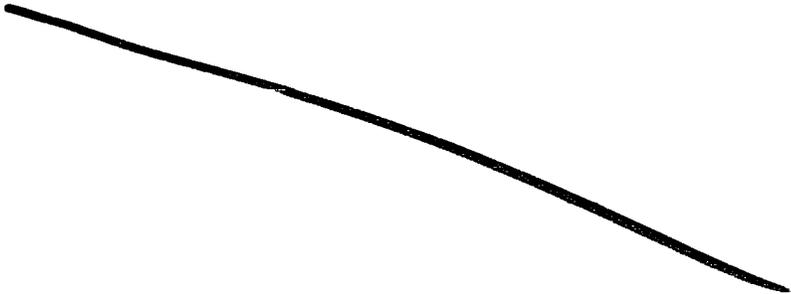
Rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, CYP2C9. An inhibitor of CYP2C8 (such as gemfibrozil) may decrease the metabolism of rosiglitazone ~~\_\_\_\_\_~~ an inducer of CYP2C8 (such as rifampin) may increase the metabolism of rosiglitazone. (These interactions were added in a 7/28/04 Changes Being Effected Amendment to the *Avandia* NDA; they were not included in the 10/31/03 proposed Prescribing Information (PI) for *Avandaryl*<sup>TM</sup>).

As stated in the label, the hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs) and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives,

phenytoin, nicotinic acid, sympathomimetics, and isoniazid may produce hyperglycemia and lead to loss of glucose control. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is not known. Potential interactions of glimepiride ~~with~~ cytochrome P450 2C9 ~~and~~

### 1.1.9 Special Populations

In the currently approved label for rosiglitazone (*Avandia*®), the sponsor reports the results of the population pharmacokinetics in patients with Type 2 diabetes mellitus, and some of the comments are quoted below.



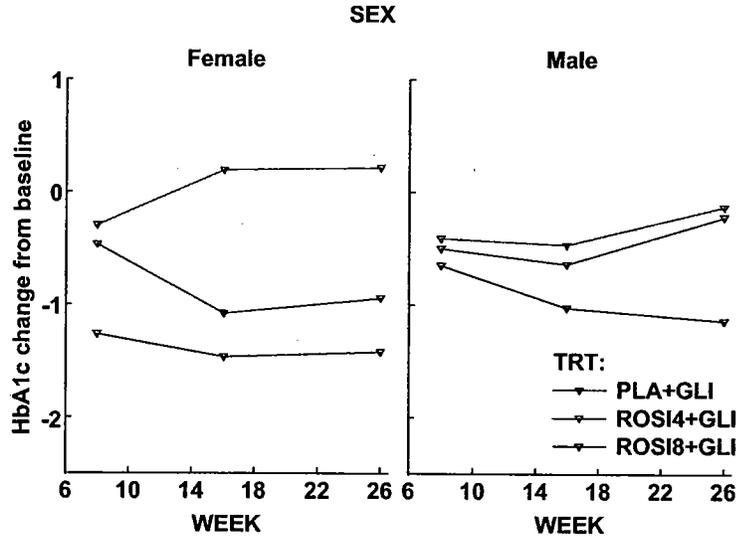
The medical review of the combination rosiglitazone and sulfonylurea therapy had noted that in Study 79 the addition of rosiglitazone to glyburide appeared to be more effective in women.

Data from Study 234 in this submission, the comparison of combination rosiglitazone and glimepiride with glimepiride indicates the greater efficacy of rosiglitazone in women, as indicated in the FDA statistician's figure below. These data support the proposed comment in the clinical pharmacology section of the *Avandaryl*<sup>TM</sup> Prescribing Information.

#### Proposed *Avandaryl* Label

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

~~For a given body mass index (BMI), females tend to have a greater fat mass than males. Since the molecular target of rosiglitazone, PPAR $\gamma$ , is expressed in adipose tissues, this differentiating characteristic may account, at least in part, for the greater response to rosiglitazone in combination with sulfonylureas in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.~~



In the analysis of Studies 096 and 079, studies which were submitted for the second line indication of rosiglitazone and sulfonylurea therapy in patients with Type 2 diabetes mellitus, descriptive statistics of several subgroups were planned per protocol and included age (<65 vs.  $\geq$  65 years), body mass index (BMI < 27 vs.  $\geq$  27 kg/m<sup>2</sup>); gender; HbA1c (<9% vs.  $\geq$  9%); FPG (<200 vs  $\geq$  200). In addition, the statistical reviewer also evaluated prior diabetes therapy and duration of diabetes, parameters which were significantly different in Study 096 only. Data in Study 096 indicate an improvement in HbA1c in patients treated with concomitantly administered rosiglitazone and sulfonylurea therapy who were previously treated with monotherapy but not in those previously treated with combination rosiglitazone and sulfonylurea. Data in Study 096 also indicate that therapy in patients with a shorter duration of Type 2 diabetes mellitus is more efficacious. No differences were observed in the age, BMI, gender, HbA1c, or FPG in the subgroup analyses.

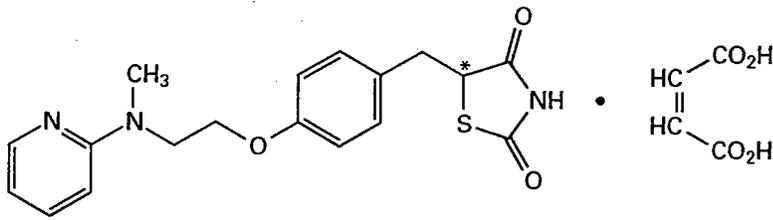
**Appears This Way  
On Original**

## 2 INTRODUCTION AND BACKGROUND

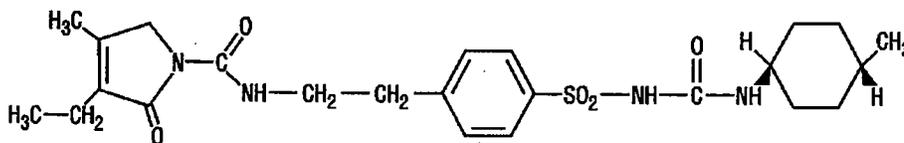
### Product Information

*Avandaryl*<sup>TM</sup> tablet contains two approved oral antidiabetic drugs in three fixed dose combinations: rosiglitazone maleate 4 mg combined with glimepiride 1 mg, 2 mg, or 4 mg. Rosiglitazone maleate is a thiazolidinedione that acts primarily by decreasing insulin resistance and increasing insulin sensitivity - "insulin sensitizer". Rosiglitazone is a proliferator-activated receptor (PPAR)-gamma agonist; activation of PPAR-gamma nuclear receptors in adipose tissue, skeletal muscle, liver regulates transcription of insulin-responsive genes and insulin action. Glimepiride, a sulfonylurea, increases insulin secretion. Like other sulfonylureas, it is most effective when administered to patients who still have pancreatic reserve, i.e., those who have shorter durations of Type 2 diabetes mellitus. The chemical names, formulae, and structures of the two compounds are outlined below.

Rosiglitazone maleate is ( $\pm$ )-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) and a molecular formula of  $C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$ . The structural formula of rosiglitazone maleate is:



Glimepiride is an oral sulfonylurea: 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea. The molecular weight 490.62, and the molecular formula for glimepiride is  $C_{24}H_{34}N_4O_5S$ . It is practically insoluble in water. The structural formula of glimepiride is:



The fixed dose combination drug product *Avandaryl*<sup>TM</sup> contain rosiglitazone, glimepiride, and the following inactive ingredients: Hypromellose 2910, lactose monohydrate, macrogol (polyethylene glycol), magnesium stearate, microcrystalline cellulose, sodium starch glycolate, titanium dioxide, and 1 or more of the following: yellow, red, or black iron oxides.

## Currently Available Treatment for Indications

Currently recommended therapy for Type 2 diabetes mellitus includes non-pharmacologic measures including, diet, exercise, weight loss; oral antidiabetic drug therapy; and insulin therapy. If diet, exercise, and weight loss toward an ideal weight are insufficient to reach glycemic targets, oral antidiabetic therapy is usually added to the diet, exercise, and weight loss program. *First-line therapy* refers to treatment of patients who are pharmacologically naïve, while *second-line therapy* refers to therapy of patients whose prior oral antidiabetic therapy was inadequate to achieve glucose goals. Oral antidiabetic drug therapy includes *monotherapy*, or treatment with one oral antidiabetic drug. *Combination therapy* includes (1) treatment with two or more oral antidiabetic drugs given concomitantly, (2) *fixed dose combinations*, and (3) combination of one or two oral antidiabetic drugs with insulin.

Oral antidiabetic drugs include sulfonylureas, the meglitinide repaglinide, the biguanide metformin, glucosidase inhibitor acarbose, and thiazolidinediones. Combination drug therapy may be more effective than monotherapy and is usually recommended after failure of the initial treatment. However, there is also a trend to initiate combination therapy earlier. Two fixed dose combination products, Glucovance® (Bristol-Myers Squibb) (metformin HCl/glyburide) and Metaglip™ (Bristol-Myers Squibb) (metformin HCl/glipizide) were studied in pharmacologically naïve patients in whom diet and exercise did not achieve adequate glycemic control, as well as in patients in whom diet, exercise, and one of the drugs in the combination did not result in adequate glycemic control. Both of these fixed dose combination products are indicated as first-line and second-line therapy. Insulin therapy, usually consisting of a combination of rapid and intermediately active insulins, is also a frequent treatment for Type 2 diabetes mellitus. Insulin therapy is also used in combination with oral antidiabetic drugs.

## Important Issues With Pharmacologically Related Products

The major safety issues associated with thiazolidinedione treatment include induction and/or exacerbation of congestive heart failure, edema, weight gain, and anemia. The risk of cardiovascular adverse events may increase when rosiglitazone is used in combination with insulin. The rates of hepatic enzyme (ALT) elevation in patients treated with rosiglitazone (0.2%) were similar in rates to patients treated with placebo (0.2%) or active comparators (0.5%) in pre-approval clinical studies, but there are post-marketing reports of three-fold and greater hepatic enzyme elevations, hepatitis, and rare hepatic failure associated with rosiglitazone use. Hypoglycemia is rare with rosiglitazone monotherapy. Combination rosiglitazone and sulfonylurea treatment is associated with hypoglycemia in rates similar to that observed with sulfonylurea treatment alone. Similar safety issues are noted with the other approved thiazolidinedione, pioglitazone.

The major safety concern with sulfonylureas is hypoglycemia. In three one-year clinical trials submitted in the original NDA for glimepiride, the risk of hypoglycemia with glimepiride was similar to that of glipizide and glyburide. The risk of hypoglycemia is greater in elderly, debilitated, or malnourished patients and in those with hepatic or renal impairment. Hypoglycemia needs to be aggressively treated. Because of the relatively long half-life ( $t_{1/2}$  ~ 5-8 hours) of glimepiride as well as other second-generation sulfonylureas including glipizide and

glyburide, severe hypoglycemia associated with alteration in consciousness or neurologic findings may persist for 24 – 48 hours, even after initial response to glucose replacement. The Overdosage section in the Prescribing Information conveys this information for these drugs. Hypoglycemia may also be exacerbated by certain drugs, such as non-steroidal anti-inflammatory drugs, and other highly protein bound drugs, including salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. In addition, beta adrenergic blocking agents may mask the symptoms of hypoglycemia.

In the preclinical glimepiride studies, two dogs developed cataracts. Cataract formation was not noted in other preclinical studies. Human ophthalmology data have not shown any significant differences between patients who were treated with glimepiride and those treated with glyburide or glipizide.

See Section 7, Integrated Review of Safety – Postmarketing Experience, for a listing of the 25 most common postmarketing adverse events reported for rosiglitazone and glimepiride.

#### Presubmission Regulatory Activity

Rosiglitazone (*Avandia*<sup>®</sup>, GlaxoSmithKline) and glimepiride (*Amaryl*<sup>®</sup>, Aventis) were approved for the treatment of Type 2 diabetes mellitus on 5/25/99 (NDA 21-071) and 11/30/95 (NDA 20-496), respectively. Concomitant use of rosiglitazone with sulfonylureas was approved on 4/3/00 (NDA 21-071 supplement) for patients inadequately treated with diet, exercise, and one of these sulfonylurea alone. IND 66,162 (submitted 11/02) presented a program for the development of rosiglitazone/glimepiride fixed dose combinations based on bioequivalence, dose proportionality, and drug interaction studies, as well as a 26-week clinical study (Study 234) comparing the efficacy of glimepiride alone and glimepiride with rosiglitazone 4 mg or 8 mg in 183 patients previously treated with oral antidiabetic therapy. In the pre-NDA meeting (6/2/03), the sponsor had proposed that approval of this combination product would be based on bioequivalence of the combination product to concomitantly administered rosiglitazone maleate and glimepiride, and bridging these results to the studies previously submitted for the combination rosiglitazone and sulfonylurea combination.

#### Other Relevant Background Information

##### Patents

The patent expiration date for glimepiride *Amaryl*<sup>®</sup>, Hoechst AG is 4/6/2005. The patent expiration dates listed under SmithKline Beecham Corporation are 8/30/2008, 4/21/2015, and 2/11/2017.

## Letter of Authorization

A letter of authorization from Aventis Pharmaceuticals authorizes the FDA to refer to the information contained in the original NDA 20-496 for *Amaryl*® Tablets (glimepiride), which was submitted 8/31/1994, in support of NDA 21-700 for *Avandaryl*<sup>TM</sup> (*Avandia*® / *Amaryl*®).

## Debarment Certification

The sponsor certifies that they have not and will not use any person debarred under section 306 of Federal Food, Drug, and Cosmetic Act in connection with this application.

## Trade Name

The Division of Medication Errors and Technical Support (DMETS) does not recommend the use of the *Avandaryl* trade name or proprietary name. According to their review, the *Avandaryl* name may potentially be confused with the following trade names: *Avandia* (rosiglitazone maleate), *Amaryl* (glimepiride), *Avandamet* (rosiglitazone maleate and metformin), and *Vanceril* (beclomethasone dipropionate inhalation aerosol). Confusion with the first three trade names may pose the greatest safety issues. The DMETS consult emphasizes many specific situations in which these drugs with “look-alike” and “sound-alike” trade names also have similar active ingredients, similar usual doses, similar scripted appearances, and similar indication for use (Type 2 diabetes mellitus), which can compound the confusion. A few comments from the consult are highlighted below.

*Post-marketing experience has shown errors occur with drug products that contain overlapping strengths, regardless of a combination ingredient versus a single ingredient. For example, Avandaryl 4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg can be prescribed as Avandaryl 1 mg, Avandaryl 2 mg, and Avandaryl 4 mg, respectively. These strengths overlap with the strength of Amaryl (1 mg, 2 mg, and 4 mg).*

*Avandia and Avandaryl will be stored in close proximity in the pharmacy. There is also the potential for computer order entry errors since the first five letters of each name is identical and the strengths are similar. If a patient receives Avandia instead of Avandaryl, he will receive only one of the two active ingredients and will likely experience hyperglycemia. DMETS believes that the overlapping product characteristics increase the risk of confusion between Avandia and Avandaryl.*

*It is likely that both Avandamet and Avandaryl will be stored in closed proximity. This has the potential to cause a medication error in a busy clinic, pharmacy or inpatient unit where the wrong product can be dispensed. DMETS is also concerned that errors will occur between Avandamet and Avandaryl with computer order entry. ...DMETS is also concerned about the potential for cognitive errors between Avandamet and Avandaryl. Since both products have the same prescriber population, indication for use, active ingredient, and similar names, post-marketing experience has shown cognitive errors occurring where the health care provider inadvertently writes one product, but intends another. Due to the overlapping product characteristics and orthographic similarities, DMETS believes that errors will occur between Avandamet and Avandaryl which can lead to a severe adverse reaction.*

*Vanceril* is an inhaler, and it is unlikely that an inhaler and tablets would be confused.

**Reviewer's recommendation:** This reviewer agrees with the objection raised by the thorough DMETS consult. Though the use of the trade name *Amaryl* may diminish when its patent expires in 2005, and patient education with an emphasis on the use of generic names in the Patient Prescribing Information could also decrease the risk of trade name confusion, the many potential causes of confusion of the trade name *Avandaryl* with the approved trade names *Avandia*, *Amaryl*, and *Avandamet* require a re-assessment of this proposed trade name. The DMETS consult should be forwarded to the sponsor.

### 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

#### CMC

The CMC recommendation and conclusion on approvability are quoted below:

*The application is APPROVABLE pending satisfactory cGMP inspection of facility used to manufacture the drug product. Currently, the status of this facility is WITHOLD pending regulatory action - Warning Letter (see page 52). A statement should be included in the SB Pharmco PR action letter regarding the drug product expiry dates*

#### Animal Pharmacology and Toxicology

Both rosiglitazone and glimepiride are approved drug products. Significant animal pharmacology and toxicology data are referenced in those NDA reviews and summarized in the respective labels. No new animal pharmacology and toxicology data were submitted in this NDA.

### 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

#### Sources of Clinical Data

The NDA 21-700 submission comprises four biopharmaceutical studies, including a dose proportionality study, a bioequivalence study, a food study, and a drug interaction study, to compare the fixed dose combination tablet of rosiglitazone and glimepiride to concomitantly administered rosiglitazone and glimepiride. These results are then "bridged" to two clinical efficacy and safety studies and one small supportive safety study in this submission, and to three clinical studies, cross-referenced in a previously approved NDA supplement (NDA 21-071 SE001) for the indication of concomitant rosiglitazone and sulfonylurea second-line therapy.

Glimepiride and rosiglitazone are administered concurrently only in one of the four clinical efficacy studies . In one of the two submitted clinical efficacy and safety studies, rosiglitazone added to glimepiride therapy is compared to glimepiride therapy alone(Study 234), and in the small supportive safety study glimepiride added to rosiglitazone therapy is compared to rosiglitazone alone(Study 4034, Aventis). The fixed dose combination drug product consisting of rosiglitazone and glimepiride was not evaluated in any of the clinical studies; instead rosiglitazone and glimepiride were administered concomitantly. In the other four studies, other sulfonylureas are studied. In the third submitted study, rosiglitazone is added to glipizide therapy (Study 135). In two of the three cross-referenced studies (Studies 015 and 096), rosiglitazone was added to sulfonylureas, and in the third study (Study 079) concomitant administration of rosiglitazone and glimepiride was compared to administration of each component. The data from the five clinical efficacy and safety studies (all except Study 4034) are referenced in the proposed prescribing information.

Tables of the biopharmaceutical and clinical studies are included in the review below.

### Tables of Clinical Studies

Table 1. Clinical Pharmacology Studies (*Source:* NDA 21-700 submission)

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/Route/ Frequency/Duration)
BRL-049653/340	Drug interaction	Effect of rosiglitazone on the PK of glimepiride	O, UC, NR	Healthy subjects, 18 - 55y inclusive;  BMI: 20-30kg/m <sup>2</sup> inclusive	15 (9M/6F)  39y (22-51y)	AVANDIA (8 mg) and Amaryl (4 mg) Commercial Tablets  Session 1: glimepiride (Amaryl) administered (single dose) on Day 1, Session 2: Rosiglitazone (AVANDIA) administered once daily for 8 days with the addition of glimepiride (single dose) on Day 8.
SB-797620/001	Dose Proportionality	To assess the dose proportionality of glimepiride in the combination formulations in a fed state	O, UC, R, XO	Healthy subjects, 18 - 55y inclusive;  BMI: 20-30kg/m <sup>2</sup> inclusive	24 (13M/11F)  31y (19-51y)	Amaryl formulations (rosiglitazone 4 mg/glimepiride 1 mg, rosiglitazone 4 mg/glimepiride 2 mg, and rosiglitazone 4 mg/glimepiride 4 mg)  Single oral dosing at each of 3 study sessions

SB-797620/002	Bioequivalence	to demonstrate the bioequivalence of the combination formulation of rosiglitazone 4 mg/glimepiride 4 mg relative to concomitant dosing of rosiglitazone 4 mg AND glimepiride 4 mg commercial tablets	O, UC, R	Healthy subjects, 18-55y inclusive; BMI:20-30kg/m <sup>2</sup> inclusive	30 (17M/13F) 31y (18-45y)	An oral combination formulation of rosiglitazone 4 mg/glimepiride 4 mg; rosiglitazone 4 mg AND glimepiride 4 mg commercial tablets  Single oral dosing at each of 2 study sessions
SB-797620/003	Food Effect/Fed Relative Bioavailability	to estimate the effect of food on the single dose pharmacokinetics of rosiglitazone and glimepiride in a rosiglitazone / glimepiride (4/4 mg) combination tablet	O, UC, R	Healthy subjects, 18-55y inclusive; BMI:20-30kg/m <sup>2</sup> inclusive	38 (15M/23F) 31y (18-54y)	An oral combination formulation of rosiglitazone 4 mg/glimepiride 4 mg; rosiglitazone 4 mg AND glimepiride 4 mg commercial tablets  Single oral dosing at each of 3 study sessions

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**Table 2. Double Blind Multicenter Clinical Trials**

(Source: Summary from current submission and NDA 21-071 SE001 statistical review)

Study* (Sites)	Design	Treatment (# randomized)	Duration of Treatment
<b>Study reports submitted in NDA 21-700</b>			
<b>234*</b> (32 Germany)  1/11/01 – 2/4/02	Rosiglitazone add-on to glimepiride	Glimepiride 3 mg + RSG placebo (57) Glimepiride 3 mg + RSG 4mg (56) Glimepiride 3 mg + RSG 8mg (59) (no RSG + glimepiride placebo arm)	26 weeks  ≤ 4-week glim titration to 3 mg 4 week run-in
<b>4034</b> [Aventis]  5/26/01–9/24/02	Glimepiride add-on to rosiglitazone	Glimepiride 1-8 mg od (forced titration) + RSG 4-8 mg (26) glimepiride placebo + RSG (15)	26 weeks  4-week RSG run-in
<b>135*</b> (39 USA;9 Canada)  5/10/99-10/20/02	Rosiglitazone add-on to glipizide	Glipizide 10 mg bid + placebo (111) RSG 4mg od+ glipizide (116)	2 years  4-week glipizide run-in
<b>Study reports submitted in NDA 21-071 SE1-001 (approved 4/00)</b>			
<b>096*</b> (33 USA)  4/97-3/98	Rosiglitazone add-on to glyburide	Glyburide • 10mg/day (115) RSG 2 mg daily + GLY (116) RSG 4 mg daily + GLY (116)	26 weeks  4-week placebo run-in 1-week FU or OLE
<b>015*</b> (54 European)  8/96-3/98	Rosiglitazone add-on to sulfonylureas	Sulfonylureas (198) [glyburide, glipizide, gliclazide] RSG 1 mg twice daily + SU (205) RSG 2 mg twice daily + SU (190)	26 weeks  2-4 week placebo + SU run-in 2-week FU or OLE
<b>079*</b> (41 USA)  4/97-3/98	Combination versus components	Glyburide 10 mg twice daily (115) RSG 2 mg twice daily (116) RSG 2 mg twice daily + GLY (116)	26 weeks  4-week glyburide run-in 7-10 day FU or OLE
*Pivotal clinical efficacy and safety studies			

### Review Strategy

The review was conducted with the electronically submitted documents and amendments. The clinical pharmacology studies and the relevant aspects of the patient label have been discussed with the primary clinical pharmacology reviewer and the clinical pharmacology team (internal conference 7/12/04). The statistical reviewer has reviewed the efficacy data from the two new pivotal clinical studies to confirm the sponsor's findings, with an emphasis on the data presentation in the prescribing information. The new clinical studies have been reviewed with an

emphasis on safety data for concomitantly administered glimepiride and rosiglitazone therapy. The second-line indication for concomitant sulfonylurea and rosiglitazone therapy was previously approved (NDA 21-700 SE1 001, 4/00). The efficacy and safety data from these three cross-referenced studies have been summarized from the statistical and clinical reviews of that submission. An integrated summary of the key efficacy and safety data from the clinical studies is presented in the review below.

### Data Quality and Integrity

The primary basis for approval of this NDA was evaluation of the pharmacokinetic data and "bridging" these data to the clinical data. The clinical pharmacology team accepted the quality of the pharmacokinetic studies. The Division of Scientific Investigation did not do any routine inspections of the new clinical sites.

### Compliance with Good Clinical Practices

Although the consent documents were not reviewed, the trials appear to have been conducted in accordance with acceptable ethical standards. The escape criteria for lack of efficacy as manifested by hyperglycemia were followed. The financial disclosure documentation appears adequate.

### Financial Disclosures

In compliance with the Final Rule on Financial Disclosure by Clinical Investigators (published 2/2/98 (63 FR 5233; revised 12/31/98 (63 FR 72171), the financial certification disclosure, OMB Form No. 0910-0396, is signed by David Wheadon, MD, Senior Vice President, US Regulatory Affairs, GlaxoSmithKline, and paragraphs (1) and (2) are checked, certifying that there were no financial agreements between the sponsor and the investigators where compensation was linked to study outcome (as defined in 21 CFR 54.2(a), and that no clinical investigator reported any proprietary interest in this product or significant equity in the sponsor (as defined in 21 CFR 54.2(b), in the GlaxoSmithKline studies (clinical pharmacology studies SB-797620/001-003, and clinical studies BRL-49653/135 and 234) and also in the Aventis Study HOE 490/4034.

The financial disclosure reports [OMB Form 0910-0396] that five investigators in Study 135 had received significant payments greater than \$25,000 of other sorts from the sponsor [21 CFR 54.4(a)(3)(ii), 54.2(f)]. The majority of these payments are identified as honoraria. The amount of compensation and the investigators' involvement in the reported clinical studies are listed below.

Investigator	Study/Site	Number Patients Enrolled (%)	Compensation Amount
1			\$49,055
2			\$91,651
3			\$78,616
4			\$134,907
5			\$77,102

A total of \_\_\_\_\_ patients were enrolled at three sites by clinical investigators who received these compensations. It is unlikely that the small number of patients enrolled at each site by these investigators would contribute significantly to the outcome of Study \_\_\_\_\_ which compares the addition of rosiglitazone to \_\_\_\_\_ therapy alone. It is a confirmatory study of the previously approved supplementary NDA \_\_\_\_\_

## 5 CLINICAL PHARMACOLOGY

The following pharmacokinetic studies were completed in healthy volunteers and were included in the NDA submission: 1) a dose proportionality study (#797620/001); 2) a bioequivalence study (#797620/002); 3) a food-effect study (#797620/003); and 4) a drug interaction study (#49653/340). An in vitro dissolution method with data and a biowaiver request for the two lower strengths 4 mg/1 mg and 4 mg/ 2 mg *Avandaryl*<sup>TM</sup> tablets were also included. These data are reviewed in the clinical pharmacology review, and the clinical pharmacology data were discussed with the primary reviewer, Jaya bharathi Vaidyanathan, Ph.D, Hank Malinowski, Ph.D., John Hunt, Ph.D., and Hae-Young Ahn, Ph.D. at the Clinical Pharmacology and Biopharmaceutics briefing meeting on 7/12/04. Data from the clinical pharmacology review and discussion are summarized below.

### Pharmacokinetics

Study 797620/001 confirmed the dose proportionality of the combination tablet formulation of rosiglitazone and glimepiride (4 mg/1 mg; or 4 mg/ 2 mg; or 4 mg/4 mg) in healthy subjects, following single dose administration of the 3 combination tablet formulations.

In the bioequivalence study (#797620/002), rosiglitazone – glimepiride drug-drug interaction was evaluated with oral medication given after a light breakfast. The effect of repeat oral doses of rosiglitazone (8 mg) on glimepiride (4 mg) pharmacokinetics and the effect of a single oral dose of glimepiride (4 mg) on multiple doses of rosiglitazone (8 mg) was tested in 14 healthy volunteers. Glimepiride (4 mg) was administered one morning, followed by a 7-day washout; then, rosiglitazone (8 mg) was administered daily for 8 days, with glimepiride (4 mg) also administered on the eighth day.

The table below summarizes rosiglitazone pharmacokinetics.

Table 3. Summary of Rosiglitazone Pharmacokinetics (sponsor's table)

Day	AUC <sub>(0-∞)</sub> (ng.h/mL) <sup>1</sup>	AUC <sub>(0-24)</sub> (ng.h/mL) <sup>1</sup>	C <sub>max</sub> (ng/mL) <sup>1</sup>	t <sub>max</sub> (h) <sup>2</sup>	t <sub>1/2</sub> (h) <sup>3</sup>
1 (n=14)	2854 [2936 (1716-4427)]	2802 [2880 (1710-4311)]	417 [427 (291-658)]	1.75 (1.00-4.00)	3.92 (2.86-4.75)
7 (n=14)	2387 [2441 (1460-3256)]	2360 [2412 (1456-3218)]	397 [415 (262-757)]	2.00 (0.50-3.33)	3.44 (2.58-4.49)
8 (n=14)	2196 [2253 (1417-3022)]	2170 [2225 (1412-2973)]	379 [394 (273-706)]	2.00 (0.50-3.00)	3.46 (2.73-5.14)

1. AUC and C<sub>max</sub> data presented as geometric mean [arithmetic mean (range)].
2. t<sub>max</sub> data presented as median (range).
3. t<sub>1/2</sub> data presented as arithmetic mean (range).

Rosiglitazone AUC was very slightly decreased following concomitant administration of rosiglitazone and glimepiride. The C<sub>max</sub>, T<sub>max</sub>, t<sub>1/2</sub> values for rosiglitazone were similar when administered alone or with glimepiride.

The table below summarizes glimepiride and the glimepiride M1 (cyclohexyl hydroxyl methyl metabolite) pharmacokinetics.

Table 4. Summary of glimepiride and M1 pharmacokinetic parameters.

Analyte	Day	AUC <sub>(0-∞)</sub> (ng.h/mL) <sup>1</sup>	C <sub>max</sub> (ng/mL) <sup>1</sup>	t <sub>max</sub> (h) <sup>2</sup>	t <sub>1/2</sub> (h) <sup>3</sup>
Glimepiride	1 (n=14)	1214 [1323 (418-2380)]	205 [221 (107-412)]	3.00 (2.50-10.03)	7.13 (3.33-11.14)
	8 (n=14)	945 [1009 (383-1866)]	157 [172 (83-330)]	4.00 (1.50-10.00)	4.83 (2.61-10.36)
M1 metabolite	1 (n=14)	581 [604 (332-949)]	63.5 [66.6 (41.0-107.0)]	6.00 (3.00-10.03)	6.22 (4.08-7.98)
	8 (n=14)	488 [510 (281-1002)]	56.8 [59.4 (42.7-96.3)]	6.00 (2.00-8.00)	4.47 (2.98-6.59)

1. AUC and C<sub>max</sub> data presented as geometric mean [arithmetic mean (range)].
2. t<sub>max</sub> data presented as median (range).
3. t<sub>1/2</sub> data presented as arithmetic mean (range).

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Glimepiride AUC<sub>(0-∞)</sub> was lower (22%) when glimepiride was given concomitantly with rosiglitazone as compared to when glimepiride was administered alone. The C<sub>max</sub> of glimepiride was also lower by 24% following concomitant administration of glimepiride and rosiglitazone. Similarly the M1 metabolite AUC<sub>(0-∞)</sub> and C<sub>max</sub> also decreased 16% and 11% in presence of rosiglitazone.

In summary, no interaction of glimepiride upon rosiglitazone was noted at steady state (i.e., day 8). A drug-drug interaction was noted when rosiglitazone was added to glimepiride on day 1, with 20% decreases in glimepiride AUC and C<sub>max</sub> and 33% increase in T<sub>max</sub> and 32% decrease in T<sub>1/2</sub>. It is not known if these changes would persist at steady state.

The bioequivalence study (#797620/002) examined the relative rate (C<sub>max</sub>) and extent of exposure (AUC) of the combination tablet formulation, *Avandaryl*<sup>TM</sup> (4 mg/ 4 mg) to concomitant dosing of *Avandia*<sup>®</sup> (rosiglitazone 4 mg) and *Amaryl*<sup>®</sup> (glimepiride 4 mg) tablets in

28 healthy subjects under fasting conditions. Results indicated that the bioequivalence was demonstrated for the rosiglitazone component in terms of AUC and  $C_{max}$ . The 90% confidence intervals for the comparisons between the combination tablet and the concomitant tablets fell within the range of 0.8 -1.25 for the AUC of rosiglitazone and glimepiride and  $C_{max}$  of rosiglitazone. However, the  $C_{max}$  of glimepiride was found to be lower following the administration of the combination tablet compared to the value obtained after concomitant dosing of the commercial tablets. If this observation persists at steady state, the clinical implication may be a slightly lower glucose lowering efficacy and potentially a lower risk of hypoglycemia of the fixed dose combination than of the concomitantly administered rosiglitazone and glimepiride.

Table 5. Summary of pharmacokinetic parameters for rosiglitazone (4 mg) and glimepiride (4 mg), by formulation [A=fixed dose combination tablet; B=concomitant dosing of rosiglitazone and glimepiride] (n=28)

Parameter (Units)	Rosiglitazone		Glimepiride	
	Regimen A	Regimen B	Regimen A	Regimen B
AUC <sub>(0-∞)</sub> (ng·h/mL)	1259 (833-2060)	1253 (756-2758)	1052 (643-2117)	1101 (648-2555)
AUC <sub>(0-8)</sub> (ng·h/mL)	1231 (810-2019)	1224 (744-2654)	944 (511-1898)	1038 (606-2337)
$C_{max}$ (ng/mL)	257 (157-352)	251 (77.3-434)	151 (63.2-345)	173 (70.5-329)
$t_{1/2}$ (h)	3.53 (2.60-4.57)	3.54 (2.10-5.03)	7.63 (4.42-12.4)	5.08 (1.80-11.31)
$t_{max}$ (h)	1.00 (0.48-3.02)	0.98 (0.48-5.97)	3.02 (1.50-8.00)	2.53 (1.00-8.03)

A = Combination Tablet; B = Concomitant dosing of rosiglitazone and glimepiride.

Data presented as geometric mean (range), except  $t_{1/2}$  which is presented as arithmetic mean (range) and  $t_{max}$  which is presented as median (range).

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The food effect study (#797620/003) demonstrated that after administration of the combination tablet (4 mg/ 4 mg), the extent (AUC) of rosiglitazone was not changed in the fed state as compared to the fasted state, but the rate of absorption was reduced (32% decrease in  $C_{max}$ ). On the other hand, glimepiride AUC<sub>(0-∞)</sub> as well as  $C_{max}$  increased 19% and 55% respectively following administration of the combination tablets in the fed state as compared in the fasted state. The rate and extent of absorption of rosiglitazone and glimepiride, in the fed state were equivalent following administration of the combination tablet compared to concomitant administration of rosiglitazone and glimepiride as the currently approved commercial formulations. The proposed package insert states that *Avandaryl*<sup>TM</sup> should be given with a meal.

Table 6. Summary of the pharmacokinetic parameters for rosiglitazone by formulation (A=Combination tablet fed; B=Concomitant administration of rosiglitazone and glimepiride tablets fed; C=combination tablets fasted) (n=34)

Parameter (Units)	Regimen A	Regimen B	Regimen C
AUC <sub>(0-∞)</sub> (ng·h/mL)	1245 <sup>1</sup> (656-1911)	1222 <sup>1</sup> (741-1948)	1351 <sup>1</sup> (788-2134)
AUC <sub>(0-4)</sub> (ng·h/mL)	1232 (647-2127)	1195 (731-1935)	1331 (770-2108)
C <sub>max</sub> (ng/mL)	218 (132-565)	204 (130-388)	321 (165-503)
t <sub>½</sub> (h)	3.36 <sup>1</sup> (2.28-4.37)	3.35 <sup>1</sup> (2.42-4.53)	3.30 <sup>1</sup> (2.34-4.28)
t <sub>lag</sub> (h)	0.00 (0.00-1.50)	0.00 (0.00-0.50)	0.00 (0.00-0.50)
t <sub>max</sub> (h)	2.00 (0.50-6.00)	2.00 (0.50-5.00)	0.55 (0.50-4.50)

1. n=33

Data presented as geometric mean (range), except t<sub>½</sub> which is presented as arithmetic mean (range), and t<sub>lag</sub> and t<sub>max</sub> which are presented as median (range).

Regimen A = Combination tablet fed; Regimen B = Concomitant administration of the rosiglitazone and glimepiride tablets fed; Regimen C = Combination tablet fasted

Table 7. Summary of pharmacokinetic parameters for glimepiride by formulation (A=Combination Tablet fed; B= Concomitant administration of the rosiglitazone and glimepiride tablets fed; C=combination tablet fasted)

Parameter (Units)	Regimen A (n=34)	Regimen B (n=32)	Regimen C (n=34)
AUC <sub>(0-∞)</sub> (ng·h/mL)	1136 <sup>1</sup> (575-2451)	1099 <sup>2</sup> (537-2312)	985 <sup>3</sup> (410-1862)
AUC <sub>(0-4)</sub> (ng·h/mL)	1056 (546-2374)	1021 (468-2223)	813 (375-1658)
C <sub>max</sub> (ng/mL)	233 (119-475)	219 (108-399)	150 (63-291)
t <sub>½</sub> (h)	3.60 <sup>1</sup> (1.93-6.99)	3.34 <sup>2</sup> (1.54-6.82)	6.63 <sup>3</sup> (2.92-10.42)
t <sub>lag</sub> (h)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-0.67)
t <sub>max</sub> (h)	2.50 (1.00-4.53)	2.26 (0.50-8.00)	2.00 (1.00-8.13)

1. n=29

2. n= 27

3. n = 16

Data presented as geometric mean (range), except t<sub>½</sub> which is presented as arithmetic mean (range), and t<sub>lag</sub> and t<sub>max</sub> which are presented as median (range).

Regimen A = Combination tablet fed; Regimen B = Concomitant administration of the rosiglitazone and glimepiride tablets fed; Regimen C = Combination tablet fasted

Since dosage form equivalence was demonstrated between strengths and dissolution was comparable between strengths, a biowaiver for the lower strengths not studies in vivo, 4 mg/1 mg and 4 mg/2 mg, was granted by the clinical pharmacology review group.

## Pharmacodynamics

No pharmacodynamic studies were submitted for the fixed dose combination of rosiglitazone and glimepiride. Pharmacodynamic studies for the individual drugs would have been submitted in those original NDAs.

## Exposure-Response Relationships

No dose-response studies were submitted for the fixed dose combination rosiglitazone and glimepiride drug product. Data for the dose response studies for the individual drugs from the original NDAs are summarized below.

The approved rosiglitazone doses are 2 mg, 4 mg, and 8 mg for monotherapy, and only 4 mg for combination therapy. The therapy is approved for once-daily ~~administration~~ administration, though the same dose divided into two-daily doses was more effective than the once daily dose. Rosiglitazone 2 mg and 4mg doses had been studied for the concomitantly administered, or combination, rosiglitazone and sulfonylurea indication. Rosiglitazone 2 mg twice daily was more effective than rosiglitazone 4 mg given once daily. The rosiglitazone 2 mg daily dose was not effective in these clinical trials.

The approved glimepiride doses are 1 mg, 2 mg, (3 mg in Europe), 4 mg, and 8 mg. In dose ranging studies reviewed in the original glimepiride NDA, glimepiride doses of 1 to 8 mg were studied in clinical trials. The effective dose was in the 2-4 mg range. Doses greater than 4 mg appeared to be effective only if the baseline HbA1c was greater than 9%.

## 6 INTEGRATED REVIEW OF EFFICACY

### Indication

The proposed indication for the fixed dose combination product rosiglitazone/glimepiride (*Avandaryl*<sup>TM</sup>) is second-line treatment of Type 2 diabetes mellitus:

~~\_\_\_\_\_~~

This combination drug product is not intended as initial pharmacologic therapy for patients with Type 2 diabetes mellitus who are inadequately treated with diet and exercise alone.

### 6.1.1 Methods

This section provides an overview of the efficacy in the submitted NDA (NDA 21-700) and previously reviewed NDA supplement (NDA 21-071 SE1-001) clinical trials. The statistical reviewer, Joy Mele, M.S., has completed a statistical labeling review to assess if the two newly submitted clinical trials provide useful information for the *Avandaryl*<sup>TM</sup> labeling. Parts of her review are included in this section.

### 6.1.2 General Discussion of Endpoints

The major question in each of the six clinical trials is “Does concomitant treatment with rosiglitazone and sulfonylurea improve glycemic control as compared to treatment with one or both components separately, in patients with Type 2 diabetes mellitus who are inadequately treated with one of the component anti-diabetic drugs alone?” The primary endpoint in all of the studies except Study 135 is the treatment effect as measured by change in HbA1c. Study 135 is a two year double-blind controlled clinical trial in which rosiglitazone added to glipizide therapy is compared to glipizide therapy alone. The primary endpoint is the time to failure of therapy, defined as a fasting plasma glucose  $\geq$  180 mg/dl, despite titration to maximal rosiglitazone (8 mg) therapy and glipizide therapy (20 mg bid).

A total of 1689 patients with Type 2 diabetes mellitus were randomized to these studies. Of these 596 (34%) were randomized to sulfonylurea therapy. Less than 10% of these patients (56) were randomized to glimepiride. One-hundred-thirty-one (7.6%) were randomized to rosiglitazone therapy alone, and 1000 (58%) were randomized to combination rosiglitazone and sulfonylurea therapy. One-hundred-thirty of the patients on combination therapy (13% of all patients on combination therapy and 7.5% of all randomized patients) were treated with rosiglitazone and glimepiride. In other words, the majority of patients were randomized to rosiglitazone and sulfonylurea combination therapy, but only a small fraction of these were randomized to sulfonylurea and glimepiride.

### 6.1.3 Study Design

The six clinical studies, including the studies in this submission and those previously submitted, comprise a total population of 1689 patients with Type 2 diabetes mellitus. In all of these studies, except the small safety study (Study 4034), rosiglitazone therapy was added to sulfonylurea therapy. The addition of sulfonylurea therapy to patients poorly controlled on rosiglitazone therapy alone was not studied. A total of 983 patients were treated with combination rosiglitazone and sulfonylurea therapy. Of these, 141 patients received combination rosiglitazone and glimepiride therapy.

The study designs are summarized for the five 26-week-as well as the two-year controlled, double-blind clinical trials in the table below. In each study a run-in period (usually 4 weeks) was followed by 26 weeks (or longer) of active therapy.

**Table 2. Double Blind Multicenter Clinical Trials**

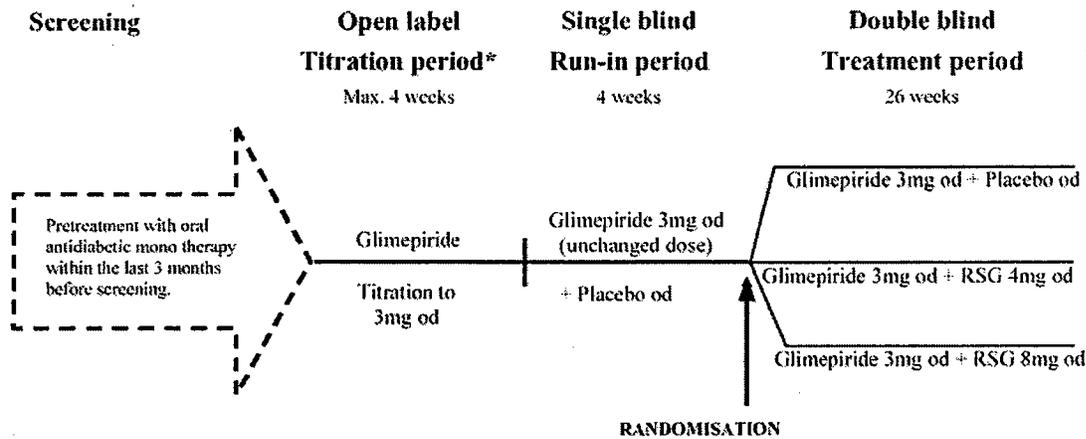
(Source: Summary from current submission and NDA 21-071 SE001 statistical review)

Study* (Sites)	Design	Treatment (# randomized)	Duration of Treatment
<i>Study reports submitted in NDA 21-700</i>			
<b>234*</b> (32 Germany)  1/11/01 – 2/4/02	Rosiglitazone add-on to glimepiride	Glimepiride 3 mg + RSG placebo (57) Glimepiride 3 mg + RSG 4mg (56) Glimepiride 3 mg + RSG 8mg (59) (no RSG + glimepiride placebo arm)	26 weeks  ≤ 4-week glim titration to 3 mg 4 week run-in
<b>4034</b> [Aventis]  5/26/01–9/24/02	Glimepiride add-on to rosiglitazone	Glimepiride 1-8 mg qd (forced titration) + RSG 4-8 mg (26) glimepiride placebo + RSG (15)	26 weeks  4-week RSG run-in
<b>135*</b> (39 USA;9 Canada)  5/10/99-10/20/02	Rosiglitazone add-on to glipizide	Glipizide 10 mg bid + placebo (111) RSG 4mg OD+ glipizide (116)	2 years  4-week glipizide run-in
<i>Study reports submitted in NDA 21-071 SE1-001 (approved 4/00)</i>			
<b>096*</b> (33 USA)  4/97-3/98	Rosiglitazone add-on to glyburide	Glyburide • 10mg/day (115) RSG 2 mg daily + GLY (116) RSG 4 mg daily + GLY (116)	26 weeks  4-week placebo run-in 1-week FU or OLE
<b>015*</b> (54 European)  8/96-3/98	Rosiglitazone add-on to sulfonylureas	Sulfonylureas (198) [glyburide, glipizide, gliclazide] RSG 1 mg twice daily + SU (205) RSG 2 mg twice daily + SU (190)	26 weeks  2-4 week placebo + SU run-in 2-week FU or OLE
<b>079*</b> (41 USA)  4/97-3/98	Combination versus components	Glyburide 10 mg twice daily (115) RSG 2 mg twice daily (116) RSG 2 mg twice daily + GLY (116)	26 weeks  4-week glyburide run-in 7-10 day FU or OLE
*Pivotal clinical efficacy and safety studies			

In the major 3-arm, controlled, double blind clinical study in this NDA submission (**Study 234**), glimepiride 3 mg is added to placebo, rosiglitazone 4 mg, or rosiglitazone 8 mg therapy in a group of 172 patients with Type 2 diabetes mellitus. The sponsor's study design is indicated below.

**Study 234**

**Figure 1 Study design**



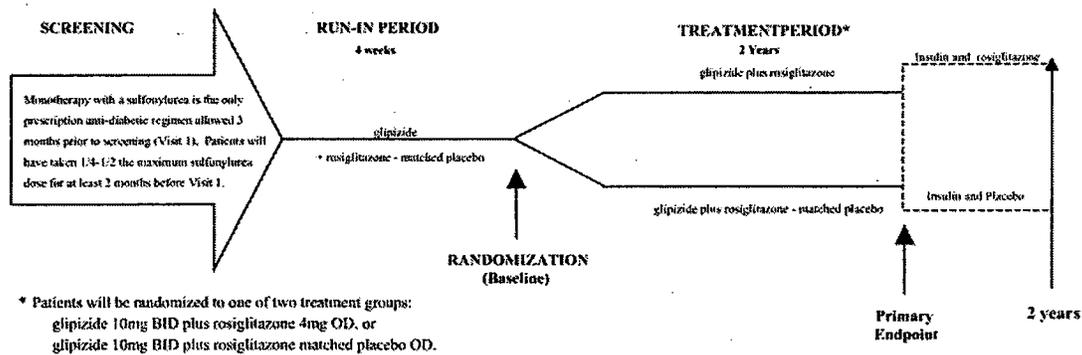
\* In patients already treated with 3mg Glimepiride the open label titration period was not required.

In study 4034, glimepiride is added to rosiglitazone in a study of only 41 patients (planned enrollment was 200). Since the sample size is small and the data are not included in the physician label, this study will be reviewed as it contributes to the safety database.

Studies 135, 096, 015 address the addition of rosiglitazone to other (non-glimepiride) sulfonylureas. The sponsor's study designs are outlined below.

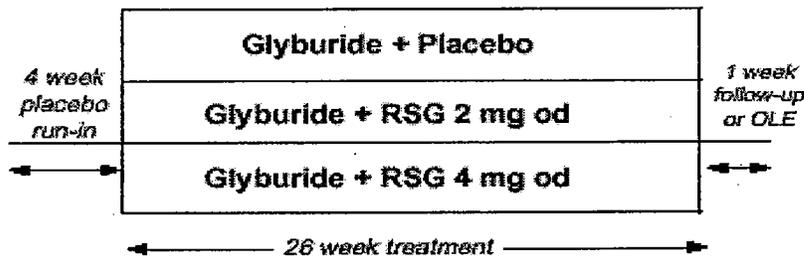
**Study 135**

**Figure 1 135 Study Design**

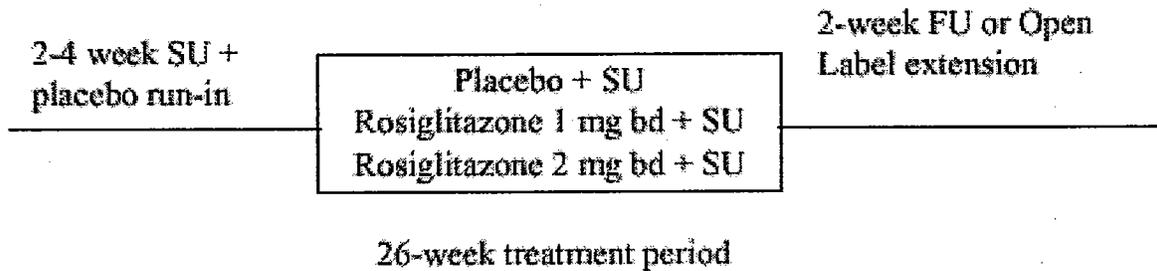


Individualize treatment goals will be encouraged. Titration of medications may be performed at anytime according to standard practice guidelines. However, patients having an FPG  $\geq 180$ mg/dL at any treatment visit after visit 4 **must** titrate their study medications. Titration of medication will continue until the patient has received the maximum recommended dosages of rosiglitazone and glipizide (4mg BID and 20mg BID, respectively). If FPG  $\geq 180$ mg/dL (upon confirmation) after patient has received maximum dosages of rosiglitazone and glipizide, patient will be withdrawn from glipizide and will receive treatment with insulin.

**Study 096**

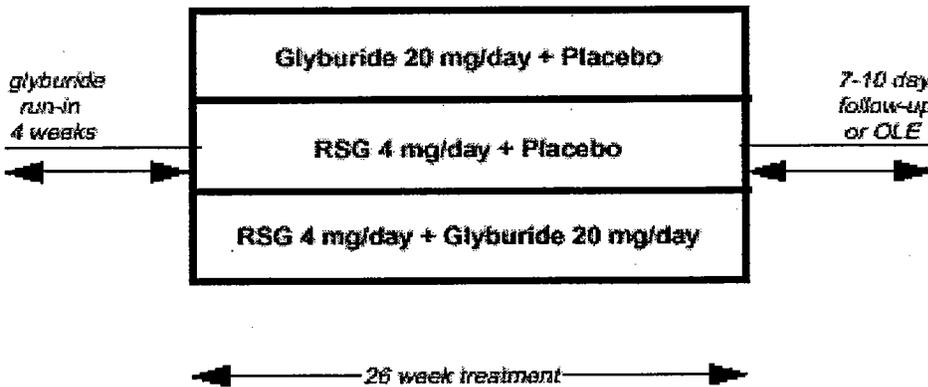


**Study 015**



The final study (Study 079) compares the administration of glyburide alone versus rosiglitazone alone versus the combination.

**Study 079**



The glycemic entry criteria were similar for the studies, except that the upper limit glucose concentration (179 mg/dl) was lower for Study 135, at a relatively lower sulfonylurea dose, suggesting that this group of patients had milder form of diabetes mellitus. The original inclusion criterion for Study 135 was an inability to use metformin. However, because of enrollment difficulties, this inclusion criterion was discontinued. All patients in the pivotal studies were treated with one or more oral anti-diabetic drug prior to randomization. Patients naïve to pharmacologic treatment for diabetes were not included in these studies.

Table 8. Inclusion Data in Clinical Studies

(Source: Summary from current submission and NDA 21-071 SE001 statistical review)

Study	HbA1c	FPG	Prior antidiabetic medications
234	≥ 7% at screen	126 ≤ FPG ≤ 270 mg/dl	1 or 2 oral antidiabetic drugs for 3 months prior to screen
4034	7.5 – 9.5 %	126 < FPG < 235 mg/dl	RSG (4 or 8 mg ) for ≥ 2 months
135		126 ≤ FPG ≤ 179 mg/dl	SU monotherapy x 3 months; ¼ - ½ max dose for last 2 months
096		140 ≤ FPG ≤ 300 mg/dl	Glyburide ≥ 10 mg/d for ≥ 2 wks prior to screen > 30% other anti diab prior to study
015	≥ 7.5%	≤ 270 mg/dl	Constant SU dose for 2 months prior to screening
079		140 ≤ FPG ≤ 300 mg/dl	Glyburide 10 mg bid for ≥ 4 wks prior to screen
<b>Conversion of glucose values from mg/dl to mmol/L (SI units):</b> 18 mg/dl = 1 mmol/L; 126 mg/dl = 7 mmol/L; 270 mg/dl = 15 mmol/L			

#### 6.1.4 Efficacy Findings

The demographic data for the five pivotal studies is also similar. The mean age was about 60 years (with a range of 32 – 81) in all the studies except Study 135. In this study, the mean age was higher (68 years), as only patients over 60 years of age were to be enrolled. Most of the patients were Caucasian and male. The known duration of diabetes (about 7 years) was similar in the different studies. Most of the patients were overweight, as noted by the body mass index above 27 kg/m<sup>2</sup>.

**Table 9. Demographic Data**

Study	N Randomized	Age Mean (range)	% age > 65	%M	Race	Body Mass Index (BMI)
234	172	63 (43-79)	47%	54%	100% Caucasian	72% with BMI > 27 kg/m <sup>2</sup>
135	227	68 (59-89)	64%	73%	91% Caucasian 7% Black 1% Hisp 1% Other	73% with BMI > 27 kg/m <sup>2</sup>
096	347	60 (36-81)		78%	90% Caucasian	88% with BMI > 27 kg/m <sup>2</sup>

015	593	61 (32-80)	42%	58%	97% Caucasian	58% BMI > 27 kg/m <sup>2</sup>
079	309	59 (38-80)	30%	66%	70% Caucasian 12% Black 19% Other	72% BMI > 27 kg/m <sup>2</sup>

The proposed doses of rosiglitazone and glimepiride for the fixed dose combination tablets of *Avandaryl*<sup>TM</sup> are compared to the doses of rosiglitazone and sulfonylureas in the clinical studies in the table below.

**Table 10. Sulfonylurea and Rosiglitazone Doses in the Clinical Trials**

*Source: Adapted from Statistical Labeling Review*

	SU	SU Dose	Rosiglitazone Dose (daily dose)
<b>Proposed Avandaryl doses</b>	<b>glimepiride</b>	<b>1 mg 2 mg 4 mg</b>	<b>4 mg 4 mg 4 mg</b>
<b>Clinical Studies</b>			
234	glimepiride	3 mg	4 mg 8 mg
135	glipizide	Start 20 mg Max 40	Start 4 Max 8
096	glyburide	≥ 10 mg	2 mg 4 mg
015	glibenclamide gliclazide glipizide	Med 15 Max 30 Med 160 Max 480 Med 15 Max 60	2 mg 4 mg
079	glyburide	20 mg	4 mg

None of the studies used the dosing combinations being proposed for *avandaryl*. Therefore, there is no clinical trial data for the to-be-marketed doses of *avandaryl*. Only one study, Study 234, used the sulfonylurea (glimepiride) contained in *Avandaryl*; this study is reviewed in the following section of this review.

The HbA1c and FPG results for the four 26-week and one 2-year studies of rosiglitazone added to sulfonylurea therapy are summarized in the table below. All the studies showed a statistically significant decrease in HbA1c for the combination (rosiglitazone and sulfonylurea) over sulfonylurea monotherapy with patients usually worsening on monotherapy.

Table 11. HbA1c and FPG results for four 26-week clinical trials and one 2-year study of rosiglitazone added to sulfonylureas (Intent to Treat Analyses with Last Observation Carried Forward) *Source: Table Adapted from Statistical Labeling Review*

	Sample Size	HbA1c Mean (%)		FPG Mean (mg/dL)	
		Baseline	Change	Baseline	Change
<i>Study Reports Submitted in NDA 21-700</i>					
<b>Study 234</b>					
Avandia 4 mg OD+Glimepiride	56	8.2	<b>-0.63*</b>	189	<b>-26</b>
Glimepiride	57	7.9	-0.08	176	+2
<b>Study 135 (2-year study)</b>					
Avandia 4 mg OD+Glipizide	115	7.6	<b>-0.65*</b>	149	<b>-25*</b>
Glipizide	110	7.4	+0.13	149	+14
<i>Study Reports Submitted in NDA 21-071 SE1-001 (approved 4/00)</i>					
<b>Study 096</b>					
Avandia 4 mg OD+Glyburide	116	9.1	<b>-0.3*</b>	214	<b>-25*</b>
Glyburide	115	8.9	+0.6	209	+23
<b>Study 015</b>					
Avandia 2 mg BID+SU	183	9.2	<b>-0.9*</b>	205	<b>-38*</b>
Sulfonylurea (SU)	192	9.2	+0.2	207	+6
<b>Study 079</b>					
Avandia 2 mg BID+Glyburide	98	9.2	<b>-0.5*</b>	222	<b>-34*</b>
Glyburide	99	9.2	+0.9	220	+24

\* Results are statistically significantly different from the control at p<0.05.

The summaries for Studies 234 and 135 are abstracted from the Statistical Labeling Review and included below.

### Study 234

Study 234 was a 26-week double-blind, placebo-controlled, randomized study. At screening, patients were removed from any pre-existing anti-diabetic medication and placed on open-label glimepiride and titrated to a maximum dose of 3 mg over a maximum of 4 weeks. Patients titrated to the maximum dose were eligible to continue into a single-blind run-in taking 3 mg of glimepiride and placebo-rosiglitazone. After 4 weeks, patients satisfying the entry criteria were randomized to placebo, rosiglitazone 4 mg or rosiglitazone 8 mg as add-on to glimepiride 3 mg; all once a day dosing. See Appendix 5.2 for a schematic of the study design.

Entry criteria included the following:

- Took oral anti-diabetic medication “within >3 months prior to screening” (Section 5.3.1 of study report)
- HbA1c ≥ 7% at screening
- 126 mg/dL ≤ FPG ≤ 270 mg/dL at Week -2
- No anti-diabetic combination therapy within 3 months of screening
- No history of chronic use of insulin

During the 26-week double blind treatment, the dose of glimepiride could be reduced to 2 mg at the discretion of the investigator; the rosiglitazone dose was not changed. Visits were scheduled every 4 weeks up to Week 20 and then at Week 26.

A total of 241 patients were screened, 174 were randomized (58:GLI+PLA; 57:GLI+ROSI 4 mg and 57:GLI+ROSI 8 mg) and 93% completed the study. Two patients in the GLI+PLA group and no patients in the ROSI groups dropped due to lack of efficacy. At the end of treatment, 5% of the patients randomized to GLI+PLA and GLI+ROSI 4 mg were on the 2 mg dose of GLI while 8.6% of the patients on GLI+ROSI 8 mg had lowered their dose to 2 mg.

The mean age of patients was 63 years (range of 43 to 79); 47% were females; and the median duration of diabetes was 6 years. The most commonly taken anti-diabetic drugs used prior to randomization were glibenclamide and glimepiride.

The applicant reported a statistically significant treatment effect for each combination versus the GLI monotherapy arm (Table 12. ANCOVA results). The HbA1c lowering for the GLI+ROSI 8 mg was significantly greater than the lowering seen for GLI+ROSI 4 mg ( $p < 0.004$ ). The 4 mg combination has about half the effect of the 8 mg combination. The results for completers are also more strongly in favor of the high dose combination ( $p < 0.0001$  compared to GLI) than the low dose combination ( $p = 0.0556$  compared to GLI). The applicant's per protocol analysis of 4 mg group versus GLI-placebo yielded a non-significant p-value of 0.12.

Table 12. Study 234 HbA1c change from baseline (LOCF)

	GLI+PLA	GLI+ROSI 4 mg	GLI+ROSI 8 mg
N	54	53	57
Baseline Mean (SD)	7.9 (1.4)	8.2 (1.4)	8.1 (1.5)
Mean change(SD)	-0.02 (1.1)	-0.64 (1.3)	-1.27 (1.5)
LS Mean change	-0.08	-0.63	-1.17
p-value vs. GLI		0.03	0.0001

The applicant reported non-significant FPG results for the 4 mg dose group ( $p = 0.088$ ) and significant results for the 8 mg group ( $p < 0.0001$ ).

The results for females were stronger than for males (see Appendix 5.3) particularly for the 4 mg combination where essentially no treatment effect is seen for males.

Overall the results for the 8 mg rosiglitazone combination dose are stronger and more robust than the results for the 4 mg combination, particularly for males. Since the 4 mg combination is close to the proposed Avandaryl doses, the limited efficacy is concerning. However, it is noteworthy that the 4 mg rosiglitazone combination is statistically significantly more effective in lowering HbA1c than GLI alone in patients inadequately treated with GLI 3 mg with a sample size of only about 50 patients in each treatment group.

### Study 135

Study 135 was a long-term study designed to determine if the combination of rosiglitazone plus glipizide delays or prevents deterioration in glycemic control compared to glipizide treatment alone. Eligible

patients entered a 4-week run-in period of glipizide 10 mg BID alone and then, were randomized to either glipizide monotherapy or glipizide and rosiglitazone 4 mg once a day. The treatment period was 2 years with a total of 16 visits (see Appendix 5.2 for the design schematic). Patients with an FPG of 180 mg/dL or greater had their doses titrated to maximum doses of rosiglitazone 4 mg BID or glipizide 20 mg BID (see Appendix 5.4 for details regarding titration). If at maximal doses, FPG remains at or above 180 mg/dL, a patient was withdrawn from glipizide and given insulin treatment; these patients were considered treatment failures. Time to treatment failure was the primary endpoint for this trial.

COENTIAL CM2003/00005/00-

To enter this trial, patients with Type 2 diabetes mellitus needed to meet the following criteria:

- prior to screening, on sulfonylurea monotherapy for at least 3 months and taking ¼ to ½ of the maximum recommended sulfonylurea dose for at least 2 months;
- at least 60 years old;
- 126≤FPG≤250 at screening;
- 126≤FPG≤179 at Week -2 (Visit 3);
- no treatment with a thiazolidinedione within 3 months of screening

A total of 357 were screened, 227 were randomized (111 to glipizide monotherapy and 116 to combination therapy). Fifty-seven (51%) monotherapy patients and 90 (78%) combination therapy patients completed 2 years on study. The reasons for withdrawal are shown below.

Table 13. Study 135 Reasons for withdrawal

	Glipizide (n=111)	RSG+Glipizide (n=116)
Adverse event	8 (7%)	13 (11%)
Lack of Efficacy	32 (29%)	3 (3%)
Protocol deviation	7 (6%)	4 (3%)
Other	7 (6%)	6 (5%)

Patients considered treatment failures, could withdraw from the study or stop glipizide treatment and initiate insulin treatment.

The average age of patients was 68 years old (range of 59-89); 73% were male and 91% were Caucasian. About 14% of the patients were intolerant or contraindicated for metformin use (this was originally an entry criteria but was changed due to difficulties in recruitment).

The applicant reported limited data on the doses taken in the study stating only in the study report that 59 completers on combination therapy remained on their initial dose and 13 combination patients and 53 monotherapy patients were titrated to the maximum dose. This reviewer determined the last dose all patients were on at the time that they either completed the full study or discontinued from the study (this dosing data was ascertained from a dataset called DOSE provided by the applicant). The majority of the patients (69%) on the combination therapy were not titrated above their starting dose while half of the patients on monotherapy were titrated to higher doses of glipizide (most to the maximum dose of 40 mg).

Table 14. Final doses for all randomized patients computed from the Applicant's dataset DOSE

Final Dose	GLIP+PLA (n=110)	GLIP+ROSI 4 mg OD (n=115)
Glip 20 mg+Rosi 4mg OD (or Pla)	35 (35%)	78 (69%)
Glip 20 mg+Rosi 4mg BID (or Pla)	14 (14%)	19 (17%)

Glip 30 mg+Rosi 4mg BID (or Pla)	10 (10%)	9 (8%)
Glip 40 mg+Rosi 4mg BID (or Pla)	40 (40%)	7 (6%)

Only 2 patients (2%) on combination therapy were treatment failures while 27 patients (29%) on monotherapy glipizide were failures (log rank test  $p < 0.0001$ ). Eleven (11) of the 27 treatment failures on monotherapy, stopped glipizide and switched to insulin.

Both the FPG and HbA1c change from baseline results showed significant treatment effects at both Week 26 and endpoint. Also the results for patients who stayed on the initial doses of combination therapy (rosiglitazone 4 mg and glipizide 10 mg daily) had results comparable to patients titrated to higher doses. So the results at endpoint shown in Table 11 of this review are representative of the results at both Week 26 and endpoint and for patients titrated and not titrated.

#### Reviewer's Comments:

Summary comments about Study 135 include the following:

- 1) The rosiglitazone and sulfonylurea therapy provides greater durability than sulfonylurea monotherapy.
- 2) Lower dosages of two medications may be more effective and have less adverse events than a higher dosage of one medication.
- 3) Titration of dosages to endpoints such as HbA1c or FPG, rather than use of just fixed dosages, may further maximize efficacy and safety.
- 4) Compliance with a reduced frequency of doses and number of medications, as with a combination fixed dose tablet, may be further enhanced by a lower cost of that therapy. The retail costs of fixed dose combination therapy appear to be less than the cost of concomitantly administered combination therapy.
- 5) It is not known if treatment durability would also be prolonged in patients with Type 2 diabetes mellitus naïve to pharmacological therapy and initially treated with a combination fixed dose tablet. Such studies have not been done.

#### 6.1.5 Efficacy Conclusions

The five controlled clinical studies (two from this submission and three from the prior submission) all indicate that treatment with rosiglitazone (4 mg) added to a sulfonylurea results in better glycemic control than treatment with the sulfonylurea alone. From baseline glycosylated hemoglobin A1c (HbA1c) values of 8 – 9% and baseline fasting plasma glucose (FPG) values of 200 – 220 mg/dl, there was a decrease in the range of 0.3 to 0.9% and 25-38 mg/dl, respectively, in the four 26-week studies.

The two-year study also showed a similar change in HbA1c and FPG, though those patients were less hyperglycemic at baseline. This study also showed that the combination rosiglitazone and sulfonylurea therapy is more durable. The primary endpoint in this study was defined as the mean time to the final action point (FAP), FPG  $\geq$  180 mg/dl, or mean time to treatment failure, when patients could be withdrawn from the study or treated with insulin. The mean duration of exposure to medication differed between the two treatment groups (644 days in the rosiglitazone and glipizide group versus 560 days in the glipizide group), as only 2 patients (2%) in the rosiglitazone and glipizide group achieved the FAP, or failed therapy, while 27 (28.7%) patients in the glipizide group achieved the FAP ( $p < 0.0001$ ).

The observation that the efficacy data for the different sulfonylureas in these clinical trials is similar is consistent with the observation of noninferiority in active-controlled one-year monotherapy trials of glimepiride and glyburide and glipizide in the original glimepiride NDA (NDA 20-496). Baseline and endpoint HbA1c values were similar for the glimepiride and control groups. The clinical studies support the second line indication of concomitantly administered rosiglitazone and sulfonylurea treatment of patients with Type 2 diabetes mellitus, who are inadequately treated with sulfonylurea treatment alone. Since the pharmacokinetic data indicate that the fixed dose combination product rosiglitazone and glimepiride is similar to concomitantly administered rosiglitazone and glimepiride, the clinical studies then also support the second line indication of fixed dose combination rosiglitazone and sulfonylurea treatment of patients with Type 2 diabetes mellitus, who are inadequately treated with sulfonylurea treatment alone.

## 7 INTEGRATED REVIEW OF SAFETY

### Methods and Findings

Safety data was reviewed in the submitted pharmacokinetic studies and the three clinical studies. The safety data for the previously submitted studies were reviewed in the medical reviews and are summarized from the Medical Review.

#### 7.1.1 Deaths

There were a total of 14 reported deaths associated with the six clinical studies. Eight patients were treated with monotherapy – five with a sulfonylurea (two of these had not been randomized and were in the run-in period) and one with rosiglitazone. The causes of death in the monotherapy group included rectal carcinoma (1), cardiac etiology (6 or 0.8% of patients on monotherapy), and subarachnoid hemorrhage (1). Six were treated with combination therapy consisting of rosiglitazone and a sulfonylurea. The causes of death in the combination therapy group included esophageal cancer (1), cardiac etiology (4 or 0.4% of patients on combination therapy), and cerebrovascular accident (1). The number of patient deaths on monotherapy and combination therapy secondary to cardiovascular etiologies did not differ greatly. It is unlikely that the cardiac and cerebrovascular deaths were related to the treatment. Two of these deaths

occurred during the run-in period, and most of these patients had extensive cardiac histories, including prior myocardial infarctions. In addition, patients with Type 2 diabetes mellitus, in general, are at 2-3 fold increased risk of cardiovascular events. The cancer deaths are also unlikely to be related to the sulfonylurea treatment.

Table 15. Patients with Fatal Adverse Events (*Source*: Case Report Forms – studies 234 and 135; Medical Review – studies 096, 015, 079)

Study	Patient ID	Treatment Group	Age Race Sex	Serious Adverse Event
234	234.018.1807	Not randomized  glimepiride	57 WM	Rectal Carcinoma  withdrew during glimepiride titration (patient received study drug in error for 2 weeks prior to randomization) when cancer diagnosed; died 3 months later
234	234.013.1301	Glimepiride+ RSG 4 mg	56 WM	Esophageal cancer diagnosed 5/17/01; randomized to study drugs 4/25/01; stopped study drugs 9/4/01 (dysphagia after chemotherapy); hospitalized and died 10/24/01
4034	[no deaths]			
135	135.011.77414	Glipizide	70 WM	Cardiac arrest at end of study
135	135.012.77293	Glipizide	75 M	Atherosclerotic heart disease
135	135.015.77301	Glipizide	75 WF	Acute myocardial infarction Died during run in phase
135	135.028.77339	Glipizide + RSG	62 BM	Cerebrovascular accident
135	135.034.76107	Glipizide	70 F	Acute myocardial infarction
135	135.051.76219	Glipizide + RSG	62 WM	Acute myocardial infarction
096	[no deaths]			
015	1 patient	SU		Subarachnoid hemorrhage
	3 patients	RSG + SU		Acute myocardial infarction
079	1 patient	RSG mono		Cardiac
	1 patient	GLY mono		Cardiac

The total number of deaths in the database submitted in the NDA (NDA 20496) for glimepiride monotherapy approval was similar for glimepiride and glyburide. In both groups, the etiology of most of the deaths was thought to be cardiovascular.

As part of the Prescribing Information for all sulfonylureas, there is a warning that describes the findings of the University Group Diabetes Program (UGDP). The UGDP was a longterm prospective clinical trial that enrolled 823 patients with Type 2 diabetes mellitus. Patients who were treated with a sulfonylurea (tolbutamide) for 5-8 years had a 2.5 higher rate of cardiovascular mortality than those treated with diet alone. There was much controversy about these findings. (University Group Diabetes Program (UGDP). *Diabetes* 1970; 19[Suppl. 2]:747-830) The United Kingdom Prospective Diabetes Study, is another longterm (20 year)

prospective study that enrolled 3867 newly diagnosed patients with Type 2 diabetes mellitus. Patients were randomized to diet, chlorpropamide (a first generation sulfonylurea), glibenclamide (a second generation sulfonylurea), and insulin. Over 10 years of followup, there were no significant differences in the diabetes related deaths, all cause mortality, myocardial infarction, fatal sudden death, and heart failure in the drug treated groups versus those treated with diet alone. ( UK Prospective Diabetes Study (UKPDS) Group, Lancet 1998; 352: 837 – 53.)

### 7.1.2 Dropouts and Other Significant Adverse Events

The safety data base comprised 1689 patients randomized to the clinical studies: 587 (35%) were randomized to sulfonylurea monotherapy, 119 (7%) were randomized to rosiglitazone monotherapy, and 983 (58%) were randomized to rosiglitazone and sulfonylurea combination therapy. There were more withdrawals due to lack of efficacy in the sulfonylurea monotherapy (14%) and rosiglitazone monotherapy (18%) than in the combination therapy groups (5%). The withdrawal rate secondary to adverse events was similar in the sulfonylurea monotherapy (7%) and combination rosiglitazone and sulfonylurea therapy (5%) and higher in the rosiglitazone monotherapy (20%).

Table 16. Withdrawal Data

(Source: NDA 21700 submission and NDA 21-071 SE001 statistical review)

Study	N screened / N ran-domized (%)	Study Arms	N /arm	N completed	N withdrew adverse event	N withdrew efficacy lack
234	241/172 (71%)	Glim 3 mg	57	53 (91%)		2 (3.4%)
		Glim3mg+RSG4mg	56	52 (91%)		
		Glim3mg+RSG8mg	59	57 (98%)		
4034	112/41 (37%)	Glim 1-8mg + RSG4-8mg	26	24		1
		RSG	15	14		1
135	357/227 (64%)	Glip10mgbid	111	57 (51%)	8 (7%)	32 (29%)
		RSG 4mg + glip	116	90 (78%)	13 (11%)	3 (3%)
096	549/347 (76%)	GLY ≥ 10 mg	115	94 (82%)	2 (2%)	9 (8%)
		GLY+RSG2mg	116	95 (82%)	5 (4%)	5 (4%)
		GLY+RSG4mg	116	102 (88%)	3 (3%)	3 (3%)
015	800/593 (74%)	SU	198	127 (64%)	23 (12%)	31 (16%)
		SU+RSG1bid	205	147 (72%)	11 (5%)	24 (12%)
		SU+RSG 2bid	190	144 (76%)	11 (6%)	16 (8%)
079	390/309 (70%)	GLY 20 mg	106	71 (67%)	10 (9%)	7 (7%)
		RSG 2mg bid	104	46 (44%)	21 (20%)	21 (20%)
		GLY+RSG 2mgbid	99	78 (79%)	7 (7%)	2 (2%)

### 7.1.3 Hypoglycemia

Serious hypoglycemia requiring the assistance of another person was reported in one patient treated with sulfonylurea monotherapy (Study 079) and two patients treated with combination rosiglitazone and sulfonylurea therapy (Studies 135 and 079). As expected, nonserious hypoglycemia tended to be more common with combination therapy (rates ranging from 2% to 32%), than with sulfonylurea monotherapy (rates ranging from 0 to 27%) in the five pivotal clinical studies. The higher rate of hypoglycemia in the combination group was consistent with the lower HbA1c in that group. Only symptomatic hypoglycemia was considered an adverse event in Studies 234 and 135; the event did not need to be confirmed with a glucose measurement. This method of ascertainment may partially account for the different rates of hypoglycemia observed in these studies.

Table 17. Hypoglycemia

(Source: Study Reports for Studies 234, 4034, 135; Medical Review for Studies 096, 015, 079)

Study	Study Arms	Serious requiring assistance  (#/% people)	Nonserious  (#/% people)
234	Glim 3 mg	0	0
	Glim3mg+RSG4mg	0	1/56 (1.8%)
	Glim3mg+RSG8mg	0	0
4034	Glim 1-8mg +RSG4-8mg	0	12/25 (48%)
	RSG	0	1/15 (7%)
135	Glip10mgbid	0	30/111 (27%)
	RSG 4mg + glip	1	37/116 (32%)
096	GLY ≥ 10 mg		2/115 (.7%)
	GLY+RSG2mg		7/116 (5%)
	GLY+RSG4mg		3/115 (2.6%)
015	SU		2%
	SU+RSG1bid		3.4%
	SU+RSG 2bid		5.3%
079	GLY 20 mg	1	6/106 (5.7%)
	RSG 2mg bid	0	0
	GLY+RSG 2mg bid	1	8/99 (8.1%)

The sponsor extensively evaluated hypoglycemia in Study 135. Part of that discussion is cited below.

Only one patient (0.9%) in the RSG+GLIP group experienced a serious adverse event of hypoglycemia. PID 135.050.76157, a 76 year-old male, was admitted to the hospital because of a low blood glucose concentration that occurred 256 days after the start of study medication. Due to a viral infection, the patient had not been able to eat for two days prior to the hospitalization. He continued to take study medication even though he was unable to eat. Treatment with study medication was not interrupted, and

the SAE was reported as resolved two days later. No patients in either treatment group withdrew from the study because of hypoglycemia.

A total of 67 patients (29.5%) experienced 235 on-therapy events of hypoglycemia. On therapy AEs of hypoglycemia occurred in a slightly higher percentage of patients in the RSG+GLIP group (31.9%) than in the GLIP group (27.0%). Of the 37 patients in the RSG+GLIP group who experienced an on-therapy hypoglycemia adverse event, 26 reported more than one occurrence, for a total of 165 events. Twenty-one of the 30 patients in the GLIP group reported more than one event, for a total of 70 events. All but six of the 235 events were either mild or moderate in nature, and only seven of the events resulted in a reduction of study medication dose. Four of the seven dose reductions occurred in the RSG+GLIP group, but per protocol, adjustments could only be made to the GLIP dose. In the majority of cases, the reduction in dose prevented a recurrence of hypoglycemia.

**Table 49 Hypoglycemia On-Therapy Adverse Events, Serious Non-Fatal Adverse Events and Withdrawals (All Randomized Patients)**

Patients with at Least 1 Event, n (%) [rate per 100 patient years]	Treatment Group		Total
	GLIP (n=111)	RSG+GLIP (n=116)	
AE <sup>1</sup>	30 (27.0), [17.62]	37 (31.9), [18.07]	67 (29.5)
SAE	0	1(0.9), [0.49]	1 (0.44)
Withdrawal Due to AE	0	0	0

1. SAEs and withdrawals are included in the AE count

Data Source: Section 15, Tables 15.2.3., 15.2.4. and 15.5.; Ad Hoc Table 875

The occurrence of hypoglycemia is often the limiting factor in achieving tight glycemic control, and treatment decisions are often guided by an analysis of risk versus benefit. Table 50 summarizes the number of patients reporting hypoglycemia as an on-therapy adverse event by treatment group and their final HbA1c. The majority of patients (20/36) in the RSG+GLIP group who experienced an on-therapy AE of hypoglycemia also achieved target HbA1c by study's end ( $\leq 7.0\%$ ). In contrast, only a minority of patients in the GLIP group who experienced an on-therapy AE of hypoglycemia achieved a near target HbA1c by study's end (10/29).

**Table 50 Subjects Reporting Adverse Events of Hypoglycemia by Treatment Group and Final HbA1c Value**

Final HbA1c	Treatment Group		Mean No. of Events/Subject
	GLIP Subjects with Hypoglycemia <sup>1</sup>	RSG+GLIP Subjects with Hypoglycemia <sup>1</sup>	
$\leq 6.5$	4	11	1.94
6.6 - $\leq 7.0$	6	9	3.25
7.1 - $\leq 8.0$	13	8	1.83
$> 8.0$	6	8	1

n = number of subjects who reported at least one on-therapy adverse event of hypoglycemia. One patient in each treatment group was excluded from the count due to lack of an on-therapy HbA1c value.

Data Source: Section 14, Table 14.2.2.1.; Section 15, Table 15.2.5.

Because of the limited safety data for glimepiride in the six clinical studies, the data for glimepiride monotherapy was reviewed. Three active-controlled 12-month monotherapy studies were reviewed in the original glimepiride NDA in which glimepiride was compared to another sulfonylurea. The rates of hypoglycemia were similar in the glimepiride and the comparator groups. The baseline and endpoint HbA1c values in the glimepiride and glyburide groups were similar (8.1% and 8.6%, respectively) in Study 2/MN/301. There was an increase in glycemia in both groups. The specific HbA1c data for the other studies are not included in the medical review. However, the severity of the hypoglycemic episodes is not described. It is not stated if a difference in the ascertainment method contributed to the 6-9 fold increased rate of hypoglycemia in Studies 8/USA/301 and 8/USA/302 as compared to Study 2/MN/301. All three studies were dose titration rather than fixed dose studies.

Table 18. Rates of Hypoglycemia in Glimepiride Trials compared to Glyburide and Glipizide  
 (Source: Medical Review of NDA 20496 (glimepiride))

Study	N randomized	Duration	Drug	Dose /day	Hypoglycemia (%)
8/USA/301	130	12 months	glimepiride	1-12 mg	18.6%
			glipizide	2.5 – 40 mg	15.9%
8/USA/302	577	12 months	glimepiride	1-16 mg	12%
			glyburide	1.25 – 20 mg	17%
2/MN/301	1041	12 months	glimepiride	1-8 mg	2%
			glyburide	2.5 – 20 mg	2%

Though no severe episode of hypoglycemia is described in the original glimepiride NDA or in the currently submitted glimepiride studies, severe, prolonged hypoglycemia has been reported in the literature in association with glimepiride therapy. A reference to treatment of prolonged hypoglycemia is included in the Overdosage Section of the *Amaryl* (glimepiride) and *Avandaryl*<sup>TM</sup> prescribing information. Similar statements are included in the overdosage sections in the glipizide and glyburide prescribing information.

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

#### 7.1.4 Common Adverse Events

Based on the data from the 120-day safety update for Studies 096, 015, and 079 (NDA supplement 21-071 SE001 for the combination rosiglitazone and sulfonylurea therapy indication), comparison of the rosiglitazone and sulfonylurea combination and sulfonylurea monotherapy treatment groups revealed that the rates of the adverse events fluid retention (4% vs. 1%, in the 2 groups, respectively), weight gain (1.5% vs. 0.6%), and anemia (2% vs 0.6%) were more common in the combination therapy groups. The reported rates for congestive heart failure and pulmonary edema were similar in the two groups in the clinical trials. New cases of congestive heart failure and exacerbations of existing congestive heart failure have been reported in postmarketing data in association with rosiglitazone monotherapy and combination therapy.

Troglitazone, the first approved thiazolidinedione, was withdrawn because of hepatic toxicity. To evaluate the risk of hepatic injury in association with rosiglitazone, another thiazolidinedione, rates of liver abnormalities (defined as ALT level > 3 x ULRR, or upper limit of the reference range) were reviewed in the rosiglitazone clinical program (both double blind and open label studies) through January 2004. Rates of liver abnormalities (ALT level > 3 x ULRR) in rosiglitazone monotherapy, (0.2 per 100 years of patient exposure) and combination rosiglitazone and sulfonylurea therapy (0.3 per 100 years of patient exposure) were lower than rates of liver abnormalities (ALT level > 3 x ULRR) in sulfonylurea monotherapy (0.5 per 100 years of patient exposure), suggesting that rosiglitazone *per se* is not associated with hepatic injury. (NDA 21071 SLR009, reviewed per Dr. Misbin 5/04) The safety data in Studies 234 and 135 in this submission were consistent with the previously reported safety data for rosiglitazone and sulfonylurea combination therapy.

#### 7.1.5 Human Reproduction and Pregnancy Data

No pregnancies were reported in these studies.

#### 7.1.6 Postmarketing Experience

The most common adverse events for rosiglitazone and glimepiride reported to the FDA Adverse Event Reporting System are listed below. The adverse events are reported as preferred terms. The most common 25 preferred terms are listed for each drug, in descending order. The number of times a preferred term is reported and the percent of total reported adverse events related to that drug are also listed. Rosiglitazone was approved in May 1999, and glimepiride was approved in November 1995.

Rosiglitazone Reported Adverse Events			Glimepiride Reported Adverse Events		
Preferred Term (PT)	Number of PTs	% of Total	Preferred Term (PT)	Number of PTs	% of Total

Weight increased	1460	19.1	Hypoglycemia	79	21.2
Oedema Peripheral	1219	15.9	Drug Interaction	30	8.1
Dyspnea	653	8.5	Hyperglycemia	18	4.8
Fatigue	620	8.1	Medication Error	18	4.8
Cardiac Failure Congestive	491	6.4	Drug Ineffective	16	4.3
Oedema	429	5.6	Diarrhea	14	3.8
Fluid Retention	359	4.7	Dizziness	14	3.8
Hypoglycemia	332	4.3	Nausea	14	3.8
Nausea	332	4.3	Abdominal Pain	13	3.5
Hyperglycemia	331	4.3	Coma	13	3.5
Headache	320	4.2	Condition Aggravated	13	3.5
Anemia	285	3.7	Diabetes Mellitus	13	3.5
Liver Function Test Abnormal	261	3.4	Liver Function Test Abnormal	13	3.5
Dizziness	255	3.3	Asthenia	12	3.2
Asthenia	213	2.8	Chest Pain	12	3.2
Abdominal Distention	202	2.6	Weight Increased	12	3.2
Condition Aggravated	198	2.6	Blood Glucose Decreased	11	3.0
Alanine aminotransferase Increased	178	2.3	Dermatitis	11	3.0
Chest Pain	176	2.3	Headache	11	3.0
Diarrhea	176	2.3	Blood Glucose Increased	10	2.7
Blood Glucose Increased	167	2.2	Dyspnea	10	2.7
Drug Ineffective	155	2.0	Thrombocytopenia	10	2.7
Myocardial Infarction	155	2.0	Cerebrovascular Accident	9	2.4
Swelling	152	2.0	Fall	9	2.4
Vomiting	145	1.9	Hemoglobin Decreased	9	2.4

The FDA Adverse Event Reporting System includes all reports since the drugs were approved. The purpose of this table is to provide an overview of postmarketing adverse events for these two drugs, which will compose the proposed fixed dose combination drug product in this NDA submission. There were a total of 7663 adverse reports for rosiglitazone and 372 adverse event reports for glimepiride. Each adverse event report may be coded into one or more preferred terms. This table comprises data from the computerized FDA Adverse Event Reporting System (AERS) Standard Reports\* (dated 8/5/04 and 8/13/04) generated by Lanh Green, Pharm. D, M.P.H., in the Office of Drug Safety. The cases have not been individually analyzed, and causality has not been established. For example, hypoglycemia is listed as a common adverse event for rosiglitazone, but it is rarely observed with rosiglitazone monotherapy in clinical trials. Most likely, these reports reflect the use of other concomitant antidiabetic drugs. This listing provides an overview of the most common postmarketing adverse events, and it includes the most common adverse events observed in the clinical trials.

\*The official AERS data set disclaimer is included below.

The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Hence, when considering these figures, it should be realized that accumulated case reports cannot be used to calculate incidence or estimates of drug risk for a particular product, as reporting of adverse events is a voluntary process, and underreporting exists. Further, because of the multiple factors which influence reporting, comparisons of drug safety cannot be made from this data. Some of these factors include the length of time a drug is marketed, the market share, size and sophistication of the sales force, publicity about an adverse reaction and regulatory actions. It should also be noted that in some of these cases, the reported clinical data was incomplete, and there is no certainty that these drugs caused the reported reactions. A given reaction may actually have been due to an underlying disease process or to another coincidental factor. Further, these data were generated using computer printouts, and some of the numbers may reflect duplicates.

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## 8. Additional Clinical Issues

### 8.1 Pediatrics

A request for a deferral of pediatric studies had originally been made in the 10/03 submission. The purpose of the 5/21/04 amendment submission was to provide additional information regarding the rationale. The sponsor's comments are quoted below:



This reviewer concurs with the plan to complete ongoing pediatric studies with rosiglitazone and glimepiride before planning pediatric studies with the fixed dose combination product *Avandaryl*.

### 8.2 Literature Review

**The limited durability of sulfonylurea monotherapy has been well known.**

For example, in the glimepiride NDA submission, the HbA1c concentration in a one-year, active (glyburide) - controlled glimepiride clinical trial, was higher at the endpoint (8.6%) than at baseline (8.1%) in both groups.

In the United Kingdom Prospective Diabetes Study, 4075 patients, aged 25 to 65 years, with newly diagnosed Type 2 diabetes mellitus, were recruited between 1977 and 1991 in the first 15 UKPDS centers. The median FPG concentration was 207 (162-259) mg/dl, HbA1c level was 9.1% (7.5%-10.7%), and mean (SD) body mass index was 29 (6) kg/m<sup>2</sup>. After 3 months on a low-fat, high-carbohydrate, high-fiber diet, patients were randomized to therapy with diet alone, insulin, sulfonylurea, or metformin. After 3 years of monotherapy with diet alone, insulin, or sulfonylurea, 19%, 52%, and 46% achieved FPG < 140 mg/dl, and 25%, 47%, and 50% , respectively, achieved HbA1c < 7%, the American Diabetes Association target. Thirty-nine percent (39% ) of obese patients treated with metformin achieved FPG < 140 mg/dl and 44% achieved HbA1c < 7%.

After 9 years of monotherapy with diet alone, insulin, or sulfonylurea, 8%, 42%, and 24% achieved FPG < 140 mg/dl, and only 9%, 28%, and 24% achieved HbA1c < 7% . Eighteen (18%) of obese patients treated with metformin had FPG < 140 mg/dl at 9 years of followup and only 13% had a HbA1c < 7%. (Turner RC et al, *JAMA* 1999; 281: 2005-2011).

In the Kaiser Permanente large, group-model, health maintenance organization, 80% of patients with Type 2 diabetes mellitus initially treated with sulfonylureas added or switched to metformin or insulin within 10 years of diagnosis. (Brown JB et al, *Clin Ther* 1999, 21:1045-1057).

**Improved compliance is associated with a fewer number of therapies and fewer dosages per day.**

Polypharmacy can inhibit ability to comply with a treatment regimen. Conversely, compliance increases with a reduction in the frequency of doses. In a study of 91 patients with Type 2 diabetes mellitus, treated with oral antidiabetic drugs, compliance was 79%, 66%, and 38% in the case of once daily, twice daily, and three times daily dosage, respectively. (Paes AHP et al, *Diabetes Care* 1997; 20:1512-1517.)

Population-based adherence to therapy declined in 2920 patients with Type 2 diabetes mellitus followed for 12 months in the United Kingdom when a combination of sulfonylurea and metformin (1060) was substituted for either sulfonylurea (1329) or metformin (531). The % adherence and adherence index, or days of drug coverage per year, were 13% and 266 days, 31% and 300 days, and 34% and 302 days in the three groups - combination therapy, sulfonylurea and metformin groups, respectively. (Morris AD et al, *Diabetes* 2000; 49:A76.)

## 9. OVERALL ASSESSMENT

The combination fixed drug product rosiglitazone and glimepiride provides a more convenient mode of treatment than concomitant treatment with the two separate drugs. The indication for this combination fixed product is as second-line therapy for patients who have failed monotherapy. The dosages of rosiglitazone (4 mg) and glimepiride (1, 2, 4 mg) in the fixed drug combination may be less than the doses of the two drugs given concomitantly. The maximal approved doses for rosiglitazone and glimepiride monotherapy are 8 mg, the maximal approved rosiglitazone combination therapy dose is 4 mg, and there is no specified maximal glimepiride dose for combination therapy. In addition, rosiglitazone is more effective when given twice daily, while the fixed drug combination product is recommended for once daily dosage. Thus, it is conceivable that the dosages of rosiglitazone and glimepiride concomitant therapy may exceed those in the proposed fixed drug combinations.

### 9.1 Conclusions

Per agreement between the sponsor and FDA before the submission of this NDA, the approval of the combination fixed product rosiglitazone maleate and glimepiride (*Avandaryl*<sup>TM</sup>) for the treatment of Type 2 diabetes mellitus would be based on pharmacokinetic data and the "bridging" of these data with the clinical data. As a result, several questions need to be answered in evaluating the appropriateness of such a proposed approval.

- 1) *Do the pharmacokinetic data indicate that the fixed dose combination product rosiglitazone and glimepiride is similar to concomitantly administered rosiglitazone and glimepiride?*

The pharmacokinetic data indicate that the fixed dose combination product rosiglitazone and glimepiride is similar to concomitantly administered rosiglitazone and glimepiride. Bioequivalence was demonstrated for the rosiglitazone component in terms of AUC and  $C_{max}$ . The 90% confidence intervals for the comparisons between the combination tablet and the concomitant tablets fell within the range of 0.8 -1.25 for the AUC of rosiglitazone and glimepiride and  $C_{max}$  of rosiglitazone. However, the  $C_{max}$  of glimepiride was found to be lower following the administration of the combination tablet compared to the value obtained after concomitant dosing of the commercial tablets. Since the  $C_{max}$  is lower in the fixed dose combination tablet, it is not a safety concern. Thus, the rosiglitazone components (fixed dose combination and concomitant administration) are bioequivalent, while the glimepiride components are similar but not bioequivalent. The 90% confidence intervals for both AUC and  $C_{max}$  need to be in the 0.8 to 1.25 range to demonstrate bioequivalence.

- 2) *To which clinical data should the pharmacokinetic data be "bridged"? The sponsor primarily cited the previously approved NDA supplement for combination rosiglitazone and sulfonylurea therapy. If that is the chosen "bridge," are other sulfonylureas similar to glimepiride? Does the only clinical safety and efficacy 26-week study comparing*

*rosiglitazone added to glimepiride and glimepiride therapy alone (Study 234) also support this "bridging?"*

Based on the data available in the original glimepiride NDA (NDA 20-496), the efficacy and safety data for glimepiride and glyburide and glipizide are similar. Postmarketing adverse event reporting is also similar for glimepiride and glyburide. On the basis of these data, it is possible to conclude that glimepiride is representative of sulfonylurea therapy, *per se*. The efficacy and safety data from the 26-week glimepiride clinical study are consistent with data from other sulfonylurea studies. These clinical data support the "bridging" of the pharmacokinetic data from rosiglitazone and glimepiride to rosiglitazone and sulfonylurea therapy in general.

3) *Is once-daily dosing appropriate based on the data?*

There are no clinical studies with the to-be-marketed fixed dose combination tablets of rosiglitazone and glimepiride. The rosiglitazone 4 mg daily dose was more effective when it was given as a divided dose (2 mg) twice daily. In the glimepiride NDA, no difference was observed between 8 mg and 16 mg daily doses given as 1 dose or as 2 divided doses. No data regarding glimepiride 4 mg or lower daily doses given in divided doses is available.

All of the clinical studies evaluate the addition of rosiglitazone to sulfonylurea therapy. No study evaluates the addition of sulfonylurea therapy to rosiglitazone. There are no head-head studies comparing the two marketed thiazolidinediones, rosiglitazone and pioglitazone. The indication for the fixed dose combination tablet should reflect the data for the concomitant administration of rosiglitazone and sulfonylureas. The indication, therefore, should be more limited:

*Avandaryl<sup>TM</sup> is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of rosiglitazone and sulfonylurea in doses comparable to or less than the rosiglitazone and glimepiride doses in Avandaryl<sup>TM</sup> or who are not adequately controlled on sulfonylurea alone.*

- 5) *The proposed indication is for second line therapy. Because of the convenience of and increased compliance with once-daily dosing with one pill rather than two separate pills, it is possible that this fixed dose combination drug would also be used as first-line therapy in patients naïve to pharmacologic therapy. Is first-line therapy with this fixed dose combination product appropriate, and more importantly, safe based on the available data?*

Studies indicate increased compliance with once-daily dosing than with twice (or more) daily dosing. Compliance also increases with a smaller number of medications. Finally, the cost of fixed dose combination therapy, though basically a convenience modality, may actually be lower than the cost of concomitant drug therapy. Other fixed dose combination anti-diabetic drugs (*Glucovance*® [metformin+glyburide] and *Metaglip*® [metformin+glipizide]) have been approved for both first and second line indications, based on studies in pharmacologically naïve patients and patients inadequately treated with one or more antidiabetic drugs. The data from the metformin and glyburide combination indicates a greater glucose lowering effect of the combination albeit at lower doses than either metformin or glyburide alone (Marre M et al, *Diabetic Medicine* 2002; 19:673-680).

Thus, it is likely that the fixed dose combination tablet *Avandaryl*<sup>TM</sup> would also be administered to patients naïve to pharmacologic therapy for Type 2 diabetes mellitus. Whether such an “off-label” indication would be associated with an increased risk of hypoglycemia, and possibly also congestive heart failure, liver function test abnormalities, and/or weight gain, in the naïve patients who have not previously been exposed to pharmacologic therapy for Type 2 diabetes mellitus, in comparison to the risk noted in second line therapy, is not known. There appear to be possible advantages of combination rosiglitazone and sulfonylurea therapy, as discussed in this review. Because of this observation and the greater convenience of one tablet and once daily dosing, the fixed dose combination may also be prescribed “off label” as first-line therapy. A clinical study to assess the safety and efficacy of the fixed dose combination tablet as first-line therapy may be worthwhile, and data could probably be collected in a clinical practice setting

As summarized in this review, the submitted data support the safety and efficacy of this fixed dose combination product as second-line therapy for the treatment of Type 2 diabetes mellitus. This reviewer recommends the approval of this fixed dose combination tablet for second line therapy, with emphasis in the Prescribing Information that first-line therapy was not evaluated, that the dosages of rosiglitazone and glimepiride in the fixed dose combination tablet may be smaller than the dosages of the two drugs in concomitant therapy, and that no clinical trials were done with the to be marketed tablet.

## 9.2 Recommendation on Regulatory Action

This reviewer recommends approval of *Avandaryl*<sup>TM</sup> (rosiglitazone maleate and glimepiride fixed dose combination product) for the following indication, with the revised labeling and change of the proposed proprietary or trade name from *Avandaryl*<sup>TM</sup>:

*Avandaryl<sup>TM</sup> is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of rosiglitazone and sulfonylurea in doses comparable to or less than the rosiglitazone and glimepiride doses in Avandaryl<sup>TM</sup> or who are not adequately controlled on sulfonylurea therapy alone.*

This reviewer agrees with the Division of Medication Errors and Technical Support (DMETS) consult, which does not recommend the use of the *Avandaryl* trade name or proprietary name. According to their review, the *Avandaryl* name may potentially be confused with the following trade names: *Avandia* (rosiglitazone maleate), *Amaryl* (glimepiride), *Avandamet* (rosiglitazone maleate and metformin), and *Vanceril* (beclomethasone dipropionate inhalation aerosol). Confusion with the first three trade names may pose the greatest safety issues.

Note also that the CMC recommendation is “approvable, pending a cGMP inspection.”

#### Recommendation on Postmarketing Actions

##### 7.1.7 Risk Management Activity

Other than the adverse events associated with rosiglitazone and sulfonylurea therapy, no specific risk has been identified that requires risk management activity.

##### 7.1.8 Required Phase 4 Commitments

There is no required Phase 4 commitment.

##### 7.1.9 Other Phase 4 Requests

There are no other Phase 4 requests.

#### Labeling Review

##### General Comments

*Note: Labeling was submitted with the electronic submission on 10/31/03. The labeling comments below and the red-line WORD documents are based on the 10/31/03 labeling submissions.*

*Revised labeling was submitted 8/10/04 by email with Changes Being Effected, relating to drug-drug interactions, liver function testing, and postmarketing reports of angioedema and urticaria in association with rosiglitazone use. This revised labeling had previously been submitted and reviewed for the Avandia® and Avandamet® labels.. The sponsor subsequently submitted these labeling changes to the electronic document room*

This reviewer's recommended changes are described in the line-by-line review as well as in the annotated, red-line copy of the Prescribing Information.

The appropriate changes in the CLINICAL STUDIES section were discussed with the statistical reviewer, Joy Mele, M.S. At first, we both thought a tabular presentation of HbA1c and FPG data for all 5 studies would be most informative. Reviewing such a table, however, we concur that there is so much consistency in the efficacy data from the various studies and that the data could (and perhaps should) be summarized in a few sentences only. Specific changes to the CLINICAL STUDIES section are included in the red-line version of the label..

The sponsor's Patient Prescribing Information (PPI) has been reviewed by the Office of Drug Safety and Division of Drug Marketing and Communication. The clinical reviewer also has made additional revisions. The wording was simplified and made consistent with the PI. Promotional language and other unnecessary information was removed. The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. The Patient Prescribing Information is in the format recommended for all patient information. The proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI." The recommended changes are described in the line-by-line review as well as in the annotated, red-line copy of the Patient Prescribing Information.

#### Comments to Applicant

- 1) The comments regarding the labeling, both PI and PPI, and red-line WORD documents of the labeling should be forwarded to the sponsor, so that they can be discussed with the sponsor prior to the PDUFA goal date.
- 2) The Division of Medication Errors and Technical Support consult regarding the trade name *Avandaryl*<sup>TM</sup> should be forwarded to the sponsor.

## 8 APPENDICES

### Review of Individual Study Reports

The clinical efficacy data and the major safety findings for Studies 234 and 135 are reviewed in the Integrated Reviews of Efficacy and Safety (Sections 6 and 7). In this section, some of the sponsor's summary safety tables are included. The safety data in Studies 234 and 135 in this submission were consistent with the previously reported safety data for rosiglitazone and sulfonylurea combination therapy.

### Study 234

The sponsor's table below lists the treatment emergent adverse events for Study 234.

Table 19 Treatment emergent adverse events affecting more than one patient in any treatment group (all patients randomised)

Body System	Treatment Group		
	Placebo + GLI n (%)	RSG 4 mg + GLI n (%)	RSG 8 mg + GLI n (%)
<b>Any TEAE</b>	<b>27 (46.6)</b>	<b>24 (42.1)</b>	<b>27 (45.8)</b>
Respiratory system disorders	12 (20.7)	11 (19.3)	8 (13.6)
Body as a whole - general disorders	4 (6.9)	8 (14.0)	7 (11.9)
Musculo-skeletal system disorders	5 (8.6)	7 (12.3)	5 (8.5)
Gastrointestinal system disorders	6 (10.3)	4 (7.0)	6 (10.2)
Central & peripheral nervous system disorders	1 (1.7)	5 (8.8)	4 (6.8)
Metabolic and nutritional disorders	3 (5.2)	5 (8.8)	1 (1.7)
Skin and appendages disorders	3 (5.2)	2 (3.5)	4 (6.8)
Resistance mechanism disorders	3 (5.2)	3 (5.3)	2 (3.4)
Urinary system disorders	4 (6.9)	1 (1.8)	3 (5.1)
Psychiatric disorders	2 (3.4)	3 (5.3)	2 (3.4)
Secondary terms - events	0	1 (1.8)	6 (10.2)
Liver and biliary system disorders	1 (1.7)	2 (3.5)	2 (3.4)
Vision disorders	1 (1.7)	2 (3.5)	2 (3.4)
Neoplasms	1 (1.7)	1 (1.8)	2 (3.4)
Vascular disorders, extracardial	3 (5.2)	0	1 (1.7)
Cardiovascular disorders, general	2 (3.4)	0	0
Myo-, endo-, pericardial & valve disorders	1 (1.7)	0	1 (1.7)
Red blood cell disorders	1 (1.7)	0	1 (1.7)
White cell and RES disorders	0	1 (1.8)	1 (1.7)

Data Source: Section 13, Table 13.4.3

The serious adverse events in Study 234 are summarized in the sponsor's table below.

Table 20 Description of all serious adverse events

No. / Sex	DOB	SAE	Intensity	Relationship	Outcome
<b>non-randomised patients</b>					
2604 / f		stroke	severe	not related	resolved
1807 / m		hospitalisation due to cancer (rectal carcinoma)	severe	not related	death
3105 / f		facial paresis left	mild	not related	resolved
3115 / m		TIA	mild	not related	resolved
		exacerbation of COPD	moderate	not related	resolved
<b>RSG placebo</b>					
3502 / f		collapse	moderate	not related	resolved
3407 / m		suspicion of TIA	moderate	unlikely	resolved
		carotid stenosis	severe	not related	resolved
<b>RSG 4 mg</b>					
2704 / m		acute right upper abdominal pain	severe	suspected	resolved
1301 / m		vomiting - cholelithiasis	severe	not related	death
		swallowing problems	severe	unlikely	death
3603 / f		oesophageal cancer	severe	unlikely	death
		lumbar disc prolapse	severe	not related	ongoing

Data Source: Section 13, Table 13.4.5 and Appendix B.L7

### Study 135

**Title:** A 2-year, Randomized, Double-blind, Parallel Group Study to Compare the Efficacy, Safety and Tolerability of Rosiglitazone Versus Placebo in Combination with Glipizide in Elderly Patients with Type 2 Diabetes Mellitus who are Inadequately Controlled on Glipizide Therapy

**On-Therapy Adverse Events Reported by  $\geq 5\%$  of Patients in Any Treatment Group (All Randomized Patients)**

AEs by Preferred Term, n(%)	GLIP (N=111)	RSG+GLIP (N=116)	Total (N=227)
No. of patients with at least 1 event	104 (93.7)	111 (95.7)	215 (94.7)
Upper respiratory tract infection	49 (44.1)	40 (34.50)	89 (39.2)
Hypoglycemia	30 (27.0)	37 (31.9)	67 (29.5)
Injury	23 (20.7)	36 (31.0)	59 (26.0)
Edema <sup>a</sup>	10 (9.0)	31 (26.7)	41 (18.1)
Hyperlipemia	10 (9.0)	22 (19.0)	32 (14.1)
Hypercholesterolemia	7 (6.3)	21 (18.1)	28 (12.3)
Arthralgia	18 (16.2)	20 (17.2)	38 (16.7)
Pain	9 (8.1)	16 (13.8)	25 (11.0)
Sinusitis	12 (10.8)	16 (13.8)	28 (12.3)
Back pain	11 (9.9)	12 (10.3)	23 (10.1)
Fatigue	14 (12.6)	11 (9.5)	25 (11.0)
Hypertension aggravated	11 (9.9)	11 (9.5)	22 (9.7)
Infection viral	11 (9.9)	11 (9.5)	22 (9.7)
Weight increase	0	11 (9.5)	11 (4.8)
Abdominal pain	7 (6.3)	10 (8.6)	17 (7.5)
Anemia	6 (5.4)	10 (8.6)	16 (7.0)
Arthritis	9 (8.1)	10 (8.6)	19 (8.4)
Diarrhea	10 (9.0)	10 (8.6)	20 (8.8)
Hypertriglyceridemia	6 (5.4)	10 (8.6)	16 (7.0)
Nausea	5 (4.5)	10 (8.6)	15 (6.6)
Dyspepsia	5 (4.5)	9 (7.8)	14 (6.2)

Bronchitis	14 (12.6)	8 (6.9)	22 (9.7)
Dizziness	8 (7.2)	8 (6.9)	16 (7.0)
Vomiting	2 (1.8)	8 (6.9)	10 (4.4)
Hyperglycemia	20 (18.0)	7 (6.0)	27 (11.9)
Hypertension	3 (2.7)	7 (6.0)	10 (4.4)
Prostatic disorder	5 (4.5)	7 (6.0)	12 (5.3)
Constipation	6 (5.4)	6 (5.2)	12 (5.3)
Coughing	7 (6.3)	6 (5.2)	13 (5.7)
Headache	9 (8.1)	6 (5.2)	15 (6.6)
Myalgia	7 (6.3)	6 (5.2)	13 (5.7)
Rash	8 (7.2)	6 (5.2)	14 (6.2)
Urinary tract infection	11 (9.9)	6 (5.2)	17 (7.5)
Asthenia	8 (7.2)	4 (3.4)	12 (5.3)
Cataract	9 (8.1)	4 (3.4)	13 (5.7)
Insomnia	6 (5.4)	4 (3.4)	10 (4.4)
Paresthesia	9 (8.1)	3 (2.6)	12 (5.3)
Periodontitis	6(5.4)	2(1.7)	8(3.5)
Cellulitis	6(5.4)	1(0.9)	7(3.1)
Neuralgia	6(5.4)	1(0.9)	7(3.1)

**Title:** A 2-year, Randomized, Double-blind, Parallel Group Study to Compare the Efficacy, Safety and Tolerability of Rosiglitazone Versus Placebo in Combination with Glipizide in Elderly Patients with Type 2 Diabetes Mellitus who are Inadequately Controlled on Glipizide Therapy

<sup>a</sup> Includes edema dependent, edema generalized, edema legs and edema peripheral

**Serious Adverse Experiences:** There were six reported deaths. One patient died prior to receiving double-blind study medication, two patients died during the study or within 30 days after the last dose of study medication (GLIP treatment) and three patients died >30 days after the last dose of study medication (two patients, RSG+GLIP, one patient, GLIP). There were 49 patients with on-therapy serious non-fatal adverse experiences: 20 (17.2%) in the RSG+GLIP group and 29 (26.1%) in the GLIP group as listed in the table below.

**Summary of On-Therapy Serious Non-Fatal Adverse Events (All Randomized Patients)**

Serious AEs by Preferred Term, n(%)	GLIP (N=111)	RSG+GLIP (N=116)	Total (N=227)
No. of patients with at least 1 event	29 (26.1)	20 (17.2)	49 (21.6)
Coronary artery disorder	2 (1.8)	4 (3.4)	6 (2.6)
Angina pectoris	0	2 (1.7)	2 (0.9)
Arthritis aggravated	1 (0.9)	2 (1.7)	3 (1.3)
Cardiac failure	3 (2.7)	2 (1.7)	5 (2.2)
Myocardial infarction	3 (2.7)	2 (1.7)	5 (2.2)
Skin neoplasm malignant	0	2 (1.7)	2 (0.9)
Therapeutic response increased	0	2 (1.7)	2 (0.9)
Aneurysm	0	1 (0.9)	1 (0.4)
Arteritis	0	1 (0.9)	1 (0.4)
Basal cell carcinoma	3 (2.7)	1 (0.9)	4 (1.8)
Cellulitis	2 (1.8)	1 (0.9)	3 (1.3)

Cerebrovascular disorder	1 (0.9)	1 (0.9)	2 (0.9)
Chest pain	3 (2.7)	1 (0.9)	4 (1.8)
Hemorrhage NOS	1 (0.9)	1 (0.9)	2
Hypoglycemia	0	1 (0.9)	1 (0.4)
Larynx neoplasm malignant	1 (0.9)	1 (0.9)	2 (0.9)
Otitis media	0	1 (0.9)	1 (0.4)
Pharyngitis	0	1 (0.9)	1 (0.4)
Urinary incontinence	0	1 (0.9)	1 (0.4)
Urinary retention	0	1 (0.9)	1 (0.4)
Vascular disorder	2 (1.8)	1 (0.9)	3 (1.3)
Anemia	1 (0.9)	0	1 (0.4)
Angina pectoris aggravated	1 (0.9)	0	1 (0.4)
Carcinoma	2 (1.8)	0	2 (0.9)
Diverticulitis	1 (0.9)	0	1 (0.4)
Duodenal ulcer hemorrhagic	1 (0.9)	0	1 (0.4)
Fever	1 (0.9)	0	1 (0.4)
Fibrillation atrial	1 (0.9)	0	1 (0.4)
Injury	1 (0.9)	0	1 (0.4)
Pancreatitis	2 (1.8)	0	2 (0.9)
Paralysis	1 (0.9)	0	1 (0.4)
Peripheral ischemia	1 (0.9)	0	1 (0.4)
Pulmonary carcinoma	1 (0.9)	0	1 (0.4)

**ble 38 Patients with Fatal Adverse Events**

Patient Number	Treatment	Age (Yrs)	Sex (M/F)	Serious AE (Preferred Term)	Verbatim Term	Intensity
135.011.77414	Glipizide	69	M	Cardiac arrest	Cardiac arrest	Severe
135.012.77293	Glipizide	75	M	--	Atherosclerotic heart disease	--
135.015.77301	Glipizide <sup>3</sup>	75 <sup>2</sup>	F <sup>2</sup>	Myocardial infarction	Myocardial infarction	--
135.028.77339	RSG+GLIP	62	M	Cerebrovascular disorder	Stroke	Severe
135.034.76107	Glipizide	70	F	Myocardial infarction	Acute myocardial infarction	Severe
135.051.76219	RSG+GLIP	72	M	Myocardial infarction	Myocardial infarction	Moderate

1. Days from start of double-blind study medication
  2. Data Source: Patient's CRF
  3. Patient died during single-blind run-in phase
- Not available

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More patients experienced at least one on-therapy SAE in the GLIP group (26.1%) than in the RSG+GLIP group (17.2%). On-therapy, non-fatal SAEs are summarized by preferred term in Table 39 and a patient listing is presented in Table 40. Detailed patient narratives are provided in Section 16.

**Table 39 Summary of On-Therapy Serious Non-Fatal Adverse Events (All Randomized Patients)**

Serious AEs by Preferred Term, n (%)	Treatment Group		
	GLIP (n=111)	RSG+GLIP (n=116)	Total (n=227)
No. of patients with at least 1 event	29 (26.1)	20 (17.2)	49 (21.6)
Coronary artery disorder	2 (1.8)	4 (3.4)	6 (2.6)
Angina pectoris	0	2 (1.7)	2 (0.9)
Arthritis aggravated	1 (0.9)	2 (1.7)	3 (1.3)
Cardiac failure	3 (2.7)	2 (1.7)	5 (2.2)
Myocardial infarction	3 (2.7)	2 (1.7)	5 (2.2)
Skin neoplasm malignant	0	2 (1.7)	2 (0.9)
Therapeutic response increased	0	2 (1.7)	2 (0.9)
Aneurysm	0	1 (0.9)	1 (0.4)
Arteritis	0	1 (0.9)	1 (0.4)
Basal cell carcinoma	3 (2.7)	1 (0.9)	4 (1.8)
Cellulitis	2 (1.8)	1 (0.9)	3 (1.3)
Cerebrovascular disorder	1 (0.9)	1 (0.9)	2 (0.9)
Chest pain	3 (2.7) <sup>1</sup>	1 (0.9)	4 (1.8)
Hemorrhage NOS	1		(0.9)
Hypoglycemia	0	1 (0.9)	1 (0.4)
Larynx neoplasm malignant	1 (0.9)	1 (0.9)	2 (0.9)
Otitis media	0	1 (0.9)	1 (0.4)
Pharyngitis	0	1 (0.9)	1 (0.4)
Urinary incontinence	0	1 (0.9)	1 (0.4)
Urinary retention	0	1 (0.9)	1 (0.4)
Vascular disorder	2 (1.8)	1 (0.9)	3 (1.3)
Anemia	1 (0.9)	0	1 (0.4)
Angina pectoris aggravated	1 (0.9)	0	1 (0.4)
Carcinoma	2 (1.8)	0	2 (0.9)
Diverticulitiis	1 (0.9)	0	1 (0.4)
Duodenal ulcer hemorrhagic	1 (0.9)	0	1 (0.4)
Fever	1 (0.9)	0	1 (0.4)
Fibrillation atrial	1 (0.9)	0	1 (0.4)
Injury	1 (0.9)	0	1 (0.4)
Pancreatitis	2 (1.8)	0	2 (0.9)
Paralysis	1 (0.9)	0	1 (0.4)
Peripheral ischemia	1 (0.9)	0	1 (0.4)
Pulmonary carcinoma	1 (0.9)	0	1 (0.4)
Sialoadentitis	1 (0.9)	0	1 (0.4)
Skin ulceration	1 (0.9)	0	1 (0.4)
Tachycardia ventricular	1 (0.9)	0	1 (0.4)
Thrombophlebitis deep	1 (0.9)	0	1 (0.4)

1. For one of these patients, the final diagnosis was gastroesophageal reflux disease, however, the SAE was not updated to reflect this.

Data Source: Section 15, Table 15.2.3.

**Table 41 Summary of Patient Withdrawals Due to On-Therapy Adverse Events (All Randomized Patients)**

AEs by Preferred Term, n (%)	Treatment Group		Total (n=227)
	GLIP (n=111)	RSG+GLIP (n=116)	
No. of patients with at least one event	8 (7.2)	11 (9.5)	19 (8.4)
Cellulitis	1 (0.9)	0	1 (0.4)
Edema <sup>1</sup>	0	2 (1.7)	2 (0.9)
Injury	1 (0.9)	0	1 (0.4)
Cardiac failure	1 (0.9)	2 (1.7)	3 (1.3)
Dyspepsia	1 (0.9)	0 (0.0)	1 (0.4)
Cardiac arrest	1 (0.9)	0	1 (0.4)
Weight increase	0	1 (0.9)	1 (0.4)
Myocardial infarction	1 (0.9)	1 (0.9)	2 (0.9)
Carcinoma	1 (0.9)	0	1 (0.4)
Pulmonary carcinoma	1 (0.9)	0	1 (0.4)
Dementia	0	1 (0.9)	1 (0.4)
Dermatitis lichenoid	0	1 (0.9)	1 (0.4)
Rash	0	1 (0.9)	1 (0.4)
Arteritis	0	1 (0.9)	1 (0.4)
Cerebrovascular disorder	0	1 (0.9)	1 (0.4)
Hemorrhage NOS <sup>2</sup>	0	1 (0.9)	1 (0.4)

1. Includes edema, edema dependent, edema generalized, edema legs and edema peripheral

2. NOS = not otherwise specified

Data Source: Section 15, Table 15.5.

## 9.1 Line-by-Line Labeling Review

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Marre M, Howlett H, Lehert P, Allavoine T. Improved glycemic control with metformin-glibenclamide combined tablet therapy (Glucovance ®) in Type 2 diabetic patients inadequately controlled on metformin. *Diabetic Medicine* 2002; 19:673-680

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8/20/04 08:08:57 PM  
MEDICAL OFFICER

David Orloff  
8/27/04 05:29:17 PM  
MEDICAL OFFICER  
concur.

# MEDICAL OFFICER REVIEW

## Filing Review

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #:NDA 21-700

Sponsor:GSK

Pharmaceutical:Hypoglycemic agent

Category:Combination drug product

Indication:Treatment of type 2 diabetes mellitus

Application Type:commercial

Proprietary Name:Avandryl

Route of Administration:oral

Generic Name & Dosage:Rosiglitazone maleate/  
Glimipiride rablet

4 mg/ 1, 2, 4 mg

Reviewer:Joanna K. Zawadzki, M.D.

Date Review Completed: 12/23/03

Chemistry Reviewer:

Pharmacology Reviewer:

Biopharmaceutics Reviewer: Jayabharati Vaidyanathan,  
Ph.D.

Statistical Reviewer:

Project Manager: Lina Aljuburi

### REVIEW SUMMARY:

Avandryl is a combination of two antidiabetic drugs, rosiglitazone maleate (R) and glimepiride (G) in a fixed dose combination (4 mg R with 1, 2, and 4 mg G). Combination therapy with rosiglitazone and sulfonylureas is approved for the treatment of DM2. A pre-NDA meeting was held on 6/2/03. The sponsor has submitted four clinical pharmacology studies for evaluation of dose proportionality, bioequivalence, food effect, dose interaction, and three controlled clinical studies – add-on studies of rosiglitazone to glipizide (2-year) (BRL 049653/135), rosiglitazone (4 or 8 mg) to glimepiride (3 mg) (26 weeks) (BRL 049653/234), and glimepiride (titration of 2 to 4 or 8 mg) to rosiglitazone (4 to 8mg) (Aventis –HOE 490/4034). The proposed indication is for the treatment of patients previously treated with a thiazolidinedione and/or sulfonylureas. This approach appears acceptable for approval of a second line indication, pending review of the NDA. It is based primarily on bioequivalence, as the clinical study (BRL 49653/234) evaluated submaximal dose of glimepiride (3 mg), combination therapy of glimepiride 3mg and rosiglitazone placebo, 4 mg, and 8mg rather than the to-be-marketed fixed dose combinations, and no separate rosiglitazone arm. The NDA can be filed.

### OUTSTANDING ISSUES:

See fileability checklist and comments from the biopharmaceutical team.

For study BRL 49653/234, bookmarking is not routinely accessible in the study report. Study narratives for serious adverse events should be provided. Please review with CTD team at FDA and then with sponsor.

### RECOMMENDED REGULATORY ACTION:

NDA, Efficacy/Label supplement:Fileable -yes

N drive location:

SIGNATURES:

Medical Reviewer: Joanna K. Zawadzki, M.D.

Date: 12/23/03

Medical Team Leader: \_\_\_\_\_ Date: \_\_\_\_\_

**45 DAY MEETING CHECKLIST**  
**NDA 21-700**

**FILEABILITY:**

On ini

**CLINICAL:**

- (1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin? yes
- (2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin? yes
- (3) On its face, is the clinical section of the NDA legible so that substantive review can begin? yes
- (4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Dose proportionality study of combination tablet is submitted.
- (5) On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Of the three supportive clinical studies submitted, the most relevant study is a submaximal dose of glimepiride (3 mg) and does not include a rosiglitazone arm. The primary emphasis of the NDA review is bioequivalence. This approach appears acceptable for approval of a second line indication, pending review of the NDA. It is based primarily on bioequivalence, as the clinical study (BRL 49653/234) evaluated submaximal dose of glimepiride (3 mg), combination therapy of glimepiride 3mg and rosiglitazone placebo, 4 mg, and 8mg rather than the to-be-marketed fixed dose combinations, and no separate rosiglitazone arm.
- (6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling? See response to #5.
- (7) Are all data sets for pivotal efficacy studies complete for all indications requested? See above.
- (8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed

draft labeling? See above.

- (9) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?

The bookmarking in study BRL 49653/234 is not always accessible.

- (10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the US population?

- (11) Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division? Case record forms for serious adverse events are submitted.

- (12) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?  
yes

- (13) Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product? yes

- (14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?  
yes

- (15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? As per the biopharm review.

- (16) From a clinical perspective, is this NDA fileable? If 'no', please state below why it is not. Yes

Joanna K. Zawadzki, M.D.  
Reviewing Medical Officer

David G. Orloff, M.D.  
Diabetes Team Leader  
Director, Division of Metabolic and Endocrine Drug Products

## NDA 21-700 Filing Review –Listing of titles of biopharmaceutical and clinical studies

Study #	Study Title
001	A dose proportionality study with a combination tablet formulation of rosiglitazone and glimepiride (4mg/1mg; or 4 mg/2mg; or 4 mg/mg) in healthy subjects)
002	A bioequivalence study with a combination tablet formulation of rosiglitazone and glimepiride 94mg/4 mg) compared to concomitant dosing of rosiglitazone 4 mg and glimepiride 4 mg (4mg +4mg) commercial tablets in healthy subjects
003	A study to assess the effect of food on pharmacokinetics of a rosiglitazone 4 mg and glimepiride 4 mg combination tablet formulation and to compare the pharmacokinetics of rosiglitazone 4 mg and glimepiride 4 mg combination tablet to concomitant dosing of rosiglitazone 4 mg and glimepiride 4 mg commercial tablets in the fed state in healthy subjects.
340	A study to estimate the effect of repeat oral doses of rosiglitazone (8mg) on the pharmacokinetics of glimepiride (4 mg) and the effect of a single oral dose of glimepiride (4 mg) on the pharmacokinetics of rosiglitazone (8mg) in healthy subjects

In addition in vitro dissolution method and results have also been provided. The dissolution was done using one pH condition, 12 units and 1 lot. Sponsor needs to submit dissolution profiles in 3 different conditions, using 3 lots (12 units/lot) in each test condition.

The above recommendation and summary is excerpted from the biopharmaceutical review.

### Clinical Studies

#### Study BRL 049653/135 (North America)

**Title:** A 2-year, Randomized, Double-blind, Parallel Group Study to Compare the Efficacy, Safety and Tolerability of Rosiglitazone Versus Placebo in Combination with Glipizide in Elderly Patients (N=357 randomized, age > 60) with Type 2 Diabetes Mellitus who are Inadequately Controlled on Glipizide Therapy

#### Study BRL 49653/234 (Germany)

**Title:** A 26-week, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of rosiglitazone in combination with glimepiride (3 mg) compared to glimepiride alone in patients with type 2 diabetes mellitus (N=174 randomized).

This clinical study is the most relevant.

The clinical study (BRL 49653/234) evaluated submaximal dose of glimepiride (3 mg), combination therapy of glimepiride 3mg and rosiglitazone placebo, 4 mg, and 8mg rather than the to-be-marketed fixed dose combinations, and no separate rosiglitazone arm.

#### Study HOE 490/4034 (Aventis)

A 26-week double-blind, placebo-controlled, parallel group study to evaluate the role of Amaryl®(glimepiride)(forced titration 1-8 mg) in improving the control of patients previously treated with Avandia® (rosiglitazone) (4-8 mg) as monotherapy (n=41)

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MEDICAL OFFICER