

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-071/S014

21-410/S009

Trade Name: Avandia Tablets
Avandamet Tablets

Generic Name: (rosiglitazone maleate)
(rosiglitazone maleate and metformin hydrochloride)

Sponsor: SM Pharmco Puerto Rico, Inc

Approval Date: January 4, 2005

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-071/S014

21-410/S009

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-071/S-014

NDA 21-410/S-009

SM Pharmco Puerto Rico, Inc. (d/b/a GlaxoSmithKline)
Attention: Willa B. Phyll, Ph.D.
Director, U.S. Regulatory Affairs
One Franklin Plaza; P.O. Box 7929
Philadelphia, PA 19101-7929

Dear Dr. Phyll:

Please refer to your supplemental new drug applications dated July 28, 2004, received July 29, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

NDA 21-071 (Avandia) for supplement 014;
NDA 21-410 (Avandamet) for supplement 009.

We acknowledge receipt of your submissions dated November 22, and December 13, 2004.

These "Changes Being Effected in 30 days" supplemental new drug applications provide for revisions to the **CLINICAL PHARMACOLOGY** section, **PRECAUTIONS** section, **Drug Interactions** subsection, and **ADVERSE REACTIONS** section of the package insert labels. Editorial changes were also implemented.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling texts.

The final printed labeling (FPL) must be identical to the labeling submitted (text for the package insert) on December 13, 2004, to NDA 21-071/S-014, and November 22, 2004, to NDA 21-410/S-009.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format - Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper.

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NDA 21-410/S-009

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Approval of these submissions by FDA is not required before the labeling is used.

If you issue a letter communicating important information about these drug products (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II Center for Drug Evaluation

Enclosure (package insert label for
NDA 21-071 and NDA 21-410)

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

/s/

David Orloff

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-071/S014

21-410/S009

LABELING

AV:LX
PRESCRIBING INFORMATION

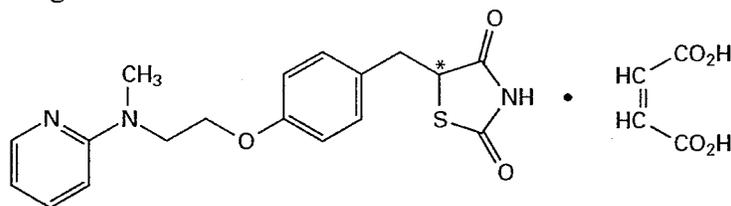
AVANDIA[®]
(rosiglitazone maleate)
Tablets

DESCRIPTION

AVANDIA (rosiglitazone maleate) is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. AVANDIA is used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). AVANDIA improves glycemic control while reducing circulating insulin levels.

Pharmacological studies in animal models indicate that rosiglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors.

Chemically, 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). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the enantiomers are functionally indistinguishable. The structural formula of rosiglitazone maleate is:



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

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

CLINICAL PHARMACOLOGY

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

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

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

Pharmacokinetics and Drug Metabolism: Maximum plasma concentration (C_{max}) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range (see Table 1). The elimination half-life is 3 to 4 hours and is independent of dose.

Table 1. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral Doses (N = 32)

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

*CL/F = Oral clearance.

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

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

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

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

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

Population Pharmacokinetics in Patients with Type 2 Diabetes: Population pharmacokinetic analyses from 3 large clinical trials including 642 men and 405 women with type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume of distribution (V_{ss}/F) were shown to increase with increases in body weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted CL/F and V_{ss}/F values varied by <1.7-fold and <2.3-fold, respectively. Additionally, rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about 15%) in female patients.

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

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

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

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

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

Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal) at baseline (see PRECAUTIONS, General, *Hepatic Effects*).

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

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

Drug Interactions:

Drugs that Inhibit, Induce, or are Metabolized by Cytochrome P₄₅₀: In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P₄₅₀ enzymes at clinically relevant concentrations. In vitro data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9.

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

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

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

Glyburide: AVANDIA (2 mg twice daily) taken concomitantly with glyburide (3.75 to 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy.

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

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

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

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

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

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

CLINICAL STUDIES

In clinical studies, treatment with AVANDIA resulted in an improvement in glycemic control, as measured by fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c), with a concurrent reduction in insulin and C-peptide. Postprandial glucose and insulin were also reduced. This is consistent with the mechanism of action of AVANDIA as an insulin sensitizer. The improvement in glycemic control was durable, with maintenance of effect for 52 weeks. The maximum recommended daily dose is 8 mg. Dose-ranging studies suggested that no additional benefit was obtained with a total daily dose of 12 mg.

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

Patients with lipid abnormalities were not excluded from clinical trials of AVANDIA. In all 26-week controlled trials, across the recommended dose range, AVANDIA as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids. These changes were statistically significantly different from placebo or glyburide controls (see Table 2).

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

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

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

Table 2. Summary of Mean Lipid Changes in 26-Week Placebo-Controlled and 52-Week Glyburide-Controlled Monotherapy Studies

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

*Once daily and twice daily dosing groups were combined.

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

Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes with inadequate glycemic control (mean baseline FPG approximately 228 mg/dL and mean baseline HbA1c 8.9%), were conducted. Treatment with AVANDIA produced statistically significant improvements in FPG and HbA1c compared to baseline and relative to placebo (see Table 3).

Table 3. Glycemic Parameters in Two 26-Week Placebo-Controlled Trials

Study A	Placebo	AVANDIA 2 mg twice daily		AVANDIA 4 mg twice daily	
N	158	166		169	
FPG (mg/dL)					
Baseline (mean)	229	227		220	
Change from baseline (mean)	19	-38		-54	
Difference from placebo (adjusted mean)	–	-58*		-76*	
Responders (≥ 30 mg/dL decrease from baseline)	16%	54%		64%	
HbA1c (%)					
Baseline (mean)	9.0	9.0		8.8	
Change from baseline (mean)	0.9	-0.3		-0.6	
Difference from placebo (adjusted mean)	–	-1.2*		-1.5*	
Responders ($\geq 0.7\%$ decrease from baseline)	6%	40%		42%	
		AVANDIA		AVANDIA	
Study B	Placebo	4 mg once daily	2 mg twice daily	8 mg once daily	4 mg twice daily
N	173	180	186	181	187
FPG (mg/dL)					
Baseline (mean)	225	229	225	228	228
Change from baseline (mean)	8	-25	-35	-42	-55
Difference from placebo (adjusted mean)	–	-31*	-43*	-49*	-62*
Responders (≥ 30 mg/dL decrease from baseline)	19%	45%	54%	58%	70%
HbA1c (%)					
Baseline (mean)	8.9	8.9	8.9	8.9	9.0
Change from baseline (mean)	0.8	0.0	-0.1	-0.3	-0.7
Difference from placebo (adjusted mean)	–	-0.8*	-0.9*	-1.1*	-1.5*
Responders ($\geq 0.7\%$ decrease from baseline)	9%	28%	29%	39%	54%

* <0.0001 compared to placebo.

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

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

The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a statistically significant improvement in glycemic control from baseline (see Figure 1 and Figure 2). At the end of week 52, the reduction from baseline in FPG and HbA1c was -40.8 mg/dL and -0.53% with AVANDIA 4 mg twice daily; -25.4 mg/dL and -0.27% with AVANDIA 2 mg twice daily; and -30.0 mg/dL and -0.72% with glyburide. For HbA1c, the difference between AVANDIA 4 mg twice daily and glyburide was not statistically significant at week 52. The initial fall in FPG with glyburide was greater than with AVANDIA; however, this effect was less durable over time. The improvement in glycemic control seen with AVANDIA 4 mg twice daily at week 26 was maintained through week 52 of the study.

Figure 1. Mean FPG Over Time in a 52-Week Glyburide-Controlled Study

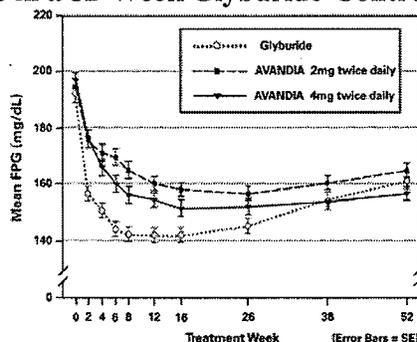
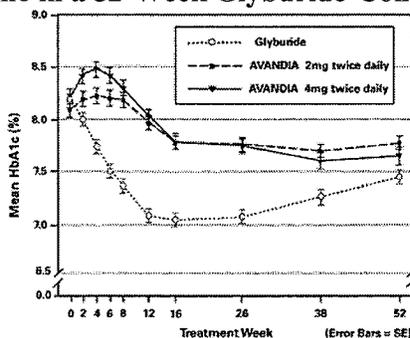


Figure 2. Mean HbA1c Over Time in a 52-Week Glyburide-Controlled Study



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

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

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

Table 4. Glycemic Parameters in a 26-Week Combination Study

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

* <0.0001 compared to metformin.

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

Patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin and who were switched to monotherapy with AVANDIA demonstrated loss of glycemic control, as evidenced by increases in FPG and HbA1c. In this group, increases in LDL and VLDL were also seen. **Combination With a Sulfonylurea:** A total of 1,216 patients with type 2 diabetes participated in three 26-week randomized, double-blind, placebo/active-controlled studies designed to assess the efficacy and safety of AVANDIA in combination with a sulfonylurea. AVANDIA 2 mg or 4 mg daily, was administered either once daily or in divided doses twice daily, to patients inadequately controlled on a sulfonylurea.

In the two placebo-controlled studies, patients inadequately controlled on sulfonylureas that were randomized to single dose or divided doses of AVANDIA 4 mg daily plus a sulfonylurea showed significantly reduced FPG and HbA1c compared to sulfonylurea plus placebo (see Table 5).

Table 5. Glycemic Parameters in Two 26-Week Combination Studies

Study C (patients on prior sulfonylurea monotherapy)	Sulfonylurea	AVANDIA 2 mg twice daily + sulfonylurea
N	192	183
FPG (mg/dL)		
Baseline (mean)	207	205
Change from baseline (mean)	+6	-38
Difference from sulfonylurea alone (adjusted mean)	-	-44*
Responders (≥ 30 mg/dL decrease from baseline)	21%	56%
HbA1c (%)		
Baseline (mean)	9.2	9.2
Change from baseline (mean)	+0.2	-0.9
Difference from sulfonylurea alone (adjusted mean)	-	-1.0*
Study D (patients on prior single or multiple therapies)	Sulfonylurea	AVANDIA 4 mg once daily + sulfonylurea
N	115	116
FPG (mg/dL)		
Baseline (mean)	209	214
Change from baseline (mean)	+23	-25
Difference from sulfonylurea alone (adjusted mean)	-	-47*
Responders (≥ 30 mg/dL decrease from baseline)	13%	46%
HbA1c (%)		
Baseline (mean)	8.9	9.1
Change from baseline (mean)	+0.6	-0.3
Difference from sulfonylurea alone (adjusted mean)	-	-0.9*

* ≤ 0.0001 compared to sulfonylurea plus placebo.

In the third study, including patients on prior single or multiple therapies, in patients inadequately controlled on the maximal dose of glyburide (20 mg daily), 2 mg of AVANDIA twice daily plus sulfonylurea significantly reduced FPG (n = 98, mean change from baseline of -31 mg/dL) and HbA1c (mean change from baseline of -0.5%) compared to sulfonylurea plus placebo (n = 99, mean change from baseline of FPG of +24 mg/dL and of HbA1c of +0.9%). The combination of sulfonylurea and AVANDIA resulted in lower levels of FPG and HbA1c than either agent alone. Patients who were switched from maximal dose of glyburide to 2 mg of AVANDIA twice daily as monotherapy demonstrated loss of glycemic control, as evidenced by increases in FPG and HbA1c.

Combination With Insulin: In two 26-week randomized, double-blind, fixed-dose studies designed to assess the efficacy and safety of AVANDIA in combination with insulin, patients inadequately controlled on insulin (65 to 76 units/day, mean range at baseline) were randomized to receive AVANDIA 4 mg plus insulin (n = 206) or placebo plus insulin (n = 203). The mean duration of disease in these patients was 12 to 13 years.

Compared to insulin plus placebo, single or divided doses of AVANDIA 4 mg daily plus insulin significantly reduced FPG (mean reduction of 32 to 40 mg/dL) and HbA1c (mean reduction of 0.6% to 0.7%). Approximately 40% of all patients treated with AVANDIA reduced their insulin dose.

INDICATIONS AND USAGE

AVANDIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. AVANDIA is indicated as monotherapy. AVANDIA is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet, exercise, and a single agent do not result in adequate glycemic control. For patients inadequately controlled with a maximum dose of a sulfonylurea or metformin, AVANDIA should be added to, rather than substituted for, a sulfonylurea or metformin.

Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but also in maintaining the efficacy of drug therapy. Prior to initiation of therapy with AVANDIA, secondary causes of poor glycemic control, e.g., infection, should be investigated and treated.

CONTRAINDICATIONS

AVANDIA is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS

Cardiac Failure and Other Cardiac Effects: AVANDIA, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. In combination with insulin, thiazolidinediones may also increase the risk of other cardiovascular adverse events. AVANDIA should be discontinued if any deterioration in cardiac status occurs.

Patients with New York Heart Association (NYHA) Class 3 and 4 cardiac status were not studied during the clinical trials. AVANDIA is not recommended in patients with NYHA Class 3 and 4 cardiac status.

In three 26-week trials in patients with type 2 diabetes, 216 received 4 mg of AVANDIA plus insulin, 322 received 8 mg of AVANDIA plus insulin, and 338 received insulin alone. These trials included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. In these clinical studies an increased incidence of edema, cardiac failure, and other cardiovascular adverse events was seen in patients on AVANDIA and insulin combination therapy compared to insulin and placebo. Patients who experienced cardiovascular events were on average older and had a longer duration of diabetes. These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of AVANDIA. In this population, however, it was not possible to determine specific risk factors that could be used to identify all patients at risk of heart failure and other cardiovascular events on combination therapy.

Three of 10 patients who developed cardiac failure on combination therapy during the double-blind part of the fixed-dose studies had no known prior evidence of congestive heart failure, or pre-existing cardiac condition.

In a double-blind study in type 2 diabetes patients with chronic renal failure (112 received 4 mg or 8 mg of AVANDIA plus insulin and 108 received insulin control), there was no difference in cardiovascular adverse events with AVANDIA in combination with insulin compared to insulin control.

Patients treated with combination AVANDIA and insulin should be monitored for cardiovascular adverse events. This combination therapy should be discontinued in patients who do not respond as manifested by a reduction in HbA1c or insulin dose after 4 to 5 months of therapy or who develop any significant adverse events. (See ADVERSE REACTIONS.)

PRECAUTIONS

General: Due to its mechanism of action, AVANDIA is active only in the presence of endogenous insulin. Therefore, AVANDIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

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

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

Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, AVANDIA should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure (see WARNINGS, Cardiac Failure and Other Cardiac Effects and PRECAUTIONS, Information for Patients).

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

Weight Gain: Dose-related weight gain was seen with AVANDIA alone and in combination with other hypoglycemic agents (see Table 6). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

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

Table 6. Weight Changes (kg) From Baseline During Clinical Trials With AVANDIA

	Duration	Control Group		AVANDIA 4 mg	AVANDIA 8 mg
			Median (25 th , 75 th percentile)	Median (25 th , 75 th percentile)	Median (25 th , 75 th percentile)
Monotherapy	26 weeks	placebo	-0.9 (-2.8, 0.9)	1.0 (-0.9, 3.6)	3.1 (1.1, 5.8)
	52 weeks	sulfonylurea	2.0 (0, 4.0)	2.0 (-0.6, 4.0)	2.6 (0, 5.3)
Combination therapy					
sulfonylurea	26 weeks	sulfonylurea	0 (-1.3, 1.2)	1.8 (0, 3.1)	–
metformin	26 weeks	metformin	-1.4 (-3.2, 0.2)	0.8 (-1.0, 2.6)	2.1 (0, 4.3)
insulin	26 weeks	insulin	0.9 (-0.5, 2.7)	4.1 (1.4, 6.3)	5.4 (3.4, 7.3)

Hematologic: Across all controlled clinical studies, decreases in hemoglobin and hematocrit (mean decreases in individual studies ≤ 1.0 gram/dL and $\leq 3.3\%$, respectively) were observed for AVANDIA alone and in combination with other hypoglycemic agents. The changes occurred primarily during the first 3 months following initiation of therapy with AVANDIA or following a dose increase in AVANDIA. White blood cell counts also decreased slightly in patients treated with AVANDIA. The observed changes may be related to the increased plasma volume observed with treatment with AVANDIA and may be dose related (see ADVERSE REACTIONS, Laboratory Abnormalities, *Hematologic*).

Ovulation: Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDIA (see PRECAUTIONS, Pregnancy, *Pregnancy Category C*). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known.

Although hormonal imbalance has been seen in preclinical studies (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility), the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with AVANDIA should be reviewed.

Hepatic Effects: Another drug of the thiazolidinedione class, troglitazone, was associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death were reported during clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations in liver enzymes (ALT $>3X$ upper limit of normal) compared to placebo. Very rare cases of reversible jaundice were also reported.

In pre-approval clinical studies in 4,598 patients treated with AVANDIA, encompassing approximately 3,600 patient years of exposure, there was no signal of drug-induced hepatotoxicity or elevation of ALT levels. In the pre-approval controlled trials, 0.2% of patients treated with AVANDIA had elevations in ALT $>3X$ the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with AVANDIA were reversible and were not clearly causally related to therapy with AVANDIA.

In postmarketing experience with AVANDIA, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established. Rosiglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death during clinical use. Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with AVANDIA undergo periodic monitoring of liver enzymes.

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

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

There are no data available from clinical trials to evaluate the safety of AVANDIA in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone.

AVANDIA should not be used in patients who experienced jaundice while taking troglitazone.

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

Liver enzyme monitoring is recommended prior to initiation of therapy with AVANDIA in all patients and periodically thereafter (see PRECAUTIONS, General, *Hepatic Effects* and ADVERSE REACTIONS, Laboratory Abnormalities, *Serum Transaminase Levels*).

Information for Patients: Patients should be informed of the following: Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but in maintaining the efficacy of drug therapy.

It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. Patients should be advised that it can take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see full effect. Patients should be informed that blood will be drawn to check their liver function prior to the start of therapy and periodically thereafter per the clinical judgement of the healthcare professional. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician. Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on AVANDIA should immediately report these symptoms to their physician.

AVANDIA can be taken with or without meals.

When using AVANDIA in combination with other hypoglycemic agents, the risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDIA (see PRECAUTIONS, Pregnancy, *Pregnancy Category C*). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known.

Drug Interactions: An inhibitor of CYP2C8 (such as gemfibrozil) may increase the AUC of rosiglitazone and an inducer of CYP2C8 (such as rifampin) may decrease the AUC of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response. (See CLINICAL PHARMACOLOGY, Drug Interactions)

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

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

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

Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

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

Pregnancy: Pregnancy Category C: There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose.

There are no adequate and well-controlled studies in pregnant women. AVANDIA should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible.

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

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

Pediatric Use: The safety and effectiveness of AVANDIA in pediatric patients have not been established.

Geriatric Use: Results of the population pharmacokinetic analysis showed that age does not significantly affect the pharmacokinetics of rosiglitazone (see CLINICAL PHARMACOLOGY, Special Populations). Therefore, no dosage adjustments are required for the elderly. In controlled clinical trials, no overall differences in safety and effectiveness between older (≥ 65 years) and younger (< 65 years) patients were observed.

ADVERSE REACTIONS

In clinical trials, approximately 4,600 patients with type 2 diabetes have been treated with AVANDIA; 3,300 patients were treated for 6 months or longer and 2,000 patients were treated for 12 months or longer.

Trials of AVANDIA as Monotherapy and in Combination With Other Hypoglycemic Agents: The incidence and types of adverse events reported in clinical trials of AVANDIA as monotherapy are shown in Table 7.

Table 7. Adverse Events (≥5% in Any Treatment Group) Reported by Patients in Double-blind Clinical Trials With AVANDIA as Monotherapy

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

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

There were a small number of patients treated with AVANDIA who had adverse events of anemia and edema. Overall, these events were generally mild to moderate in severity and usually did not require discontinuation of treatment with AVANDIA.

In double-blind studies, anemia was reported in 1.9% of patients receiving AVANDIA compared to 0.7% on placebo, 0.6% on sulfonylureas, and 2.2% on metformin. Edema was reported in 4.8% of patients receiving AVANDIA compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. Overall, the types of adverse experiences reported when AVANDIA was used in combination with a sulfonylurea or metformin were similar to those during monotherapy with AVANDIA. Reports of anemia (7.1%) were greater in patients treated with a combination of AVANDIA and metformin compared to monotherapy with AVANDIA or in combination with a sulfonylurea.

Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anemia in these studies (see ADVERSE REACTIONS, Laboratory Abnormalities, *Hematologic*).

In 26-week double-blind, fixed-dose studies, edema was reported with higher frequency in the AVANDIA plus insulin combination trials (insulin, 5.4%; and AVANDIA in combination with insulin, 14.7%). Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with AVANDIA (see WARNINGS, Cardiac Failure and Other Cardiac Effects).

In postmarketing experience with AVANDIA, adverse events potentially related to volume expansion (e.g., congestive heart failure, pulmonary edema, and pleural effusions) have been reported.

Hypoglycemia was the most frequently reported adverse event in the fixed-dose insulin combination trials, although few patients withdrew for hypoglycemia (4 of 408 for AVANDIA plus insulin and 1 of 203 for insulin alone). Rates of hypoglycemia, confirmed by capillary blood glucose concentration ≤50 mg/dL, were 6% for insulin alone and 12% (4 mg) and 14% (8 mg) for insulin in combination with AVANDIA.

In postmarketing experience with AVANDIA, angioedema and urticaria have been reported rarely.

Laboratory Abnormalities: Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in patients treated with AVANDIA (mean decreases in individual studies up to 1.0 gram/dL hemoglobin and up to 3.3% hematocrit). The time course and magnitude of decreases were similar in patients treated with a combination of AVANDIA and other hypoglycemic agents or AVANDIA monotherapy. Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin combination studies and may have contributed to the higher reporting rate of anemia. White blood cell counts also decreased slightly in patients treated with AVANDIA. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with AVANDIA.

Lipids: Changes in serum lipids have been observed following treatment with AVANDIA (see CLINICAL STUDIES).

Serum Transaminase Levels: In clinical studies in 4,598 patients treated with AVANDIA encompassing approximately 3,600 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevated ALT levels.

In controlled trials, 0.2% of patients treated with AVANDIA had reversible elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. Hyperbilirubinemia was found in 0.3% of patients treated with AVANDIA compared with 0.9% treated with placebo and 1% in patients treated with active comparators.

In the clinical program including long-term, open-label experience, the rate per 100 patient years exposure of ALT increase to >3X the upper limit of normal was 0.35 for patients treated with AVANDIA, 0.59 for placebo-treated patients, and 0.78 for patients treated with active comparator agents.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. In postmarketing experience with AVANDIA, reports of hepatic enzyme elevations 3 or more times the upper limit of normal and hepatitis have been received (see PRECAUTIONS, General, *Hepatic Effects*).

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

The management of antidiabetic therapy should be individualized. AVANDIA may be administered either at a starting dose of 4 mg as a single daily dose or divided and administered in the morning and evening. For patients who respond inadequately following 8 to 12 weeks of treatment, as determined by reduction in FPG, the dose may be increased to 8 mg daily as monotherapy or in combination with metformin. Reductions in glycemic parameters by dose and regimen are described under CLINICAL STUDIES. AVANDIA may be taken with or without food.

Monotherapy: The usual starting dose of AVANDIA is 4 mg administered either as a single dose once daily or in divided doses twice daily. In clinical trials, the 4 mg twice daily regimen resulted in the greatest reduction in FPG and HbA1c.

Combination Therapy: When AVANDIA is added to existing therapy, the current dose of a sulfonylurea, metformin, or insulin can be continued upon initiation of AVANDIA therapy.

Sulfonylurea: When used in combination with sulfonylurea, the recommended dose of AVANDIA is 4 mg administered as either a single dose once daily or in divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin: The usual starting dose of AVANDIA in combination with metformin is 4 mg administered as either a single dose once daily or in divided doses twice daily. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with AVANDIA.

Insulin: For patients stabilized on insulin, the insulin dose should be continued upon initiation of therapy with AVANDIA. AVANDIA should be dosed at 4 mg daily. Doses of AVANDIA greater than 4 mg daily in combination with insulin are not currently indicated. It is recommended that the insulin dose be decreased by 10% to 25% if the patient reports hypoglycemia or if FPG concentrations decrease to less than 100 mg/dL. Further adjustments should be individualized based on glucose-lowering response.

Maximum Recommended Dose: The dose of AVANDIA should not exceed 8 mg daily, as a single dose or divided twice daily. The 8 mg daily dose has been shown to be safe and effective in clinical studies as monotherapy and in combination with metformin. Doses of AVANDIA greater than 4 mg daily in combination with a sulfonylurea have not been studied in adequate and well-controlled clinical trials. Doses of AVANDIA greater than 4 mg daily in combination with insulin are not currently indicated.

AVANDIA may be taken with or without food.

No dosage adjustments are required for the elderly.

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

Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy) (see PRECAUTIONS, General, *Hepatic Effects* and CLINICAL PHARMACOLOGY, Special Populations, *Hepatic Impairment*). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with AVANDIA and periodically thereafter (see PRECAUTIONS, General, *Hepatic Effects*).

There are no data on the use of AVANDIA in patients younger than 18 years; therefore, use of AVANDIA in pediatric patients is not recommended.

HOW SUPPLIED

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

2 mg bottles of 30: NDC 0029-3158-13

2 mg bottles of 60: NDC 0029-3158-18

2 mg bottles of 100: NDC 0029-3158-20

2 mg bottles of 500: NDC 0029-3158-25

2 mg SUP 100s: NDC 0029-3158-21

NDA 21-071/S-014

NDA 21-410/S-009

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4 mg bottles of 30: NDC 0029-3159-13
4 mg bottles of 60: NDC 0029-3159-18
4 mg bottles of 100: NDC 0029-3159-20
4 mg bottles of 500: NDC 0029-3159-25
4 mg SUP 100s: NDC 0029-3159-21

8 mg bottles of 30: NDC 0029-3160-13
8 mg bottles of 100: NDC 0029-3160-20
8 mg bottles of 500: NDC 0029-3160-25
8 mg SUP 100s: NDC 0029-3160-21

STORAGE

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

REFERENCE

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



GlaxoSmithKline

GlaxoSmithKline
Research Triangle Park, NC 27709

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Month, Year

AV:LX

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-071/S014

21-410/S009

MEDICAL REVIEW(S)

MEDICAL OFFICER LABELING REVIEW

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

Application #: NDA 21-071/S-014 Electronic submission Sponsor: GlaxoSmithKline Pharmaceutical: 3031400 Category: oral antidiabetic drug Indication: Treatment of Type 2 Diabetes Mellitus Reviewer: Joanna K. Zawadzki, M.D.	Application Type: commercial Proprietary Name: Avandia (rosiglitazone maleate) Route of Administration: oral Dosage: 2, 4, 8 mg tablets Date Review Completed: August 3, 2004
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REVIEW SUMMARY:

The sponsor has submitted labeling revisions as CBE's (changes being effected) to the *AVANDIA* (rosiglitazone maleate) PRECAUTIONS section on 7/28/04, including the final printed label, for labeling changes that will be implemented on the sponsor's website within one week and in Packaging Operations in 6 months. The proposed labeling changes include the following:

- (1) Revisions to PRECAUTIONS, Drug Interactions subsection, regarding interactions of rosiglitazone with gemfibrozil (pharmacologic study) and rifampin (cited published reference), describing P450(CYP)2c8 inhibition and induction, respectively. Question for clinical pharmacology: is a published reference adequate for inclusion in the label, if the data have not been reviewed here?
- (2) Addition of PRECAUTIONS, Pediatric Use and Geriatric subsections;
- (3) Addition of postmarketing reports of angioedema and urticaria under ADVERSE EVENTS.

The revisions are discussed further in the text. Clinical pharmacology comments regarding (1) and postmarketing (Office of Drug Safety) comments regarding (3) are pending. This reviewer notes that the CBE revisions are acceptable.

OUTSTANDING ISSUES:

Clinical pharmacology and postmarketing reviews are pending.

RECOMMENDED REGULATORY ACTION:

New clinical studies _____	Clinical Hold _____	Study May Proceed _____
NDA, Efficacy/Label supplement: _____	Approvable _____	Not Approvable _____
<input checked="" type="checkbox"/> Approve		

N drive location:

SIGNATURES:	Medical Reviewer: <u>Joanna K. Zawadzki, M.D.</u>	Date: 8/3/04 _____
	Medical Team Leader: David G. Orloff, M.D. And Division Director	Date: _____

Supportive Data for Labeling Revisions in the Prescribing Information (AV:L11)

The sponsor has submitted labeling revisions as CBE's (changes being effected) to the *AVANDIA* (rosiglitazone maleate) PRECAUTIONS section on 7/28/04, including the final printed label, for labeling changes that will be implemented on the sponsor's website within one week and in Packaging Operations in 6 months. The proposed labeling changes include the following:

- (1) Revisions to PRECAUTIONS, Drug Interactions subsection, regarding interactions of rosiglitazone with gemfibrozil (pharmacologic study) and rifampin (cited published reference), describing P450(CYP)2c8 inhibition and induction, respectively. Question for clinical pharmacology: is a published reference adequate for inclusion in the label, if the data have not been reviewed here?

“Drug Interactions: *Drugs Metabolized by Cytochrome P₄₅₀*: In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P₄₅₀ enzymes at clinically relevant concentrations. In vitro data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9. An inhibitor of CYP2C8 (such as gemfibrozil) may decrease the metabolism of rosiglitazone and an inducer of CYP2C8 (such as rifampin) may increase the metabolism of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response.”

Gemfibrozil: Concomitant administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone AUC by 2 fold, compared to the administration of rosiglitazone (4 mg once daily) alone. Given the potential for dose-related adverse events with rosiglitazone, a decrease in the dose of rosiglitazone may be needed when gemfibrozil is introduced.

The highlighted [blue] sections have been added on the basis of a clinical pharmacology study (for gemfibrozil) and a published reference (for rifampin). A Phase 1 Clinical Study BRL-049653/902, an open-label study to evaluate safety, tolerability, and pharmacokinetics of rosiglitazone when co-administered with gemfibrozil in 14 healthy adult subjects, was conducted 1/5/04 – 2/12/04. Rosiglitazone 4mg QD was administered by mouth (*per os*, PO) on days 1 through 7 in the first treatment, there was a 7-day washout, and gemfibrozil 600mg BID was administered PO on Days 3 through 7 and rosiglitazone 4mg QD was administered PO in addition to the gemfibrozil, from Days 1 through 7 in the second treatment. Terminal phase half-life of rosiglitazone 4mg was between 2.21 and 4.86 hours and increased to 5.63 and 11.91 hours after repeat-dose gemfibrozil 600mg bid. “Based on AUC(0-∞) of rosiglitazone 4mg QD, there was an average increase of 127% following 7 days of concomitant administration of repeat-dose gemfibrozil 600mg and rosiglitazone 4mg. For AUC(0-∞), the 90% confidence interval of the ratio gemfibrozil 600mg + rosiglitazone 4mg: rosiglitazone 4mg lies completely outside of the equivalence range (0.80 to 1.25) indicating an effect of gemfibrozil on AUC(0-∞) of rosiglitazone.” “Conclusions: Administration of repeat-dose gemfibrozil 600 mg with concomitant rosiglitazone 4 mg for 7 days resulted in a 2.27-fold and 1.16-fold increase on Day 7 rosiglitazone AUC and C_{max}, respectively. Rosiglitazone t_{1/2} was increased approximately 2-fold.”

The summary of the rifampin study is excerpted below.

Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects

Ji-Young Park, MD, PhD, Kyoung-Ah Kim, PhD, Mun-Ho Kang, MD, PhD, Su-Lyun Kim, BS, and Jae-Gook Shin, MD, PhD *Incheon and Busan, Korea*

Background and Objective: Rifampin (INN, rifampicin) causes several drug interactions with coadministered antidiabetic drugs. Rosiglitazone is a novel thiazolidinedione antidiabetic drug, but little is known about the drug interaction between rifampin and rosiglitazone. Our objective was to investigate the effect of rifampin on the pharmacokinetics of rosiglitazone in humans. **Method:** In an open-label, randomized, 2-way crossover study, 10 healthy Korean male subjects were treated once daily for 6 days with 600 mg rifampin or with placebo. On day 7, a single dose of 8 mg rosiglitazone was administered orally. Plasma rosiglitazone concentrations were measured. **Results:** Rifampin significantly decreased the mean area under the plasma concentration–time curve for rosiglitazone by 65% (2947.9 ng · h/mL versus 991.5 ng · h/mL, $P < .001$) and the mean elimination half-life from 3.9 to 1.5 hours ($P < .001$). The peak plasma concentration of rosiglitazone was significantly decreased by rifampin (537.7 ng/mL versus 362.3 ng/mL, $P < .01$). The apparent oral clearance of rosiglitazone increased about 3-fold after rifampin treatment (2.8 L/h versus 8.5 L/h, $P < .001$).

Conclusion: This study showed that rifampin affected the disposition of rosiglitazone in humans, probably by the induction of cytochrome P450 (CYP) 2C8 and, to a lesser extent, CYP2C9. Therefore caution should be exercised during the coadministration of rifampin and rosiglitazone. (*Clin Pharmacol Ther* 2004;75: 157-62.)

(2) Addition of PRECAUTIONS, Pediatric Use and Geriatric subsections;

Pediatric Use: The safety and effectiveness of AVANDIA in pediatric patients have not been established.
Geriatric Use: Results of the population pharmacokinetic analysis showed that age does not significantly affect the pharmacokinetics of rosiglitazone (see CLINICAL PHARMACOLOGY, Special Populations). Therefore, no dosage adjustments are required for the elderly. In controlled clinical trials, no overall differences in safety and effectiveness between older (≥ 65 years) and younger (< 65 years) patients were observed.

These comments were previously under CLINICAL PHARMACOLOGY/Special Populations.

(3) Addition of postmarketing reports of angioedema and urticaria under ADVERSE EVENTS.

In postmarketing experience with AVANDIA, angioedema and urticaria have been reported rarely.

To support this addition, the sponsor has submitted a report, which includes the cv of the author, Margaret O. Sowell, MD, PhD. The sponsor estimates that the marketed exposure to rosiglitazone is 4,406,027 patient years (from launch to 8/03, IMS data) and approximately 47,900 patients have received rosiglitazone in clinical trials or

postmarketing studies. For the MedDRA terms angioedema, urticaria, and terms suggestive of hypersensitivity-type reactions, 375 reports were noted in the world-wide database, with 80 cases reported as either anaphylaxis, angioedema, and/or urticaria. Of the 375 reports, 105 were identified as key cases, and 16 of the key cases were identified as pivotal. In addition, one pivotal case was identified in clinical trial data, out of 23 reports. The reporting rate for angioedema/urticaria is considered very rare according to CIOMS III guidelines (<0.01% or <1/10,000).

The clinical trial report is quoted below:

A0347738A: A 27-year-old female in a phase I open-label study experienced an urticarial rash within 24 hours after the second dose of study medication (7 days after the first dose). The rash cleared within 6 hours. Twenty-one days after the first dose of the study medication, the patient received a third dose of rosiglitazone. Several hours later, the patient developed a rash (positive rechallenge). The event resolved the following day. No confounding history or concurrent medications are noted.

The pivotal postmarketing cases are summarized in the sponsor's tables below:

Case Id; Age; Gender; Country	Adverse Events	TTO	Outcome	Concurrent Drugs	Comment
A0380506A 62 Y; Female USA	Angioneurotic oedema, itching, oropharyngeal swelling, face swelling, rash	Same day	Positive rechallenge	glipizide, loratadine, aspirin, conjugated estrogen + medroxyprogesterone, valdecoxib	Started aspirin on the same day as the initial event. Worsening of symptoms when RSG resumed three days later. Not a medically verified report.
A0385806A 50 - 59 Y; Female; USA	Anaphylactic reaction	Several Weeks	Positive rechallenge	metformin, glibenclamide	No event while on RSG 4 mg for several weeks. Experienced events (swelling of lips and tightness in chest) after RSG increased to 8 mg. Positive rechallenge with 1/4 tablet of RSG administered by MD. Not a medically verified report.
B0287405A 46 Y; Female; Netherlands	Urticaria, pruritus	9 Days	Positive rechallenge	glimepiride	Glimepiride continued and event resolved. RSG restarted (unknown date) and events recurred (unknown dates). Nonserious case. Not a medically verified report.
A0324748A 49 Y; Female; USA	Anaphylactic reaction, dyspnoea, erythema, swollen tongue, urticaria	8 hours	Resolved	Not specified.	History of hypersensitivity -allergies to #2 dye, codeine, aspirin, PCN, tape, amitriptyline and wool. Treated in ER with atropine, fluid and "shots". Diagnosed as having a severe anaphylactic reaction. Patient was not admitted to hospital. RN from MD's office thought reaction may have been related to allergy to #2 red dye.
A0388380A 65 Y; Male; USA	Urticaria	10 Days	Resolved	allopurinol, HCTZ, sildonafile, aspirin	History of dermatological hypersensitivity reactions. Co-suspect medications included rampiril 5 mg. Rash did not resolve until after RSG arm of trial was discontinued. Rash did NOT reoccur when rampiril was restarted.

Case Id; Age; Gender; Country	Adverse Events	TTO	Outcome	Concurrent Drugs	Comment
A0412287A 43 Y; Female; USA	Anaphylactic reaction	1 Days	Resolved	lisinopril, acetraline	Suspect medication rosiglitazone-metformin. History of rash due to pioglitazone. Start date of lisinopril unknown. Diagnosed in ER with drug-reaction anaphylaxis (throat and tongue swelling).
B0246354A 65 Y; Male; UK	Angioneurotic oedema	2 weeks	Resolved	Not specified.	Patient was unable to breath or talk with swollen tongue and lips. He was admitted to ICU. Treatment included cefuroxime, IV chlorpheniramine, hydrocortisone and nebulised salbutamol.
B0250417A 43 Y; Male; UK	Urticaria	2 days	Resolved	metformin, gliclazide	Rec'd from Regulatory Authority. Acute urticaria noted to be incapacitating and disabling.
B0262631A 79 Y; Female; Switzerland	Exanthema (face), eyelid oedema	4 Hours	Resolved	metformin, gliclazide, ACE inhibitor (not specified)	Nonserious case. Four hours after first dose of RSG, patient developed exanthema of face and swelling of her eyelids.
B0302693A 54 Y; Female; France	Pharyngeal oedema; headache, itching, respiratory difficulties	4 Days	Resolved	lytacand, urapidil, amlodipine, metformin, clopidogrel, naproxen, pevasatin	Unspecified history of allergies. RSG discontinued and the event resolved 2 days later. Naproxen was discontinued 7 days after the events had completely resolved.
B0307414A 79 Y; Female; France	Angioneurotic oedema, itching	Same day.	Resolved	amlodipine, fenofibrate, paracetamol	Nonserious case. Patient experienced left hemiface angioedema and moderate itching. RSG discontinued and the events resolved the same day.

Case Id; Age; Gender; Country	Adverse Events	TTO	Outcome	Concurrent Drugs	Comment
B0309310A 72 Y; Male; UK	Lip swelling	2 Days	Resolved	lisinopril, metformin, bendroflumazide, gliclazide	- Rec'd from Regulatory Authority. Patient was on other medication "for years" without incident.
B0309810A 56 Y; Female; France	Angioneurotic oedema	1 day	Resolved	repaglinide, glimepiride	- Nonserious case. Within 24 hours of first dose of RSG, patient experienced giant urticaria (angioedema) and itching.
B0309856A 53 Y; Female; France	Angioneurotic oedema (Quinke's edema with suffocation feeling, infiltration of face and pharyngeal discomfort)	8 days	Resolved	pevasatin, aspegic, thyroxine	- Allergies to penicillin and cephalosporin. Co-suspect medication of glibenclamide which the patient had been on for approximately 5 years at the time of the event.
B0312746A 53 Y; Male; UK	Angioneurotic oedema (throat swelling and pain)	Same day	Resolved	fluoxetine, ramipril, aspirin, gliclazide	- Rec'd from Regulatory Authority. Unknown therapy dates for ramipril and aspirin.
B0314150A 44 Y; Female; Netherlands	Angioneurotic oedema, itching	1 Day	Resolved	human short-acting insulin, rosuvastatin, flvoxamine, omeprazole	- Rec'd from Regulatory Authority. One day after the first dose of RSG, the patient experienced angioedema of tongue and throat with excessive itching all over the body.

Reviewer's Comments

There are other drugs, including ace inhibitors and aspirin, in some of these reports that may also contribute to angioedema. The relation of rosiglitazone dose and the symptoms and timing of the associated symptoms and the positive rechallenges support the association of rosiglitazone and angioedema and urticaria and the proposed labeling. Pending clinical pharmacology comments regarding change (1) and postmarketing

(Office of Drug Safety) comments regarding change (3), the proposed CBE revisions are acceptable.

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/s/

Joanna Zawadzki
8/4/04 10:15:07 AM
MEDICAL OFFICER

David Orloff
8/27/04 05:24:22 PM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-071/S014

21-410/S009

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA:	21-071-S014
Submission Date(s):	July 28, 2004
Brand Name:	Avandia / Avandamet
Generic Name:	Rosiglitazone maleate
Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Hae-Young Ahn, Ph.D.
OCPB Division:	DPE-2
ORM division:	DMEDP
Sponsor:	GlaxoSmithKline
Relevant IND(s):	
Submission Type:	Supplement for CBE, labeling
Formulation:	Oral tablets
Indication:	Treatment of Type 2 Diabetes Mellitus

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-2) reviewed the supplement and finds it acceptable provided by labeling agreement. This recommendation and labeling comments should be sent to the sponsor as appropriate.

1.2 Phase IV Commitments

N/A

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The effect of gemfibrozil on rosiglitazone PK was evaluated in an open-label, non-randomized, 2-period, fixed-sequence study in healthy adult subjects (n=14; female=4, male=10).

Rosiglitazone 4mg was administered once a day (QD) at approximately 8AM from Day 1 through Day 7 during dosing period 1. Gemfibrozil 600mg BID was administered from Day -3 through Day 7 and rosiglitazone 4mg QD was administered from Day 1 through Day 7 during dosing period 2. Pharmacokinetics of rosiglitazone was estimated on Day 1, 2, and 4 through 8 during both dosing periods.

Results were summarized in the following tables.

Table 1 Summary of rosiglitazone PK parameters: geometric mean (95% CI)

Day 1						
Treatment	N	C _{max} (ng/mL)	T _{max} ^a (hr)	AUC(0-τ) (ng·hr/mL)	AUC(0-∞) (ng·hr/mL)	t _{1/2} (hr)
Rosiglitazone 4mg QD	13	315 (278, 358)	0.50 (0.50 - 2.00)	1356 (1188, 1550)	1376 ^a (1177, 1609)	3.51 ^b (2.98, 4.14)
Gemfibrozil 600mg BID + Rosiglitazone 4mg QD	13	283 (246, 328)	1.00 (1.00 - 3.00)	2599 (2246, 3007)	3087 ^a (2527, 3771)	8.13 ^c (7.09, 9.33)
Day 7						
Treatment	N	C _{max} (ng/mL)	T _{max} ^a (hr)	AUC(0-τ) (ng·hr/mL)		t _{1/2} (hr)
Rosiglitazone 4mg QD	13	287 (251, 316)	0.50 (0.48 - 3.00)	1271 (1089, 1482)		3.73 ^d (3.04, 4.57)
Gemfibrozil 600mg BID + Rosiglitazone 4mg QD	13	334 (299, 373)	1.00 (0.50 - 3.00)	2887 (2359, 3534)		7.38 ^d (6.37, 8.56)

a. presented as median (range)
 b. N = 11
 c. N = 12
 d. N = 10

Table 2 Summary of statistical analyses on PK results

Rosiglitazone	Comparison	Point Estimate	90% CI	CVw%
Day 7				
AUC(0-τ) ^a	B:A	2.27	(2.09, 2.48)	13.01
C _{max} ^a	B:A	1.16	(1.04, 1.30)	16.86
t _{1/2} ^a	B:A	1.99	(1.76, 2.26)	17.22
T _{max} ^b (h)	B:A	0.25	(0.00, 0.50)	
Day 1				
AUC(0-∞) ^a	B:A	2.24	(2.01, 2.51)	14.44
C _{max} ^a	B:A	0.90	(0.85, 1.00)	16.86
t _{1/2} ^a	B:A	2.29	(2.02, 2.58)	17.22
T _{max} ^b (h)	B:A	0.50	(0.25, 0.75)	
CI=confidence interval a. Represents the ratio of geometric means between regimens. b. Represents the median difference between regimens. Regimen A=Rosiglitazone 4mg QD Regimen B=Gemfibrozil 600mg BID + rosiglitazone 4mg QD				

Gemfibrozil increased exposure of rosiglitazone by 124% for AUC on Day 1. Individual exposure changes were summarized in the following figures and it appeared to be no atypical trends except the effect of gemfibrozil. Rosiglitazone AUC change by gemfibrozil was similar between Day 1 (2.24-fold increase) and Day 7 (2.27-fold increase), and the results indicate that there was no significant effect of gemfibrozil on accumulation of rosiglitazone.

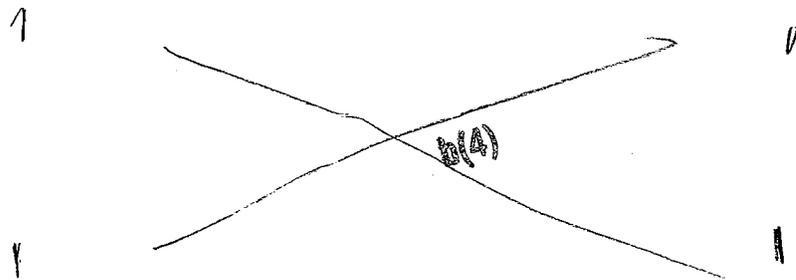


Figure 1 Individual stick plot for rosiglitazone AUC for Day 7 (left panel) and Day 1 (right panel)

In addition, the sponsor proposed a general statement in PRECAUTION for effect of rifampin, a metabolic enzyme inducer, on rosiglitazone based on the following publication:

Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects, Park *et al.*,
Clin. Pharmacol. Ther. 75:157-162, 2004

Removed

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2 Labeling Comments

It is recommended to move the description of Drug Interactions from PRECAUTION to CLINICAL PHARMACOLGY. In addition, study results of rifampin effect on rosiglitazone exposure are recommended to include in Drug Interactions as follow:

(~~Strikethrough text~~ is recommended to be deleted and underlined text is recommended to be added.)

CLINICAL PHARMACOLOGY

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

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

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

Pharmacokinetics and Drug Metabolism: Maximum plasma concentration (C_{max}) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range (see Table 1). The elimination half-life is 3 to 4 hours and is independent of dose.

Table 1. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral Doses (N = 32)

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

CL/F = Oral clearance.

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

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

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

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

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

Population Pharmacokinetics in Patients with Type 2 Diabetes: Population pharmacokinetic analyses from 3 large clinical trials including 642 men and 405 women with type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume of distribution (V_{ss}/F) were shown to increase with increases in body weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted CL/F and V_{ss}/F values varied by <1.7-fold and <2.3-fold, respectively. Additionally, rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about 15%) in female patients.

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

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

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

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

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

Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal) at baseline (see PRECAUTIONS, General, *Hepatic Effects*).

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

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

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

Drug Interactions: Drugs Metabolized by Cytochrome P₄₅₀: In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P₄₅₀ enzymes at clinically relevant concentrations. In vitro data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9.

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

Glyburide: AVANDIA (2 mg twice daily) taken concomitantly with glyburide (3.75 to 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy.

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

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

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

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

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

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

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

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

Reviewer's comment: The study results for the effect of rifampin on rosiglitazone are from a well controlled clinical study and thus it is recommended to update the results in labeling. The results were based on Korean subjects. However, there was no ethnic difference in rosiglitazone PK according to the labeling and thus the results seem to be acceptable for labeling.

PRECAUTIONS

~~**Drug Interactions: Drugs Metabolized by Cytochrome P₄₅₀:** In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P₄₅₀ enzymes at clinically relevant concentrations. In vitro data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9. An inhibitor of CYP2C8 (such as gemfibrozil) may~~

~~decrease the metabolism increase the exposure of rosiglitazone and an inducer of CYP2C8 (such as rifampin) may increase the metabolism decrease the exposure of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response.~~

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

~~**Glyburide:** AVANDIA (2 mg twice daily) taken concomitantly with glyburide (3.75 to 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy.~~

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

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

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

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

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

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

~~**Gemfibrozil:** Concomitant administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone AUC by 2 fold, compared to the administration of rosiglitazone (4 mg once daily) alone. Given the potential for dose-related adverse events with rosiglitazone, a decrease in the dose of rosiglitazone may be needed when gemfibrozil is introduced.~~

Attachment starts here.

3 Appendix

3.1 Study Synopsis (BRL-049653/902)

CONFIDENTIAL

RM2004/00079/00
BRL-049653/902

Synopsis

Document Number: RM2004/00079/00 Study Number: BRL-049653/902

Title: An Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Rosiglitazone when Co-administered with Gemfibrozil in Healthy Adult Subjects	
Investigator(s): 1 investigator in the US received IRB approval to enroll subjects in the study.	
Study center(s): 1 investigational site in the US received study drug for participation in the study.	
Publication(s): None	
Study period: 05 January 2004 - 12 February 2004	Phase of Development: 1
<p>Objectives: The primary objective of the study was to evaluate the effect of repeat oral doses of gemfibrozil on the pharmacokinetics of repeat oral doses of rosiglitazone. The secondary objectives were to evaluate the effect of repeat oral doses of gemfibrozil on the pharmacokinetics of a single oral dose of rosiglitazone and assess the safety and tolerability of concomitant oral dosing of rosiglitazone and gemfibrozil.</p> <p>If at any time it appeared there was potential variability in rosiglitazone response or handling in the study, the following objectives were to be investigated (assuming sample number was adequate and the availability of genotyping assays): relationship between genetic variants and the pharmacokinetics, safety and/or tolerability, and efficacy of the investigational product.</p>	
<p>Methodology: This was an open-label, non-randomized, 2-period, fixed-sequence study in 14 healthy adult subjects. The duration of study participation from screening to follow-up was approximately 8 weeks. Each subject participated in 2 dose periods, separated by a 7 to 10 day washout period. In Dose Period 1, subjects received rosiglitazone alone for Days 1 through 7. In Dose Period 2, following gemfibrozil pre-treatment for 3 days, subjects received concomitant rosiglitazone treatment for Days 1 through 7. Pharmacokinetic measurements were obtained on Days 1, 2, and 4 through 8 during both dose periods.</p>	
<p>Number of subjects: A total of 14 subjects were enrolled in the study. Of which, 13 completed all study sessions and provided evaluable pharmacokinetic data for inclusion in the statistical analyses.</p>	
<p>Diagnosis and main criteria for inclusion: The population selected for this study was comprised of 14 healthy male and female subjects aged 18 to 60 years who were free of Hepatitis B antigen, Hepatitis C antibody and human immunodeficiency virus antibody, and were not taking any prescription or over the counter medications or herbal supplements within 1 week prior to dosing.</p>	

Title: An Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Rosiglitazone when Co-administered with Gemfibrozil in Healthy Adult Subjects

Treatment administration: Subjects received oral doses of rosiglitazone (4mg once a day [*quoque die*, QD]) and gemfibrozil (600mg twice a day [*bis in die*, BID]) during the study. During both dose periods, study drug was administered in a fasted state on Days 1 and 7; study drug was administered on Days 2 through 6 without regard to food intake. The description and order of treatments administered were as follows:

Dose Period 1, Treatment A: rosiglitazone 4mg QD was administered by mouth (*per os*, PO) at approximately 8AM from Days 1 through 7.

Dose Period 2, Treatment B: gemfibrozil 600mg BID was administered PO at approximately 8AM and 8PM from Days -3 through 7 AND rosiglitazone 4mg QD was administered PO at approximately 8AM, in addition to the gemfibrozil, from Days 1 through 7.

Criteria for evaluation:

Pharmacokinetics: During each dose period, pharmacokinetic samples were collected according to the following schedule.

- Pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours post-dose, from approximately 8AM on Day 1 through 8AM on Day 2
- Pre-dose on Days 4 through 6
- Pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours post-dose, from approximately 8AM on Day 7 through 8AM on Day 8

The planned pharmacokinetic analysis included full pharmacokinetic profiles of rosiglitazone on Days 1 and 7; trough rosiglitazone measurements on Days 4 through 6; and gemfibrozil measurements at 2 and 4 hours post-dose on Day 7 of Dose Period 2. The following parameters were log_e-transformed prior to formal statistical analysis: AUC(0- τ), AUC(0- ∞), C_{max}, and t_{1/2} of rosiglitazone.

Pharmacogenetics: If at any time it appeared there was potential variability in rosiglitazone response or handling in the study, the relationship between genetic variants and the pharmacokinetics, safety and/or tolerability, and efficacy of the investigational product were to be investigated.

Safety and Tolerability: Safety assessments were based on medical review of adverse event reports; the results of vital sign and electrocardiogram measurements; clinical laboratory test results; and physical examination findings.

Statistical methods: The target sample size was 14 subjects. Sample size calculations were based on pooled within-subject estimates of variability (CV_w%) across Clinical Pharmacology studies in the rosiglitazone drug development program in normal healthy volunteers (16.0% for AUC, 21.7% for C_{max}). Based on the largest of the within-subject estimates of variability (21.7% for C_{max}) and a sample size of 14 subjects, it was estimated that the precision for the lower and upper bounds of the 90% confidence intervals for the ratios of the comparisons of interest was no more than 15% of the observed point estimate.

Title: An Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Rosiglitazone when Co-administered with Gemfibrozil in Healthy Adult Subjects

After \log_e -transformation, AUC(0- τ), Cmax, and t1/2 of rosiglitazone were separately analyzed by analysis of variance (ANOVA) with terms for subject, regimen, and day (regimen). Point estimates and associated 90% confidence intervals for the difference (B minus A) on Day 7 and Day 1 were constructed using the appropriate error term. These point estimates and confidence intervals were then exponentially backtransformed to obtain point estimates and 90% confidence intervals for the ratio B:A on Day 7 and Day 1.

After \log_e -transformation, AUC(0- ∞) (Day 1) of rosiglitazone was analyzed by analysis of variance (ANOVA) with terms for subject and regimen. The point estimate and associated 90% confidence interval for the difference (B minus A) on Day 1 was constructed using the appropriate error term. This point estimate and confidence interval was then exponentially backtransformed to obtain a point estimate and 90% confidence interval for the ratio B:A on Day 1.

Distributional assumptions underlying the statistical analyses were assessed by visual inspection of residual plots. Normality was examined by normal probability plots, while homogeneity of variance was assessed by plotting the studentised residuals against the predicted values for the model. Estimates of within-subject variability for AUC(0- τ), AUC(0- ∞), and Cmax of rosiglitazone also were provided.

Tmax was analyzed nonparametrically using the Wilcoxon's Matched Pairs Method. The point estimates and 90% confidence intervals for the median differences were calculated for the difference (B minus A) for Day 7 and Day 1.

Descriptive statistics (n, arithmetic mean and corresponding 95% confidence interval, standard deviation [SD], median, minimum and maximum, and CVb%) were calculated for all pharmacokinetic endpoints by regimen. For tmax, CVb% also was calculated for each regimen.

For AUC(0- τ), AUC(0- ∞), Cmax, and t1/2, geometric means and between-subject CVs (CVb[%]) were calculated for each regimen as follows. Corresponding 95% confidence intervals for the geometric means also were produced.

Descriptive statistics of the rosiglitazone trough concentration data (N, arithmetic mean, standard deviation, median, minimum and maximum) were calculated by regimen, where appropriate. For rosiglitazone, trough concentration samples were obtained on Days 4 through 6 of each dose period. For gemfibrozil, descriptive statistics were presented for concentration data from Day 7 of Dose Period 2.

Subject demographics (including age, gender, ethnic origin, height, and weight) and adverse events were summarized. Extent of exposure, vital sign measurements, physical examination findings, and serious adverse events were listed by subject.

Title: An Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Rosiglitazone when Co-administered with Gemfibrozil in Healthy Adult Subjects

Summary: A total of 14 subjects received study drug (10 [71.4%] males and 4 [28.6%] females) and ranged in age from 21 to 59 years with a mean of 38 years. Mean height and weight were 175.0cm and 82.4kg, respectively. Caucasian was the predominant ethnic origin comprising 92.9% of the population.

Pharmacokinetics: On Day 1, the following results were observed:

- Terminal phase half-life of rosiglitazone 4mg was between 2.21 and 4.86 hours; while the terminal phase half-life of rosiglitazone after repeat-dose gemfibrozil 600mg was between 5.63 and 11.91 hours. Estimates of percent of the area under the concentration-time curve extrapolated to infinity (% extrapolated) were generally less than 20%; although generally higher after the concomitant administration of repeat-dose gemfibrozil 600mg and rosiglitazone 4mg.
- Based on AUC(0-∞) of rosiglitazone 4mg, there was an average increase of 124% when administered after repeat dosing of gemfibrozil 600mg. For AUC(0-∞), the 90% confidence interval of the ratio gemfibrozil 600mg + rosiglitazone 4mg : rosiglitazone 4mg lies completely outside of the equivalence range (0.80 to 1.25) indicating an effect of gemfibrozil on AUC(0-∞) of rosiglitazone following a single dose.
- Based on Cmax of rosiglitazone 4mg, there was an average decrease of 10% when administered after repeat dosing of gemfibrozil 600mg. For Cmax, the 90% confidence interval of the ratio gemfibrozil 600mg + rosiglitazone 4mg : rosiglitazone 4mg lies within the equivalence range (0.80 to 1.25) indicating no effect of gemfibrozil on Cmax of rosiglitazone.

On Day 7, the following results were observed:

- Maximum rosiglitazone concentrations were observed between 0.48 and 3 hours after dosing, following 7 days of oral administration of rosiglitazone 4mg and concomitant administration of repeat-dose gemfibrozil 600mg and rosiglitazone 4mg. Thereafter, plasma concentrations decreased in a monoexponential manner.
- Terminal phase half-life of rosiglitazone 4mg was between 2.18 and 7.38 hours; while the terminal phase half-life of rosiglitazone after 7 days of concomitant administration of repeat-dose gemfibrozil 600mg and rosiglitazone 4mg was between 4.80 and 9.63 hours.
- Based on AUC(0-r) of rosiglitazone 4mg QD, there was an average increase of 127% following 7 days of concomitant administration of repeat-dose gemfibrozil 600mg and rosiglitazone 4mg. For AUC(0-r), the 90% confidence interval of the ratio gemfibrozil 600mg + rosiglitazone 4mg : rosiglitazone 4mg lies completely outside of the equivalence range (0.80 to 1.25) indicating an effect of gemfibrozil on AUC(0-r) of rosiglitazone.

Title: An Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Rosiglitazone when Co-administered with Gemfibrozil in Healthy Adult Subjects

- Based on C_{max} of rosiglitazone 4mg, there was an average increase of 16% following 7 days of concomitant administration of repeat-dose gemfibrozil 600mg and rosiglitazone 4mg. For C_{max}, the 90% confidence interval of the ratio gemfibrozil 600mg + rosiglitazone 4mg: rosiglitazone 4mg was not entirely contained within the equivalence range (0.80 to 1.25) indicating an effect of gemfibrozil on C_{max} of rosiglitazone.
- Following 7 days of concomitant administration of repeat-dose gemfibrozil 600mg and rosiglitazone 4mg, rosiglitazone t_{1/2} approximately doubled, while T_{max} was increased by less than 1 hour.

Pharmacogenetics: No variability in rosiglitazone response or handling was observed during the study. Therefore, no pharmacogenetic analysis was performed.

Safety:

- Each treatment was well tolerated with few adverse events after each treatment. A single subject withdrew due to an adverse event of moderate urticaria reported following 4 days of rosiglitazone treatment; the event was considered by the investigator to be unrelated to rosiglitazone.
- Headache and somnolence were the most common adverse events among the 3 treatment regimens.
- All adverse events were considered to be of mild or moderate intensity and all adverse events resolved.
- Most adverse events were considered unrelated to study drug.
- No hypoglycemia occurred.
- No serious adverse events or deaths were reported.

Conclusions: Administration of repeat-dose gemfibrozil 600 mg with concomitant rosiglitazone 4 mg for 7 days resulted in a 2.27-fold and 1.16-fold increase on Day 7 rosiglitazone AUC and C_{max}, respectively. Rosiglitazone t_{1/2} was increased approximately 2-fold.

All treatments were generally well tolerated in these healthy subjects with few AEs after each treatment. All AEs were considered to be of mild or moderate intensity and all AEs resolved. No serious adverse events or deaths occurred during the study. A single subject withdrew due to an adverse event of moderate urticaria following 4 days of rosiglitazone treatment; the event was considered by the investigator to be unrelated to rosiglitazone. One subject was reported with AEs of increased ALT and AST, with peak ALT and AST <2 fold ULN following treatment with rosiglitazone and gemfibrozil, resolving 1 week after treatment cessation. No hypoglycemia was noted.

Date of Report: June 2004

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*See, Effect of rifampin on the pharmacokinetics of
rosiglitazone in healthy subjects, Park et.al, Clin. Pharmacol.
Ther. 75:157-162, 2004.*

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/s/

Sang Chung
8/11/04 04:56:28 PM
PHARMACOLOGIST

Hae-Young Ahn
8/12/04 10:34:31 AM
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-071/S014

21-410/S009

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-071/S-014

SB Pharmco Puerto Rico, Inc. (d/b/a GlaxoSmithKline)
Attention: Margaret M. Kreider, Ph.D.
Director, US Regulatory Affairs
One Franklin Plaza; 200 North 16th Street FP-1005
Philadelphia, PA 19102

Dear Dr. Kreider:

We acknowledge receipt of your February 21, 2005, submission containing final printed labeling in response to our January 4, 2005, letter approving your supplemental new drug application for Avandia (rosiglitazone maleate) Tablets, 2 mg, 4 mg and 8 mg.

We have reviewed the labeling that you submitted in accordance with our January 4, 2005, letter and we find it acceptable.

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jena Weber

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Division of Metabolic and Endocrine Drug Products, HFD-510

PROJECT MANAGER LABELING REVIEW

Application Numbers and Submission Dates:

NDA 21-071/S-014 Avandia® (rosiglitazone maleate)

NDA 21-410/S-009 Avandamet™ (rosiglitazone maleate and metformin HCl)

Sponsor: SB Pharmco Puerto Rico, Inc. (dba GlaxoSmithKline, Inc).

Submission Dates: February 23, 2005

Receipt Dates: February 24, 2005

Material Reviewed: FPL for both products.

Background and Summary Description: Avandamet™ is a fixed-dose combination product of two different active ingredients consisting of rosiglitazone maleate and metformin hydrochloride tablets. Avandia® (rosiglitazone maleate) was approved under NDA 21-071 on May 25, 1999. Glucophage (metformin HCl) was approved under NDA 20-357, on March 5, 1995. The combination product Avandamet was approved October 10, 2002.

Avandia and/or Avandamet are indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes

Review – Package Insert is acceptable as per approval letters issued with labeling on January 4, 2005.

Conclusion: Issue acknowledge and retain letter for both NDA supplements.

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Jena Weber

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CSO



NDA 21-071/S-014

CBE-30/CBE-0 SUPPLEMENT

GlaxoSmithKline
Attention: Sharon Shapowal, R.Ph.
Senior Director, U.S. Regulatory Affairs
One Franklin Plaza; 200 N. 16th Street
Philadelphia, PA 19101-7929

Dear Ms. Shapowal:

Name of Drug Product: Avandia® (rosiglitazone maleate) Tablets
2 mg, 4 mg and 8 mg.

NDA Number: 21-071

Supplement number: S-014

Date of supplement: July 28, 2004

Date of receipt: July 29, 2004

This supplemental application, submitted as "Supplement - Changes Being Effectuated" provides for revisions to the **PRECAUTIONS** section, **Drug Interactions: Drugs Metabolized by Cytochrome P450** subsection, and miscellaneous editorial changes to the package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 27, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be **January 25, 2004**.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Document Room 8B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-071/S-014

Page 2

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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