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Approval Package for:

APPLICATION NUMBER:

NDA 21-071/S-004

Trade Name: AVANDIA

Generic Name: rosiglitazone maleate

Sponsor: SmithKline Beecham

Approval Date: February 27, 2003

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APPLICATION NUMBER:

NDA 21-071/S-004

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APPLICATION NUMBER:

NDA 21-071/S-004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-071/S-004

SmithKline Beecham Pharmco Puerto Rico, Inc. d/b/a
GlaxoSmithKline
Attention: Sharon W. Shapowal, R.Ph.
Director, Avandia USRA
One Franklin Plaza; P.O. Box 7929
Philadelphia, PA 19101

Dear Ms. Shapowal:

Please refer to your supplemental new drug application dated February 7, 2000, received February 8, 2000, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for Avandia® (rosiglitazone maleate) Tablets, 2 mg, 4 mg and 8 mg.

We acknowledge receipt of your submissions dated May 5, 11, and 26, 2000, June 29, October 6, November 1 and 8, 2000, February 15, May 11, and August 26, 2002, and February 19, 20, and 27, 2003.

Your August 26, 2002, submission constituted a complete response to our February 8, 2001, action letter.

This supplemental new drug application proposes a new indication for the use of Avandia in combination with insulin for the treatment of patients with Type 2 diabetes mellitus.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling.

The final printed labeling (FPL) must be identical to the draft labeling (text for the package insert) submitted on February 27, 2003, and be formatted in accordance with the requirements of 21 CFR 201.66.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-081/S-004." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (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, HF-2
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 301-208-9354.

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 and Research

Enclosure: package insert (final draft submitted on February 27, 2003).

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
2/27/03 05:03:59 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-071/S-004

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug
Administration
Rockville MD 20857

NDA 21-071/S-004

SmithKline Beecham
Attention: Sharon W. Shapowal, R.Ph.
Director, Avandia U.S. Regulatory Affairs
One Franklin Plaza - P.O. Box 7929
Philadelphia, PA 19101

AE
2/8/01

Dear Ms. Shapowal:

Please refer to your supplemental new drug application dated February 7, 2000, received February 8, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avandia® (rosiglitazone maleate) Tablets, 2 mg, 4 mg, and 8 mg.

We acknowledge receipt of your submissions dated May 5, 11, and 25, June 29, October 6, and November 1, and 8, 2000.

This supplemental new drug application proposes a new indication for the use of Avandia in combination with insulin for the treatment of patients with Type 2 diabetes mellitus.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

> Because of the observed increased incidence of cardiovascular adverse events in patients treated with the combination of Avandia and insulin in the controlled trials reviewed as part of supplement 004, including edema, dyspnea, congestive heart failure, and events related to myocardial ischemia, additional studies and/or information are needed to address these safety issues. Investigations of the mechanism(s) by which such events are precipitated, information enabling prospective identification of patients at risk for such events, strategies for prevention, and algorithms for clinical management of fluid overload and congestive heart failure in patients using combination Avandia and insulin are all needed in order to permit safe and effective use of these drugs in combination in the treatment of patients with Type 2 diabetes mellitus.

This approvable action is being taken simultaneously with an Approval action on supplement 006. Supplement 006 provides for changes to the package insert for Avandia in the **PRECAUTIONS** section, **Hepatic Effects** subsection, with the addition of post-marketing safety information related to hepatic adverse events associated with Avandia use. In addition, based upon the review of the safety information submitted with supplement 004 related to Avandia-insulin combination therapy, the labeling approved with supplement 006 also contains changes in several other sections of the package insert. These changes include a new **CLINICAL STUDIES** section, a new **WARNINGS**

section and **Cardiac Failure and Other Cardiac Effects** subsection, and revisions to the **PRECAUTIONS** section **Edema** and **Weight Gain** subsections, and in the **ADVERSE REACTIONS** section.

Your complete response to this letter should, in addition to the information above, include revised draft labeling which must contain all previous revisions as reflected in the most recently approved labeling for your product. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

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 and Research

/s/

David Orloff
2/8/01 04:10:21 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-071/S-004

LABELING

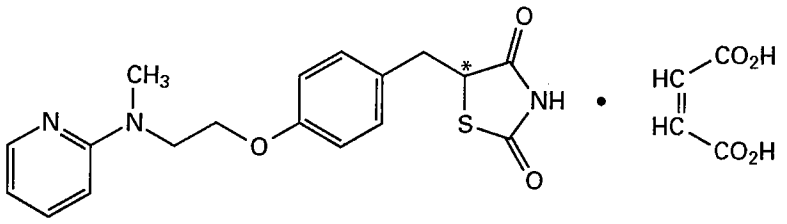
AVANDIA®
(rosiglitazone maleate)
Tablets

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 (±)-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 is:



Rosiglitazone maleate

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 (PPARγ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPARγ-responsive genes also participate in the regulation of fatty acid metabolism.

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

In animal models, 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
$AUC_{0\text{-inf}}$ [ng.hr./mL]	358 (112)	733 (184)	2971 (730)	2890 (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 (Vss/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

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

In vitro data demonstrate that rosiglitazone is predominantly metabolized by Cytochrome P_{450} (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway.

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

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

Special Populations: ***Age:*** 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 PPARγ is expressed in adipose tissues, this differentiating characteristic may account, at least in part, for the greater response to AVANDIA in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.

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

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

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

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

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 Week 26			Glyburide-controlled Study 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%
HbAlc (%)			
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 (≥0.7% decrease from baseline)	6%	40%	42%

Study B	Placebo	AVANDIA		AVANDIA	
		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 (≥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

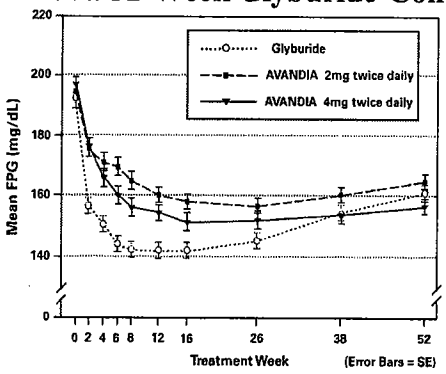
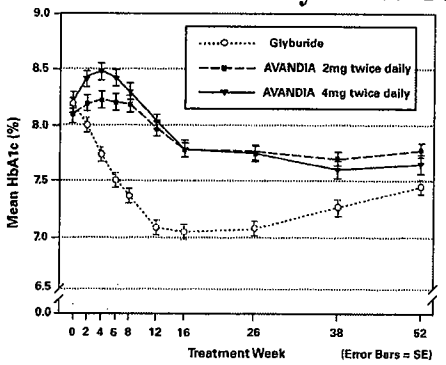


Figure 2. Mean HbA1c Over Time in a 52-Week Glyburide-Controlled Study



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 (≥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 67 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 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

		Control Group		AVANDIA 4 mg	AVANDIA 8 mg
Monotherapy	Duration		Median (25^{th}, 75^{th} percentile)	Median (25^{th}, 75^{th} percentile)	Median (25^{th}, 75^{th} percentile)
	26 weeks	placebo	-0.9 (-2.8, 0.9)	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 ≤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. Therapy with AVANDIA should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). In patients with normal baseline liver enzymes, following initiation of therapy with AVANDIA, it is recommended that liver enzymes be monitored every 2 months for the first 12 months, and periodically thereafter. Patients with mildly elevated liver enzymes (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with AVANDIA should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with AVANDIA in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including 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.

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.

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.

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 every 2 months for the first 12 months, and periodically thereafter. 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: *Drugs Metabolized by Cytochrome P_{450}:* In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P_{450} 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.

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.

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 = 2526	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 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.

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*).

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.

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.

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

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.

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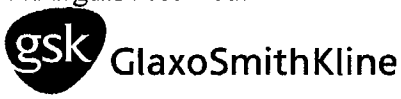


GlaxoSmithKline
Research Triangle Park, NC 27709
AV:L9

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-071/S-004

MEDICAL REVIEW(s)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: February 26, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 27-072/S-004
Avandia (rosiglitazone maleate)
New indication for combined use with insulin

SUBJECT: NDA review issues and recommended action

Background

NDA 21-071/S-004 was originally submitted on 2-7-00 and included the efficacy and safety data from two 6-month trials comparing the effect of rosiglitazone (R) to placebo (pbo) in patients not adequately controlled on insulin alone. The sponsor proposed an indication for combined use of R 4 mg ——— and insulin. The addition of R was effective in lowering HbA1c and insulin requirments relative to pbo, by a mean ~1 percentage unit across the two trials. The safety experience showed that the combination was fraught with greater risk for adverse events associated with fluid accumulation, including edema and CHF, than was insulin alone. The application received an "approvable" action; changes to the label were effected to convey warnings about the potential adverse cardiac effects of the combination. Before the application could be approved and a new indication granted, the sponsor was required to address prospective identification of those at increased risk for the complications, preventive strategies, and management of events related to fluid accumulation, should they occur. In addition, the sponsor was asked to discuss possible mechanisms accounting for the fluid accumulation, which is a known effect of the TZD class.

On 8-26-02, the sponsor submitted a complete response to the AE letter which did address the issues above. The application included the safety and efficacy data from two additional 6-month studies of R vs. pbo in addition to background insulin therapy. The first (085) was a study of insulin dose-sparing (as opposed to efficacy per se) and the second (136) was an efficacy and safety study in poorly controlled diabetics with pre-dialysis renal insufficiency.

Avandia, as well as other TZDs, is known to cause fluid accumulation, manifest as edema, or signs and symptoms of overt CHF. Both Actos and Avandia are so labelled. It is also clear, from studies with both drugs, that the combination of TZD plus insulin is associated with a higher frequency of events related to fluid retention (and/or overall cardiac AEs potentially related to fluid accumulation) than insulin alone. One hypothesis that has been advanced is that the insulin sensitizer, as it were, simply exacerbates the effect of insulin to cause salt and water retention via renally mediated mechanisms. The current submission, which expands the

controlled experience with Avandia in combination with insulin, does not contradict earlier findings, but does provide further information that in the majority of cases, effects attributable to fluid accumulation are gradual in onset, mild in severity, manageable, reversible, and may, in part, be obviated by exclusion of patients with prior cardiac histories and by limiting the dose of Avandia to 4 mg.

Clinical

Efficacy and safety findings

The original trials submitted in support of this indication (082, 095) were parallel group, fixed dose trials (pbo, 4, 8 mg R added to insulin). These have been reviewed previously.

Study 085 was a forced-titration study in which patients received 4 mg daily for the first 8 to 12 weeks and then received 8 mg daily for the duration. The majority of patients were up-titrated to 8 mg. Thus the efficacy data have not been pooled with the 4 mg efficacy data proposed in the label in the section describing insulin-R combination therapy. Furthermore, as stated above, this was not a study designed to assess effects on glycemic control, but rather on insulin requirements. Indeed, in Study 085 the addition of R was effective in this regard and did effect an approximate 0.5% mean reduction in HbA1c relative to pbo. Significantly, in this trial in which glucometer-generated home blood glucose measurements were not collected, the percentage of patients reporting hypoglycemia was similar between the two treatment groups (~14% pbo, ~17% R). In this study, the rates of edema were similar between the two groups (~15% R, ~12% pbo), consistent with the small numerical differences in total cardiovascular adverse events--a composite that includes CHF, hypertension, bundle branch block, atrial fibrillation, palpitations, tachycardia, angina, and MI—(10 events Pbo+insulin; 13 events R+insulin) and CHF (1 pbo; 3 R). Only 2 patients withdrew due to CHF, one in each treatment group. Overall, about 10% of R-insulin combination patients experienced a cardiovascular AE, the majority of which were not serious.

Study 136 was in patients with pre-dialysis renal insufficiency. This was another forced-titration study in which about half of the ~100 R-treated patients received 8 mg daily after the first 8 to 12 weeks. The efficacy of the combination was similar to that seen in other trials (~0.5% HbA1c reduction relative to pbo). Hypoglycemia occurred at about double the rate in the combination therapy group than in the insulin-alone group (22% vs. 11%) though virtually all instances were mild to moderate in severity and readily managed by insulin dose adjustments. Likewise, edema occurred with double the frequency among those treated with R plus insulin relative to insulin alone (20% vs. 10%) and 5 patients in the R group withdrew due to edema. Significantly, in this patient population at increased risk for CV events (and confirmed by rates of CV AEs increased overall), the rates of all cardiovascular events--same as composite above—(13% pbo, 11% R) and CHF (~3% for pbo and R) were not different between treatment groups. Note that edema is not included in the CV composite.

Identification of patients at risk

The sponsor presents tables of the incidence of edema and CHF across the double-blind clinical trials database for R, showing that 1) the risk of CHF for R monotherapy or in combination with metformin or SFU is low (< <1%) and not different from placebo or from monotherapy with metformin or SFU. By contrast, rates of CHF when R is added to insulin (particularly at the 8

mg dose) exceed those with insulin alone (2.5% vs. 1 %). This is not new information. Likewise, 15% of patients treated with the combination developed edema compared to 5% treated with insulin alone.

The sponsor notes that use of insulin is itself a risk factor for prevalent and incident CHF, as are age, duration of diabetes, ischemic heart disease, and renal insufficiency. The use of insulin thus marks a population with a risk of edema and CV event greater than those in the populations treated with oral agents alone. This is borne out in the adverse event data across the different Avandia trials, summarized in the submission. The implication is that patients inadequately controlled on insulin, in whom the addition of a TZD may have therapeutic benefit, there must be an expectation of a risk of edema, and potentially CHF due in part to the TZD themselves and to the increased susceptibility of the patient population to these events in the first place.

There were two deaths in one study, one each on placebo and R, and 3 deaths in the second study, one during the run in. Both other patients were in the R group and had significant histories of CAD and CHD.

Summary

On balance, while the signal of increased risk for edema, CHF, and other CV adverse events persits in these follow up trials (indeed, there was no expectation that it was a fluke of the earlier trials and would disappear in subsequent studies), a strategy of careful patient selection (e.g., no history of cardiac compromise), judicious titration, and monitoring may obviate some of the fluid-related AEs of the combination. Approximately 10% of patients treated with rosiglitazone and insulin experienced cardiac AEs across the trials to date. The majority of events are non-serious. Furthermore, with fluid accumulation leading to edema as the premonitory event in most patients, the potential CV risks of R alone and in combination with insulin are monitorable and manageable.

Comparative cardiac safety data, studies 082, 095, 085, 136 (from JZ)

Study	082 and 095 pooled		085 and 136 pooled	
	Placebo	Rosi	Placebo	Rosi
N	203	408	248	250
Cardiac Aes	10	43	24	25
CHF	2	10	5	8
MI	0	2	1	3
Cardiac arrest	0	2	0	1

Labeling

Final labeling for the supplement has been negotiated and will be attached to the action letter in DFS.

Recommendation
AP, with labeling changes.

Appears This Way
On Original

Appears This Way
On Original

NDA # 21-071/S-004
Drug: Avandia
Proposal: Combination use with insulin
03/05/03

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
3/5/03 01:40:59 PM
MEDICAL OFFICER

Memorandum

FEB 7 2001

Date: 11/29/00

From: Saul Malozowski
Medical Team Leader

Subject: Avandia, rosiglitazone (NDA 21071-S004). Team leader recommendations: Avandia in combination with insulin.

To: David Orloff
Division Director, DMEDP

Efficacy

Two double blind placebo controlled studies (n~600) of 26 weeks duration, support the claim that Avandia in combination therapy with insulin at daily doses of 4 mg / / results in improvement of glycemic control in patients poorly controlled on insulin alone. Statistically significant improvements in HbA1C compared to the placebo treated groups were seen in subjects receiving Avandia. Similar changes were seen in fasting plasma glucose (FPG) levels. The relative decrease in median HbA1C compared to the placebo-treated group ranged between 0.5% to 0.8% (study 095, 4 and 8 mg, once a daily dosing respectively) and 0.7% to 1.3% (study 082, 4 and 8 mg in divided dosing respectively). There was not a difference in HbA1C improvement between the 4 and 8 mg doses given once daily ($p<0.066$). Similar dosing divided into two daily doses appear to be more effective than once a day dosing (4 mg OD= 05%, 4 mg QD=0.7%, 8 OD=0.8% and 8 mg QD=1.3%). These results, however, being from two distinct clinical trials, although strongly suggestive of a difference in efficacy between twice and once a day dosing, do not fully clarify this issue.

As in previous studies with Avandia (either in monotherapy or in combination) improvements in FPG appeared to be maximal after 8 to 12 weeks of therapy while maximal changes in HbA1C were delayed and not seen until 12 to 26 weeks. The efficacy of the Avandia and insulin combination therapy was maintained during the 26-week study period.

Avandia treatment also resulted in reductions in insulin needs.

Subgroup analyses showed that the Avandia's efficacy in combination with insulin was independent of age in subjects younger or older than 65 years old. As previously shown, female patients, overweight patients (BMI $\geq$ 27kg/m2) and patients poorly controlled at the start of therapy, FBG ($\geq$ 200mg/dL) or HbA1C ($\geq$ 9%), showed greater treatment effects, measured as a median decrease in HbA1C.

Safety

The disease progression in patients in these studies was longer than in previous studies (~18 years vs ~4 years (monotherapy) or ~8 years (combination with metformin). The randomization (2:1 for Avandia) was balanced and the controlled group was similar to the Avandia treated groups. The two supporting studies of combination therapy with Avandia and insulin showed, in order of frequency, the following adverse events: hypoglycemia (53% -71%), anemia (4%-17%), edema (2%-10%), hyperlipidemia (1% to 9%), weight gain (0%-7%), dyspnea (4%-5%, study 082 only) and cardiac failure (2%-4%, study 095 only). The approximated time of exposure to Avandia in the controlled part of the studies was 200 patient/years for a total of ~400 subjects for 26 weeks. Due to the study design the patients years for patients treated with insulin and placebo was ~100 with ~200 patients treated for 26 weeks.

Deaths

All four deaths in the studies occurred only in subjects receiving Avandia. No deaths were tallied in the control group. One case was related to a hypoglycemic episode, another to a MI, a third a case was attributed to a ruptured aneurysm and the fourth was secondary to a stroke.

Because in these studies Avandia has been shown to act in an additive manner in reducing glucose levels, it is clear that the reported death associated with hypoglycemia, could be clearly attributed to Avandia. The report in this case indicates that the patient was not eating properly and this may have further precipitated his demise. I think this scenario will indeed repeat itself during Avandia marketing because this is a common occurrence in subjects with diabetes.

All other deaths may have been triggered by Avandia. Avandia is known to induce fluid retention and intravascular expansion. All three episodes could, in part, be explained by these mechanisms. Attribution, however, is difficult to determine.

Six more deaths were reported in the extension studies. Four of them were cardiac in nature (two cardiac failures, one arrhythmia, and one cardiac arrest). An additional case was secondary to an intracranial hemorrhage and the sixth report was due to a hepatic neoplasm.

It is not possible to clearly attribute the deaths in the controlled and open label parts of these studies to Avandia.

Withdraws and serious adverse events

In study 082 withdraws were almost four times more frequent in patients receiving Avandia at either dose when compared to the control group. Only two patients on placebo abandoned the study while a total of 15 subjects on Avandia did.

In study 095, four patients in the control group withdrew while 14 patients on Avandia did (three times more frequent for the Avandia treated subjects). Nine of these patients were receiving the 8-mg dose of Avandia.

explanation for the anemia. This has not been explored in humans. Both the observation of reductions in Hb and leukocyte counts support this alternative hypothesis.

I think, that the label could properly reflect the changes observed in Hb levels.

Edema
Both insulin and Avandia in monotherapy are known to be associated with the development of edema. In combination therapy the increased incidence of edema was additive and dose related. As previously stated patients with edema had an increased incidence of concurrent anemia (9/59=15%). In addition, patients with edema had an increased incidence of concurrent adverse cardiac events (7/59=12%.)
The sponsor has not properly addressed the mechanism leading to edema, although thousand of patients have been exposed to Avandia.. Although mechanistic studies are not required by the Agency for drug approval, I strongly believe that the sponsor should clarify this issue as soon as possible, to provide a better understanding of this process and a better basis for the treatment of this common adverse reaction.

Hyperlipidemia
Small increases in total cholesterol, LDL-cholesterol and HDL-cholesterol were seen with combination therapy with Avandia and insulin. These resulted in minimal changes in the ratios of total cholesterol/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol. At the same time, small decreases in free fatty acids and mixed changes in serum triglycerides were seen with combination therapy with Avandia and insulin.
It seems that despite the While improvements in glucose control, HbA1C levels and markers of insulin sensitivity are usually accompanied by improvements in lipid profiles, Avandia's pharmacological characteristics do not lead to benefits in this arena.

Weight Increase
Both insulin and Avandia in monotherapy are associated with weight increase. Combination therapy of Avandia and insulin, however, results in additive weight gain. The incidence of weight increase was dose related and the mean weight of patients on combination therapy continued to increase throughout the studies. This was previously observed in monotherapy studies and in combination of Avandia with other oral hypoglycemic agents.

Contrary to the plateau observed in the control of HbA1C that may show deterioration with time, weight gain continues to accrue during treatment with Avandia.
Little attention has been given by the academic community and the heath care professionals to this troublesome finding. Although everybody recognizes the need to obtain better glucose control, it is not known how much this weight increment may over time, negatively impact on the cardiovascular health of patients treated with this compound. Similar concerns should be raised for other compounds in this class that lead to significant weight gain. The sponsor has not characterized the nature of this weight gain with Avandia. We still do not know where the fat is accumulated. This knowledge is critical to the risk and benefit assessment, particularly in patients prone to atherosclerosis and cardiac problems.

The mean weight increase in the double blind phase of the studies ranged from 4 to 7kg, while individual weight gains as high as 27.5kg were seen. It is important to note that all

currently approved antidiabetic drugs stress in the label the need to initiate therapy with the diet and exercise (it is implicit that weight reductions will ensue). However, treatment with Avandia results in weight gain.

In these clinical studies weight gain was associated with edema and anemia, but it was not predictive of risk for cardiac failure. Out of the 23 patients with the largest weight gain in these studies 12/23=53% had edema, 5/23=22% had anemia but none had cardiac failure.

Cardiac Related Events

There was a marked increase in total adverse cardiac events, serious adverse cardiac events, and adverse cardiac events leading to withdrawal in patients on insulin and Avandia combination therapy compared to insulin alone (14 % vs < 5%respectively). Most of the cardiac events involved cardiac failure. In the double blind part of the study cardiac failure was seen with Avandia 5/100 pt-years vs insulin alone 2/100 pt-years.

There was a significant increase in the incidence of arrhythmias in the patients on insulin and Avandia combination therapy compared to insulin alone. Patients at highest risk of cardiac events were older, had a longer duration of diabetes and were on the higher 8mg daily dose of Avandia. The majority of patients on combination therapy (18/24=75%) who developed heart failure had predisposing risk factors (history of congestive heart failure, cardiac ischemia, edema, or left ventricular hypertrophy), but they represent only 18/200=9% of the patients with one or more predisposing cardiovascular risk factors. It is important to stress that patients with CHF staged as >NY2 were excluded from these studies. T

. We do not know whether patients in the control group had a similar degree of predisposing cardiac factors, but the randomization should have addressed this issue.

Hepatic Events

The findings of these studies do not add to the current understanding of this issue in patients with diabetes treated with Avandia. The changes recently implemented in this section by the division properly reflect what we have learned from review of data submitted by the sponsor and from postmarketing reports.

Summary

Avandia in combination with insulin significantly decreases HbA1C levels when compared to patients receiving insulin alone. These effects are seen after several weeks of treatment and the effectiveness of the drug appears to plateau with time. At the same time this improvement in glucose control is accompanied with significant weight increase, anemia, and edema. The weight gain is seen early on during therapy and there is no indication that there is plateau effect. Patients continue to gain weight throughout the study. The location of this fat accumulation remains to be elucidated. A similar pattern of the increase in reports of anemia with time also emerged from the studies. Hypoglycemia was more frequent in patients treated with Avandia. No hepatic adverse events emerged throughout the studies.

The effects on lipids appeared to be neutral. The rate of patient withdrawals from the studies as well as the number and severity of adverse events were also more frequent in the Avandia treated group. However of greater concern was the more than doubling in the incidence of congestive heart failure in patients receiving Avandia and the reports of cardiac arrhythmias only in the Avandia treated group. Deaths during the blinded and open label parts of the study were clustered in the Avandia treated group, but it is not possible to establish a cause and effect relationship from the available data.

Recommendations

I recommend not approving this application. Although the sponsor has shown that Avandia is effective in providing better glucose control when added to insulin, the safety information that emerged from the studies is quite troublesome. The data indicate that the risks of using this combination outweigh the limited benefits offered by glucose control.

My recommendation does not imply that this balance of risks and benefits is similar for all patients that may need this combination, but I think that an approval will provide a false sense of security. Attempts to label this drug for its use with insulin will fail to convey all the risks that emerged during the clinical trials. In this context, and because the drug is currently available and physicians can, despite the lack of an approved indication, prescribe Avandia in combination with insulin, it is imperative to modify the current label. This update should convey what has been learned from these studies.

We should also consider requesting the sponsor to send a Dear Dr. letter to communicate this information.

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

Application #: 21,071-SE1 004 BZ	**Application Type: NDA Labeling Supplement**
Sponsor: Glaxo SmithKline	**Proprietary Name: Avandia™**
Investigator: Multiple	**USAN Name: Rosiglitazone maleate**
Category: thiazolidinedione	**Route of Administration: oral**
Reviewer: Joanna K. Zawadzki, M.D.	**Review Date: 2/07/03**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
8/26/02	8/27/02	NDA Supplement	New indication- Use of rosiglitazone (4 mg) in combination with insulin for the treatment of patients with type 2 diabetes mellitus.

RELATED APPLICATIONS (If applicable)

Document Date	Application Type	Comments
5/25/99	NDA 21071	**Approval of Avandia**
2/7/00	NDA 21071 – S004	New indication- Use of rosiglitazone in combination with insulin for the treatment of patients with type 2 diabetes mellitus – reviewed per W. Lubas, M.D., Ph.D.
5/30/00	NDA 21071-S006	Hepatic Effects Labeling Supplement
6/30/00	SE1-004-BM	European Agency Labeling for Avandia

REVIEW SUMMARY: See next page

DRAFT

DRAFT

OUTSTANDING ISSUES: 1) Proposed labeling changes (see review). 2) Financial disclosure information pending

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies _____ **Clinical Hold** _____ **Study May Proceed**

NDA, Efficacy/Label supplement: _____ **Approvable** ___x___ **Not Approvable**

SIGNATURES:

Medical Reviewer: Joanna K. Zawadzki, M.D. **Date:** _____.

Medical Team Leader: _____. **Date:** _____.

Division Director David. G. Orloff, M.D.

TABLE OF CONTENTS

NDA 21-071/S-004 (8/26/02)
Avandia® (rosiglitazone maleate) Tablets

REVIEW SUMMARY

The thiazolidinedione rosiglitazone maleate (Avandia) has been approved for the treatment of patients with type 2 diabetes mellitus as monotherapy and as combination therapy with sulfonylureas and metformin. On 2/7/00, the sponsor had submitted an application for the treatment of diabetes mellitus with combination insulin and rosiglitazone. This application had indicated an increased risk of cardiovascular events and the application was deemed "approvable." The sponsor submitted two additional 26-week studies in patients treated with combination rosiglitazone and insulin. The sponsor requested an indication for combination low dose rosiglitazone (4 mg) and insulin treatment in patients with type 2 diabetes.

The 2/7/00 NDA supplement submission had shown that combination therapy with rosiglitazone and insulin was effective at improving HbA1C and fasting plasma glucose (FPG) in patients inadequately controlled on insulin monotherapy (FPG≥140mg/dL, HbA1C≥7.5% and fasting C-peptide ≥0.4ng/mL) in two 26-week studies (082, 095). The relative median decrease in HbA1C compared to the placebo-treated group ranged from 0.5% to 1.3%, with the greatest improvement in glycemic control in patients who received 8mg of rosiglitazone per day and were dosed twice daily. However, combination therapy with rosiglitazone and insulin resulted in an increased incidence of hypoglycemia, anemia, hyperlipidemia, edema, weight gain, and cardiac events, including cardiac failure, ischemic heart disease and arrhythmias in the combination therapy group compared to the placebo. The incidence of anemia, edema, weight gain and cardiac failure was dose related. No increase in adverse cardiac events had been previously reported in clinical trials with the other thiazolidinediones, troglitazone (Rezulin). Four episodes of congestive heart failure were observed in patients treated with pioglitazone (Actos) and insulin, and no episodes of heart failure in patients treated with placebo and insulin. The incidence of the non-cardiac adverse events had been previously seen with other thiazolidinediones, though the incidence with combination therapy with insulin was substantially higher than seen with rosiglitazone monotherapy or combination therapy with rosiglitazone and other oral antidiabetic agents. Because of the cardiac adverse events, the indication for combination rosiglitazone and insulin therapy was deemed "approvable" on 2/8/01. The FDA requested additional information regarding cardiovascular events and fluid retention to support the benefit-risk assessment for the indication.

On 8/26/02, GSK submitted two European 26-week studies (085 and 136) which evaluated the use of rosiglitazone with insulin. The mean age was higher (61 and 66, respectively), the duration of diabetes (13.4 and 14.6 years) was longer than in the prior studies, and patients in Study 136 also had chronic renal failure. The mean age and known duration of diabetes mellitus were slightly sicker than in studies 082 and 095. Rosiglitazone was initially given at 4mg od and the dose was increased to 8mg at 8 or 12 weeks. Both studies showed that combination therapy with rosiglitazone and insulin was effective at lowering insulin dose and improving HbA1c and FPG. Safety adverse effects of combination rosiglitazone and insulin included an increased incidence of hypoglycemia, anemia, hyperlipidemia, edema, weight gain. The percent of patients with hypoglycemia was increased in the patients treated with rosiglitazone and insulin, but the rates were lower (about 20%) than in studies 082 and 095 (50-67%). A slight increased risk of cardiac events, especially cardiac failure and myocardial infarction – but

less than in studies 082 and 095 - was suggested in Study 085. The data suggest that rosiglitazone may potentiate fluid retention, especially in susceptible individuals, and thus exacerbate the risk of cardiac adverse events.

The sponsor also submitted additional analyses of the insulin combination data to identify potential risk factors for fluid-related adverse events, hypotheses regarding mechanism(s) of thiazolidinedione-related fluid retention, and evaluation of clinical management of thiazolidinedione-induced fluid retention. The sponsor requested a limited indication for the low dose (4mg) of rosiglitazone in combination with insulin and provided labeling which incorporates the safety information from studies 082 and 095 for both the 4mg / / of rosiglitazone.

In conclusion, patients with type 2 diabetes mellitus who are treated with rosiglitazone and insulin are at increased risk of cardiac adverse events, as has been shown by these three studies. The risk may be lower with the lower dose of Avandia, though it still persists.

INTRODUCTION

Rosiglitazone maleate (Avandia) is a member of the thiazolidinedione class of oral antidiabetic agents. Thiazolidinediones improve glycemic control by increasing insulin sensitivity, thereby decreasing insulin resistance, which is a common feature of type 2 diabetes. Rosiglitazone has been approved in the US as an adjunct to diet and exercise for the treatment of type 2 diabetes. It has been approved as monotherapy, as well as combination therapy with metformin or sulfonylureas. An NDA supplement previously submitted (2/7/00) presented two pivotal studies (082, 095) for the combination rosiglitazone and insulin indication.

Combination therapy with rosiglitazone and insulin was effective at improving HbA1C and fasting plasma glucose (FPG) in patients inadequately controlled on insulin monotherapy (FPG≥140mg/dL, HbA1C≥7.5% and fasting C-peptide ≥0.4ng/mL) in two 26-week studies (082, 095). The relative median decrease in HbA1C compared to the placebo-treated group ranged from 0.5% to 1.3%, with the greatest improvement in glycemic control in patients who received 8mg of rosiglitazone per day and were dosed twice daily. However, combination therapy with rosiglitazone and insulin resulted in an increased incidence of hypoglycemia, anemia, hyperlipidemia, edema, weight gain, and cardiac events, including cardiac failure, ischemic heart disease and arrhythmias in the combination therapy group compared to the placebo. The incidence of anemia, edema, weight gain and cardiac failure was dose related. The cardiac adverse effects from Studies 082 and 095 are summarized in the table below from Dr. William Lubas's review of that NDA supplement. Among the patients treated with rosiglitazone and insulin who developed congestive heart failure, there were six patients treated with rosiglitazone 8 mg and four patients treated with rosiglitazone 4 mg. Patients who were more responsive to the combination insulin and rosiglitazone treatment appeared to be more at risk for these complications.

Table 6: On-therapy Reports of Cardiovascular Events* for OD and BD Regimens – Rosiglitazone (RSG) in Combination with Insulin (INS), Double-blind Population

	RSG+INS		Insulin	
	N = 408		N = 203	
Preferred Term **	**n**	**%**	**n**	**%**
Dyspnea	10	2.5	2	1.0
Cardiac failure	10	2.5	2	1.0
Total arrhythmias	7	1.7	0	0.0
Cerebrovascular disorder	5	1.2	2	1.0
Coronary artery disorder	5	1.2	1	0.5
Myocardial ischemia	4	1.0	0	0.0
Peripheral ischemia	4	1.0	2	1.0
Angina pectoris	2	0.5	2	1.0
Angina pectoris aggravated	2	0.5	1	0.5
Cardiac arrest	2	0.5	0	0.0
Myocardial infarction	2	0.5	0	0.0

Cardiomegaly	1	0.2	1	0.5
Total Patients†† w/Cardiovascular AEs	43	10.5	10	4.9

* A patient could have more than one cardiovascular event
** Sorted by descending order of preferred term frequency, RSG+INS – BD
† One patient (082.027.13978) also had an on-therapy AE of pulmonary edema which began 22 days after the onset of the on-therapy cardiac failure.
†† Patients counted only once, regardless of number of preferred terms.
Data Source: ISS Table 4.2.4.2.a and 4.2.4.2.b; Appendix 4.0a **Modified Table 8.H.4.10**

ON THERAPY ADVERSE EVENTS IN THE DOUBLE BLIND POPULATION

Adverse Event	**Responders** HbA1C>=0.7%					**NonResponders** HbA1C<0.7%					
	RSG+INS N=204		INS N=36		Relative % RSG+INS/ INS	RSG+INS N=197		INS N=162		Relative % RSG+INS/ INS	%Resp/ %NonResponders
	N	%	N	%		N	%	N	%		
Edema	39	19	3	8	2.3	21	11	8	5	2.2	1.7
Anemia	27	13	1	3	4.7	17	9	6	4	2.3	1.4
CV event	23	11	1	3	4.0	13	7	8	5	1.3	1.6
Wt gain	12	6	0	0	∞	7	4	3	2	1.9	1.5
Cardiac failure	7	3	0	0	∞	3	1.5	2	1.2	1.2	2.0
Total AEs	82	40	5	14	2.9	52	26	20	12	2.1	1.5

Following this review, an "approvable" letter (2/7/01) was sent to the sponsor:

"Because of the observed increased incidence of cardiovascular adverse events in patients treated with the combination of Avandia and insulin in the controlled trials reviewed as part of supplement 004, including edema, dyspnea, congestive heart failure, and events related to myocardial ischemia, additional studies and/or information are needed to address these safety issues. Investigations of the mechanism(s) by which such events are precipitated, information enabling prospective identification of patients at risk for such events, strategies for prevention, and algorithms for clinical management of fluid overload and congestive heart failure in patients using combination Avandia and insulin are all needed in order to permit safe and effective use of these drugs in combination in the treatment of patients with Type 2 diabetes mellitus."

Thus, the sponsor was asked to comment regarding the management of these risks and provide an approach to manage fluid overload and congestive heart failure in patients on combination rosiglitazone and insulin. At the time the increased risk of cardiac adverse effects was observed with combination rosiglitazone and insulin treatment, there was no known association of increased risk of cardiac adverse events with the other thiazolidinediones, troglitazone and pioglitazone, which had both been approved for combination use with insulin. Subsequent review of the controlled double blind clinical study data revealed that there were four cases of congestive heart failure in combination pioglitazone and insulin therapy (two on 15 mg and two on 45 mg of pioglitazone), but no cases in the group treated with insulin and placebo.
This NDA supplement presents two European double-blind pivotal studies 085 and 136 to assess the safety and efficacy of rosiglitazone in combination with insulin in patients with type 2

diabetes who are inadequately controlled by insulin monotherapy. Both studies were initiated before 2/01.

In conclusion, safety concerns have been raised with combination therapy of rosiglitazone and insulin, specifically in the areas of edema, weight gain, anemia, incidence of hypoglycemia, and cardiac adverse effects. Three studies (082, 095, and now also 085) show an increased incidence of cardiac adverse effects with combination insulin and rosiglitazone therapy. At the 4 mg dose of rosiglitazone, there is no significant difference in the rates of emergent congestive heart failure. Adverse cardiac effects, particularly myocardial infarction and congestive heart failure, were seen in patients with previously both known and unknown cardiac disease, and mostly at the higher dose of rosiglitazone (8 mg) but also at the lower dose of rosiglitazone. Patients with type 2 diabetes mellitus are at significantly increased risk of cardiac disease. Treatment of type 2 diabetes mellitus with combination rosiglitazone (4mg) and insulin may result in a lower risk of cardiac adverse events, but the combination treatment of rosiglitazone and insulin would have to be labeled to appropriately include this risk. The final risk benefit analysis suggests that combination rosiglitazone and insulin treatment of patients with type 2 diabetes may be effective but adequately safe only with greater diligence.

EFFICACY REVIEW

Protocol 085-*A 26 week randomized, double-blind multicenter study to evaluate the effects of rosiglitazone on insulin requirements in insulin treated type 2 diabetic patients*
(33 European centers 5/9/00-6/21/01)

The primary objective of this study was to compare the effectiveness of rosiglitazone therapy in reducing daily insulin requirements in patients with type 2 diabetes mellitus treated with subcutaneous insulin, and the primary efficacy parameter was the percent change from baseline in total daily insulin dose at week 26.

The study enrolled 277 patients between ages 36-79 years with type 2 diabetes receiving $\geq$30 units of total insulin as at least twice daily injections for at least 3 months prior to baseline. Subjects had to have fasting plasma glucose (FPG) $\leq$ 180mg/dL. HbA1C specifically was not an enrollment criterion. Patients with unstable or severe angina requiring continual nitrate treatment for symptomatic relief, coronary insufficiency, or congestive heart failure (NYHA class I to IV inclusive) were excluded. Patients with anemia, severe renal, or hepatic were excluded.

Males (54%) out numbered females. Most patients were Caucasian (99.6%). The average age of patients was 61 years (range 36-79), with a smaller proportion of subjects over 65 years (40%) in all treatment groups. The average duration of diabetes was 13.4 $\pm$ 8.1 years in the insulin and placebo group and slightly longer 14.6 $\pm$7.8 years in the insulin and rosiglitazone group. Baseline HgbA1c was similar in the treatment groups (8 $\pm$ 1). A total of 252 (79%) patients completed the study, with a similar number of patients (20 to 24) withdrawing from each treatment group. The mean baseline FPG was slightly higher in the insulin and rosiglitazone

group 167.2 (±52.3) mg/dl compared to the insulin and placebo group 157.2 (±50.8) mg/dl. Baseline mean (±SD) total daily insulin dose was 63 (±30) in the insulin only group and 68 (±36) in the insulin and rosiglitazone group. At baseline both treatment groups received similar numbers of insulin injections each day: 2.9 (1.1) in the insulin placebo group and 3.1 (1.1) in the insulin and rosiglitazone group.

The study protocol divided patients into two treatment groups ie. Placebo or 2mg bid rosiglitazone. At week 8 or week 12 the dose was increased to 4mg bid until the end of the study (and stayed at this level in 90.4%). Patients with symptoms of congestive heart failure were maintained on the 4mg dose longer. The dose could be reduced from 8mg to 4mg. The insulin dose for all patients was maintained at the start of therapy and decreases in insulin dose were done at study visits by 5 to 10% if glucose concentration fell below 90% of baseline or <30mg/dl. Of note, the dose of rosiglitazone was introduced more slowly than in studies 082 and 095 and the insulin dose was also reduced more.

After 26 weeks of treatment, rosiglitazone reduced the mean total daily insulin dose by 16.5% (p=0.0001) by 14.9 units and 32% of patients in the rosiglitazone group had a reduction in total daily insulin dose of >30%, and only 15/137 patients (11%) reduced the number of injections taken. No patients discontinued insulin therapy completely. Mean decrease in HbA1C was 0.07% in the rosiglitazone group at 26 weeks and there was an increase of HbA1c of 0.45% in the placebo group.

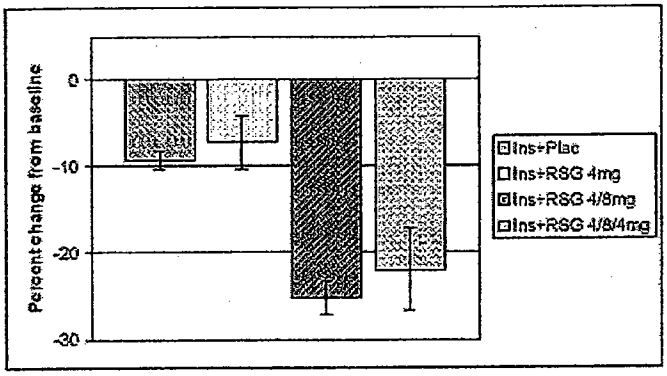
Week 26 (ITT with LOCF Population)

	Treatment Group	
	Ins + Placebo (n = 139)	Ins + RSG (n = 137)
Insulin (units)		
Baseline (Geometric mean-SE, Geometric mean+SE)	57.4 (55.42, 59.48)	60.9 (58.60, 63.28)
Week 26 (Geometric mean-SE, Geometric mean+SE)	52.1 (50.09, 54.13)	46.6 (44.59, 48.66)
% Change from Baseline (Geometric mean-SE, Geometric mean+SE)	-9.3 (-10.38, -8.23)	-23.5 (-25.23, -21.75)
95% CI	-11.4, -7.2	-26.9, -20.0
p-value	<0.0001	<0.0001
Difference from placebo		
adjusted mean difference	-	-16.5
95% CI	-	-20.5, -12.2
p-value	-	0.0001

Data Source: Section 14, Table 14.2.1.3, 14.3.4; Appendix B, Listing B.1.3; Appendix C, Listing C.1.2B

The percent change from baseline in insulin dose at week 26 is shown in the sponsor's table below. There was a slightly smaller percent change from baseline in insulin dose in those who reverted to the rosiglitazone 4 mg dose after the 8 mg dose.

Figure 3 Percent Change from Baseline in Insulin Dose at Week 26 (ITT with LOCF Population)

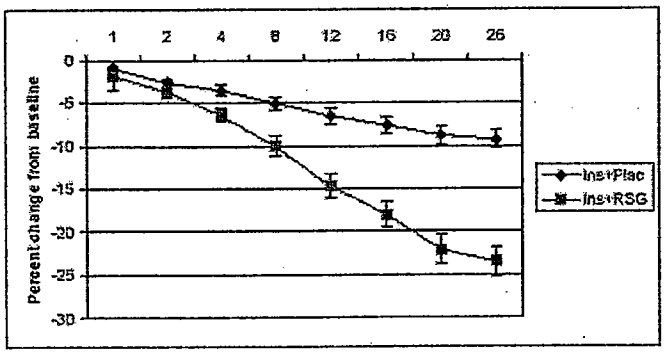


	Ins + Plac	Ins+RSG 4mg	Ins+RSG 4/8mg	Ins+RSG 4/8/4mg
n	138	12	118	3
Geometric mean	-9.3	-7.2	-25.2	-22.0
Geometric mean – SE	-10.42	-10.31	-27.12	-26.72
Geometric mean + SE	-8.26	-4.15	-23.35	-17.04

Data source: Section 14, Table 14.2.1B
Error bars = Geometric mean-SE, Geometric mean+SE

The percent change from baseline to week 26 in total daily insulin dose for each center is shown in the sponsor's Figure 4 below. A greater percentage decrease in insulin dose is noted in the group treated with rosiglitazone as compared to those treated with placebo. The separation of the two groups occurs mostly after 8 weeks, which is when the majority of the patients were switched to rosiglitazone 8 mg in combination with the insulin.

Figure 4 Percent Change from Baseline in Total Daily Insulin Dose Over Time (ITT with LOCF Population)



Data source: Section 14, Table 14.2.1A
Error bars = Geometric mean-SE, Geometric mean+SE

The reduction in total insulin is shown numerically the sponsor's table 13 below. Though the insulin dose was decreased over the course of the study, the number of insulin injections did not change.

Table 13 Total Insulin Dose at Each Visit (ITT with LOCF Population)

	Treatment Group	
	Ins + Plac (n = 139)	Ins + RSG (n = 137)
Insulin (Units)		
Baseline (Mean ± SD)	63.0 ± 30.08	67.8 ± 35.94
Week 4 (Mean ± SD)	61.1 ± 29.57	64.2 ± 35.51
Week 8 (Mean ± SD)	60.4 ± 29.79	62.3 ± 35.64
Week 12 (Mean ± SD)	59.5 ± 29.62	58.5 ± 30.54
Week 16 (Mean ± SD)	58.9 ± 29.69	56.3 ± 29.07
Week 20 (Mean ± SD)	58.2 ± 29.49	53.8 ± 28.07
Week 26 (Mean ± SD)	58.1 ± 29.64	52.9 ± 28.07
Change from baseline to week 26 (Mean ± SD)	-4.9 ±7.62	-14.9 ± 17.62

Data Source: Section 14 Table 14.2.2A, Appendix C, Listing C.1.2

A third of the patients treated with insulin and rosiglitazone decreased the mean total daily insulin dose by ≥30%.

Table 15 Proportion of Patients Who Had a Reduction in Mean Total Daily Insulin Dose (ITT with LOCF Population)

	Treatment Group	
	Ins + Plac (n = 139)	Ins + RSG (n = 137)
Total Number of Patients with no Reduction n(%)	62 (48.6)	32 (23.4)
Reduction <10%	27 (19.4)	15 (10.9)
Reduction 10 - <20%	28 (20.1)	24 (27.5)
Reduction 20 - <30%	14 (10.1)	22 (16.1)
Reduction 30 - <40%	4 (2.9)	20 (14.6)
Reduction 40 - <50%	4 (2.9)	14 (10.2)
Reduction ≥50%	0	10 (7.3)
Total Number of Patients with Reduction ≥30%	8 (5.8)	44 (32.1)

Data Source: Section 14 Table 14.3.8, Appendix C, Listing C.1.2

Thus, it is not surprising that less than a third of the patients treated with insulin and rosiglitazone had a reduction in HbA1c ≥ 0.7%

Table 17 Proportion of Patients Who Responded in HbA1c with a Reduction of 0.7% or More (ITT with LOCF Population)

	Treatment Group	
	Ins + Plac (n = 135)	Ins + RSG (n = 126)
Number of Patients with Reduction ≥0.7% n(%)	11 (8.1)	34 (27.0)
Reduction <0.5%	119 (88.1)	81 (64.3)
Reduction 0.5 - <0.7%	5 (3.7)	11 (8.7)
Reduction 0.7 - <1.0%	4 (3.0)	11 (8.7)
Reduction 1.0 - <1.5%	4 (3.0)	14 (11.1)
Reduction 1.5 - <2.0%	1 (0.7)	6 (4.8)
Reduction ≥2.0%	2 (1.5)	3 (2.4)

Data Source: Section 14 Table 14.3.8A, Appendix C, Listing C.1.1

Protocol 136-*A 26 week randomized, double-blind multicenter placebo-controlled study to evaluate the efficacy, safety, and tolerability of rosiglitazone with concurrent insulin therapy and/or a sulfonylurea in type 2 diabetic patients* with chronic renal failure (not on dialysis) (47 European centers 7/30/99-6/07/01)

The primary objective of this study was to compare the efficacy of rosiglitazone with that of placebo in combination with background insulin and/or a sulfonylurea in reducing HbA1c in patients with type 2 diabetes mellitus and chronic renal failure (not on dialysis).

The study enrolled 294 patients (291 were randomized) between 35 and 80 years of age, with type 2 diabetes mellitus (with FPG ≥ 7 mmol/l and <12mmol/l) who had chronic renal failure (not on dialysis) as defined by an estimated creatinine clearance (using the Cockcroft-Gault equation) of <79 ml/min. Patients with unstable or severe angina requiring continual nitrate treatment for symptomatic relief, coronary insufficiency, or congestive geart heart failure (NYHA class I to IV inclusive) were excluded. Patients with anemia, severe renal, or hepatic were excluded.

Males (61%) outnumbered females. Most patients were Caucasian (97.6%). The average age of patients was 66 + 7.7 (SD) years and the majority (59.7% overall and 62.2 % in the placebo group and 57.2% in the rosiglitazone group) was over 65. The mean (SD) duration of diabetes was 14.6 ±8.7 years (range 0-47 years), with a mean (SD) baseline HbA1c in the placebo and rosiglitazone groups of 8.3 ±1.2 % and 8.2 ±1.2%, respectively and a mean (SD) baseline FPG of 170.8 ±48.3 mg/dL and 174.1±66.2 mg/dL,respectively. There were no marked differences between treatment groups in any of the baseline characteristics. At entry, 201 (69.1%) patients had been treated with insulin alone, 71 (24.4%) with a sulfonylurea alone and 19 (6.5%) with insulin and a sulfonylurea. The mean dose (SD) of insulin at baseline, for all patients who took insulin, was comparable between the treatment groups (56.5 ±42.31 units/day in the placebo group and 54.4 ±39.87 units/day in the rosiglitazone group) (Section 11, Table 13.7.4A). A higher sulfonylurea mean dose (SD) in all patients who took a sulfonylurea, was found in patients in the rosiglitazone group (192.2 ±880.00). Mean BMI was 29.9kg/m^2 ±5.2 (SD) range 17.0-50.4 kg/m^2. The distribution of antidiabetic insulin and sulfonylurea therapy (gliclazide, glibenclamide, glimepiride, glipizide, acarbose, tolbutamide, metformin hydrochloride, repaglinide, gliquidone) were similar in the two treatment groups

The study protocol divided patients into two treatment groups placebo or rosiglitazone 4mg od. The patient population was stratified by severity of renal failure (estimated using the Cockcroft-Gault equation) at the screening visit (i.e. mild CrCl 60-79ml/min; moderate CrCl 30-59 ml/min; severe (CrCl < 29ml/min). If fasting capillary blood glucose > 6.1 mmol/l (measured by glucometer) or if patients did not achieve adequate glycemic control at week 8 or 12, the medication was increased to placebo bd or rosiglitazone 4mg bd. The dose of insulin or suflonylurea could be reduced by the investigator if hypoglycemia occurred or if pronounced edema or congestive heart failure occurred. Insulin or sulfonylurea could not be initiated after entry to the study. The goal was to recruit >25% of patients into each stratum of severity of

renal failure, but only 48 (16.7%) patients had severe renal failure at screening, with 138 (47.9%) patients with moderate and 93 (32.3%) patients with mild renal failure at screening.

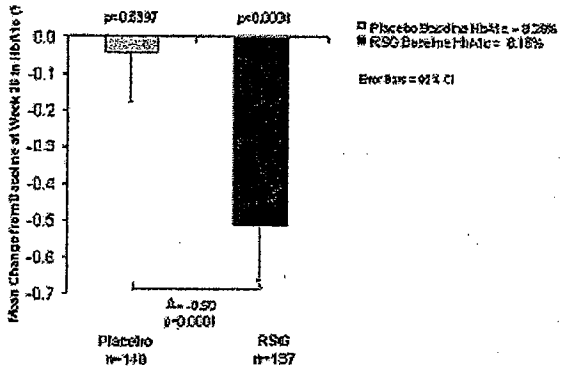
After 26 weeks of treatment, rosiglitazone (4mg to 8mg/day) in combination with insulin and/or a sulfonylurea was associated with a 0.5% decrease from baseline in HbA1c compared with placebo plus insulin and/or a sulfonylurea (p=0.0001). These results were similar despite the degree of renal impairment at screening. Fasting plasma glucose decreased by 8±60 gm/dl in the placebo group and by 32±67 mg/dl in the rosiglitazone group. The decrease was statistically significant in the patients with moderate renal failure at entry.

Table 21 Change in HbA1c at Study Endpoint (Week 26) Compared to Baseline and Placebo (ITT Population with LOCF)

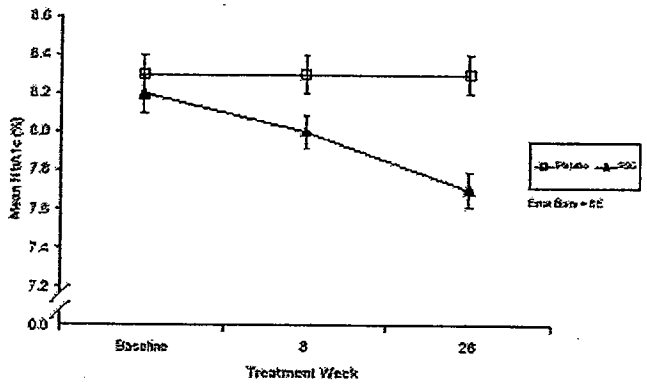
	Treatment Group	
	Placebo (n=140)	RSG (n=137)
HbA1c (%)*		
Baseline (mean ± SD)	8.3±1.24	8.3±1.23
Week 26 (mean ± SD)	8.3±1.22	7.7±1.08
Change from baseline**†		
mean ± SD	-0.03±0.88	-0.5±0.92
95% CI	(-0.18,0.11)	(-0.66, -0.35)
p-value†	0.6397	<0.0001
Difference from placebo		
adjusted mean difference	-	-0.5
95% CI	-	(-0.70, -0.31)
p-value††		0.0001

* SIGN reference range: <6.5%
** All values calculated are only for those patients who had a baseline and on-therapy value (last on-therapy observation carried forward if week 26 is missing)
† From paired t-test
†† Significance level is 0.05
Data Source: Section 12, Table 14.3.1A; Appendix C, Listing C.1.1

Figure 2 Mean Change in HbA1c at Study Endpoint (Week 26) Compared to Baseline and Placebo Group (ITT Population with LOCF)



Data Source: Section 12, Tables 14.3.1A



Data Source: Section 12, Tables 14.2.1A

As in Study 085, the greatest decrease in HgbA1c occurred after 8 weeks when the majority of patients treated with rosiglitazone and insulin were on the 8 mg dose.

SUMMARY OF EFFICACY REVIEW

Rosiglitazone in combination therapy with insulin at daily doses of 8 mg (4 mg in a minority of patients) improves glycemic control in patients previously poorly controlled on insulin. HgA1c in the rosiglitazone and insulin group decreased by 0.07% (versus 0.45% increase in the placebo group) in study 085 with a modest (16.5%) decrease in the insulin requirement (the primary efficacy variable) of 14.9 units. HgA1c decreased by 0.5% compared to the placebo group in study 136. The major improvement in glycemia occurred after the 8 weekpoint when the dose of rosiglitazone was increased to 8 mg in the majority of patients.

These decreases in HgA1c are lower than those that were observed in studies 082 and 095, respectively. The relative decrease in median HbA1c compared to the placebo-treated group was 0.5% to 0.8% (study 095) and 0.7% to 1.3% (study 082), for rosiglitazone 4 and 8 mg doses. The lower efficacy in studies 082 and 136 may have reflected the somewhat older population with longer duration of diabetes mellitus and more underlying disease, including renal failure in study 0136. The conduct of the study, the slower introduction of rosiglitazone and maintenance of less strict glycemic control, may have also contributed to the lower efficacy.

SAFETY REVIEW

Protocol 085-*A 26 week randomized, double-blind multicenter study to evaluate the effects of rosiglitazone on insulin requirements in insulin treated type 2 diabetic patients*

138 patients were exposed to rosiglitazone in this study, with 66% exposed for 180-270 days, 22% exposed for 91-180 days, and 12.3% exposed for 90 days or less. The majority of patients(118/136, 86.8%) received rosiglitazone 8mg after 8 weeks of treatment and only 9.6% (13/136) of the patients stayed on rosiglitazone 4mg. In 7 patients, the dose was not advanced because of an adverse effect.

The most commonly reported adverse events included hypoglycemia, edema, and hypercholesterolemia.

Table 21 On-therapy Adverse Experiences Reported by ≥5% of Patients in Any Treatment Group by Preferred Term (All Randomised Patients)

AEs by Preferred Term, n (%)	Treatment Group		
	Ins + Plac (n=139)	Ins + RSG (n=138)	Total (n=277)
Total Patients with at least 1 AE	81 (58.3)	92 (66.7)	173 (62.5)
Hypoglycaemia	19 (13.7)	24 (17.4)	43 (15.5)
Upper Respiratory Tract Infection	8 (5.8)	10 (7.2)	18 (6.5)
Oedema	6 (4.3)	9 (6.5)	15 (5.4)
Oedema legs	4 (2.9)	9 (6.5)	13 (4.7)
Hypercholesterolaemia	1 (0.7)	8 (5.8)	9 (3.2)
Viral Infection	4 (2.9)	8 (5.8)	12 (4.3)
Hyperglycaemia	9 (6.5)	5 (3.6)	14 (5.1)
Injury	11 (7.9)	4 (2.9)	15 (5.4)

Note: AEs sorted by descending order of RSG group
Data Source: Section 15, Tables 14.5.2.4; Appendix 19, Listing 19.1.2

DEATHS

Two patients died during the study. One patient (PID 085.751.76932) was a 77 year old female treated with insulin and placebo. The patient had had a history of atrial fibrillation since 1995 and died of a cerebral infarction approximately 5 months after treatment with study drug. The other patient (PID 085.813.76589) was a 66-year-old female treated with insulin and rosiglitazone. Prior medical history had included hypertension and she had angina pectoris 3 months after the initiation of the study drug. During the cardiac catheterization, she had an acute myocardial infarction and complete atrioventricular block, resulting in cardiorespiratory arrest and death. The investigator doubted the relation of these events and the study drug. The association of the events with the patient's underlying hypertension and combination rosiglitazone and insulin cannot be excluded.

WITHDRAWALS

The number of withdrawals due to adverse experiences was 12 (9.4%) in the insulin and rosiglitazone group versus 6 (4.3%) in the insulin and placebo group. There were 6 withdrawals due to cardiac events in the rosiglitazone and insulin group compared to 1 patient in the insulin and placebo group. There was one withdrawal due to edema in each group, and there wee no withdrawals because of hepatic adverse events. A summary of patient withdrawals and a listing of the withdrawn patients are listed below.

Table 32 Summary of Patient Withdrawals Due to On-Therapy Adverse Experiences (All Randomised Patients)

AE leading to withdrawal by preferred term, n (%)	Treatment Group		
	Ins + Placebo (n=139)	Ins + RSG (n=138)	Total (n=277)
No. of patients with at least 1 event leading to withdrawal	6 (4.3)	13 (9.4)	19 (6.9)
Angina pectoris	0	2 (1.4)	2 (0.7)
Myocardial infarction	0	2 (1.4)	2 (0.7)
Cerebrovascular disorder	2 (1.4)	2 (1.4)	4 (1.4)
Allergic reaction	0	1 (0.7)	1 (0.4)
Cellulitis	0	1 (0.7)	1 (0.4)
Oedema	0	1 (0.7)	1 (0.4)
Dyspnoea	1 (0.7)	1 (0.7)	2 (0.7)
Retinal disorder	0	1 (0.7)	1 (0.4)
Pain	0	1 (0.7)	1 (0.4)
Cardiac failure	1 (0.7)	1 (0.7)	2 (0.7)
Dizziness	0	1 (0.7)	1 (0.4)
Headache	0	1 (0.7)	1 (0.4)
Palpitation	0	1 (0.7)	1 (0.4)
Oedema generalised	1 (0.7)	0	1 (0.4)
Hyperglycaemia	1 (0.7)	0	1 (0.4)
Upper respiratory infection	1 (0.7)	0	1 (0.4)
Rash erythematous	1 (0.7)	0	1 (0.4)

NOTE. Patient could be withdrawn due to more than 1 adverse experience
Data Source: Section 15, Table 15.3, Appendix D, Listing D.1.4

Table 31 Patients with On-therapy Serious Nonfatal Adverse Experiences

Patient Number	Treatment Group	Age (yrs)	Sex (M/F)	Day of Onset* (days)	Serious Adverse Experience (Preferred Term)	Intensity	Relationship
085 [illegible] 37202	RSG 4 mg	51	Male	109	Myocardial infarction	Severe	Unlikely
085 433 37181	RSG 4 mg	71	Male	155	Cerebrovascular disorder	Severe	Unlikely
085 433 37182	RSG 4 mg	72	Male	28	Chest pain	Moderate	Unlikely
085 434 77501	Placebo	57	Female	57	Pancreatitis	Moderate	Unlikely
085 434 37203	RSG 4 mg	60	Female	153	Bundle branch block	Moderate	Unlikely
				155	Myocardial infarction	Moderate	Unlikely
085 438 37233	RSG 4 mg	72	Male	27	Carcinoma	Severe	Not related
085 439 77258	RSG 4 mg	63	Female	4	Biliary pain	Moderate	Not related
				172	Pneumonia	Moderate	Not related
085 450 37264	RSG 4 mg	47	Male	124	Oedema leg	Moderate	Suspected
085 503 76458	RSG 4 mg	68	Female	93	Hyperglycaemia	Moderate	Suspected
085 601 87626	Placebo	66	Female	136	Cardiac failure	Severe	Suspected
085 703 78651	Placebo	73	Female	121	Injury	Severe	Unlikely
085 708 76082	RSG 4/8 mg	63	Female	134	Cardiac failure	Moderate	Possible
085 728 76385	RSG 4 mg	66	Male	125	Pneumonia	Moderate	Not related
085 776 77023	Placebo	53	Male	8	Skin ulceration	Moderate	Not related
				8	Infection	Moderate	Not related
				93	Retinal haemorrhage	Severe	Unlikely
085 776 77024	Placebo	63	Male	29	Embolism cerebral	Moderate	Unlikely
				29	Cerebrovascular disorder	Moderate	Unlikely
085 777 37051	RSG 4 mg	56	Male	13	Angina pectoris	Moderate	Unlikely
				11	Dyspnoea	Moderate	Unlikely
085 801 76471	Placebo	62	Female	88	Cerebrovascular disorder	Moderate	Unlikely
085 803 76569	RSG 4 mg	71	Male	82	Myocardial infarction	Severe	Unlikely
085 804 76525	RSG 4 mg	77	Male	29	Cerebrovascular disorder	Severe	Unlikely
085 806 76532	RSG 4 mg	69	Male	29	Cardiac failure	Severe	Unlikely
				29	Cellulitis	Severe	Unlikely
085 813 76580	RSG 4 mg	66	Female	91	Angina pectoris	Severe	Not related
085 922 76311	RSG 4 mg	65	Male	45	Chin edema	Moderate	Unlikely

Of note, four patients treated with insulin and rosiglitazone 4 mg withdrew because of cardiac failure, edema, angina, and cerebrovascular disorder 14 to 86 days after the initiation of therapy with rosiglitazone and insulin.

SERIOUS ADVERSE EVENTS

The incidence of on-therapy serious non-fatal adverse experiences was higher in the insulin and rosiglitazone group (11.6%) compared to the insulin and placebo group (5%). A greater number of cardiac-related adverse events, including angina, myocardial infarction, edema, and cardiac failure, occurred in the rosiglitazone and insulin group.

Table 30 Summary of On-therapy Serious Nonfatal Adverse Experiences (All Randomised Patients)

Serious AEs by Preferred Term, n (%)	Treatment Group		
	Ins + Placebo (n=139)	Ins + RSG (n=138)	Total (n=277)
Total Patients with at least 1 serious AE	7 (5.0)	16 (11.6)	23 (8.3)
Myocardial infarction	1 (0.7)	3 (2.2)	4 (1.4)
Angina pectoris	0	2 (1.4)	2 (0.7)
Cardiac failure	1 (0.7)	2 (1.4)	3 (1.1)
Cerebrovascular disorder	2 (1.4)	2 (1.4)	4 (1.4)
Pneumonia	0	2 (1.4)	2 (0.7)
Biliary pain	0	1 (0.7)	1 (0.4)
Bundle branch block	0	1 (0.7)	1 (0.4)
Carcinoma	0	1 (0.7)	1 (0.4)
Cellulitis	0	1 (0.7)	1 (0.4)
Chest pain	0	1 (0.7)	1 (0.4)
Dyspnoea	0	1 (0.7)	1 (0.4)
Oedema legs	0	1 (0.7)	1 (0.4)
Hypoglycaemia	0	1 (0.7)	1 (0.4)
Otitis externa	0	1 (0.7)	1 (0.4)
Embolism cerebral	1 (0.7)	0	1 (0.4)
Infection	1 (0.7)	0	1 (0.4)
Injury	1 (0.7)	0	1 (0.4)
Pancreatitis	1 (0.7)	0	1 (0.4)
Retinal haemorrhage	1 (0.7)	0	1 (0.4)
Skin ulceration	1 (0.7)	0	1 (0.4)

Data Source: Section 15, Table 15.2.3, x15.2.3, Appendix 13, Listing D.1.6

CARDIAC-RELATED ADVERSE EVENTS

There were significant cardiac-related adverse events associated with combination rosiglitazone and insulin therapy. A total of 23 patients (8.3%) experienced cardiac-related AEs, with 13 (9.4%) in the rosiglitazone group and 10 (7.2%) in the placebo group. 7 patients were withdrawn from the study as result of the cardiac event and in 9 patients the event was classified as an SAE.

Table 22 On-therapy Cardiac-Related Adverse Experiences by Body System and Preferred Term (All Randomised Patients)

AEs by Body System &Preferred Term, n (%)	Treatment Group		
	Ins+Plac (n=139)	Ins+RSG (n=138)	Total (n=277)
Cardiovascular General	6 (4.3)	6 (4.3)	12 (4.3)
Cardiac Failure	1 (0.7)	3 (2.2)	4 (1.4)
Hypertension	2 (1.4)	3 (2.2)	5 (1.8)
Hypertension aggravated	3 (2.2)	0	3 (1.1)
Heart Rate and Rhythm	3 (2.2)	2 (1.4)	5 (1.8)
Bundle branch block	0	1 (0.7)	1 (0.4)
Fibrillation atrial	2 (1.4)	0	2 (0.7)
Palpitation	1 (0.7)	1 (0.7)	2 (0.7)
Tachycardia	1 (0.7)	0	1 (0.4)
Myocardial, Endocardial, Pericardial, Valve	2 (1.4)	6 (4.3)	8 (2.9)
Angina pectoris	1 (0.7)	3 (2.2)	4 (1.4)
Myocardial Infarction	1 (0.7)	3 (2.2)	4 (1.4)

Data Source: Section 15, Table 15.2.1; Appendix 13, Listing D.1.2

There were 4 cases of cardiac failure, 3 in the rosiglitazone group and 1 in the placebo group. The incidence of ischaemic events (angina pectoris and myocardial infarction) was also greater in the rosiglitazone group (3 cases of each) than in the placebo group (1 case of each event).

The table below lists the patients with congestive heart failure and myocardial infarction. Of the 9 patients with congestive heart failure and myocardial infarction, 2 were in the placebo group

and 7 (7/138 or 5%) were in the rosiglitazone group. One of the rosiglitazone-treated patients had a myocardial infarction and died (see above also).

Study 085: Serious adverse events – Myocardial infarction and congestive heart failure
(Data abstracted from Table 23 and pages 77-80)

Treatment Received (plus insulin)	Patient Number	Age Sex	Adverse Event	Withdrawal	Day of Onset	Prior Cardiac Condition
RSG 4/8 mg	085.450.87702	77 M	Myocardial infarction	WD	103	Hypertension hypecholesterolemia
placebo	085.601.87624	66 F	Cardiac failure	WD	138	Hypertension Myocardial infarction Aortic valve prosthesis
RSG 4/8 mg	085.454.77203	61 F	Myocardial infarction		155	Myocardial infarction
RSG 4/8/4 mg	085.703.76982	63 F	Cardiac failure		138	Angina pectoris Hypertension hyperlipidimia
RSG 4/8/4mg	085.703.76983	72 F	Cardiac failure		100	No known prior cardiac history Hypertonia neuropathy
RSG 4/8 mg	085.803.76503	71 M	Myocardial Infarction Cardiac failure	WD	82	Angina Coronary heart disease Carotid atherosclerosis (bilateral) Atrial fibrillation Dyslipidemia hypertension
RSG 4 mg	085.805.76532	69 M	Cardiac failure	WD	29	No known prior cardiac disease Diabetic retinopathy Diabetic nephropathy
RSG 4/8 mg	085.813.76589	66 F	Myocardial infarction Atrioventricular block Death during cardiac catheterization	WD/death	95	hypertension
Placebo	085.925.87720	78 M	Myocardial infarction		116	Angina pectoris hypertension

Brief summaries of the above cases of congestive heart failure and myocardial infarction are listed below (in same order as above table):

(PID 085.450.87702) 77 year old male with history of hypertension and hypercholesterolemia who presented with angina pectoris and was diagnosed with myocardial infarction three months after initiation of combination rosiglitazone (RSG 4/8mg) and insulin therapy. Treatment with study medication was stopped, and patient underwent myocardial revascularization and coronary artery bypass. Treatment was thought to be unrelated to study drug by the investigator.

(PID 085.601.87624) 66 year old female with history of hypertension, myocardial infarction, angina pectoris, aortic valve prosthesis and surgery for arterial stenosis in the left leg who experienced edema one day after starting study treatment (placebo; patient had been on insulin for 6 years). Five months after initiation of study medication, she developed dyspnea and cardiac decompensation. The patient was treated with furosemide and isosorbide dinatrate and recovered 5 days later. She was withdrawn from the study. Treatment was thought to be possibly related to study drug by the investigator.

(PID 085.454.77203) 61 year old female with history of chest pain and myocardial infarction who developed chest pain 5 months after starting treatment drug (rosiglitazone 4/8 mg). A diagnosis of myocardial infarction was made. Symptoms resolved 21 days later, though the new left bundle branch block persisted. Treatment was thought to be probably unrelated to study drug by the investigator.

(PID 085.703.76982) 63 year old female with history angina, hypertension, hyperlipidemia, and snoring with apnea tendency who experienced pedal edema and suspected angina pectoris four months after initiation of the treatment drug (rosiglitazone). A diagnosis of congestive heart failure was made, the patient was treated with furosemide and the dose of treatment drug was reduced, and the event resolved the following day. Treatment was thought to be possibly related to study drug by the investigator.

(PID 085.703.76983) 72 year old female with history of hypertonia and neuropathy who developed edema (swollen feet) 3 months after initiation of treatment drug (rosiglitazone). Heart failure was suspected and he was treated with spironolactone and furosemide and the dose of rosiglitazone was reduced. The event resolved after 4 days. Treatment was thought to be probably related to study drug by the investigator.

(PID 085.803.76503) 71 year old male with history of asymptomatic peripheral vascular disease, bilateral carotid atherosclerosis, episodic atrial fibrillation, dislipemia, hypertension, history left carotid endarterectomy, angina, and subclinical heart disease in the past, who presented with an abrupt increase in dyspnea and ankle edema three months after the initiation of treatment drug (rosiglitazone). A diagnosis of congestive heart failure and subendocardial myocardial infarction was made. The patient withdrew from the study and recovered about 18 days later. Treatment was thought to be probably unrelated to study drug by the investigator.

(PID 085.805.76532) 69 year old male with history of diabetic nephropathy and diabetic retinopathy but no prior known cardiac disease, who developed exertional dyspnea, paroxysmal nocturnal dyspnea, increased edema of the lower limbs, and worsening cellulitis of left lower limb 21 days after the initiation of the treatment drug (rosiglitazone). The patient was treated for the diagnoses of congestive heart failure with ciprofloxacin and clindamycin. Study medication was stopped and the patient was withdrawn from the study. Treatment was thought to be probably related to study drug by the investigator.

(PID 085.813.76589) [This summary is also above under Deaths.]
66-year-old female treated with insulin and study treatment rosiglitazone. Prior medical history had included hypertension and she had angina pectoris 3 months after the initiation of the study drug. During the cardiac catheterization, she had an acute myocardial infarction and complete atrioventricular block, resulting in cardiorespiratory arrest and death. The investigator doubted the relation of these events and the study drug.

(PID 085.925.87720) 78 year old male with history hypertension, hyperlipidemia, and bilateral diabetic maculopathy, treated with placebo, who experienced anterior myocardial infarction four months after starting study medication (placebo). Treatment with treatment drug was interrupted for 12 days. Treatment was thought to be unrelated to study drug by the investigator.

Reviewer's Comment: The association of the above events with the patient's treatment combination rosiglitazone and insulin or placebo and insulin cannot be excluded, though preexisting cardiovascular history in the majority of the cases was a contributing factor. In the patients with no prior known cardiovascular history with a long duration of diabetes mellitus, a prior undiagnosed cardiovascular history cannot be excluded.

A full listing of the cardiac-related on-therapy adverse experiences is shown in Table 23.

Table 23 Randomised Patients with Cardiac-Related On-therapy Adverse Experiences

Treatment Received	Patient Number	AE (Preferred Term)	Drug relationship	Intensity	Day of Onset*	SAE/Withdrawal/ Death	Prior/Presenting cardiac condition	Corrective therapy	Outcome
RSG 8/8mg	085.450.87702	Myocardial infarction	Unlikely	Severe	102	SAE/WD	Hypertension	Yes	Resolved
Placebo	085.455.77130	Tachycardia	Unlikely	Moderate	42	"	Hypertension	No	Resolved
		Angina pectoris	Unlikely	Moderate	42	"	Tachycardia	No	Resolved
RSG 4/8mg	085.455.77193	Hypertension	Not related	Moderate	17	"	Hypertension	No	Resolved
RSG 8/8mg	085.454.77305	Bundle branch block	Unlikely	Moderate	155	SAE	Hypertension	Yes	Ongoing
		Myocardial infarction	Unlikely	Moderate	155	SAE		Yes	Ongoing
Placebo	085.501.87624	Cardiac failure	Suspected	Severe	198	SAE/WD	Aortic valve prosthesis Hypertension Myocardial infarction	Yes	Resolved
RSG 8/8mg	085.703.76982	Cardiac failure	Probable	Moderate	138	SAE	Angina pectoris	Yes	Resolved
RSG 4/8mg	085.703.76983	Cardiac failure	Probable	Moderate	190	"	"	Yes	Resolved
RSG 4/8mg	085.727.76366	Hypertension	Suspected	Mild	37	"	"	Yes	Ongoing
RSG 8mg	085.727.76575	Palpitation	Probable	Moderate	1	WD	Hypertension Myocardial infarction	No	Resolved
RSG 4mg	085.776.77028	Hypertension	Suspected	Severe	7	"	Angina pectoris Hypertension Quinnes	Yes	Resolved
Placebo	085.776.77029	Hypertension aggravated	Suspected	Moderate	57	"	Hypertension	Yes	Ongoing
Placebo	085.776.77031	Hypertension aggravated	Suspected	Moderate	4	"	Angina pectoris Hypertension	Yes	Resolved
Placebo	085.776.77034	Atrial fibrillation	Unlikely	Mild	30	"	Atrial fibrillation	Yes	Ongoing
RSG 4mg	085.777.77051	Angina pectoris	Unlikely	Moderate	11	SAE/WD	Cardiac failure Coronary bypass Hypertension Ischaemic heart disease	Yes	Resolved
RSG 4/8mg	085.773.77068	Angina pectoris	Probable	Mild	112	"	Hypertension	Yes	Ongoing
RSG 4/8mg	085.805.76905	Myocardial infarction	Unlikely	Severe	82	SAE/WD	Atrial fibrillation Left carotid surgery Hypertension	Yes	Resolved
RSG 4mg	085.805.76552	Cardiac failure	Probable	Severe	20	SAE/WD	"	Yes	Resolved
Placebo	085.805.76557	Hypertension	Unlikely	Mild	57	"	"	Yes	Ongoing
Placebo	085.805.76542	Hypertension	Suspected	Mild	140	"	"	Yes	Ongoing
Placebo	085.812.76564	Atrial fibrillation	Suspected	Mild	12	"	Atrial fibrillation	No	Resolved
		Palpitation	Not related	Mild	5	"		No	Ongoing
RSG 4/8mg	085.813.76589	Angina pectoris	Not related	Severe	95	SAE/WD/DEATH	Hypertension	Yes	Resolved
Placebo	085.924.76541	Hypertension aggravated	Unlikely	Moderate	66	"	Hypertension	Yes	Ongoing

In summary, 13/138 (9%) patients treated with rosiglitazone and insulin had cardiac-related adverse events as compared to 10/139 (7%) patients treated with placebo and insulin. 7/138 (7%) patients treated with rosiglitazone and insulin had more severe cardiac-related adverse events, including myocardial infarction and heart failure, as compared to 2/139 (2%) patients treated with placebo and insulin. (These rates of cardiac-related adverse events are not significantly different by the Fischer's exact test.)

ECHOCARDIOGRAPHY DATA

Echocardiograms were taken at baseline and at the end of treatment. However, only about half of the enrolled patients had evaluable echocardiograms at both times, because of non-evaluable or missing echocardiograms.

Table 36 Patients With and Without Evaluable Echocardiogram at Baseline (All Randomised Patients)

Number of patients at baseline: n (%)	Treatment Group		
	Ins + Placebo (n=139)	Ins + RSG (n=138)	Total (n=277)
With evaluable echocardiogram	83(59.7)	82 (59.4)	165 (59.6)
With non-evaluable echocardiogram	2 (1.4)	3 (2.2)	5 (1.8)
With missing echocardiogram	54(38.8)	53 (38.4)	107 (38.6)

Data Source: Section 15, Table 15.11

The sponsor concludes that treatment with rosiglitazone and insulin does not have any intrinsically deleterious effect on the myocardium/endocardium, as there were no changes in left ventricular mass, end diastolic volume, end systolic function, ejection fraction or cardiac index. The change from baseline for patients who had a baseline and week 26 value are shown the sponsor's table 38.

Table 38 Change in Echocardiogram Parameters from Baseline to Study Endpoint (Week 26) (All Randomised Patients)

	Treatment Group	
	Ins + Plac (n=139)	Ins + RSG (n=139)
Left Ventricular Mass (LVM) (g)		
n	60	57
Baseline (mean ± SD)	166.55 ± 60.35	165.3 ± 48.4
Week 26 (mean ± SD)	173.5 ± 63.5	165.85 ± 44.8
Change from Baseline	6.95 ± 53.65	0.55 ± 44.4
Left Ventricular Mass Index (LVMI) (g/m²)		
n	60	57
Baseline (mean ± SD)	84.7 ± 23.45	84.05 ± 23.00
Week 26 (mean ± SD)	87.9 ± 26.05	83.1 ± 19.30
Change from Baseline	3.2 ± 27.35	-0.95 ± 23.45
Left Ventricular End Diastolic Volume (LVEDV) (mL)		
n	60	56
Baseline (mean ± SD)	98.45 ± 28.25	95.45 ± 27.85
Week 26 (mean ± SD)	92.55 ± 34.4	95.15 ± 24.0
Change from Baseline	-5.95 ± 33.45	-0.3 ± 27.95
Left Ventricular End Diastolic Volume Index (LVEDVI)		
n	60	56
Baseline (mean ± SD)	50.45 ± 12.15	48.65 ± 13.70
Week 26 (mean ± SD)	47.05 ± 13.35	48.05 ± 12.50
Change from Baseline	-3.35 ± 16.75	-0.6 ± 14.3
Left Ventricular End Systolic Volume (LVESV) (mL)		
n	60	56
Baseline (mean ± SD)	36.55 ± 15.2	35.55 ± 12.9
Week 26 (mean ± SD)	33.1 ± 16.65	34.3 ± 12.1
Change from Baseline	-3.45 ± 14.35	-1.25 ± 14.45
Left Ventricular End Systolic Volume Index (LVESVI)		
n	60	56
Baseline (mean ± SD)	18.8 ± 6.9	18.1 ± 6.25
Week 26 (mean ± SD)	16.8 ± 7.95	17.25 ± 5.9
Change from Baseline	-1.8 ± 7.05	-0.85 ± 7.35
Left Ventricular Ejection Fraction (LVEF) (%)		
n	60	56
Baseline (mean ± SD)	63.15 ± 8.4	62.4 ± 7.05
Week 26 (mean ± SD)	64.8 ± 7.7	64.1 ± 6.75
Change from Baseline	1.6 ± 8.1	1.75 ± 8.6
Cardiac Index (CI)		
n	60	56
Baseline (mean ± SD)	2.25 ± 0.8	2.25 ± 0.7
Week 26 (mean ± SD)	2.15 ± 0.7	2.25 ± 0.65
Change from Baseline	-0.1 ± 0.95	0 ± 0.75

ASSESSMENT OF BRAIN NATURIETIC PEPTIDE

Brain natriuretic peptide may be a useful marker for detecting cardiac dysfunction in patients with diabetes mellitus. In this study, patients treated with insulin and rosiglitazone had a slightly larger mean change in BNP (4.1pg/ml) after 26 weeks compared to patients treated with insulin and placebo (0.9pg/ml).

Table 42 Change in Brain Naturietic Peptide at Study Endpoint (Week 26) Compared to Baseline (All Randomised Patients)

	Treatment Group	
	Ins+ Plac (n = 139)	Ins+ RSG (n = 138)
BNP (pg/ml)*		
Baseline (mean ± SD)	17.75 ± 20.7	14.25 ± 7.4
Week 26 (mean ± SD)	18.65 ± 21.15	18.35 ± 20.65
Change From Baseline	0.9 ± 14.25	4.1 ± 20.7

* Reference range < (n) = 42 pg/ml
Data Source: Section 15, Table 15.10.2, Appendix F, Listing F.L1, F.L2

ON-THERAPY EDEMA-RELATED ADVERSE EVENTS

A total of 36 patients experienced edema during the study – 16 (11.5%) in the insulin and placebo group and 20 (14.5%) in the insulin and rosiglitazone group. There were more patients with leg edema in the rosiglitazone and insulin group (9 versus 4). Only 4 of the 36 patients had a prior history of edema. Two patients were withdrawn from the study because of edema (one from each group). In four patients, the dose of rosiglitazone was not increased from 4 to 8mg because of edema, and in another patient the dose was decreased from 8mg to 4mg because of edema. Eleven patients were treated with a diuretic and in 4/11, the treatment was corrective.

Table 25 On-therapy Oedema-Related Adverse Experiences by Preferred Term (All Randomised Patients)

	Treatment Group		
AEs by Preferred Term, n (%)	Ins+ Placebo (n=139)	Ins+ RSG (n=138)	Total (n=277)
Total Patients with at least 1 oedema-related AE*	16 (11.5)	20 (14.5)	36 (13.0)
Oedema	6 (4.3)	9 (6.5)	15 (5.4)
Oedema dependent	3 (2.2)	1 (0.7)	4 (1.4)
Oedema generalised	2 (1.4)	0	2 (0.7)
Oedema legs	4 (2.9)	9 (6.5)	13 (4.7)
Periorbital oedema	1 (0.7)	0	1 (0.4)
Peripheral oedema	3 (2.2)	1 (0.7)	4 (1.4)

* Comprises: oedema, oedema dependent, oedema generalised, oedema legs, periorbital oedema and peripheral oedema
Data Source: Section 15, Table 15.2.1, Appendix D, Listing D.L2

WEIGHT

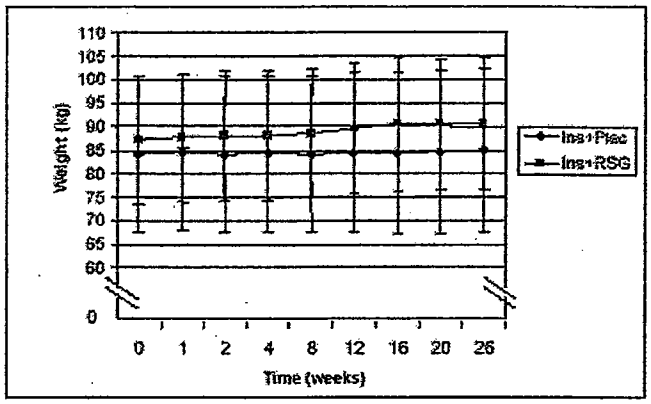
There was a 3kg weight gain in the rosiglitazone and insulin group, compared to 0.14kg in the insulin and placebo group. The greatest weight gain occurred after 8 weeks when the rosiglitazone dose was increased from 4mg to 8mg.

Table 39 Change in Weight at Study Endpoint (Week 26) Compared to Baseline (All Randomised Patients)

	Treatment Group	
	Ins + Placebo (n=139)	Ins + RSG (n=138)
Weight (kg)		
Baseline (mean ± SD)	84.04 ± 16.58	87.09 ± 13.76
Week 26 (mean ± SD)	84.96 ± 17.30	90.52 ± 13.99
Change from baseline* (n)	126	113
mean ± SD	0.14 ± 2.41	3.08 ± 3.39

* Those patients who had both a baseline and a week 26 value
Data Source: Section 15, Tables 15.9.3, Appendix E, Listings E.L1.A, E.L2A

Figure 5 Mean Body Weight Over Time (All Randomized Patients)



Data Source: Section 15, Table 15.6.3, Appendix E, Listings E.1.1A, E.1.2A
Error bars = Geometric mean-SE, Geometric mean+SE

Assessment of hemoglobin and hematocrit revealed a decrease of .86g/dl and 2.65 %, respectively, during the study in patients treated with insulin and rosiglitazone, versus negligible changes in the other group. Most of the decrease occurred after the increase to the 8 mg dose.

No patients had values of AST, ALT, alkaline phosphatase 3 times the upper reference limit or total bilirubin 1.5 times the upper reference limit.

HYPOGLYCEMIA

A total of 44 patients (15.9%) experienced hypoglycemia, 20 (14.4%) in the insulin and placebo group and 24 (17.4%) in the insulin and rosiglitazone group. Only one of these was considered a serious adverse event (a patient in the rosiglitazone and insulin group), and it resulted in a hospitalization.

LIPID PARAMETERS

Small mean increases in total cholesterol, LDL cholesterol, and HDL-cholesterol were noted in the rosiglitazone and insulin group as compared to the placebo and insulin group.

Table 46 Percent Change in Lipid Parameters at Study Endpoint (Week 26) Compared to Baseline (All Randomised Patients)

	Treatment Group	
	Ins + Plac (n = 139)	Ins + RSG (n = 138)
Total Cholesterol (mg/dL)		
n*	121	107
Baseline, geometric mean **	202.9 (199.82, 206.02)	210.1 (206.79, 213.49)
Week 26, geometric mean **	199.9 (196.57, 203.39)	224.7 (220.37, 229.15)
Change from baseline (%) geometric mean **	-0.1 (-1.15, 1.02)	5.6 (4.01, 7.21)
HDL-cholesterol (mg/dL)		
n*	129	105
Baseline, geometric mean **	51.4 (50.33, 52.48)	51.2 (50.19, 52.16)
Week 26, geometric mean **	51.2 (50.08, 52.27)	52.8 (51.57, 54.02)
Change from baseline (%) geometric mean **	0.2 (-1.05, 1.43)	3.1 (1.32, 4.99)
LDL-cholesterol (mg/dL)		
n*	115	91
Baseline, geometric mean **	120.4 (117.73, 123.19)	124.2 (121.35, 127.18)
Week 26, geometric mean **	116.3 (113.69, 118.95)	134.9 (131.37, 138.46)
Change from baseline (%) geometric mean **	-1.7 (-3.27, -0.05)	4.2 (2.37, 6.08)
Triglycerides (mg/dL)		
n*	121	107
Baseline, geometric mean **	129.2 (121.39, 137.50)	127.3 (119.68, 135.36)
Week 26, geometric mean **	132.8 (125.53, 139.68)	143.4 (135.84, 151.31)
Change from baseline (%) geometric mean **	6.7 (3.46, 10.07)	8.3 (4.47, 12.46)
Free Fatty Acids (mg/dL)		
n*	117	109
Baseline, geometric mean **	13.6 (13.45, 14.62)	14.5 (13.95, 15.12)
Week 26, geometric mean **	14.2 (13.68, 14.80)	13.4 (12.86, 14.03)
Change from baseline (%) geometric mean **	3.8 (-1.59, 8.05)	-8.3 (-12.70, -3.95)

* Change from baseline calculated only for those patients who had both a baseline and a Week 26 visit (= n)
** Geometric mean (geometric mean ± SE, geometric mean +SE)
NOTE: All laboratory values are fasting
Data Source: Section 15, Table 15.7.7, Appendix 8, Listings F L1 and F L2

Protocol 136-*A 26 week randomized, double-blind multicenter placebo-controlled study to evaluate the efficacy, safety, and tolerability of rosiglitazone with concurrent insulin therapy and/or a sulfonylurea in type 2 diabetic patients with chronic renal failure (not on dialysis)*

In this study, 148 patients were exposed to rosiglitazone, 112 to insulin and rosiglitazone and 36 to a sulfonylurea and rosiglitazone. This population comprised patients with renal failure, long-standing history of type 2 diabetes, and many had significant cardiac disease at presentation. ((The inclusion criteria excluded NYHA I-IV, but many patients with cardiac disease may be asymptomatic)) During the screening period, 239 (82.1%) patients had hypertension, 17 (5.8%) had angina pectoris, and 12 of 221 (5.4%) of the patients on insulin had heart failure. 51% of the rosiglitazone-treated patients wee exposed to the drug for more than 180 days, 34% were exposed for 91-180 days, and 14.2% for less than 90 days. The exposure was similar in patients treated with placebo.

The most common adverse events, those experienced by >5% of patients, included hypoglycemia, edema, respiratory disorder, and anemia, all of which were more common in the rosiglitazone-treated than in the placebo-treated group.

Table 43 On-therapy Adverse Experiences Reported by ≥5% of Patients in Any Treatment Group by Preferred Term (All Randomised Patients)

AEs by Preferred Term, n (%)	Treatment Group		
	Placebo N=143	RSG N=148	Total N=291
Total Patients with at least one AE	97 (67.8)	111 (75.0)	208 (71.5)
Hypoglycaemia	17 (11.9)	33 (22.3)	50 (17.2)
Oedema†	13 (9.1)	28 (18.9)	41 (14.1)
Respiratory Disorder	3 (2.1)	9 (6.1)	12 (4.1)
Anaemia	7 (4.9)	8 (5.4)	15 (5.2)
Infection Viral	3 (2.1)	8 (5.4)	11 (3.8)
Injury	3 (2.1)	8 (5.4)	11 (3.8)
URTI	9 (6.3)	6 (4.1)	15 (5.2)
Hyperglycaemia	12 (8.4)	5 (3.4)	17 (5.8)
Hypertension	8 (5.6)	1 (0.7)	9 (3.1)

† Comprises oedema, oedema dependent, oedema legs, oedema generalised and oedema peripheral
NOTE: Sorted by highest dose of rosiglitazone
Data Source: Section 13, Table X15.2.8; Appendix D, Listing D.L2

DEATHS

There were three deaths during this study: one of these deaths (patient 136.951.74467) was during the placebo run-in period. The other two deaths occurred in patients treated with rosiglitazone. Patient 136.701.74549 was a 78 year old male who died from a suspected myocardial infarction 26 days after the first dose of rosiglitazone in combination with a sulfonylurea. The patient had a history of atrial flutter, hypertension, chronic renal failure, and two prior myocardial infarctions. Patient 136.778.74643 was a 73 year old male who died from pneumonia and cardiac insufficiency 5 months after initiating rosiglitazone therapy. He was also on insulin, and he had a history of chronic renal failure, hyperlipidemia, coronary heart disease (myocardial infarction 5 years previously), and hypertension.

WITHDRAWALS

Withdrawals due to adverse experiences included 9 (6.3%) patients in the placebo group and 14 (9.5%) patients in the rosiglitazone group. 13 of the 14 patients who and were on rosiglitazone were also on insulin. Three of these patients had mild renal failure at entry, five had moderate renal failure, and four had severe renal failure. All the placebo-treated patients who withdrew were on insulin, and one had mild renal failure, five had moderate renal failure, and three had severe renal failure at study entry. Causes for withdrawal included edema (5 in rosiglitazone group; 0 in placebo group), cardiac failure (3 in the rosiglitazone group; 2 in the placebo group), fluid overload (1 in placebo group only); myocardial infarction (1 in rosiglitazone group; 0 in placebo group).

Table 59 Summary of Patient Withdrawals Due to On-Therapy Adverse Experiences (All Randomised Patients)

AEs leading to withdrawal by Preferred Term, n (%)	Treatment Group: Placebo (n=143)	Treatment Group: RSG (n=148)	Total (n=291)
No. of patients with at least one event	9 (6.3)	14 (9.5)	23 (7.9)
Implantation complication	1 (0.7)	0 (0.0)	1 (0.3)
Drug level increased	1 (0.7)	0 (0.0)	1 (0.3)
Oedema	0 (0.0)	3 (2.0)	3 (1.0)
Oedema Dependent	0 (0.0)	1 (0.7)	1 (0.3)
Oedema Generalised	0 (0.0)	1 (0.7)	1 (0.3)
Fever	0 (0.0)	1 (0.7)	1 (0.3)
Cardiac Failure	2 (1.4)	3 (2.0)	5 (1.7)
Fluid Overload	1 (0.7)	0 (0.0)	1 (0.3)
Migraine	0 (0.0)	1 (0.7)	1 (0.3)
Diarrhoea	1 (0.7)	1 (0.7)	2 (0.7)
Vomiting	1 (0.7)	0 (0.0)	1 (0.3)
Jaundice	0 (0.0)	1 (0.7)	1 (0.3)
Hyperglycaemia	2 (1.4)	0 (0.0)	2 (0.7)
Hyperkalaemia	1 (0.7)	0 (0.0)	1 (0.3)
Weight Increase	0 (0.0)	1 (0.7)	1 (0.3)
Myocardial Infarction	0 (0.0)	1 (0.7)	1 (0.3)
Adenocarcinoma NOS	0 (0.0)	1 (0.7)	1 (0.3)
Pancreas Neoplasm Malignant	0 (0.0)	1 (0.7)	1 (0.3)
Anaemia	3 (2.1)	1 (0.7)	4 (1.4)
Pneumonia	0 (0.0)	1 (0.7)	1 (0.3)
Respiratory Disorder	1 (0.7)	0 (0.0)	1 (0.3)
Rash Pustular	0 (0.0)	1 (0.7)	1 (0.3)
Renal Failure Acute	1 (0.7)	0 (0.0)	1 (0.3)

NOTE: Patient could be withdrawn due to more than one adverse experience
Data Source: Section 13, Table 15.5; Appendix D, Listing D.14

Table 60 Patients Withdrawn From the Study Due to On-Therapy Adverse Experiences

Patient Number	Treatment Group	On Insulin?	Severity at Renal Failure at Entry	Age (yrs)	Gender (M/F)	Adverse Experience(s) Leading to Withdrawal Preferred Term	Intensity	Relationship To Study Medication
134 704 79418	Placebo	Yes	Severe	68	M	Anaemia	Moderate	Unlikely
134 483 79417	Placebo	Yes	Moderate	72	M	Cardiac Failure	Severe	Unlikely
134 403 79517	Placebo	Yes	Moderate	62	F	Hyperglycaemia	Severe	Not related
134 484 79916	Placebo	Yes	Mild	57	M	Hyperglycaemia Implantation Complication	Moderate Moderate	Not related Not related
134 905 79512	Placebo	Yes	Severe	59	M	Renal Failure Acute	Moderate	Not related
134 901 79423	Placebo	Yes	Severe	42	M	Diarrhoea Vomiting	Severe Severe	Unlikely Unlikely
134 912 79412	Placebo	Yes	Moderate	74	M	Hyperkalaemia Drug Level Increased	Moderate Moderate	Unlikely Unlikely
134 906 79478	Placebo	Yes	Moderate	61	M	Anaemia	Severe	Unlikely
132 901 78350	Placebo	Yes	Moderate	79	M	Fluid Overload Anaemia Respiratory Disorder Cardiac Failure	Severe Moderate Moderate Moderate	Unlikely Unlikely Unlikely Unlikely
134 804 79481	Rosiglitazone	Yes	Moderate	57	M	Rash Pustular	Moderate	Unlikely
134 813 79502	Rosiglitazone	Yes	Moderate	75	M	Oedema Generalised Cardiac Failure	Severe Mild	Unlikely Unlikely
134 407 79502	Rosiglitazone	Yes	Mild	59	F	Oedema	Moderate	Unlikely
134 407 79503	Rosiglitazone	Yes	Mild	66	F	Weight Increase Oedema	Mild Mild	Unlikely Unlikely
134 901 79527	Rosiglitazone	Yes	Moderate	75	F	Anaemia	Moderate	Not related
134 813 79459	Rosiglitazone	Yes	Severe	68	M	Jaundice Pancreas Neoplasm Malignant	Severe Severe	Not related Not related
134 423 79503	Rosiglitazone	Yes	Mild	69	F	Migraine	Moderate	Not related
134 503 79574	Rosiglitazone	Yes	Moderate	67	M	Adenocarcinoma NOS	Severe	Not related
134 503 79575	Rosiglitazone	Yes	Severe	61	F	Diarrhoea Fever	Severe Severe	Not related Not related
134 701 79519	Rosiglitazone	No	Moderate	77	M	Myocardial Infarction	Severe	Unlikely
134 708 79418	Rosiglitazone	Yes	Severe	61	M	Oedema	Moderate	Unlikely
134 708 79503	Rosiglitazone	Yes	Severe	72	M	Pneumonia Cardiac Failure	Severe Severe	Unlikely Unlikely

CARDIAC-RELATED ADVERSE EVENTS

The incidence of cardiac-related adverse experiences was similar in the two groups, irrespective of concomitant use of insulin or the degree of renal impairment at screening. Four patients in the placebo group and 4 patients in the rosiglitazone group had on-therapy adverse experiences of cardiac failure. Two patients treated with rosiglitazone (one with insulin and one with a

sulfonylurea) had pulmonary edema. In the former patient, the pulmonary edema occurred 21 days after the rosiglitazone dose was increased to 8mg/day, while in the second patient the pulmonary edema was associated with the receiving of a blood transfusion. Of the 6 patients in the rosiglitazone group who reported cardiac failure or pulmonary edema, five were on a maximal dose of rosiglitazone of 4mg. Another patient with a history of heart failure also had mild congestive heart failure post therapy. Thus, 7 patients on rosiglitazone and 4 patients on placebo reported cardiac failure. Only three of the 12 patients who had cardiac failure at entry into the study reported cardiac failure as an on-therapy adverse experience.

Five patients (all on insulin) withdrew due to an adverse experience of cardiac failure, 3 on rosiglitazone (one of whom died) and 2 in the placebo group.

Table 44 On-therapy Cardiac-related Adverse Experiences by Body System and Preferred Term (All Randomised Patients)

AEs by Body System & Preferred Term, n (%)	Treatment Group: Placebo insulin (n=109)	Placebo not on insulin (n=34)	RSG insulin (n=112)	RSG not on insulin (n=36)	Total insulin (n=221)	Total not on insulin (n=70)
Cardiovascular General	14 (12.8)	5 (14.7)	12 (10.7)	3 (8.3)	26 (11.8)	8 (11.4)
Cardiac Failure, Cardiac Failure Left	4 (3.7)	0 (0.0)	4 (3.6)	0 (0.0)	8 (3.7)	0 (0.0)
Pulmonary oedema	0 (0.0)	0 (0.0)	1 (0.9)	1 (2.8)	1 (0.5)	1 (1.4)
Fluid Overload	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Heart Disorder	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)	0 (0.0)
Hypertension, Hypertension Aggravated	9 (8.3)	4 (11.8)	5 (4.5)	1 (2.8)	14 (6.3)	5 (7.1)
Hypotension	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)	0 (0.0)
Syncope	0 (0.0)	1 (2.9)	0 (0.0)	1 (2.8)	0 (0.0)	2 (2.9)
Heart Rate and Rhythm	1 (0.9)	0 (0.0)	1 (0.9)	1 (2.8)	2 (0.9)	1 (1.4)
Fibrillation, Atrial	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	1 (1.4)
Tachycardia	1 (0.9)	0 (0.0)	1 (0.9)	1 (2.8)	2 (0.9)	1 (1.4)
Myocardial, Endocardial, Pericardial, Valve	1 (0.9)	0 (0.0)	1 (0.9)	1 (2.8)	2 (0.9)	1 (1.4)
Angina Pectoris	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)	0 (0.0)
Coronary Disorder	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Myocardial Infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	1 (1.4)

Data Source: Section 13, Tables 15.2.4.1 and 15.2.4.NI; Appendix D, Listing D.1.2

Table 45 Patients with On-therapy Cardiac Failure/Pulmonary Oedema Adverse Experience (All Randomised Patients)

Patient Number	Treatment Group (dose)	Concomitant Insulin?	Severity of Renal Failure at Entry	Intensity	Relationship	Withdrawn due to AE?	CHF at entry?
236 403 73477	Placebo	Yes	Moderate	Severe	Susp/Prob	Yes	Yes
236 902 73495	Placebo	Yes	Moderate	Mild	Susp/Prob	No	No
236 951 73998	Placebo	Yes	Moderate	Moderate	Unlikely	Yes	No
236 902 74480	Placebo	Yes	Severe	Severe	Unlikely	No	Yes
136 104 74412	Rosiglitazone 4mg	Yes	Mild	Moderate	Susp/Prob	No	Yes
136 105 74562	Rosiglitazone 4mg	Yes	Moderate	Mild	Susp/Prob	Yes	No
136 778 73643	Rosiglitazone 4mg	Yes	Severe	Severe	Unlikely	Yes - died	No
136 904 74099	Rosiglitazone 4mg	Yes	Moderate	Severe	Susp/Prob	Yes	No
136 420 74697	Rosiglitazone 8mg	Yes	Moderate	Mild	Not Related	No	No
136 307 74582	Rosiglitazone 8mg	No	Severe	Severe	Susp/Prob	No	No

Data Source: Section 11, Table 13.5.2; Section 13, Tables X15.2A, 15.2.1, 15.2.2, 15.2.4.1, 15.2.4.NI and 15.5.
Note: One patient, previously on rosiglitazone, with a history of heart failure and receiving insulin therapy (136.104.74436) had mild congestive heart failure post-therapy. Data source: Appendix B, Listings B.1.3, B.1.4, Appendix D, Listing D.1.3, .

Table 46 On-therapy Cardiac Failure/Pulmonary Oedema Adverse Experiences by Severity of Renal Failure at Entry (All Randomised Patients)

Severity of Renal Failure at Entry, n (%)*	Treatment Group: Placebo Insulin (n=109)	Placebo Not on Insulin (n=34)	RSG Insulin (n=112)	RSG Not on Insulin (n=36)	Total Insulin (n=221)	Total Not on Insulin (n=70)
≥80 ml/min	n=2	n=0	n=4	n=3	n=6	n=3
	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (16.7)	0 (0.0)
Mild	n=35	n=8	n=32	n=19	n=67	n=27
	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	1 (1.5)	0 (0.0)
Moderate	n=54	n=19	n=56	n=9	n=110	n=28
	3 (5.6)	0 (0.0)	3 (5.4)	0 (0.0)	6 (5.5)	0 (0.0)
Severe	n=18	n=7	n=20	n=5	n=38	n=12
	1 (5.6)	0 (0.0)	1 (5.0)	1 (20.0)	2 (5.3)	1 (8.3)

* Renal Failure at Entry: Mild = CrCl 60-79mL/min, moderate = CrCl 30-59mL/min, severe = CrCl ≤ 29mL/min
Creatinine clearance estimated using the Cockcroft-Gault equation
Data Source: Sections 13 and 14, Tables X15.2A.E, 15.2A.NI, 15.2.4.1, 15.2.4.NI and Ad Hoc Table 751; Appendix D, Listing D.1.2

Four patients with renal failure at entry were in the placebo group (3 moderate and 1 severe) and 5 patients with renal failure at entry in the rosiglitazone group were distributed 1 mild, 3 moderate, 1 severe. One patient on rosiglitazone had normal renal function and cardiac failure.

EDEMA

At baseline, three patients in each of the placebo and rosiglitazone groups had edema. Diuretic use pre-screening occurred in 75 (52.4%) patients in the placebo group, and 70 (47.3%) patients in the rosiglitazone group. Concomitant diuretic use occurred in 84 (58.7%) patients in the placebo group, and in 81 (54.7%) patients in the rosiglitazone group. Thirteen patients (12 on insulin) in the placebo group reported edema, while 28 patients (25 were on insulin) in the rosiglitazone group reported edema. No patient in the placebo group withdrew because of edema, while five patients in the rosiglitazone group withdrew because of edema.

Table 48 On-therapy Oedema-related Adverse Experiences by Preferred Term (All Randomised Patients)

AEs by Preferred Term, n (%)	Treatment Group: Placebo Insulin (n=109)	Placebo Not on Insulin (n=34)	RSG Insulin (n=112)	RSG Not on Insulin (n=36)	Total Insulin (n=221)	Total Not on Insulin (n=70)
Total patients with at least one oedema-related AE*	12 (11.0)	1 (2.9)	25 (22.3)	3 (8.3)	37 (16.7)	4 (5.7)
Oedema	5 (4.6)	0 (0.0)	15 (13.4)	1 (2.8)	20 (9.0)	1 (1.4)
Oedema Dependant	4 (3.7)	1 (2.9)	5 (4.5)	1 (2.8)	9 (4.1)	2 (2.9)
Oedema Generalised	2 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)	3 (1.4)	0 (0.0)
Oedema Legs	1 (0.9)	0 (0.0)	5 (4.5)	1 (2.8)	6 (2.7)	1 (1.4)
Oedema Peripheral	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	1 (1.4)

* includes 2 patients in the RSG group who each experienced two episodes of oedema during the study (patients 138 165.74762 and 138.375.74654)
Data Source: Section 13, Tables 15.2.4.1 and 15.2.4.NI; Appendix D, Listing D.1.2

Table 49 On-therapy Oedema-related Adverse Experiences by Severity of Renal Failure at Entry (All Randomised Patients)

Severity of Renal Failure at Entry, n (%)*	Treatment Group: Placebo Insulin (n=109)	Placebo Not on Insulin (n=34)	RSG Insulin (n=112)	RSG Not on Insulin (n=36)	Total Insulin (n=221)	Total Not on Insulin (n=70)
≥80 mL/min	n=2	n=0	n=4	n=3	n=6	n=3
	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (16.7)	0 (0.0)
Mild	n=35	n=8	n=32	n=19	n=67	n=27
	7 (20.0)	0 (0.0)	7 (21.9)	1 (5.3)	14 (20.9)	1 (3.7)
Moderate	n=54	n=19	n=56	n=9	n=110	n=28
	4 (7.4)	0 (0.0)	13 (23.2)	1 (11.1)	17 (15.5)	1 (3.6)
Severe	n=18	n=7	n=20	n=5	n=38	n=12
	1 (5.6)	1 (14.3)	4 (20.0)	1 (20.0)	5 (13.2)	2 (16.7)

* Renal Failure at Entry. Mild = CrCl 60-79mL/min, moderate = CrCl 30-59mL/min, severe = CrCl ≤ 29mL/min
Creatinine clearance estimated using the Cockcroft-Gault equation
Data Source: Sections 13 and 14, Tables X15.2A.3, 15.2A.NI, 15.2.4.1, 15.2.4.NI and Ad Hoc Table 73I; Appendix D, Listing D.1.2

ANEMIA-RELATED ADVERSE EXPERIENCES

A similar number of anemia-related adverse experiences was reported in the two groups: seven (4.9%) in the placebo group and 8 (5.4%) in the rosiglitazone group.

HYPOGLYCEMIA

Thirty-three (22.3%) patients treated with rosiglitazone and 17 patients (11.9%) treated with placebo reported hypoglycemia during the study. These were independent of the renal failure status. Of the 33 patients in the rosiglitazone group, 16 had a maximum dose of 4mg and 17 had a maximum dose of 8mg. Two adverse events of hypoglycemia from patients on rosiglitazone with were classified as severe. Twelve (8.4%) patients in the placebo group and 26 (17.6%) patients in the rosiglitazone group who had an episode of hypoglycemia had a decrease in insulin and/or sulfonylurea dose. However, nine patients (6.3%) in the placebo group and 14 (9.5%) in the rosiglitazone group also had dose reductions without an episode of hypoglycemia.

Table 53 Patients with On-therapy Adverse Experiences of Hypoglycaemia (All Randomised Patients)

	Treatment Group		
Adverse Experience, n (%)	Placebo (n=143)	RSG (n=148)	Total (n=291)
Hypoglycaemia	17 (11.9)	33 (22.3)	50 (17.2)
Hypoglycaemia with FPG<50mg/mL	2 (1.4)	5 (3.4)	7 (2.4)
Hypoglycaemia with Third Party Intervention/Hospitalisation	0 (0.0)	1 (0.7)	1 (0.3)

Data Source: Section 13, Table 15.2.5; Appendix D, Listing D.1.2

Hemoglobin and hematocrit both decreased (by 0.8 g/dl and 2.4%, respectively) during the study in the patients treated with rosiglitazone as compared to placebo.

A weight gain of 2.7 kg was observed in the rosiglitazone-treated group and 0.6 kg in the placebo group.

SUMMARY OF SAFETY REVIEW

A total of 250 patients (138 in study 085 and 112 in study 136) were exposed to combination rodiglitazone and insulin treatment. The main adverse effects included hypoglycemia, edema, anemia, weight gain (about 3 kg), and cardiac adverse events. The percent of patients treated with combination rosiglitazone and insulin who presented with hypoglycemia was 17.4% versus 13.7% in the placebo group (study 085) and 18.9% versus 11.9% in the placebo group (study 136). For comparison, 63% of the patients in studies 082 and 095 (408 patients exposed to combination rosiglitazone and insulin therapy) had hypoglycemia as emergent adverse events (as compared to 41.4% in the insulin placebo group. Cardiac-related adverse events comprised 13 patients on combination rosiglitazone and insulin therapy in study 085 and 12 patients in study 0136, as compared to 10 and 14 patients on insulin and placebo, respectively. However, the number of cases of cardiac failure were 3 in the rosiglitazone group versus 1 in the placebo group in study 085 and 5 in the rosiglitazone group (including a case of pulmonary edema plus one post-therapy case of CHF) versus 4 in the insulin and placebo group in study 136. In comparison, there were 10 cases of CHF in the rosiglitazone and insulin treated groups in studies 082 and 095, versus two cases in the control group. There were three cases of myocardial infarction in the rosiglitazone and insulin group and one case in the placebo group (study 085). Thus, despite less intensive glycemic control, as manifested by less incidence of hypoglycemia and a smaller decrease in HgA1c, there is still an excess of congestive heart failure and myocardial infarction in study 085.

SPONSOR'S SUMMARY OF BENEFITS AND RISKS

The sponsor summarized the data from studies 082, 095, 085, and 136 with a special emphasis on the emergent adverse events of cardiac failure. Other cardiac-related adverse events were not always included or at least not highlighted. The sponsor's analysis is written in support of the lower dose of rosiglitazone 4mg. In studies 082 and 095, in patients with HbA1c $\geq$ 7.5%, rosiglitazone 4mg was associated with a decrease in HbA1c of 0.6% (4mg qd) and 0.7% (2 mg bd).

Table 1 Numbers of Patients with On-therapy Adverse Events (082, 095)

	RSG 4mg qd + insulin N=99	RSG 2mg bd + insulin N=107	Placebo + insulin N=203
Hypoglycemic symptoms[1]	61	57	84
Edema	19	14	11
Cardiovascular AE (total)[2]	10	7	9
CHF (total)	2	2	2
CHF (SAE)	0	1	1
CHF (withdrawn)	0	0	0

[1] Symptoms or signs of hypoglycemia with or without documented capillary or plasma glucose <50mg/dl.
[2] Included: CHF, chest pain, coronary artery disorder, angina pectoris, angina pectoris aggravated, cardiac arrest, brain disorder, cardiomegaly, myocardial infarction, myocardial ischemia.
Data source: Insulin cNDA, Item 28, ISS Tables 11.2.4.1b and 11.2.4.1c

It is important to note that the n in the placebo group is about twice the n in the rosiglitazone groups. Thus, the rates for the adverse events of edema, cardiovascular adverse events, and CHF in the rosiglitazone groups are about twice the rates for these events in the placebo group.

The rate of emergent CHF in the rosiglitazone and insulin group was three times the rate in the placebo group.

Table 2 Numbers of Patients with On-therapy Cardiac-related Adverse Events, Serious Adverse Events of CHF and CHF Events Leading to Withdrawal (085)

	RSG + insulin N=138	Placebo + insulin N=139
Cardiovascular AE (total)*	13	10
CHF (total)	3	1
CHF (SAE)	2	1
CHF (withdrawn)	1	1

*Included: CHF, hypertension, aggravated, Sinus bradycardia, atrial fibrillation, palpitations, tachycardia, angina pectoris, myocardial infarction
Data Source: Study 085 Clinical Trial Report, Section 12, Tables 12.2.1, 12.2.3 and 12.2.5; Appendix 2, Listings 2.1.2, 2.1.4 and 12.2.6

There was a smaller excess of CHF in study 136.

Table 4 Baseline Characteristics (136)

	RSG N=345	Placebo N=343
Treatment		
Insulin alone	99 (68%)	99 (68%)
SU alone	36 (25%)	35 (25%)
Insulin + SU	10 (7%)	9 (6%)
Baseline HbA1c	8.2%	8.3%
Mean Duration of Diabetes	14 yrs	16 yrs
Screening Cl_{creat}		
≥ 80 mL/min (normal)	7 (5%)	2 (1%)
50-79 mL/min (mild CRF)	50 (34%)	43 (30%)
30-49 mL/min (mod CRF)	68 (45%)	75 (51%)
≤ 29 mL/min (severe CRF)	23 (16%)	25 (18%)

Data Source: Study 136 Clinical Trial Report, Section 12, Tables 12.3.2, 12.4.3

Table 5 Numbers of Patients with Cardiac-related Adverse Events, Serious Adverse Events of CHF and CHF Events Leading to Withdrawal (136)

	RSG + Insulin/SU N=148	Placebo + Insulin/SU N=143
Cardiovascular AE (total)*	17	19
CHF (total)	5**	4
CHF (SAE)	3	3
CHF (withdrawn)	3	2

*Includes: cardiac failure, cardiac failure left, heart disorder, hypertension, hypertension aggravated, atrial fibrillation, tachycardia, angina pectoris, coronary disorder, myocardial infarction
**Includes one post-therapy CHF event
Data Source: Study 136 Clinical Trial Report, Section 15, Tables 15.2.3, 15.2.4, 15.5; Appendix D, Listings D.12, D.14, D.15

The sponsor concludes that in susceptible patients, fluid retention may lead to congestive heart failure but that it is monitorable and treatable.

The small number of events of CHF on rosiglitazone 4mg added to exogenous insulin from Studies 082, 095, 085 and 136 described in this document clearly support the assertions that, in susceptible patients (ie. patients unable to tolerate modest increases in plasma volume), fluid retention may lead to congestive heart failure, and that patients with known cardiovascular disease and those felt to be at high risk for cardiac disease, should be closely monitored for signs and symptoms of fluid overload. These events did not present as acute pulmonary edema and generally were accompanied or preceded by other signs of fluid retention such as peripheral edema and excessive weight gain. These observations, in addition to the fact that standard medical management was generally effective, further support an appropriate role for patient monitoring and education when rosiglitazone is added to insulin therapy.

In summary, the risk of developing fluid-related adverse events when rosiglitazone is added to exogenous insulin appears to be gradual, dose-related and affected by host characteristics, increased in older patients and in patients with long-standing diabetes (likely surrogates for prevalent co-morbid cardiovascular conditions), as well as in patients with established cardiovascular disease including CHF. This appears to be a class effect of PPAR gamma activators, which sensitize peripheral tissues to the effects of insulin, and thereby are hypothesized to potentiate the fluid retaining properties of insulin. The identification of risk factors and the presence of a dose-relationship indicate that this is a potentially predictable side effect which can be readily monitored for intervention if necessary.

The sponsor proposes a mechanism of action for thiazolidinedione-induced fluid retention. This appendix 1 is reproduced below.

3 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 21-071
5004

FINANCIAL DISCLOSURE FOR STUDIES 082 AND 095)

Form 3454, CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS, had not been submitted by David Wheadon, V.P. & Director of Regulatory Affairs and Product Professional Services was not submitted in the electronic NDA. The financial disclosure has been requested.

CONCLUSION OF STUDY RESULTS

Clinical Studies of Combination Rosiglitazone and Insulin Treatment				
Study	082	095	085	136
Rosiglitazone Dose	0, 4, or 8 mg	0, 4, or 8 mg	0 or 4/8 mg (or 4/8/4 mg)	0 or 4/8 mg (or 4/8/4 mg)
n	319	292	277	221
age	56-58	57-59	61	66
Age > 65	20-23%	25-34%	40%	60%
% male	56	59-64	54	61
% Caucasian	68-72	68-73	99	98
Duration of DM	12.3	13.1	13.4 and 14.6	14.6
Cardiac exclusion	NYHA 3-4	NYHA 3-4	NYHA 1-4	NYHA 1-4
Baseline HbA1c	8.9 – 9.1%	9.1 – 8.8%	8	8.3 – 8.2
FPG	195-212	199-203	157-167	170-174
Change in HbA1c (%) for 8 mg dose	-1.2	-0.7	-0.07 (placebo +.45)	-0.5
baseline insulin dose	70-78	65-76	57-61	54-56
Decrease in insulin dose (8 mg) adjusted for placebo	12.6%	14.7%	16.5%	(not given)
% Patients with Hypoglycemia (rosiglitazone vs placebo)	67% vs 38%	71% vs 45%	17.4% vs 13.7%	22.3% vs 11.9%

Incidence of Cardiac Related Adverse Events in Double-blind Population
Number of patients with events in **rosiglitazone** and insulin group are compared to events in **placebo** and insulin groups.

Study	**082 and 095** (combined)	**085**	**136**
N (#patients)	408 vs 203	138 vs 139	112 vs 109
Cardiac AEs	43 vs 10	13 vs 10	12 vs 14
CHF	10 vs 2	3 vs 1	5 (6) vs 4
MI	2 vs 0	3 vs 1	0 vs 0
Cardiac arrest	2 vs 0	1 vs 0	0 vs 0

RECOMMENDATIONS
This application adequately supports the safety of the combination rosiglitazone and insulin therapy in type 2 diabetes mellitus, pending appropriate labeling.

Recommendation code: Approveable

SIGNATURE PAGE

Reviewed by:

(2/7/03)

Joanna K. Zawadzki, M.D.
FDA/CDER/OND/ODEII/DMEDP
Medical Officer

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Medical Team Leader
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cc: Original NDA (NDA Archive DMEDP)
HFD-510/Division File
HFD-510/Zawadzki /Orloff/Weber

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: February 7, 2001 FEB 8 2001

FROM: David G. Orloff, M.D. 2-8-07
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-071/S-004, S-006

SUBJECT: sNDA review issues and action

Administrative background

These supplements are being acted upon simultaneously on February 8, 2001. Supplement S-004 was submitted February 8, 2000 and proposed a new indication for the combined use of Avandia and insulin in Type 2 DM based on the results of two 26-week, randomized, double-blind trials. Supplement S-006 was submitted May 26, 2000 proposed changes, based on post-marketing safety information, to the PRECAUTIONS section of the label to modify the safety information related to edema, use in patients with heart failure, and hepatic effects, in light of the number and nature of cases reported in open-market use. Corresponding changes were also proposed in the Information for Patients subsection. This supplement (006) was converted to a prior approval labeling supplement, and FDA and the sponsor met in October 2000

Proceeding in parallel, review of supplement 004 for insulin plus Avandia revealed safety concerns, specifically related to fluid overload and cardiac adverse events that outweigh any benefit of the combination relative to insulin alone, leading to the conclusion that the combined use of Avandia and insulin cannot be recommended at this time. The safety issues related to the combination, however, do merit treatment in labeling, in order to warn users of the potential hazards of the combination. Labeling that addresses both supplements has been successfully negotiated. As S-004 will not be approved (but rather an Approvable action will be taken), the safety labeling related to insulin-Avandia combination therapy is being approved as part of S-006.

Medical issues

Safety

S-004. Dr. Lubas has thoroughly reviewed the safety data. The major issue raised in the review of the two clinical trials of Avandia plus insulin combination therapy relates to a marked increase

in the incidence of cardiovascular adverse events with the combination relative to insulin alone. Indeed, the overall incidence of cardiovascular AEs in the double-blind and open-label portions of these studies was approximately 15% for the combination therapy groups and approximately 5% for the insulin monotherapy groups. Most of the events were CHF and dyspnea, with many of the patients experiencing both, as well as those apparently related to myocardial ischemia, whether MI, angina, thus perhaps more aptly classified as acute coronary syndromes. In cross-study comparisons, the rate of CHF in the Avandia plus insulin patients far exceeded that observed with insulin alone and in any of the other trials of Avandia, metformin, or SFU monotherapy or of Avandia in combination with these other oral agents. In addition, the incidence of edema and the incidence and severity of weight gain in the combination arms likewise exceeded those with insulin alone. Up to 20% of patients on combination therapy developed edema compared to 5% on insulin alone. Mean weight gains of 7-8 kg over the 6-month treatment period were observed in patients treated with Avandia 8 mg daily in combination with insulin.

Note that the issue has been raised that the high rate of CV adverse events in the combination studies may in part be due to the population studied, specifically that the average age and duration of diabetes exceeds those in previous trials, and may mark a population with a higher rate of underlying or incipient coronary and/or myocardial disease. In addition, the design of the trials, in which insulin dose was held constant unless a patient experienced profound or repeated hypoglycemia, may also have increased the risk to these perhaps more fragile patients. Such discussion, while theoretically quite reasonable, only suggests hypotheses that require testing. For now, the safety data stand as they are, and as such, they support a significant increased risk of CV adverse events related to volume overload and to myocardial ischemia in patients on combination Avandia and insulin compared to insulin alone.

S-006

Dr. Zawadzki's review of S-006 presents the post-marketing adverse event reporting data for hepatic events and CHF. Four cases of acute liver failure associated with Avandia therapy were reported from 6/99 to 3/00. The rate calculated by OPDRA is about 11 per million person-years. The rate calculated for troglitazone prior to its withdrawal was 60-100 per million person-years. There were 51 cases of hepatitis, of which 30% were asymptomatic, 24% were in patients previously treated with troglitazone, and 80% of whom recovered, with no fatalities. The current label recommends that patients who developed jaundice on troglitazone not be treated with Avandia.

Efficacy

S-004. Two clinical studies were submitted in support of the indication for combined Avandia-insulin. [redacted] ∴ Drs. Lubas and Mele have thoroughly reviewed the efficacy data. These were double-blind, placebo-controlled studies of 26 weeks' duration in relatively old patients with longstanding diabetes not adequately controlled on insulin. A total of approximately 400 patients were treated with insulin in combination with Avandia for at least 26 weeks across the two studies. The trials were identical save that in one the Avandia was given as a split dose morning and evening, and in the other, it was given as a once daily dose. Patients were stabilized on insulin for 4 weeks and then randomized to continue

insulin alone at a constant dose or to receive, in addition, Avandia 4 or 8 mg daily. The primary outcome variable was change from baseline in HbA1c. The results showed that there was a dose-related incremental reduction in HbA1c in patients treated with the combination compared to insulin alone, up to 1.3% reduction in the 4mg BID group. The divided dose appeared more effective than the once daily dose. Likewise, there were dose-related reductions in FPG in the Avandia groups as well.

Labeling
S-006, Hepatic Effects
Although the risk of serious liver disease with Avandia appears small, particularly in comparison to that with troglitazone, inclusion of additional information in the labeling is warranted and has been negotiated.

S-004
In addition, as explained above, based upon the review of the safety information submitted with S-004 related to Avandia-insulin combination therapy, further labeling has been negotiated to include changes in several other sections of the package insert. These changes include a new CLINICAL STUDIES section, a new WARNINGS section and Cardiac Failure and Other Cardiac Effects subsection, and revisions to the PRECAUTIONS section Edema and Weight Gain subsections, and in the ADVERSE REACTIONS section. These changes address safety issues related to the combined use of Avandia and insulin, summarized above.

Biopharmaceutics
No new biopharmaceutics studies were submitted.

Pharmacology/Toxicology
No new pharm/tox data were submitted.

Chemistry/ Microbiology
A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

DSI/Data Integrity
No DSI audit was requested. No labeling related to efficacy is being granted, and the safety data do not bear auditing by DSI for obvious reasons.

Financial disclosure
The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

Conclusions
As above, the labeling related to hepatic and cardiovascular adverse events with particular attention in the latter case to the risks of combined use with insulin has been successfully

negotiated. A new WARNINGS section has been added to the label addressing cardiac adverse effects of Avandia alone and in combination with insulin. A bolded statement that Avandia is not indicated in combination with insulin is included.

The sponsor is currently discussing internally the form of notification of health care providers of these changes to the Avandia label.

Recommendation

S-004. Approvable pending the sponsor's adequately addressing the increased risk of cardiovascular adverse events associated with the combination of insulin and Avandia. Investigations of the mechanism(s) by which such events are precipitated, information enabling prospective identification of patients at risk for such events, strategies for prevention, and algorithms for clinical management of fluid overload and congestive heart failure in patients using combination Avandia and insulin are all needed in order to permit safe and effective use of these drugs in combination in the treatment of patients with Type 2 diabetes mellitus. This will be conveyed in the action letter.

S-006. Approved. The final label contains labeling based on the review of S-004, as discussed above.

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

Application #: 21,071-S004	**Application Type: NDA Labeling Supplement**
Sponsor: SmithKline Beecham	**Proprietary Name: Avandia™**
Investigator: Multiple (Not named)	**USAN Name: Rosiglitazone maleate**
Category: Thiazolidinedione	**Route of Administration: oral**
Reviewer: William A. Lubas MD-PhD	**Review Date: 2/6/2001**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
2/7/2000	2/8/2000	NDA Supplement	New indication- Use of rosiglitazone in combination with insulin for the treatment of patients with type 2 diabetes mellitus.

RELATED APPLICATIONS (If applicable)

Document Date	Application Type	Comments
5/30/00	NDA 21071-S006	Hepatic Effects Labeling Supplement
6/30/00	SE1-004-BM	European Agency Labeling for Avandia

REVIEW SUMMARY:

Combination therapy with *Avandia* and insulin was effective at improving HbA1C and fasting plasma glucose (FPG) in patients inadequately controlled on insulin monotherapy (FPG≥140mg/dL, HbA1C≥7.5%, fasting C-peptide ≥0.4ng/mL). The relative median decrease in HbA1C compared to the placebo-treated group ranged from 0.5% to 1.3%. Improvement in glycemic control was greatest in patients who received 8mg of *Avandia* per day and were dosed twice daily. The efficacy of this combination therapy was maintained during the entire 26-week study period. Similar efficacy was observed for both men and women, and for patients above and below 65 years of age. Patients who were overweight or more poorly controlled at the start of therapy were more likely to show a greater benefit, measured as a median decrease in HbA1C.

Combination therapy with *Avandia* and insulin was associated with an increased incidence of hypoglycemia (53%-71%), anemia (4%-17%), edema (2%-10%), hyperlipidemia (1%-9%) and weight gain (0%-7%). All of these adverse events have previously been seen with thiazolidinediones. However, the incidence of these adverse events with *Avandia* and insulin combination therapy was substantially higher than seen with *Avandia* monotherapy or combination therapy with *Avandia* and other oral antidiabetic agents. There was no data to suggest that combination therapy with insulin increases the small risk of hepatotoxicity seen with *Avandia* monotherapy and previously associated with other thiazolidinediones. The incidence of hypoglycemia was dose related and more frequent with once daily dosing. In addition, there was an increase in the incidence of cardiac events including cardiac failure, ischemic heart disease and arrhythmias in the combination therapy group compared to placebo. In preclinical studies cardiac hypertrophy, plasma volume expansion and drug-related early death due to heart dysfunction have been seen with thiazolidinediones. But an increase in adverse cardiac events had not been previously reported in clinical trials with *Actos* or *Rezulin*. In post marketing experience with *Avandia, Actos* and *Rezulin,* adverse events potentially related to volume expansion (such as congestive heart failure, pulmonary edema and pleural effusions) have been reported. Dose related increases in the incidence of anemia, edema, weight gain and cardiac failure, were seen in these clinical studies with combination therapy of *Avandia* and insulin. Patients with anemia were more likely to have edema concurrently during the trials. Patients with edema were more likely to have concurrent anemia or adverse cardiac events. Adverse cardiac events occurred more frequently in patients who were older, had a longer duration of diabetes or were on the higher 8mg dose of *Avandia*. While most patients who developed cardiac failure had predisposing risk factors including a history of congestive heart failure, cardiac ischemia, edema, or left ventricular hypertrophy, a substantial percentage (25%-30%) did not. Therefore, it is not possible to identify all patients who might be at risk of cardiac failure on combination therapy with *Avandia* and insulin.

In conclusion, since diabetics with a history of anemia, edema, or cardiac disease, are at increased risk of adverse events on combination therapy with *Avandia* and insulin, the use of combination therapy in these patients requires an individual case by case risk benefit analysis. While the adverse events of edema, anemia and weight gain are treatable and therefore less likely to cause significant acute morbidity, they can increase the long-term risk for cardiovascular adverse events in type 2 diabetics. In this reviewer's judgement the small improvements in the surrogates, HbA1C and FPG, do not at this time justify the increased risk of cardiac failure and other adverse cardiovascular events seen in these type 2 diabetics on combination therapy. Double blind placebo-controlled clinical trials for a period of time longer than 26 weeks would be needed to confirm that the improvement in glycemic control in these patients on combination therapy with *Avandia* and insulin results in a long term decrease in morbidity and mortality. Therefore, the indication of combination therapy of *Avandia* and insulin is not recommended but changes in the *Avandia* label incorporating appropriate safety information should be approved.

OUTSTANDING ISSUES: 1) Proposed labeling changes (see review).

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies _____	**Clinical Hold**	_____	**Study May Proceed**
NDA, Efficacy/Label supplement: X	**Approvable**	_____	**Not Approvable**

SIGNATURES:

Medical Reviewer: William Talbot **Date:** 2/8/01

Medical Team Leader: _____ **Date:** _____

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INTRODUCTION

Avandia (Rosiglitazone maleate) is a member of the thiazolidinedione class of oral antidiabetic agents. Thiazolidinediones improve glycemic control by increasing insulin sensitivity, thereby decreasing insulin resistance, which is a common feature of type 2 diabetes. Avandia has been approved in the US as an adjunct to diet and exercise for the treatment of type 2 diabetes. It has been approved as monotherapy, as well as combination therapy with metformin or sulfonylureas. This NDA supplement presents two double blind pivotal studies 082 and 095 as well as some preliminary data from an ongoing open label extension 114. The purpose of these studies is to assess the safety and efficacy of Avandia in combination with insulin for the treatment of patients with type 2 diabetes who are inadequately controlled by insulin monotherapy. This review will deal primarily with the completed double blind placebo controlled studies 082 and 095.

At present Avandia is approved in Europe only as combination therapy with metformin or sulfonylureas. It has not been approved there as monotherapy [redacted]. Actos the only other currently available thiazolidinedione has been approved in the US as monotherapy and as combination therapy with metformin, sulfonylureas or insulin. Rezulin, the first thiazolidinedione to be approved, was indicated as combination therapy with metformin, sulfonylureas or insulin, before it was withdrawn from the US market because of concern that it was associated with an increased incidence of hepatitis and liver failure.

Premarketing clinical trials of Actos in combination therapy with insulin showed that 15.3% of the Actos-treated patients compared to 7.0% of the placebo-treated patients developed edema, which was generally mild to moderate in intensity. In these trials no increase in serious adverse cardiac events potentially related to volume expansion were observed. But patients with NYHA Class III and IV cardiac status were not included in these trials. In recent postmarketing analysis, a trend showing an increase in cardiac events related to volume expansion has been observed. In clinical trials Rezulin was associated with a 6% to 8% increase in plasma volume in normal controls compared to placebo. But no increase in serious adverse cardiac events potentially related to volume expansion was observed. As in the studies with Actos, patients with NYHA Class III and IV cardiac status were not included in the Rezulin trials. In postmarketing analysis adverse events of congestive heart failure, edema and weight gain were seen with Rezulin but a causal relationship was not established.

Clinical trials of Actos in combination therapy with insulin showed an increased incidence of hypoglycemia. This ranged from 8% (15mg of Actos) to 15% (30mg of Actos) compared to a 5% incidence in placebo-treated patients. A similar increase in the incidence of hypoglycemia (5% to 8%) was seen in combination studies with Rezulin plus insulin compared to the incidence in the placebo-treated group (4%, Study 991-068). A clinical review of the trials with the Rezulin combination therapy concluded that the method of adjustment of insulin dosage appeared to minimize the occurrence of hypoglycemia.

Clinical trials with Actos or Rezulin in combination therapy with insulin showed a 2% to 4% reduction in hematocrit compared to a 1 to 2 % reduction in those treated with placebo. This small change in hematocrit was not associated with a significant increase in the incidence of anemia in patients treated with combination therapy compared to the placebo-treated group.

In conclusion, safety concerns have been raised with combination therapy of thiazolidinediones and insulin, specifically in the areas of edema, weight gain, anemia and incidence of hypoglycemia. However, the final risk benefit analysis determined that when used appropriately this combination was both safe and effective for the treatment of a subset of patients with type 2 diabetes.

EFFICACY REVIEW

Protocol 082-*A 26 week randomized, double-blind multicenter study to evaluate the safety, efficacy, and tolerability of Avandia administered twice daily to patients with type 2 diabetes who are inadequately controlled on insulin therapy.*

The primary objective of this study was to evaluate the change in HbA1C in insulin-treated type 2 diabetic patients who were inadequately controlled on insulin monotherapy, with treatment of either placebo, 2mg or 4 mg of Avandia twice daily for 26 weeks.

The study enrolled 319 patients with type 2 diabetes receiving $\geq$ 30 units of total insulin as twice daily injections. Subjects had to have fasting plasma glucose (FPG) $\geq$140mg/dL, HbA1C $\geq$ 7.5% and fasting C-peptide $\geq$ 0.4ng/mL in order to be enrolled in the study. Patients with anemia, severe renal, hepatic or cardiac disease (NYHA class III/IV) including evidence of left ventricular hypertrophy, ST-T segments changes or those taking beta-blockers were excluded. Males (56%) outnumbered females. Most patients were Caucasian (68% to 72%), only 15% to 19% were black. The average age of patients was 56 to 58 years (range 26-80), with a similar proportion of subjects over 65 years (20% to 23%) in all treatment groups. The average duration of diabetes was 12.3 years, again similar in all treatment groups. A total of 252 (79%) patients completed the study, with a similar number of patients (20 to 24) withdrawing from each treatment group. The mean baseline HbA1C (8.9% to 9.1%) and FPG (195 to 212mg/dL) were similar across all treatment groups.

The study protocol divided patients into three treatment groups ie. placebo, 2mg bid Avandia or 4mg bid Avandia. The insulin dose for all patients was maintained at the start of therapy. Changes in insulin dose were permitted only for patients who had a seven-day mean capillary glucose of <100 mg/dL or who reported severe or recurrent hypoglycemic episodes during the study.

Mean decreases in HbA1C were significantly greater ($p<0.0001$) for both groups given Avandia, 2mg bid (-0.6%) and 4mg bid (-1.2%), compared to placebo (+0.1%) see Table

1 below. And the higher Avandia dose 4mg bid produced a significantly greater decrease in HbA1C than the 2mg-bid dose ($p<0.0001$).

Table 1 Change from Baseline in HbA1c at Week 26
(Intent-to-Treat Population)

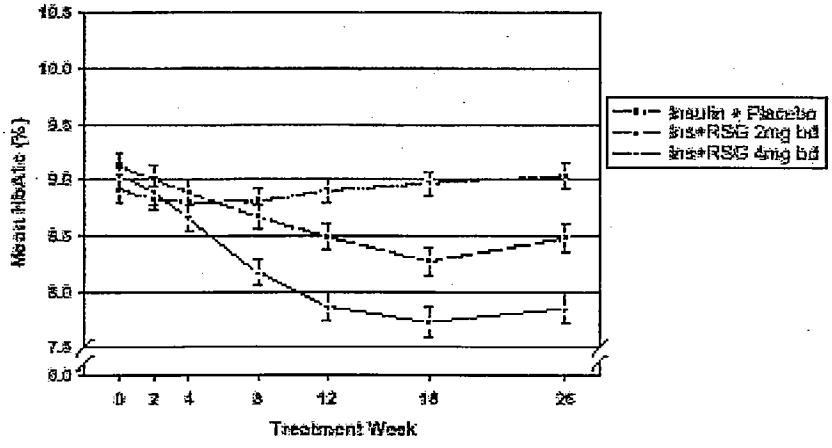
	Treatment Group		
HbA1c (%)	**Insulin + Placebo**	**Insulin + RSG**	**Insulin + RSG**
Reference range:<6.5		**2mg bid**	**4mg bid**
N	103	106	103
Baseline (mean ± SD)	8.9±1.07	9.1±1.28	9.0±1.27
Median	8.6	8.9	9.0
Week 26 (mean ± SD)	9.0±1.21	8.5±1.36	7.9±1.39
Median	8.9	8.3	7.5
Change From Baseline (mean±SD)	0.1±0.98	-0.6±1.07	-1.2±1.06
95% CI	(-0.1, 0.3)	(-0.8, -0.4)	(-1.4, -1.0)
p-value†	0.2032	<0.0001	<0.0001

Data taken from Table 15 Vol. 3, 082

Similarly, responders defined as those patients who achieved a reduction from baseline of HbA1C of at least 0.7%, were significantly higher ($p<0.0001$) for the 4mg bid Avandia group (68%), compared to the 2mg bid Avandia group (45%), and placebo (18%) (see NDA, study 082, Vol. 3, Table 16, pg. 70).

A time course of the change in HbA1C is shown below in Fig. 3, taken from study 085, Vol. 3. Changes in HbA1C can be observed at the earliest time tested, 2 weeks, and appear to maximize between 12-26 weeks.

Figure 3 Mean HbA1c over Time (ITT Population)



(ROSIGLITAZONE/082 - ITT Population) (Error Bars = SE)

Data Source: Section 14, Table 14.2.1.A

Similar results were obtained with fasting plasma glucose (FPG). Both 2mg and 4mg bid of Avandia resulted in lower FPG than placebo ($p<0.0001$) see Table 2 below.

Table 2 Change from Baseline in Fasting Plasma Glucose at Week 26
(Intent-to-Treat Population)

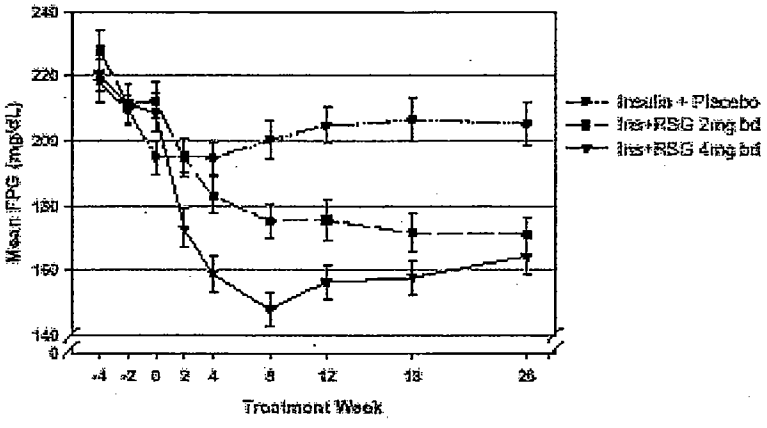
	Treatment Group		
	Insulin + Placebo	**Insulin + RSG 2mg bid**	**Insulin + RSG 4mg bid**
Fasting Plasma Glucose (mg/dL)			
Reference range: 13-50 years, 70-115; ≥50 years, 70-125			
N	104	106	103
Baseline (mean ± SD)	195±52.92	212.4±58.23	208.7±58.01
Median	185.5	204.0	202.0
Week 26 (mean ± SD)	205.2±65.43	170.9±57.74	164.3±59.49
Median	203.0	164.0	155.0
Change From Baseline(mean ± SD)	10.3±68.13	-41.5±70.74	-44.4±60.17
95% CI	(-3.0, 23.5)	(-55.1, -27.8)	(-56.2, -32.6)
p-value** from paired t-test	0.1273	<0.0001	<0.0001

Data from Table 17 Vol. 3, 082

Responders, defined as those patients who achieved a reduction from baseline of FPG of at least 30mg/dL, were significantly higher ($p<0.0001$) for the 4mg bid dose (63%), compared to 2mg bid (55%), and placebo (29%) (see NDA, study 082, Vol. 3, Table 19, pg. 76).

A time course of the change in FPG during the study is shown below in Fig. 6, taken from study 082 Vol. 3. Changes in FPG can be observed at the earliest time tested, 2 weeks, and appear to approach maximal reductions by 4-8 weeks. These maximal changes in FPG are seen well before they are reflected in similar changes in HbA1C levels (see Fig. 3 above).

Figure 6 Mean Fasting Glucose over Time (ITT Population)



(ROSIGLITAZONE/082 - ITT Population) (Error Bars = SE)

Data Source: Section 14, Table 14.3.1A

There were no significant differences among treatment groups in C-peptide level relative to baseline (see NDA, study 082, Table 20, pg. 78).

Insulin dose was decreased for significantly more patients in the Avandia 4mg bid and 2mg bid groups compared to placebo. There was no significant difference between the two Avandia treatment groups in the proportion of patients who had a decrease in their insulin dose. A total of 34% (2mg bid) to 44% (4mg bid) of the patients on Avandia had to decrease their insulin dose compared to 14% of the patients in the placebo group, see Table 3 below. Although not statistically significant, the data show a trend that more patients receiving the higher Avandia dose of 4mg bid required their insulin dose decreased, and that these patients also required a higher % decrease in the baseline insulin dose.

Table 3 Change from Baseline and Percent Change from Baseline in Insulin Dose and Number (%) of Patients with Changes in Total Daily Insulin Dose (Intent-to-Treat Patients)

	Treatment Group		
	Insulin + Placebo	**Insulin + RSG 2mg bid**	**Insulin + RSG 4mg bid**
N	104	106	103
Baseline (Mean ± SD; units)	70.1 ± 30.43	71.3 ± 43.75	77.7 ± 36.41
Week 26 (Mean ± SD; units)	69.7 ± 31.05	66.5 ± 38.16	68.3 ± 36.69
Change from Baseline (Mean ± SD; units)	-0.4 ± 5.61	-4.8 ± 14.64	-9.4 ± 16.67
% Change from Baseline (Mean ± SD; %)	-0.6 ± 8.24	-5.6 ± 15.90	-12.0 ± 20.21
Patients [n, (%)] with:			
Increase in Dose	9 (8.7%)	3 (2.8%)	3 (2.9%)
No Change in Dose	81 (77.9%)	67 (63.2%)	55 (53.4%)
% Decrease in Dose of			
>0% to ≤10%	7 (6.7%)	13 (12.3%)	7 (6.8%)
>10% to ≤20%	4 (3.8%)	8 (7.5%)	13 (12.6%)
>20% to ≤30%	2 (1.9%)	6 (5.7%)	6 (5.8%)
>30% to ≤40%	0	5 (4.7%)	8 (7.8%)
>40% to ≤50%	1 (1.0%)	3 (2.8%)	5 (4.9%)
>50% to ≤100%	0	1 (0.9%)	6 (5.8%)
Total Patients with a Decrease in Dose	14 (13.5%)	36 (34.0%)	45 (43.7%)

Data taken from NDA, study 085 Vol.3, Table 22, pg. 86

SUBGROUP ANALYSES

The trends in reductions in HbA1C and FBG were similar in patients <65 years and ≥65 years (see Table 23, study 082). In general the reductions were greatest with 4mg bid of Avandia and intermediate with 2mg bid Avandia.

The trends in reductions in HbA1C and FBG were similar in both men and women, although the reductions tended to be greater in women (see Table 23, study 082). In general the reductions were greatest with 4mg bid of Avandia and intermediate with 2mg bid Avandia.

Patients with higher BMI (≥ 27kg/m2), higher baseline HbA1C (≥ 9%) or higher baseline FBG (≥ 200mg/dL) had greater mean decreases in HbA1C and FBG with the Avandia and insulin combination (see Table 23, study 082). In general the reductions were greatest with 4mg bid of Avandia and intermediate with 2mg bid Avandia. These data suggest that patients that are more overweight or more poorly controlled are likely to show a greater benefit from combination therapy.

Protocol 095-*A 26 week randomized, double-blind multicenter study to evaluate the safety, efficacy, and tolerability of Avandia administered once daily to patients with type 2 diabetes who are inadequately controlled on insulin therapy.*

The primary objective and studies designs were similar to study 082. In study 082 patients on insulin therapy were started on placebo, 2mg or 4mg Avandia twice daily so that the total daily Avandia dose was 4mg or 8mg. In this study, 095, patients on insulin therapy were given the entire 4mg or 8mg of Avandia as a single daily dose.

The study enrolled 292 patients with type 2 diabetes receiving ≥ 30 units of total insulin as twice daily injections. The same general entry criteria were used as in the previous study, 082. Males outnumbered females (59% to 64%) in the two groups receiving Avandia in combination with insulin, similar to study 082. However, females outnumbered males (55%) in the Avandia and placebo combination. Most patients were Caucasian (68% to 73%) and only 15% to 16% were black which was similar to study population in 082. The average age of patients was 57 to 59 years (range 24 to 84), with a similar proportion of patients over 65 years in the 8mg Avandia group (25%) as seen in the earlier study, but there were more elderly patients (32%-34%) in the placebo and 4mg Avandia groups. The average duration of diabetes was 13.1 years, similar in all three treatment groups and to the patients in the earlier study 082. A total of 228 (79%) completed the study, with somewhat more withdrawals from the 8mg Avandia group (26%), than the 4mg Avandia group (21%), than the placebo group (17%). Following the same pattern, there was a higher incidence of adverse events in the 8mg Avandia group (10%), compared to the 4mg Avandia group (6%), and placebo (4%). The mean baseline

HbA1C (8.8%-9.1%) and FPG (199 to 203md/dL) were similar in the patients in all three treatment groups and to the patients in study 082.

The study protocol was similar to study 082. The baseline insulin dose was maintained as study medication was introduced. Changes in insulin dose were permitted only for patients who had a seven-day mean capillary glucose of < 100mg/dL or who reported severe or recurrent hypoglycemic episodes during the study.

Mean decreases in HbA1C were significantly greater ($p<0.0001$) for both groups given Avandia, 4mg (-0.4%) and 8mg (-0.7%), compared to placebo (+0.1%), see Table 4 below. The higher Avandia dose of 8mg did not produce a statistically greater decrease in HbA1C than the 4mg dose but the trend was suggestive ($p<0.066$).

Table 4 Change from Baseline in HbA1c at Week 26
(Intent-to-Treat Population)

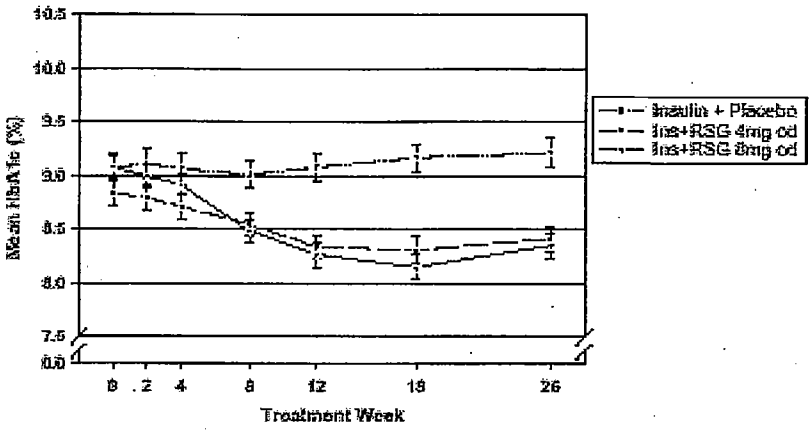
	Treatment Group		
HbA1c (%)	**Insulin + Placebo**	**Insulin + RSG 4mg od**	**Insulin + RSG 8mg od**
Reference range:<6.5			
N	95	97	95
Baseline (mean ± SD)	9.1 ± 1.24	8.8 ± 1.10	9.1 ± 1.01
Median	9.0	8.7	9.1
Week 26 (mean ± SD)	9.2 ± 1.34	8.4 ± 1.17	8.4 ± 1.14
Median	9.1	8.2	8.2
Change From Baseline (mean ± SD)	0.1 ± 0.95	-0.4 ± 0.96	-0.7 ± 0.96
95% CI	(-0.1, 0.3)	(-0.6,-0.2)	(-0.9, -0.5)
p-value †	0.1738	<0.0001	<0.0001

Data taken from NDA Vol. 12 Table 15 study 095

Responders, defined as those patients who achieved a reduction from baseline of HbA1C of at least 0.7%, were significantly higher for the 8mg Avandia group (53%, $p<0.0001$), and the 4mg Avandia group (37%, $p<0.002$) compared to placebo (19%) (see NDA study 095, Vol. 12 Table 16, pg.69). Again the higher 8mg daily dose did not produce a statistically greater increase in HbA1C than the 4mg dose, but the trend was suggestive ($p<0.067$).

A time course of the change in HbA1C during the study is shown below in Figure 3, study 095, Vol. 12. Changes in HbA1C can be observed at the earliest time tested, 2 weeks and appear to maximize between 12-26 weeks. Both curves for Avandia in this study overlap and are very similar to the curve seen with 2mg of Avandia given twice daily in study 082. However, these changes are less than seen with 4mg twice daily in study 082, where mean HbA1c drops to below 8.0%. If these differences are statistically significant it suggests that the most effective dosing regime is 4mg bid, used in study 082. The 4mg bid-dosing regime had previously been shown to be most effective with Avandia monotherapy, as well.

Figure 3 Mean HbA1c over Time (ITT Population)



Both 4mg ($p<0.0003$) and 8mg ($p<0.0001$) of Avandia resulted in lower FPG than placebo see Table 5 below, although the higher Avandia dose did not produce a statistically greater decrease in FPG ($p<0.24$).

Table 5 Change from Baseline in Fasting Plasma Glucose at Week 26
(Intent-to-Treat Population)

	Treatment Group		
	Insulin + Placebo	**Insulin + RSG 4mg od**	**Insulin + RSG 8mg od**
Fasting Plasma Glucose (mg/dL)			
Reference range: 13-50 years, 70-115; ≥51 years, 70-125			
N	95	97	95
Baseline (mean ± SD)	203.0 ± 57.26	199.1 ± 66.26	198.8 ± 61.32
Median	202.0	184.0	193.0
Week 26 (mean ± SD)	209.1 ± 62.81	174.1 ± 61.06	164.6 ± 60.07
Median	204.0	162.0	146.0
Change From Baseline(mean ±SD)	6.0 ± 64.56	-25.1 ± 66.02	-34.2 ± 65.33
95% CI	(-7.1, 19.2)	(-38.4, -11.8)	(-47.5, -20.9)
p-value** from paired t-test	0.3657	0.0003	<0.0001

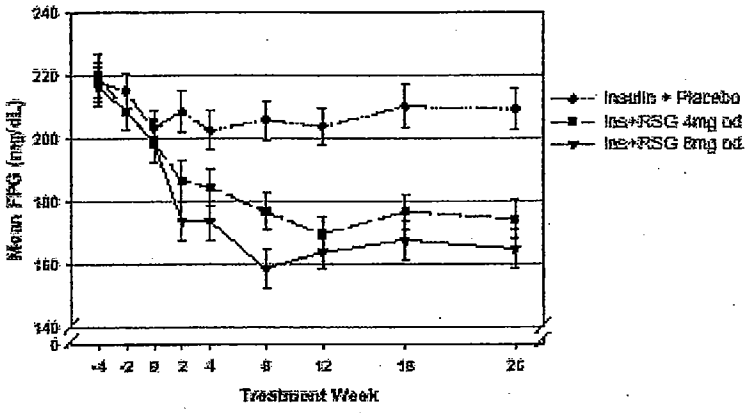
Data from Table 17, Vol. 12, study 095

Responders, defined as those patients who achieved a reduction from baseline FPG of at least 30 mg/dL, were significantly higher for the 4 mg od group (47%, $p<0.0044$) and the 8mg od group (46%, $p<0.0075$) compared to placebo (30%) (see NDA, study 095, Vol. 12, Table 19, pg. 75).

A time course of the change in FPG during the study is shown in Fig. 6 below, taken from study 095 Vol. 12. Changes in FPG can be observed at the earliest time tested, 2 weeks,

and appear to approach maximal reductions by 8 weeks. These maximal changes in FPG are seen before they are reflected in similar changes in HbA1C levels (see Fig. 3 above). The time course of these changes is similar to what had been seen in the previous study 082.

Figure 6 Mean Fasting Glucose over Time (ITT Population)



(ROSIGLITAZONE095 - ITT Population) (Error Bars = SE)

Data Source: Section 14, Table 14.2.1.A

There were no significant differences among treatment groups in C-peptide level relative to baseline (see NDA, study 095 Table 20, pg. 76).

Insulin dose was decreased for significantly more patients in the Avandia 4mg od and 8mg od groups compared to placebo ($p<0.001$). There was no significant difference between the two Avandia treatment groups in the proportion of patients who had a decrease in their insulin dose. A total of 47% (4mg od) to 53% (8mg od) of the patients on Avandia had to decrease their insulin dose compared to 16% of the patients in the placebo group, see Table 6 below.

Table 6 Change from Baseline and Percent Change from Baseline in Insulin Dose and Number (%) of Patients with Changes in Total Daily Insulin Dose (Intent-to-Treat Patients)

	Treatment Group		
	Insulin + Placebo	**Insulin + RSG 4mg od**	**Insulin + RSG 8mg od**
N	95	97	95
Baseline (Mean ± SD; units)	64.7 ± 29.33	76.4 ± 44.80	73.9 ± 29.42
Week 26 (Mean ± SD; units)	63.7 ± 27.69	69.1 ± 44.20	63.9 ± 31.65
Change from Baseline (Mean ± SD; units)	-1.0 ± 8.19	-7.3 ± 16.03	-10.0 ± 15.59
% Change from Baseline (Mean ± SD; %)	0.2 ± 14.03	-9.1 ± 16.20	-14.5 ± 23.24

Table 6 Change from Baseline and Percent Change from Baseline in Insulin Dose and Number (%) of Patients with Changes in Total Daily Insulin Dose (Intent-to-Treat Patients)

	Treatment Group		
	Insulin + Placebo	**Insulin + RSG 4mg od**	**Insulin + RSG 8mg od**
Patients [n, (%)] with:			
Increase in Dose	12 (12.6%)	5 (5.2%)	3 (3.2%)
No Change in Dose	68 (71.6%)	46 (47.4%)	42 (44.2%)
% Decrease in Dose of			
>0% to ≤10%	7 (7.4%)	15 (15.5%)	15 (15.8%)
>10% to ≤20%	1 (1.1%)	14 (14.4%)	8 (8.4%)
>20% to ≤30%	6 (6.3%)	7 (7.2%)	12 (12.6%)
>30% to ≤40%	0	5 (5.2%)	3 (3.2%)
>40% to ≤50%	1 (1.1%)	1 (1.0%)	3 (3.2%)
>50% to ≤100%	0	4 (4.1%)	9 (9.5%)
Total Patients with a Decrease in Dose	15 (15.8%)	46 (47.4%)	50 (52.6%)

Data taken from NDA, study 095 Vol. 12, Table 22, pg. 84

SUBGROUP ANALYSES

In contrast to study 082 where reductions in HbA1C and FBG were similar in patients <65 years and ≥65 years in study 095, mean decreases in HbA1C were greater in patients <65 years while mean decreases in FBG were greater in patients ≥65 years (see Table 23 study 095). Since the mean decreases in HbA1C and FBG for both age groups are all within one standard deviation of each other, the data does not suggest that there is any statistical difference in efficacy for patients <65 years and ≥65 years.

In contrast to study 082 where reductions in HbA1C and FBG tended to be greater in women, in study 095, the results were mixed with no significant trend consistently favoring either sex (see Table 23 study 095). However, in the statistical review combining data from both studies, females continued to show a larger treatment effect as had been previously seen with Avandia monotherapy.

Similar to study 082, where patients with higher baseline HbA1C (≥ 9%) or higher baseline FBG (≥ 200mg/dL) had greater mean decreases in HbA1C and FBG on Avandia and insulin combination therapy, in study 095 patients with higher FBG (≥ 200mg/dL) and most patients with higher baseline HbA1C (≥ 9%) continued to have greater mean decreases in HbA1C and FBG. These data suggest that patients with worse control, measured as baseline HbA1C and FBG, were more likely to show a greater benefit from combination therapy.

In the earlier study 082, patients with higher BMI (≥ 27kg/m2) had greater mean decreases in HbA1C and FBG on Avandia and insulin combination therapy, similar to what had been previously seen with Avandia monotherapy. In this study, 095, the results were mixed. Patients with higher BMI (≥ 27kg/m2), had greater mean decreases in HbA1C, while patients with lower BMI (≤ 27kg/m2), had greater mean decreases in FBG (see Table 23 study 095). However, in the statistical review combining data from both studies, Joy Mele found that while patients with higher baseline BMIs had larger treatment effects, BMI was not a good predictor of response.

SUMMARY OF EFFICACY REVIEW

Avandia in combination therapy with insulin at daily doses of 4mg to 8mg results in improvement of glycemic control in patients poorly controlled on monotherapy. Patients with FPG ≥ 140mg/dL, HbA1C ≥ 7.5% and fasting C-peptide ≥0.4ng/mL had statistically significant decreases in FPG and HbA1C compared to the placebo treated groups. No statistically significant changes in C-peptide were observed. The relative decrease in median FPG compared to the placebo-treated group at 26 weeks of therapy ranged between 31 to 40mg/dL (study 095, Table 5) and 52 to 55 mg/dL (study 082, Table 2). The relative decrease in median HbA1C compared to the placebo-treated group ranged between 0.5% to 0.8% (study 095, Table 4) and 0.7% to 1.3% (study 082, Table 1). Improvements in FPG and HbA1C were greatest in study 082 with twice daily dosing compared to once a day dosing in study 095. With twice daily dosing, 8mg of Avandia in combination with insulin resulted in statistically greater improvements in FPG and HbA1c than 4mg of Avandia. With once a day dosing there was a trend suggesting that the 8mg dose was more effective than the 4 mg dose but it was not statistically significant ($p<0.066$).

Improvements in FPG appeared to be maximal after 8 to 12 weeks of therapy while maximal changes in HbA1C were delayed and not seen until 12 to 26 weeks. The efficacy of the Avandia and insulin combination therapy was maintained during the 26-week study period.

In subgroup analysis the efficacy with Avandia and insulin combination therapy was independent of age (> or < 65 years). However, females, overweight patients (BMI ≥ 27kg/m2) and patients poorly controlled at the start of therapy, FBG (≥ 200mg/dL) or HbA1C (≥ 9%), showed greater treatment effects, measured as a median decrease in HbA1C.

SAFETY REVIEW

Protocol 082-*A 26 week randomized, double-blind multicenter study to evaluate the safety, efficacy, and tolerability of Avandia administered twice daily to patients with type 2 diabetes who are inadequately controlled on insulin therapy.*

A total of 212 patients received at least one dose of Avandia. The median duration of exposure was 182 days for each of the three treatment groups. The adverse events that occurred more frequently in the Avandia groups compared to the placebo-treated control are highlighted in Table 7 below. These events are considered by this reviewer to be potentially related to the study medication. Reports of hypoglycemia, anemia, weight gain, edema and hyperlipidemia have been previously reported with the use of thiazolidinediones in combination with insulin therapy and are consistent with these findings.

ON-THERAPY ≥3% INCIDENCE OF ADVERSE EVENTS

Table 7 On-therapy Adverse Experiences Reported by ≥3% of Patients in Any Treatment Group

	Treatment Group		
AEs by Preferred Term, n (%)	**Insulin + Placebo (N = 107)**	**Insulin + RSG 2mg bid (N = 107)**	**Insulin + RSG 4mg bid (N = 105)**
Patients with at Least One Adverse Experience	88 (82.2%)	98 (91.6%)	98 (93.3%)
Hypoglycemia	41 (38.3%)	57 (53.3%)	70 (66.7%)
Upper respiratory tract infection	21 (19.6%)	24 (22.4%)	22 (21.0%)
Anemia	1 (0.9%)	4 (3.7%)	13 (12.4%)
Injury	10 (9.3%)	4 (3.7%)	12 (11.4%)
Infection viral	12 (11.2%)	9 (8.4%)	11 (10.5%)
Edema dependent	3 (2.8%)	3 (2.8%)	10 (9.5%)
Hyperlipemia	4 (3.7%)	4 (3.7%)	9 (8.6%)
Headache	7 (6.5%)	4 (3.7%)	8 (7.6%)
Urinary tract infection	10 (9.3%)	2 (1.9%)	8 (7.6%)
Sinusitis	7 (6.5%)	7 (6.5%)	7 (6.7%)
Coughing	3 (2.8%)	4 (3.7%)	6 (5.7%)
Arthralgia	2 (1.9%)	9 (8.4%)	5 (4.8%)
Pain	6 (5.6%)	6 (5.6%)	5 (4.8%)
Weight increase	2 (1.9%)	6 (5.6%)	5 (4.8%)
Dizziness	4 (3.7%)	2 (1.9%)	5 (4.8%)
Bronchitis	4 (3.7%)	8 (7.5%)	4 (3.8%)
Edema legs	1 (0.9%)	8 (7.5%)	4 (3.8%)
Nausea	3 (2.8%)	5 (4.7%)	4 (3.8%)
Dyspnea	2 (1.9%)	5 (4.7%)	4 (3.8%)
Diarrhea	5 (4.7%)	3 (2.8%)	4 (3.8%)
Constipation	1 (0.9%)	3 (2.8%)	4 (3.8%)
Cellulitis	3 (2.8%)	2 (1.9%)	4 (3.8%)
Back pain	6 (5.6%)	5 (4.7%)	3 (2.9%)
Rhinitis	3 (2.8%)	4 (3.7%)	3 (2.9%)
Hypertension aggravated	6 (5.6%)	6 (5.6%)	2 (1.9%)
Infection	6 (5.6%)	4 (3.7%)	2 (1.9%)
Fatigue	4 (3.7%)	1 (0.9%)	2 (1.9%)
Rash	4 (3.7%)	4 (3.7%)	1 (1.0%)
Hyperglycemia	3 (2.8%)	4 (3.7%)	1 (1.0%)
Respiratory disorder	1 (0.9%)	4 (3.7%)	1 (1.0%)
Retinal disorder	0	4 (3.7%)	1 (1.0%)

Table 8 Summary of Patient Withdrawals Due to On-therapy Adverse Experience

Renal function abnormal	0	1 (0.9%)	0
Cerebrovascular disorder	0	1 (0.9%)	0
Retinal disorder	0	1 (0.9%)	0
Asthenia	1 (0.9%)	0	0
Cellulitis	1 (0.9%)	0	0
Malaise	1 (0.9%)	0	0
Sepsis	1 (0.9%)	0	0

* In addition, two patients (082.030.14086 and 082.026.13839), both in the insulin plus rosiglitazone 4mg bid group, withdrew due to weight gain, which was not reported as an AE.

** PID 082.012.13531, in the insulin plus Rosiglitazone 2mg bid group, withdrew from the study while on therapy due to a pretherapy AE of hepatitis that started on day -46. Patient 082.025.14211, in the insulin plus Rosiglitazone 4mg bid group, withdrew on day 54, when he had an SAE of peripheral ischemia. These AE's are not included in the AE withdrawal tables. See also Table 18.0, Errata.

Data Source: Section 15, Table 15.5; Appendices B and D, Listings B.L1, D.L1, and D.L2

Data Taken from Table 40 Vol. 3 pg. 139 study 082

The withdrawal rate was almost 4 times as high in both Avandia groups as in the placebo treated group. The adverse events possibly related to the study medication are highlighted in Table 8 above. There are 8 such cases in the 8mg Avandia group, compared to 2 cases in the 4mg Avandia group and 1 case in the placebo treated group. The higher Avandia dose is associated with an increased incidence in adverse events possibly related to the study medication.

SERIOUS ON-THERAPY ADVERSE EVENTS

Table 9 Summary of Serious Nonfatal On-therapy Adverse Experiences

	Treatment Group		
Preferred Term, n (%*)	**Insulin + Placebo**	**Insulin + RSG 2mg bid**	**Insulin + RSG 4mg bid**
	(N = 107)	**(N = 107)**	**(N = 105)**
Patients with at least one serious nonfatal AE	5 (4.7%)	8 (7.5%)	9 (8.6%)
Cellulitis	2 (1.9%)	1 (0.9%)	2 (1.9%)
Cerebrovascular disorder	0	0	2 (1.9%)
Pneumonia	0	1 (0.9%)	1 (1.0%)
Anemia	0	0	1 (1.0%)
Arthralgia	0	0	1 (1.0%)
Cardiac arrest	0	0	1 (1.0%)
Necrosis ischemic	0	0	1 (1.0%)
Osteomyelitis	0	0	1 (1.0%)
Peripheral gangrene	0	0	1 (1.0%)
Peripheral ischemia	0	0	1 (1.0%)
Pulmonary edema	0	0	1 (1.0%)
Rash	0	0	1 (1.0%)
Cardiac failure	0	1 (0.9%)	0
Dyspnea	0	1 (0.9%)	0
GI hemorrhage	0	1 (0.9%)	0
Hyperkalemia	0	1 (0.9%)	0
Hypoxia	0	1 (0.9%)	0
Neoplasm malignant	0	1 (0.9%)	0
Pancreatitis	0	1 (0.9%)	0

Table 9 Summary of Serious Nonfatal On-therapy Adverse Experiences

	Treatment Group		
Pulmonary carcinoma	0	1 (0.9%)	0
Sarcoidosis	0	1 (0.9%)	0
Renal calculus	0	1 (0.9%)	0
Renal function abnormal	0	1 (0.9%)	0
Respiratory disorder	0	1 (0.9%)	0
Schizophrenic reaction	0	1 (0.9%)	0
Urinary retention	0	1 (0.9%)	0
Depression aggravated	1 (0.9%)	0	0
Infection	1 (0.9%)	0	0
Injury	1 (0.9%)	0	0
Sepsis	1 (0.9%)	0	0
Suicide attempt	1 (0.9%)	0	0

* Number of patients reporting an AE / number of patients receiving double-blind medication X 100
Data Source: Section 15, Table 15.2.3; Appendix D, Listing D.L6
Data taken from Table 38 Vol. 3 pg. 132 study 082

The number of patients with on-therapy serious adverse events was twice as high in both Avandia groups as in the placebo treated group. The adverse events possibly related to the study medication are highlighted in Table 9 above. There are 3 such cases in the 8mg Avandia group, compared to 1 case in the 4mg Avandia group and 0 cases in the placebo treated group. Again the higher Avandia dose is associated with an increased incidence in adverse events possibly related to the study medication.

Protocol 095-*A 26 week randomized, double-blind multicenter study to evaluate the safety, efficacy, and tolerability of Avandia administered once daily to patients with type 2 diabetes who are inadequately controlled on insulin therapy.*

A total of 196 patients received at least one dose of Avandia. The median duration of exposure was 182 days for each of the three treatment groups. The adverse events that occurred more frequently in the high dose Avandia group or in both Avandia groups compared to the placebo-treated control are highlighted in Table 10 below. Such adverse events may be potentially related to the study medication. The adverse events of hypoglycemia, anemia, weight gain, edema and hyperlipidemia occurred more frequently in the Avandia groups in both this study 095, and the earlier study 082. Additional adverse events, which also occurred more frequently in the Avandia groups in this study include, cardiac failure, hypercholesterolemia and hypertriglyceridemia. It is uncertain why these adverse events were no seen in the previous study 082, Table 7. One possibility is that they were labeled differently by the physicians involved at the different centers in these two studies. For example, hypercholesterolemia and hypertriglyceridemia may have been grouped together under the term hyperlipidemia in the earlier study. Another possibility is that these events occurred at an incidence of less than 3% (082) or 4% (095) and so they were not listed in the incidence Tables.

ON-THERAPY ≥4% INCIDENCE OF ADVERSE EVENTS

Table 10 On-therapy Adverse Experiences Reported by ≥4% of Patients in Any Treatment Group

	Treatment Group		
AE's by Preferred Term, n (%)	**Insulin + Placebo (n = 96)**	**Insulin + RSG 4mg od (n = 99)**	**Insulin + RSG 8mg od (n = 97)**
Patients with at Least One Adverse Experience	87 (90.6)	88 (88.9)	90 (92.8)
Hypoglycemia	43 (44.8)	61 (61.6)	69 (71.1)
Upper Respiratory Tract Infection	20 (20.8)	22 (22.2)	20 (20.6)
Anemia	6 (6.3)	11 (11.1)	16 (16.5)
Infection Viral	4 (4.2)	7 (7.1)	9 (9.3)
Urinary Tract Infection	10 (10.4)	6 (6.1)	9 (9.3)
Injury	8 (8.3)	13 (13.1)	8 (8.2)
Edema Legs	4 (4.2)	2 (2.0)	7 (7.2)
Weight Increase	1 (1.0)	0	7 (7.2)
Hyperlipemia	2 (2.1)	1 (1.0)	6 (6.2)
Edema Dependent	0	5 (5.1)	5 (5.2)
Bronchitis	3 (3.1)	3 (3.0)	5 (5.2)
Coughing	3 (3.1)	1 (1.0)	5 (5.2)
Sinusitis	8 (8.3)	7 (7.1)	4 (4.1)
Infection	1 (1.0)	3 (3.0)	4 (4.1)
Cardiac Failure	1 (1.0)	2 (2.0)	4 (4.1)
Edema Generalized	1 (1.0)	2 (2.0)	4 (4.1)
Pain	4 (4.2)	2 (2.0)	4 (4.1)
Fatigue	0	1 (1.0)	4 (4.1)
Hypercholesterolemia	0	0	4 (4.1)
Back Pain	2 (2.1)	5 (5.1)	3 (3.1)
Headache	8 (8.3)	5 (5.1)	3 (3.1)
Hypertriglyceridemia	1 (1.0)	4 (4.0)	3 (3.1)
Arthritis	4 (4.2)	2 (2.0)	3 (3.1)
Diarrhea	9 (9.4)	2 (2.0)	3 (3.1)
Hypertension Aggravated	5 (5.2)	1 (1.0)	3 (3.1)
Gastritis	0	4 (4.0)	2 (2.1)
Retinal Disorder	3 (3.1)	4 (4.0)	2 (2.1)
Arthralgia	5 (5.2)	3 (3.0)	2 (2.1)
Abdominal Pain	4 (4.2)	0	0
Dizziness	4 (4.2)	0	0

NOTE: Sorted by highest dose of Rosiglitazone

Data Source: Section 15, Table 15.2.4; Appendix D, Listing D.L2 Data Taken from Table 26 Vol. 12 pg. 93 study 095

One other adverse event, viral infection, occurred more frequently in both Avandia groups compared to placebo in this study (095). This reviewer considers this adverse event unlikely to be related to the study medication. There is no preclinical data to support such a finding and in the earlier study (082) the opposite result was seen, with viral infection occurring more frequently in the placebo group compared to the Avandia groups (see Table 7).

DEATHS

There was one death in this study, which occurred in the 8mg Avandia and insulin combination therapy group. The death was likely due to hypoglycemic shock following a prolonged fast. The study medication may have contributed to the incidence of hypoglycemia. The incidence of hypoglycemia was 67% in the 8mg Avandia and insulin combination therapy group compared to 38% in the placebo-treated group receiving insulin monotherapy.

WITHDRAWALS DUE TO ADVERSE EFFECTS

Table 11 Summary of Patient Withdrawals Due to On-therapy Adverse Experience

	Treatment Group		
Adverse Experience* leading to Withdrawal by Preferred Term, n (%)	**Insulin + Placebo (N = 96)**	**Insulin + RSG 4mg od (N = 99)**	**Insulin + RSG 8mg od (N = 97)**
Patients with AE's leading to withdrawal	4 (4.2)	5 (5.1)	9 (9.3)
Anemia	0	0	5 (5.2)
Hypoglycemia	0	1 (1.0)	1 (1.0)
Retinal disorder	0	1 (1.0)	1 (1.0)
Cardiac failure	0	0	1 (1.0)
Hypertension pulmonary	0	0	1 (1.0)
Encephalopathy	0	0	1 (1.0)
Cardiac arrest	0	0	1 (1.0)
SGOT increased	0	0	1 (1.0)
SGPT increased	0	0	1 (1.0)
Dyspnea	0	0	1 (1.0)
Hot flushes	0	1 (1.0)	0
Injury	0	1 (1.0)	0
Angina pectoris aggravated	0	1 (1.0)	0
Cellulitis	1 (1.0)	0	0
Pancreatitis	1 (1.0)	0	0
Arthritis	1 (1.0)	0	0
Polymyalgia rheumatica	1 (1.0)	0	0
Synovitis	1 (1.0)	0	0
Rash	1 (1.0)	0	0
Cerebrovascular disorder	1 (1.0)	0	0

* In addition, patient 095.026.12493 withdrew because of "asymptomatic low blood sugars", which the investigator classified as a withdrawal reason of "other" and patient, 095.007.12143, was withdrawn on-therapy for an AE (Hepatic Enzymes Increased) that began pre-therapy. These patients are not included in the above totals.
Data Source: Section 15, Table 15.5; Appendices B and D, Listings B.L1, D.L1, and D.L2
Data Taken from Table 40 Vol. 12 pg. 132, study 095

Twice as many patients withdrew from the study in the 8mg Avandia group compared to the 4mg Avandia and placebo-treated groups. The adverse events possibly related to the study medication are highlighted in Table 11 above. There are 11 such cases of adverse events that lead to patient withdrawal in the 8mg Avandia group, compared to 2 such cases in the 4-mg Avandia group and none in the placebo-treated group. Again as seen in

the previous study, the higher dose is associated with an increased incidence in adverse events possibly related to the study medication.

SERIOUS ON-THERAPY ADVERSE EVENTS

Table 12 Summary of Serious Nonfatal On-therapy Adverse Experiences

	Treatment Group		
Preferred Term, n (%*)	**Insulin + Placebo**	**Insulin + RSG 4mg od**	**Insulin + RSG 8mg od**
	(N = 96)	**(N = 99)**	**(N = 97)**
Patients with serious AE's	8 (8.3)	7 (7.1)	9 (9.3)
Cardiac failure	1 (1.0)	0	3 (3.1)
Anemia	0	1 (1.0)	1 (1.0)
Angina pectoris aggravated	0	1 (1.0)	1 (1.0)
Back pain	0	1 (1.0)	1 (1.0)
Injury	0	1 (1.0)	1 (1.0)
Arthritis rheumatoid	0	0	1 (1.0)
Embolism pulmonary	0	0	1 (1.0)
Hypertension pulmonary	0	0	1 (1.0)
Infection	0	0	1 (1.0)
Neoplasm NOS	0	0	1 (1.0)
Thrombophlebitis deep	0	0	1 (1.0)
Cerebrovascular disorder	2 (2.1)	1 (1.0)	0
Dehydration	0	1 (1.0)	0
Diabetes mellitus aggravated	0	1 (1.0)	0
Gastritis	0	1 (1.0)	0
Gastrointestinal disorder NOS**	0	1 (1.0)	0
Hot flushes	0	1 (1.0)	0
Myalgia	1 (1.0)	1 (1.0)	0
Pain	0	1 (1.0)	0
Pneumonia	0	1 (1.0)	0
Angina pectoris	1 (1.0)	0	0
Asthma	1 (1.0)	0	0
Cellulitis	1 (1.0)	0	0
Pancreatitis	1 (1.0)	0	0
Rash	1 (1.0)	0	0

* Number of patients reporting an AE / number of patients receiving double-blind medication X 100
** NOS = not otherwise specified
Data Source: Section 15, Table 15.2.3; Appendix D, Listing D.L6
Data Taken from Table 38 Vol. 12 pg.127 study 095

The number of patients with serious on-therapy adverse events was similar in all three groups. The serious adverse events possibly related to the study medication are highlighted in Table 12 above. There are 5 cases in the 8mg Avandia group, 2 cases in the 4mg Avandia group and 2 cases in the placebo-treated group. Again as seen in the previous study, the higher dose of Avandia is associated with an increased incidence in adverse events possibly related to the study medication.

SUMMARY OF NDA SAFETY STUDIES

Two deaths in the two studies are potentially related to the study medication, one due to hypoglycemia and the other to a myocardial infarction. Although these deaths correspond to only 0.3% (2/600) of the patients in these studies, this could represent a large number of patients once Avandia and insulin combination therapy is approved for general use, with the estimated 16 million type 2 diabetics in the US.

In both studies withdrawals due to adverse events and serious adverse events were most common in the high dose Avandia group. Events that occurred more frequently in the Avandia groups may be potentially related to the study medication. These are in order of frequency in which they occurred, hypoglycemia (53% -71%), anemia (4%-17%), edema (2%-10%), hyperlipidemia (1% to 9%), weight increase (0%-7%), dyspnea (4%-5%, study 082 only) and cardiac failure (2%-4%, study 095 only).

These adverse events will be discussed in more detail in the order of the frequency with which they were seen in these studies.

HYPOGLYCEMIA
The incidence of hypoglycemia in the combined double blind and open label population (N=644) was increased in the Avandia groups (61%) compared to the placebo-treated groups (41%). It appeared greater in the 8mg Avandia group (higher dose) and in the once daily dose groups (study 095). Even if these differences are not statistically significant they show a trend suggesting that higher single doses of Avandia are more likely to cause hypoglycemia.

Table 13	**Incidence of hypoglycemia in the double-blind population**		
Study	Placebo	4mg Avandia	8mg Avandia
082 (twice daily)	38%	53%	67%
095 (once daily)	45%	62%	71%

The increased incidence of hypoglycemia seen with Avandia and insulin combination therapy compared to insulin alone was partially due to the strict guidelines for the adjustment of the starting insulin dose in these treatment protocols. Reduction in the starting insulin dose was permitted only in response to sustained hypoglycemic (mean capillary glucose <100 mg/dL for 7 days), or severe or recurrent episodes of hypoglycemia. It is likely therefore, that the incidence would be lower under less restrictive general use, with patients receiving individualized instruction from their personal physician.

Few patients (4/541 = 0.7%) withdrew from the studies due to hypoglycemia, and most of the events were described as mild to moderate in intensity. Out of the patients on Avandia and insulin combination therapy 12/541=2.2 % had one or more episode of FBG

<50mg/dL based on the patients diary cards or scheduled lab assessment, compared to 2/203=1% patients on insulin monotherapy.

One patient died during the study as a consequence of hypoglycemia because of a prolonged fast after taking medication. This death may have been prevented if the patient had eaten appropriately and so this death cannot be attributed solely to the study medication.

It is this reviewer's recommendation that the labeling be written to describe the increased incidence of hypoglycemia with insulin and Avandia combination therapy. Patients who may have difficulty controlling hypoglycemia or in self treating these episodes need to assess their risk benefit before starting this combination therapy. If therapy is initiated in these patients, it would be best that they start on a dose of 2mg bid to try to minimize the risk of hypoglycemia.

ANEMIA

Both studies 082 and 095 showed a dose-dependent reduction in hemoglobin in patients receiving combination therapy with Avandia and insulin (see Table 30 in studies 082 and 095). The magnitude of the decrease in the mean change from baseline of hemoglobin ranged from –1.0g/dL for combination therapy with insulin or metformin to –0.7g/dL for combination therapy with sulfonylureas. This is similar to the change of –1.0g/dL seen with Avandia monotherapy (see Table 1.8) suggesting that the entire decrease in hemoglobin which is seen may be attributed to Avandia therapy alone.

Patients enrolled in the combination therapy studies with metformin and insulin had lower baseline hemoglobin values (14.1 and 14.2 g/dL respectively) compared to patients on placebo (14.6 g/dL) or Avandia monotherapy (14.6 g/dL) (see Table 1.8). This partially explains why a higher incidence of anemia was observed in the combination therapy studies with metformin (7.1%) and insulin (10.8%) compared to placebo (0.7%) and Avandia monotherapy (1.0%).

New cases of anemia were seen as early as 15 to 28 days, with the greatest mean decreases in hemoglobin and hematocrit seen at 197 to 280 days in the studies reviewed in this NDA (see Tables 8.H.8.2 and 8.H.8.3). New occurrences of anemia continued to develop throughout the studies (see Table 30 in studies 082 and 095).

Seven patients were withdrawn from these studies for anemia and two cases were characterized as serious adverse experiences. The observed changes in anemia maybe related to increased plasma volume, which has been seen with Avandia therapy. 23% (10/44) of the patients with an AE of anemia during the study also developed edema while on Avandia and insulin combination therapy (see Table 29 in studies 082 and 095). Analysis of the cases of anemia confirmed them to be normocytic, consistent with the proposed mechanism of plasma expansion.

Patients with a low baseline hematocrit who might be at risk of anemia should have their hemoglobin monitored closely while on therapy with Avandia. Patients who are already anemic should have their anemia corrected before being started on therapy.

EDEMA
Thiazolidinediones have previously been shown to cause fluid retention resulting in edema. The incidence of edema was 4.8% with Avandia monotherapy compared to 1.3% in the placebo group (see Table 1.9). Combination therapy with Avandia and sulfonylureas (3.0%) or metformin (4.4%) did not substantially change the incidence of edema compared to Avandia alone (4.8%), suggesting that these other oral hypoglycemic agents are not associated with fluid retention.

Insulin therapy, however, like monotherapy with Avandia is also associated with an increase in the incidence of edema (5.4%) (see Table 1.9). Combination therapy with Avandia and insulin is additive with respect to the incidence of edema. So in the double blind and open-label population the incidence of edema was 19.8% (107/541) (see Table 8.H.4.14) compared to only 5.4% (11/203) in patients treated with insulin alone.

In studies 082 and 095 there was as dose-dependent association with combination therapy with Avandia plus insulin and edema (see Table 28 in studies 082 and 095).

Table 14
Incidence of edema in the double-blind population

Avandia (mg)	% of Patients with edema	
	Study 082	Study 095
0	4.7	5.2
4	13.1	10.1
8	16.2	18.6

There were no withdrawals or serious adverse events due to edema in these studies. The majority of events were labeled as mild to moderate in intensity. However, eleven patients between the two studies had two or more occurrences of edema reported. Out of the 10 patients who had both edema and anemia 9 had them concurrently and 2 were withdrawn from the study due to the anemia. In addition 7 patients had edema concurrently with cardiac AE's. In study 082, one patient withdrew due to pulmonary edema and a cardiac arrest. In study 095, two of the cardiac-related AE's were considered serious and but only one patient withdrew from the study due to the cardiac event. So while most episodes of edema can be adequately treated and are not in and of themselves serious, they help identify a subset of the population that maybe at increased risk of recurrent edema, anemia or cardiac related events. The labeling should inform physicians of this possibility. The labeling should also mention that edema may be dose-related so physicians should consider limiting patients at potential risk of edema, anemia or cardiac events to the lower 4mg daily dose.

HYPERLIPIDEMIA

Elevations in total cholesterol, and LDL-cholesterol or decreased levels of HDL have been associated with the development of atherosclerosis. The independent effect of lowering triglycerides or free fatty acids on atherosclerotic disease is still unresolved. Since diabetics have an increased risk of much more severe and extensive atherosclerosis than nondiabetics of the same age and gender, it is important to control their lipid profiles to limit the progression of the disease. Thiazolidinediones have previously been shown to have mixed results on lipid profiles. Avandia monotherapy was shown to increase total and LDL cholesterol in addition to HDL cholesterol. So that at 26 or 52 weeks of therapy there was no significant change in the LDL/HDL ratio compared to placebo. The clinical significance of these mixed changes in the lipid profile is not known.

In these two studies with Avandia in combination therapy with insulin similar results were observed. There were small increases in total, LDL and HDL cholesterol. The net result was there was a minimal difference in the median change from baseline for total cholesterol/HDL cholesterol or LDL/HDL cholesterol ratios in the two Avandia groups compared to insulin monotherapy. Small decreases in free fatty acids (-0.2 to –2.3 mg/dL) were seen in the Avandia groups, while changes in triglycerides were mixed and not consistently different between any of the groups (see Table 21, studies 082 and 095).

No lipid-related AE's were serious and no patients withdrew from the studies due to hypercholesterolemia or hypertriglyceridemia. Two patients withdrew from the study due to hyperlipemia, which was not considered an AE.

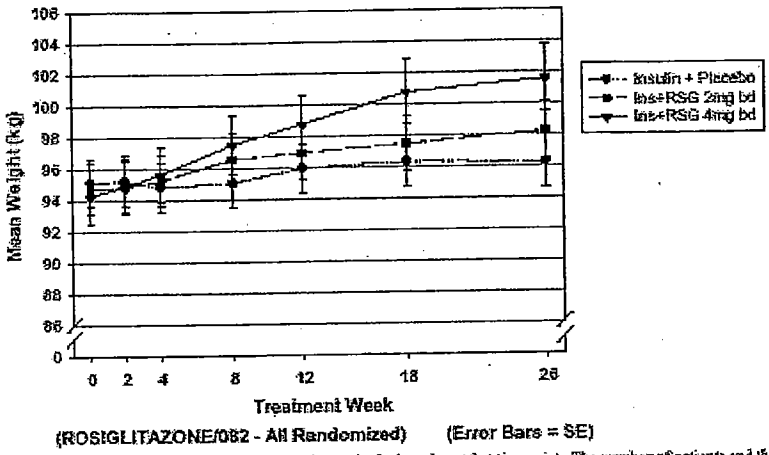
The Avandia label already describes the changes seen in lipid profiles with monotherapy and combination therapy with sulfonylureas. It would be adequate to say that similar changes are seen with Avandia and insulin combination therapy. Again as mentioned previously the clinical significance of these mixed changes is not known at this time.

WEIGHT GAIN

In the combined double blind and open-label population there was a greater prevalence of weight gain with Avandia and insulin combination therapy (5.7%) compared to insulin monotherapy (1.5%) (see Table 8.H.4.1). This increase was higher than had been previously reported for Avandia alone or in combination therapy with metformin or sulfonylureas (see NDA 20-071, Item 8.H.4). Individual weight changes for patients on combination therapy ranged from –10.8kg to +25.7kg. The mean weight gain over time for all patients in studies 082 and 095 was greatest for patients on the 8mg dose of Avandia (7-8kg) and intermediate on the 4mg daily dose (3-4kg), see Fig 10 and Fig 11 below. A similar dose dependent increase in AE's had been previously shown for edema and anemia. Fluid retention may be a common contributing factor to all of these conditions.

The increase in mean weight continued over the entire 26 weeks of the study, suggesting that weight gain will need to be monitored regularly for patients on Avandia and insulin combination therapy.

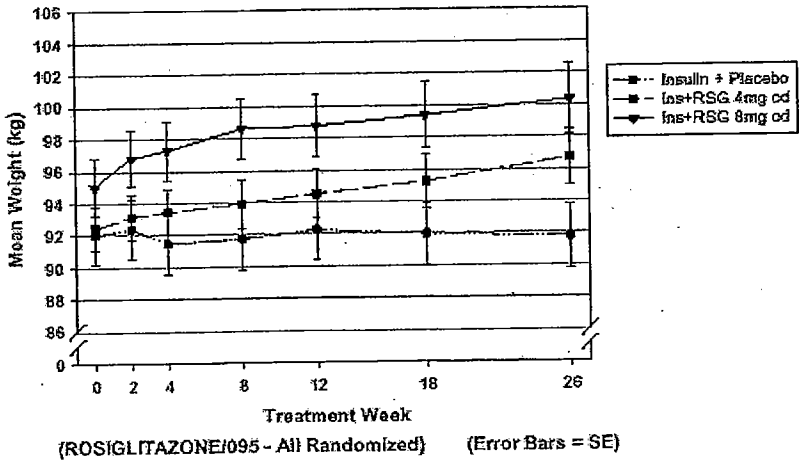
Figure 11 Mean Weight (kg) over Time in All Randomized Patients



(ROSIGLITAZONE/082 - All Randomized) (Error Bars = SE)

NOTE: The population at each timepoint is all patients who had a value at that timepoint. The number of patients and the baseline means are therefore different from those in Table 47.
Data Source: Section 15, Table 15.6.3

Figure 10 Mean Weight (kg) over Time in All Randomized Patients



(ROSIGLITAZONE/095 - All Randomized) (Error Bars = SE)

NOTE: The population at each timepoint is all patients who had a value at that timepoint. The number of patients and the baseline means are therefore different from those in Table 47.
Data Source: Section 15, Table 15.6.3

No weight gain AE's were serious. Two patients in the Avandia (8mg) and insulin combination therapy group withdrew from the studies due to weight gain that was not reported as an AE. Weight gain from the use of thiazolidinediones may be multifactorial

including fluid retention and increase in fat tissue. Patients with preexisting cardiac conditions that may be aggravated by fluid retention will need to be monitored regularly by their physician.

Out of the 23 patients with the largest weight gain 12/23=53% had edema, 5/23=22% had anemia, 0/23=0% had cardiac failure, 8/23=35% had cardiac events-6 aggravated hypertension, 2 chest pain, 1 hypotension, 1 bundle branch block (10 events in 8 patients) While weight gain is associated with adverse events, total weight gain does not seem to be a useful marker for cardiac failure. Sudden increases in weight are likely to be more predictive of risk for cardiac failure then total weight gain.

CARDIAC RELATED EVENTS (Cardiac failure, dyspnea, MI etc.)
The overall duration of diabetes (12-13yrs) was longer in the insulin and Avandia combination studies than in previous monotherapy studies with Avandia (4 –5 yrs) or in combination studies with Avandia and metformin or sulfonylureas (7 – 8 yrs). The patients in these studies, therefore had a higher baseline incidence of macrovascular disease (ie. congestive heart failure, ischemic heart disease and vascular disease) and microvascular disease (ie. retinopathy and peripheral neuropathy) than patients in the previous studies (see Tables 1.3 and 1.4). This would account for the higher incidence of cardiac related events observed in this study. However, since patients were randomly assigned to the insulin monotherapy or insulin plus Avandia combination therapy groups the relative baseline risk for cardiac events should be the same in all groups.

There were many more patients with adverse cardiac events (77/541=14.2%) in the insulin and Avandia combination therapy groups compared to the insulin monotherapy group (10/203=4.9%) in the double blind and open-label populations (see Table 8.H.4.9). Most of the events in the combination therapy group were due to heart failure (n=24, 4.4%) and dyspnea (n=23, 4.3%) and these typically occurred concomitantly, so that 60% of patients with heart failure also reported dyspnea.

Compared to insulin monotherapy (2.2/100 pt years, 95%CF 0.3-7.9) there was more than a 3 fold higher rate of heart failure with Avandia and insulin combination therapy in the double blind and open-label populations (7.4/100 pt years, 95%CF 4.8-11.1) (see Table 1.10).

There was one death and a total of 36 non-fatal serious adverse cardiac events in (27/541=5.0%) patients on insulin and Avandia combination therapy in the combined double blind and open label phases of this study. This is compared to no deaths and only 4 non-fatal serious adverse cardiac events in (4/203=2.0%) patients on insulin monotherapy. Most of the events in the combination therapy group were due to heart failure (n=12, 2.2%) and ischemic heart disease (n=10, 1.8%).

There was a total of 22 patients withdrawn due to cardiac events in the Avandia and insulin combination group (n=541) compared to 1 such withdrawal in the insulin monotherapy group (n=203) in the combined double blind and open label populations.

There were 15 patients that reported arrhythmias in the open-label and double blind population that were described as generally mild or moderate in intensity. All 15 were from the Avandia and insulin combination group (n=541). No such events were seen in the insulin alone placebo group (n=203). Two patients withdrew from the study due to arrhythmias.

Most of the patients with cardiac events treated with Avandia and insulin were receiving the higher 8mg/day dose. This suggests that it may be possible to minimize the risk to these patients by treating them with the lower 4mg daily dose. The contribution of the higher dose to the risk for cardiac events, may be partially overestimated since more patients were exposed to the higher dose for longer periods of time, but in general the risk seems to be dose related.

Patients in the Avandia and insulin combination group that experienced heart failure were on average 7 years older (64 vs. 57 yrs) and had a longer duration of diabetes (18 vs. 12.5 yrs) than those who did not experience heart failure. However, it was not possible to find specific risk factors that could be used to identify all patients at risk of heart failure on combination therapy. Data analysis from both the double blind (6-month) and open label (10-month) populations in which 24 patients developed cardiac failure on Avandia plus insulin combination therapy showed that:

- None of the 23 patients with the highest weight gain in these studies had cardiac failure.
- Only 4 of the 40 patients in the Avandia treatment group with a history of edema had an on therapy episode of cardiac failure.
- Only 5 of the 22 patients in the Avandia treatment group with a history of heart failure had a subsequent episode on therapy.

Therefore a prior history of edema, or heart failure identified at most 9/24=38% of the patients in the double blind and open label populations who had heart failure during the study.

Since patients with type 2 diabetes are at increased risk of cardiovascular disease it is important to compare patients on combination therapy only to placebo treated patients treated for a similar duration. At 26 weeks the incidence of cardiac failure is only 2.5% for the combination therapy group compared to 1% for the insulin only placebo-treated group. This 1.5-% difference may not seem large but it might have continued to increase if patients were followed for a longer duration. Unfortunately, in these studies all patients were switched to combination therapy during the open label phase. So while the percent of patients with cardiac failure continued to increase to 4.4% at 10 months into the open label phase of the studies it is not possible to know what the incidence would have been for patients maintained on insulin alone. In any case should combination therapy of

Avandia with insulin be approved the 1.5% increase in the incidence of heart failure would still represent a significant number of patients in the general population.

In conclusion, there was a marked increase in total adverse cardiac events, serious adverse cardiac events, and adverse cardiac events leading to withdrawal in patients on insulin and Avandia combination therapy compared to insulin alone. Most of the cardiac events involved cardiac failure and ischemic heart disease. There were also significantly more arrhythmias of all types with the insulin and Avandia combination therapy compared to insulin alone. Patients at highest risk of cardiac events were older, had a longer duration of diabetes and were on the higher 8mg daily dose of Avandia. The majority of patients (18/24=75%) who developed heart failure had predisposing risk factors (history of congestive heart failure, cardiac ischemia, edema, or left ventricular hypertrophy). However a significant number of patients (6/24=25%) did not. This would make if difficult to identify all patients at increased risk of cardiovascular events. These findings should be included in the label under *PRECAUTIONS, Cardiac Effects.*

HEPATIC EVENTS
Since the first marketed thiazolidinedione, troglitazone, was removed from the US market because it was associated with an increased risk of hepatitis and liver failure, there is an increased scrutiny of hepatic related adverse events in other members of this drug class. No patients in these studies 082 or 095 developed SGOT or SGPT elevations greater than three times the upper limit of normal due to combination therapy. One patient was withdrawn from the studies due to elevated transaminases that were noted on the initial day of the study and continued for 12 days on therapy. These transaminase elevations presumably occurred prior to the administration of the initial dose of study medication but the investigator involved suspected that they might be due to the study medication.

It needs to be mentioned that there were only 644 patients enrolled in these double blind studies which lasted for 26 weeks. This is too small of a patient population to rule out hepatotoxicity. Pooling data from all clinical studies with Avandia, the sponsor calculated that the incidence of SGPT which was greater than three times the upper limit of normal was only 13/4948=0.26%. This is slightly more than seen in the placebo group 1/156=0.18% but less than seen in other combination studies with insulin and sulfonylureas or metformin 5/1238=0.40% (see Table 8.H.8.18).

In post marketing analysis three cases of hepatic failure have been seen as of 9/2000. OPDRA calculated that the rate of acute liver failure was about 10.8 per million person-yrs, which is lower than the rate estimated for troglitazone 60-107 per million person-yrs, but higher than the background rate of 1 per million person-yrs. In addition 51 cases of hepatitis, described as serum transaminase levels greater than three times the upper limit of normal, have been associated with the use of Avandia. These findings have been used to amend the label in supplement S006. From the limited number of patients in studies 082 and 095 there is no data to suggest that combination therapy with insulin increases the risk of hepatotoxicity seen with Avandia.

SAFETY UPDATE 2000 PART I-Rosiglitazone in Combination with Insulin
This safety update summarizes data for 549 patients exposed to Avandia in combination with insulin with a clinical cut off date of July 7, 2000. This includes 18 months of additional information for patients followed in the open label extension.

Deaths
There were 6 more deaths reported since the end of studies 082 and 095 in the open label extension study 114. Two due to cardiac failure, one due to arrhythmia and one due to cardiac arrest, which may possibly be related to the study drug combination. One death due to an intracranial hemorrhage might also be related to the study medication. In this case the patient fell and struck his head while at home resulting in the intracranial hemorrhage. The patient never regained consciousness, so it is unclear if a cardiovascular event may have precipitated the fall. One death due to a hepatic neoplasm is unlikely to be related to combination therapy with Avandia plus insulin.

Serious Non-Fatal Adverse Events
There was a slight increase in the incidence of coronary heart disease in the Safety Update 2000 compared to the incidence reported in this NDA. Most other serious non-fatal cardiovascular events, however, decreased in rate or remained unchanged including cardiac failure, myocardial infarction, dyspnea, angina pectoris aggravated, and chest pain. There was a decrease in the rate of serious non-fatal adverse events due to anemia as well.

Adverse Events leading to Withdrawals
There were slight decreases in the percent of patients withdrawn from the study due to cardiac failure, anemia and hypoglycemia in the Safety Update 2000 compared to the rates reported in this NDA. Most other withdrawals due to adverse events occurred at similar rates in both reports.

Adverse Events occurring in ≥ 5% of the Population
There was a decrease in the incidence of cardiac failure, dyspnea, all types of edema, anemia, hypoglycemia, hypercholesterolemia, and hyperlipemia in the Safety Update 2000 compared to the incidence reported in this NDA.

Conclusion
It is encouraging that there was a decrease in the incidence of most adverse events, including those that were considered serious or resulted in patient withdrawals in the Safety Update 2000. However, it is difficult to assess the clinical value of these data since only 27% of the patients originally enrolled in the trial were left after 2 years of open label follow up and included in the Safety Update 2000. It is likely that with time only the healthier patients elected to continue in the study.

The continued incidence of deaths due to cardiovascular events and possibly related to the study medication is concerning. Since no placebo group was studied for the same duration of time, it is not possible to know if this increase in mortality is due to

combination therapy with Avandia plus insulin or if it is part of the normal progression of cardiovascular disease seen as a consequence of type 2 diabetes. Ideally a new clinical trial could be set up to compare patients on combination therapy to placebo for a longer duration of treatment. It might be helpful to include another treatment arm for patients started on more intensive insulin therapy. Also it would be worth considering the exclusion of all patients with a history of edema, cardiac failure or significant cardiac disease.

CONCLUSION OF STUDY RESULTS

I) Combination therapy with Avandia and insulin was effective at improving glycemic control in patients inadequately controlled on insulin therapy.

1) Patients with FPG $\geq$ 140mg/dL, HbA1C $\geq$ 7.5% and fasting C-peptide $\geq$0.4ng/mL had statistically significant decreases in FPG and HbA1C compared to the placebo treated groups.
2) The relative decrease in median FPG compared to the placebo-treated group at 26 weeks of therapy ranged between 31 to 40mg/dL (study 095, Table 5) and 52 to 55 mg/dL (study 082, Table 2).
3) The relative median decrease in HbA1C compared to the placebo-treated group ranged between 0.5% to 0.8% (study 095, Table 4) and 0.7% to 1.3% (study 082, Table 1).
4) No statistically significant changes in C-peptide were observed.
5) Improvements in FPG and HbA1C were greatest in study 082 with twice daily dosing compared to once a day dosing in study 095.
6) Improvements in FPG appeared to be maximal after 8 to 12 weeks of therapy while maximal changes in HbA1C were delayed and not seen until 12 to 26 weeks.
7) The efficacy of the Avandia and insulin combination therapy was maintained during the 26-week study period.
8) In subgroup analysis the efficacy with Avandia and insulin combination therapy was independent of age (> or < 65 years) and sex.
9) Patients, who were more overweight (BMI $\geq$ 27kg/m2) or more poorly controlled at the start of therapy, FBG ($\geq$ 200mg/dL) and HbA1C ($\geq$ 9%) were more likely to show a greater benefit, measured as a median decrease in HbA1C.

II) Combination therapy with Avandia and insulin was relatively well tolerated in the studies presented in this NDA. However, there was an increased frequency of the following adverse events: hypoglycemia (53%-71%), anemia (4%-17%), edema (2%-10%), hyperlipidemia (1%-9%), weight increase (0%-7%), dyspnea (4%-5%, study 082 only) and cardiac failure (2%-4%, study 095 only).

1) Hypoglycemia
   a) Hypoglycemia was the most common adverse event in the combined double blind and open-label phases of these studies. It occurred in 331/541=61% of the patients on Avandia and insulin combination therapy, compared to 84/203=41% of patients on insulin and placebo.
   b) Episodes of FBG < 50mg/dL, based on the patients diary cards or scheduled lab assessment, were much less common. Only 12/541=2.2 % of the patients on Avandia and insulin combination therapy had one or more such episodes, compared to 2/203=1% patients on insulin monotherapy.
   c) The high incidence of events was likely due to the strict protocol guidelines which did not permit reduction in the baseline insulin dose unless the patient had sustained hypoglycemia (mean capillary glucose <100mg/dL for 7 days) or severe or recurrent episodes of hypoglycemia.
   d) The incidence of hypoglycemia was dose related and occurred more frequently with once a day dosing.

2) Anemia
   a) The magnitude of the mean decrease in hemoglobin seen with combination therapy with Avandia and insulin was 1g/dL which is similar to what had been previously seen with Avandia monotherapy or combination therapy with Avandia and other oral antidiabetic agents.
   b) However, patients on combination therapy had individual decreases in hemoglobin of up to 3.6g/dL substantially greater than the mean decrease of 1g/dL. The lowest hemoglobin reported in patients on therapy that may be solely attributed to therapy was 9.5g/dL. (One patient whose clinical course was complicated with a bleeding gastric ulcer had a decrease in her hemoglobin of 5g/dL from 13.9 to 8.9g/dL.)
   c) The risk of developing anemia during combination therapy with Avandia and insulin was greater compared to patients on placebo or Avandia monotherapy. But this was largely due to the lower baseline hemoglobin (-0.4g/dL) seen in the patients enrolled in combination therapy compared to those on placebo and Avandia monotherapy.
   d) New occurrences of anemia were seen throughout the 26 weeks of the studies.
   e) The incidence of anemia was dose related.
   f) Patients with anemia had an increased incidence of concurrent edema (9/44=20%)
   g) The anemia was primarily normocytic as would be expected with volume expansion.

3) Edema
   a) Both insulin and Avandia in monotherapy are associated with edema. In combination therapy the increased incidence of edema was additive.
   b) The incidence of edema was dose related.
   c) In the double blind phase of these studies 59/408=14.5% of all patients on the Avandia and insulin combination had adverse events of edema.
   d) Patients with edema had an increased incidence of concurrent anemia (9/59=15%)

e) Patients with edema had an increased incidence of concurrent adverse cardiac events (7/59=12%)
f) In the open label extension, study 114, the incidence of new adverse events of edema in patients on combination therapy was essentially unchanged at 58/389=14.9%.

4) Hyperlipidemia
   a) Small increases in total cholesterol, LDL-cholesterol and HDL-cholesterol were seen with seen with combination therapy with Avandia and insulin. These resulted in minimal changes in the ratios of total cholesterol/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol.
   b) Small decreases in free fatty acids and mixed changes in serum triglycerides were seen with combination therapy with Avandia and insulin.
   c) The clinical significance of the lipid changes associated with Avandia therapy is not known.

5) Weight Increase
   a) Both insulin and Avandia in monotherapy are associated with weight increase. In combination therapy the effect on weight increase was additive.
   b) The incidence of weight increase was dose related.
   c) Mean weight in patients on combination therapy with Avandia and insulin increased over the entire 26 week study period.
   d) The mean weight increase in the double blind phase of the studies ranged from 4 to 7kg, while individual weight gains as high as 27.5kg were seen.
   e) Weight gain was associated with edema and anemia, but was not predictive of risk for cardiac failure. Out of the 23 patients with the largest weight gain in these studies 12/23=53% had edema, 5/23=22% had anemia but none had cardiac failure.

6) Cardiac Related Events
   a) Type 2 diabetics on insulin therapy typically have had diabetes for a longer time and are likely to be at higher risk for cardiovascular complications. In this study patients were randomly assigned to treatment groups in order to control for this.
   b) There was a marked increase in total adverse cardiac events, serious adverse cardiac events, and adverse cardiac events leading to withdrawal in patients on insulin and Avandia combination therapy compared to insulin alone.
   c) Most of the cardiac events involved cardiac failure and ischemic heart disease.
   d) There was a significant increase in the incidence of arrhythmias of all types in the insulin and Avandia combination therapy compared to insulin alone. However, it was not possible to identify specific arrhythmias that were more commonly associated with combination therapy.
   e) Patients at highest risk of cardiac events were older, had a longer duration of diabetes and were on the higher 8mg daily dose of Avandia.
   f) While the majority of patients on combination therapy (18/24=75%) who developed heart failure had predisposing risk factors (history of congestive heart

failure, cardiac ischemia, edema, or left ventricular hypertrophy), a significant proportion (6/24=25%) did not. And only 18/200=9% of the patients with one or more predisposing cardiovascular risk factors on combination therapy developed heart failure. This means that it is not possible to distinguish patients at increased risk of cardiovascular adverse events by medical history.

7) Hepatic Events
   a) Non of the 644 patients enrolled in these studies developed elevations in SGOT or SGPT > three times the upper limit of normal due to combination therapy. One patient had elevations of 3.1 to 3.9 times the upper limit of normal noted on the first day of study 095. This was presumably before he received any study medication. The patient was withdrawn from the study on day 12 due to persistently elevated transaminases.
   b) Pooling data from all clinical studies with Avandia, the sponsor calculated that the incidence of SGPT > three times the upper limit of normal is only 13/4948=0.26%. This is slightly more than placebo 1/156=0.18% but less than seen in combination studies with insulin and sulfonylureas or metformin 5/1238=0.40% (see Table 8.H.8.18).
   c) In post marketing analysis, three cases of hepatic failure have been seen with Avandia as of 9/2000. OPDRA calculated that the rate of acute liver failure was about 10.8 per million person-yrs, which is lower than the rate estimated for troglitazone 60-107 per million person-yrs, but higher than the background rate of 1 per million person-yrs.
   d) In post marketing analysis 51 cases of hepatitis have been seen with Avandia as of 9/2000. Hepatitis was determined as serum transaminase levels > three times the upper limit of normal that could not be accounted for by another cause.
   e) From the limited number of patients in studies 082 and 095 there is no data to suggest that combination therapy with insulin increases the risk of hepatotoxicity seen with Avandia.

16 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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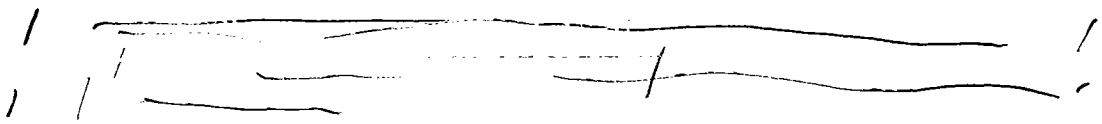

FINANCIAL DISCLOSURE FOR STUDIES 082 AND 095

Form 3454, CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS, was submitted by David Wheadon, V.P. & Director of Regulatory Affairs and Product Professional Services.

For study 082, 174 clinical investigators from 41 different sites are listed as having submitted completed financial information with no financial information to disclose. 14 clinical investigators (7%) did not respond to the request for financial information, but the sponsor has copies of 2 letters of notification on file for each of these investigators.

For study 095, 125 clinical investigators from 40 different sites are listed as having submitted completed financial information. 113 of these investigators are listed as having no financial information to disclose. 24 clinical investigators (15%) did not respond to the request for financial information, but the sponsor has copies of 2 letters of notification on file for each of these investigators. 8 clinical investigators (5%), from centers 21 and 22, did not have any information listed in the NDA, because they were no longer employed at the centers. The clinical centers submitted letters confirming that they had been unable to contact these investigators to obtain their signatures.

Reviewer's Comments
The data presented in this NDA was obtained from two large placebo-controlled double-blinded multicenter trials at 40 to 41 different sites including 188 to 157 different clinical investigators. None of the clinical investigators who responded had financial information, which needed to be disclosed. Of the remaining 7% to 20% of the investigators, who did not respond to the sponsor's request for financial information, there is a low likelihood that they could have effected the outcome of these placebo-controlled double-blinded multicenter trials.

RECOMMENDATIONS

The proposed new indication for the treatment of type 2 diabetics with *Avandia* and insulin in combination therapy should not be approved at this time. This indication may be reevaluated following longer double blind placebo controlled clinical trials that can provide additional information on the long-term benefits of this combination therapy. Acceptable endpoints would be cardiovascular mortality or total mortality.

The proposed labeling changes, describing appropriate safety information about combination therapy with *Avandia* and insulin, should be adopted.

Recommendation code: AE

SIGNATURE PAGE

Reviewed by:

(2/6/01)

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cc: Original NDA (NDA Archive DMEDP)
HFD-510/Division File
HFD-510/Lubas/Malozowski/Orloff/Weber

APPENDIX

References:

Buckingham, R.E., Al-Barazanji, C.D., Toseland N., Slaughter, M., Connor, S.C., West, A., Bond, B., Turner, N.C. and Clapham, J.C. Peroxisome Proliferator-Activated Receptor-γ Agonist, Rosiglitazone, Protects Against Nephropathy and Pancreatic Islet Abnormalities in Zucker Fatty Rats *Diabetes*, **47**:1326-1334, 1998

Tables from NDA

Table 1.3: Incidence of Selected Presenting Conditions Related to Macrovascular Disease in the Rosiglitazone Double Blind Population

Table 1.4: Incidence of Selected Presenting Conditions Related to Microvascular Disease in the Rosiglitazone Double Blind Population

Table 1.8 Incidence of Anemia in the Rosiglitazone Clinical Program (Double Blind Population)

Table 1.9: Incidence of Edema in the Rosiglitazone Clinical Program (Double-Blind Population)

Table 1.10: Rate of Heart Failure in the Rosiglitazone Phase 3 Program

Table 8.H.4.1: On-therapy Adverse Experiences (≥3% in Any Treatment Group) by WHO (ART) Preferred Term - Rosiglitazone in Combination with Insulin, Double-blind and Open-label Population

Table 8.H.4.14: On-therapy Reports of Edema* - Rosiglitazone in Combination with Insulin, Double-blind and Open-label Population

Table 8.H.4.15: On-therapy Reports of Edema* for OD and BID Regimens-Rosiglitazone in Combination with Insulin, Double-blind Population

Table 8.H.4.9: On-therapy Reports of Cardiovascular Events* -Rosiglitazone in Combination with Insulin, Double-blind and Open-label Population

Table 8.H.8.18: Rates of ALT Levels >3X ULRR* in the Rosiglitazone Clinical Program

Table 8.H.8.2: Mean Change from Baseline in Hemoglobin and Hematocrit Over Time – Rosiglitazone in Combination with Insulin, Double-blind, and Open-label Population

Table 8.H.8.3: Mean Change from Baseline in Hemoglobin and Hematocrit by Regimen– Rosiglitazone in Combination with Insulin, Double-blind Population

Table 23 Mean Change from Baseline in HbA1c and FPG at Week 26 by Subgroups- Intent-to-Treat Patients Study 082

Table 23 Mean Change from Baseline in HbA1c and FPG at Week 26 by Subgroups - Intent-to-Treat Patients Study 095

Table 28 Randomized Patients with On-therapy Adverse Experiences of Edema Study 082/095

Table 30 On-therapy Adverse Experiences of Anemia by Time of First Occurrence Study 082/095

Table 8.H.8.2: Mean Change from Baseline in Hemoglobin and Hematocrit Over Time – Rosiglitazone in Combination with Insulin, Double-blind, and Open-label Population

	RSG + INS			INS		
Hemoglobin (g/dL)	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline*	541	14.1	1.34	203	14.1	1.28
1 days	0	0	0	0	0	0
2-30 days	390	-0.5	0.62	150	-0.1	0.62
31-60 days	446	-0.7	0.67	174	0.0	0.66
61-90 days	437	-0.8	0.77	179	-0.1	0.67
91-196 days	443	-1.0	0.78	175	-0.2	0.68
197-280 days	268	-1.3	0.88	13	0.1	0.66
281-378 days	158	-0.9	0.95	0	0	0
379-560 days	36	-0.7	1.04	0	0	0
Hematocrit (%)	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline*	541	41.9	3.88	203	41.8	3.73
1 days	0	0	0	0	0	0
2-30 days	390	-1.4	2.05	150	-0.5	1.98
31-60 days	446	-2.0	2.17	174	-0.3	2.10
61-90 days	437	-2.6	2.41	179	-0.5	2.16
91-196 days	443	-3.1	2.41	175	-1.1	2.07
197-280 days	268	-3.9	2.69	13	-0.3	1.77
281-378 days	158	-3.1	3.00	0	0	0
379-560 days	36	-2.6	3.24	0	0	0

* Time intervals expressed in days
Data Source: ISS Table 8.2.4.1.1a

Table 8.H.8.3: Mean Change from Baseline in Hemoglobin and Hematocrit by Regimen – Rosiglitazone in Combination with Insulin, Double-blind Population

	RSG + INS OD			RSG + INS BID			INS		
Hemoglobin (g/dL)	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline*	196	14.2	1.41	212	14.0	1.30	203	14.1	1.28
1 days	0	0	0	0	0	0	0	0	0
2-30 days	142	-0.4	0.64	153	-0.4	0.60	150	-0.1	0.62
31-60 days	165	-0.6	0.64	184	-0.6	0.66	174	0.0	0.66
61-90 days	152	-0.8	0.74	183	-0.7	0.73	179	-0.1	0.67
91-196 days	164	-1.0	0.74	187	-1.0	0.74	175	-0.2	0.68
197-280 days	16	-0.3	0.84	14	-0.7	0.76	13	0.1	0.66
Hematocrit (%)	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline*	196	42.0	4.08	212	41.8	3.80	203	41.8	3.73
1 days	0	0	0	0	0	0	0	0	0
2-30 days	142	-1.2	2.14	153	-1.3	1.97	150	-0.5	1.98
31-60 days	165	-1.9	2.10	184	-2.1	2.07	174	-0.3	2.10
61-90 days	152	-2.5	2.40	183	-2.5	2.30	179	-0.5	2.16
91-196 days	164	-3.1	2.30	187	-3.3	2.15	175	-1.1	2.07
197-280 days	16	-0.7	3.17	14	-2.0	2.34	13	-0.3	1.77

* Time intervals expressed in days return to Safety Summary Anemia
Data Source: ISS Table 8.2.4.2.1a return to text 7)Precautions return to text 14) Laboratory

Table 30 On-therapy Adverse Experiences of Anemia by Time of First Occurrence Study 082									
Time from Start of Study Medication	Treatment Group								
	Insulin + Placebo (N = 107)			Insulin + RSG 2mg bid (N = 107)			Insulin + RSG 4mg bid (N = 105)		
(days)	N at Risk	N with Event	Cum.%	N at Risk	N with Event	Cum.%	N at Risk	N with Event	Cum.%
1-14	107	0	0.0	107	0	0.0	105	0	0.0
15-28	102	0	0.0	105	0	0.0	103	1	1.0
29-42	100	0	0.0	104	0	0.0	102	1	2.0
43-56	100	0	0.0	103	1	1.0	99	4	6.0
57-84	100	1	1.0	99	1	2.0	92	2	8.0
85-112	96	0	1.0	97	1	3.0	90	1	9.1
113-182	91	0	1.0	91	1	4.6	84	4	14.9

N at risk = number of patients still taking study medication minus patients who had at least one AE of anemia reported at a prior visit.
Cum. % = Cumulative % of patients with AE of anemia adjusted for number of withdrawn patients
Data Source: Section 15, Table 15.2.5; Appendix D, Listing D.L2
SAS output is presented in Section 15, Table 15.2.7.

Table 30 On-therapy Adverse Experiences of Anemia by Time of First Occurrence Study 095									
Time from Start of Study Medication	Treatment Group								
	Insulin + Placebo (N = 96)			Insulin + RSG 4mg od (N = 99)			Insulin + RSG 8mg od (N = 97)		
(days)	N at Risk	N with Event	Cum.%	N at Risk	N with Event	Cum.%	N at Risk	N with Event	Cum.%
0-14	96	0	0.0	99	0	0.0	97	0	0.0
15-28	94	1	1.1	98	0	0.0	95	0	0.0
29-42	90	0	1.1	95	2	2.1	91	2	2.2
43-56	89	0	1.1	93	1	3.2	88	5	7.8
57-84	85	3	4.6	90	1	4.3	82	3	11.2
85-112	80	0	4.6	83	1	5.5	76	4	16.0
113-182	79	2	7.9	80	4	11.8	70	2	19.3
≥183	34	0	7.9	35	2	21.3	30	0	19.3

N at risk = number of patients still taking study medication minus patients who had at least one AE of anemia reported at a prior visit.
Cum. % = Cumulative % of patients with AE of anemia adjusted for number of withdrawn patients
Data Source: Section 15, Table 15.2.5; Appendix D, Listing D.L2
SAS output is presented in Section 15, Table 15.2.7.

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Table 28 Randomized Patients with On-therapy Adverse Experiences of Edema Study 082						
Treatment group	**PID**	**Preferred term**	**Verbatim term**	**Intensity**	**Relationship to Study Medication**	**Outcome**
Insulin + Placebo	082.021.13957	Edema peripheral	Increased swelling (l) hand + (l) foot	Mild	Unlikely	Ongoing
"	082.022.14001	Edema dependent	Trace pedal edema	Mild	Not related	Ongoing
"	082.026.13968	Edema dependent	Edema both feet	Moderate	Not related	Resolved 7 days
"	082.033.14139	Edema dependent	Pedal edema both feet fluid retention	Mild	Suspected	Ongoing
"	082.039.13778	Edema legs	Edema (r) leg + foot	Moderate	Not related	Ongoing
Ins+RSG 2mg bid	082.003.13551	Edema legs	Edema–lower extremities	Mild	Suspected	Resolved 5 days
"	082.003.14216*	Edema legs	Edema lower extremities	Mild	Suspected	Resolved 71 days
"		Edema periorbital	Swelling eyes	Mild	Suspected	Resolved 59 days
"		Edema periorbital	Swelling; bilateral hands, feet/ankle and eyes	Mild	Unlikely	Resolved 5 days
"		Edema peripheral	Swelling; bilateral hands, feet/ankle and eyes	Mild	Unlikely	Resolved 5 days
"	082.006.13573	Edema dependent	Edema to feet	Mild	Unlikely	Resolved 7 days
"	082.006.13918	Edema legs	Swelling to lower legs	Mild	Unlikely	Resolved 3 days
"	082.008.13722**	Edema legs	Edema left lower extremity	Mild	Unlikely	Resolved 5 days
"	082.010.13963	Edema legs	Trace pitting edema, lower 1/3 legs	Mild	Not related	Ongoing
"	082.012.13531	Edema legs	Leg edema	Mild	Not related	Ongoing
"	082.015.13868	Edema dependent	Bilateral edema of ankles	Mild	Unlikely	Ongoing
"	082.017.13756	Edema generalized	Fluid retention	Mild	Suspected	Ongoing
"	082.025.13943	Edema legs	Bilateral lower leg edema	Mild	Unlikely	Ongoing
"	082.027.13770	Edema	Worsening edema	Mild	Suspected	Ongoing
"	082.030.14088	Edema peripheral	2+ pitting edema peripheral	Moderate	Unlikely	Resolved 125 days
"	082.031.13680**	Edema legs	(r) leg discomfort with +3 pitted edema	Moderate	Not related	Resolved 16 days

(table continues)
* Patient subsequently developed ECG abnormalities
** Patient had presenting condition of edema
† Edema resolved after the last dose of study medication.
†† Edema resolved after the end of study but while patient was on study medication since the patient continued into the open-label study.
‡ Patient withdrew from study on day 36 due to an SAE of pulmonary edema and cardiac arrest.
Data Source: Section 15, Table 15.2.4, and Appendix D, Listing D.L2.

Table 28 (continued) Randomized Patients with On-therapy Adverse Experiences of Edema Study 082						
Treatment group	**PID**	**Preferred term**	**Verbatim term**	**Intensity**	**Relationship to Study Medication**	**Outcome**
Ins+RSG 2mg bid	082.033.14082	Edema dependent	Pedal edema	Mild	Unlikely	Ongoing
(continued)						
Ins+RSG 4mg bid	082.003.13552 †	Edema dependent	Edema–bilateral feet	Mild	Suspected	Resolved 118 days
"	082.004.13695	Edema dependent	Increased edema of ankles	Mild	Unlikely	Ongoing
"	082.007.13856	Edema legs	Leg edema	Moderate	Suspected	Ongoing
"	082.008.13721	Edema dependent	Ankle edema [left]	Mild	Probable	Ongoing
"	082.009.13832 ††	Edema peripheral	Bilateral hand and leg edema	Mild	Not related	Resolved 18 days
"	082.027.13974	Edema	1+ bilateral edema	Moderate	Probable	Ongoing
"	082.027.13978 ‡	Edema dependent	(l) ankle 1+ edema	Moderate	Unlikely	Ongoing
"		Edema dependent	(r) ankle 1+ edema	Moderate	Unlikely	Resolved 190 days
"	082.028.13808 ††	Edema dependent	Slightly worsening edema of left foot	Mild	Not related	Resolved 102 days
"	082.028.13910 †	Edema dependent	Swelling in ankles (edema)	Moderate	Unlikely	Resolved 50 days
"		Edema dependent	Swelling in feet (edema)	Moderate	Unlikely	Resolved 50 days
"		Edema peripheral	Swelling in left hand (edema)	Moderate	Unlikely	Resolved 50 days
"	082.028.14109	Edema dependent	Swelling bottom left foot	Mild	Unlikely	Ongoing
"	082.029.14019	Edema generalized	Gen swelling	Mild	Not related	Resolved 1 day
"	082.032.13813**	Edema legs	Edema, bilateral both legs	Mild	Unlikely	Ongoing
"	082.034.13661	Edema dependent	Feet swollen	Mild	Not related	Ongoing
"	082.036.13945*	Edema legs	Lower bilateral peripheral edema	Mild	Unlikely	Ongoing
"	082.038.13993	Edema dependent	Edema (ankles)	Moderate	Not related	Ongoing
"	082.041.13935**	Edema legs	Leg edema (worsening) (worsening from baseline)	Moderate	Unlikely	Ongoing
"	082.041.13936	Edema dependent	(r) foot swelling	Mild	Unlikely	Resolved 16 days

* Patient subsequently developed ECG abnormalities
** Patient had presenting condition of edema
† Edema resolved after the last dose of study medication.
†† Edema resolved after the end of study but while patient was on study medication since the patient continued into the open-label study.
‡ Patient withdrew from study on day 36 due to an SAE of pulmonary edema and cardiac arrest.
Data Source: Section 15, Table 15.2.4, and Appendix D, Listing D.L2.

Table 28 Randomized Patients with On-therapy Adverse Experiences of Edema Study 095						
Treatment group	**PID**	**Preferred term**	**Verbatim term**	**Intensity**	**Relationship to Study Medication**	**Outcome**
Ins+Placebo	095.010.12429	Edema legs	Lower extremities swelling	Mild	Suspected	Resolved (31 days)
Ins+Placebo	095.010.12433	Edema legs	Swelling to lower extremities	Mild	Unlikely	Ongoing
Ins+Placebo	095.026.12129	Edema legs	Worsening edema in legs and feet	Moderate	Not Related	Ongoing
Ins+Placebo	095.034.12701	Edema legs	1 (+) lower extremity edema	Mild	Not Related	Ongoing
Ins+Placebo	095.038.12390	Edema generalized	Fluid retention intermittent	Mild	Not Related	Resolved (160 days)
Ins+RSG 4mg od	095.005.12384	Edema dependent	Edema (ankles)	Mild	Suspected	Resolved (57 days)
Ins+RSG 4mg od	095.007.12188	Edema dependent	Left pitting pretibial ankle edema	Mild	Not Related	Resolved (8 days)
		Edema dependent	Pitting pretibial ankle edema – Rt.	Mild	Not Related	Ongoing
Ins+RSG 4mg od	095.008.12033	Edema legs	Lower extremity edema	Mild	Suspected	Ongoing
Ins+RSG 4mg od	095.013.12485	Edema peripheral	Edema, both hands	Mild	Not Related	Resolved (3 days)
Ins+RSG 4mg od	095.013.12588	Edema dependent	Pedal edema – bilateral	Mild	Not Related	Ongoing
		Edema generalized	Weight gain (due to generalized edema)	Moderate	Suspected	Ongoing
Ins+RSG 4mg od	095.013.12695	Edema dependent	Trace pedal edema	Mild	Suspected	Resolved (160 days)
Ins+RSG 4mg od	095.024.12094	Edema dependent	Mild dependent edema	Mild	Not Related	Ongoing
Ins+RSG 4mg od	095.026.12130	Edema peripheral	Edema in arms + legs	Mild	Not Related	Ongoing
Ins+RSG 4mg od	095.027.12201	Edema generalized	Fluid retention (9 lb. weight gain)	Mild	Suspected	Ongoing
Ins+RSG 4mg od	095.032.12445	Edema legs	Bilateral lower leg edema	Moderate	Not Related	Resolved (19 days)
Ins+RSG 8mg od	095.002.12015	Edema dependent	Edema both feet (L) > R	Moderate	Not Related	Ongoing
Ins+RSG 8mg od	095.003.12601	Edema dependent	Edema bilateral feet	Mild	Not Related	Resolved (32 days)
Ins+RSG 8mg od	095.005.12385	Edema generalized	Weight gain >10% from screening	Mild	Suspected	Ongoing
		Edema Peripheral	Edema of hands and feet	Moderate	Suspected	Resolved (17 days)
Ins+RSG 8mg od	095.005.12439	Edema generalized	Generalized edema	Mild	Suspected	Ongoing
		Edema generalized	Increased weight due to generalized edema	Mild	Suspected	Resolved (118 days)
		Edema generalized	Increased weight due to generalized edema	Moderate	Suspected	Ongoing

(table continues)
Data Source: Section 15, Table 15.2.4, and Appendix D, Listing D.L2.

Table 28 (continued) Randomized Patients with On-therapy Adverse Experiences of Edema Study 095						
Treatment group	**PID**	**Preferred term**	**Verbatim term**	**Intensity**	**Relationship to Study Medication**	**Outcome**
Ins+RSG 8mg od	095.006.12230	Edema dependent	Bilateral pedal edema	Mild	Unlikely	Ongoing
Ins+RSG 8mg od	095.007.12527	Edema legs	Bilateral lower extremity edema	Mild	Unlikely	Ongoing
Ins+RSG 8mg od	095.010.12423	Edema legs	Edema to lower extremities	Moderate	Probable	Resolved (25 days)
Ins+RSG 8mg od	095.010.12639	Edema legs	Swelling to lower extremities at end of work day	Mild	Suspected	Resolved (50 days)
Ins+RSG 8mg od	095.013.12009	Edema dependent	"Lt. Foot swollen" aka pedal edema	Mild	Not related	Resolved (47 days)
Ins+RSG 8mg od	095.013.12300	Edema	Weight gain due to increased edema	Moderate	Not Related	Ongoing
Ins+RSG 8mg od	095.013.12687	Edema legs	Edema legs	Mild	Suspected	Resolved (179 days)
		Face edema	(L) face swollen	Mild	Not Related	Resolved (1 day)
Ins+RSG 8mg od	095.020.12539	Edema legs	Edema in right leg	Mild	Not Related	Ongoing
Ins+RSG 8mg od	095.022.12211	Edema legs	In patients history now worse. Bilateral leg edema	Moderate	Not Related	Ongoing
		Edema peripheral	(R) hand edema	Moderate	Not Related	Ongoing
Ins+RSG 8mg od	095.028.12138	Edema generalized	Generalized edema	Moderate	Suspected	Ongoing
Ins+RSG 8mg od	095.030.12605	Edema periorbital	Periorbital edema	Mild	Not Related	Resolved (113 days)
Ins+RSG 8mg od	095.032.12447	Edema dependent	Left foot edema	Mild	Not Related	Ongoing
Ins+RSG 8mg od	095.036.12458	Edema legs	Edema of lower extremities	Moderate	Not Related	Resolved (5 days)
		Edema legs	Lower extremities trace edema	Mild	Suspected	Ongoing
Ins+RSG 8mg od	095.038.12249	Edema generalized	Fluid retention	Moderate	Probable	Ongoing
		Edema generalized	Left and right leg edema/feet edema/ abdomen/edema	Moderate	Suspected	Ongoing
Data Source: Section 15, Table 15.2.4, and Appendix D, Listing D.L2. return to text						

Table 8.H.4.1: On-therapy Adverse Experiences (≥3% in Any Treatment Group) by WHO (ART) Preferred Term - Rosiglitazone in Combination with Insulin, Double-blind and Open-label Population

Preferred Term*	RSG + INS N = 541		Insulin N = 203	
	n	%	n	%
Total Patients w/AEs	**501**	**92.6**	**175**	**86.2**
Hypoglycemia	331	61.2	84	41.4
Upper Resp Tract Infection	115	21.3	41	20.2
Anemia	75	13.9	7	3.4
Injury	50	9.2	19	9.4
Infection Viral	47	8.7	16	7.9
Sinusitis	42	7.8	16	7.9
Edema Dependent	41	7.6	3	1.5
Edema Legs	39	7.2	5	2.5
Headache	37	6.8	15	7.4
Urinary Tract Infection	37	6.8	20	9.9
Arthralgia	36	6.7	7	3.4
Hyperlipemia	32	5.9	6	3.0
Weight Increase	31	5.7	3	1.5
Pain	29	5.4	11	5.4
Back Pain	27	5.0	8	3.9
Hypertension Aggravated	25	4.6	12	5.9
Bronchitis	24	4.4	7	3.4
Cardiac Failure	24	4.4	2	1.0
Dyspnea	23	4.3	2	1.0
Fatigue	23	4.3	4	2.0
Nausea	22	4.1	4	2.0
Coughing	20	3.7	6	3.0
Diarrhea	20	3.7	14	6.9
Edema Generalized	20	3.7	2	1.0
Infection	20	3.7	8	3.9
Edema Peripheral	18	3.3	1	0.5
Cellulitis	16	3.0	4	2.0
Chest Pain	16	3.0	2	1.0
Hypercholesterolemia	16	3.0	0	0.0
Rash	16	3.0	7	3.4
Arthritis	15	2.8	8	3.9
Dizziness	15	2.8	8	3.9
Allergy	11	2.0	8	3.9

* Sorted by RSG + INS, descending order of frequency of preferred term.
Data Source: ISS Table 4.2.4.1.a , ISS Table 4.2.4.1.b; Appendix 4.0a

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Table 8.H.4.14: On-therapy Reports of Edema* - Rosiglitazone in Combination with Insulin, Double-blind and Open-label Population

Preferred Term **	RSG + INS N = 541		INS N = 203	
	n	%	n	%
Edema Dependent	41	7.6	3	1.5
Edema Legs	39	7.2	5	2.5
Edema Generalized	20	3.7	2	1.0
Edema Peripheral	18	3.3	1	0.5
Edema	3	0.6	0	0.0
Pulmonary Edema	1	0.2	0	0.0
Total Patients† with Edema AEs	107	19.8	11	5.4

* A patient could have more than one edema AE.
** Sorted by descending order of preferred term frequency, RSG+INS.
† Patients counted only once, regardless of number of preferred terms.
Data Source: ISS Table 4.2.4.1.a and 4.2.4.1.b; Appendix 4.0a

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Table 8.H.4.15: On-therapy Reports of Edema* for OD and BID Regimens – Rosiglitazone in Combination with Insulin, Double-blind Population

Preferred Term **	RSG+INS BID N = 212		RSG+INS OD N = 196		Insulin N = 203	
	n	%	n	%	n	%
Edema Dependent	13	6.1	11	5.6	3	1.5
Edema Legs	12	5.7	9	4.6	5	2.5
Edema Generalized	3	1.4	6	3.1	2	1.0
Edema Peripheral	4	1.9	4	2.0	1	0.5
Edema	2	0.9	1	0.5	0	0.0
Pulmonary Edema	1	0.5	0	0.0	0	0.0
Total Patients† with Edema AEs	32	15.1	28	14.3	11	5.4

* A patient could have more than one edema AE.
** Sorted by descending order of preferred term frequency, RSG+INS.
† Patients counted only once, regardless of number of preferred terms.
Data Source: ISS Table 4.2.4.2.a, ISS Table 4.2.4.2.b; Appendix 4.0a

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Table 1.8 Incidence of Anemia in the Rosiglitazone Clinical Program (Double Blind Population)*

	Baseline Hemoglobin	***Hgb (Mean Change from baseline)*** **	***AE of Anemia***	***Value of Potential Clinical Concern**** **
	(gm/dL)	***(gm/dL)***	***(% of patients)***	***(% of patients)***
RSG monotherapy	14.6	*-1.0*	*1.9*	*0.9*
Placebo	14.6	*-0.2*	*0.7*	*0.4*
RSG + Metformin	14.2	*-1.0*	*7.1*	*1.5*
Metformin	14.2	*-0.3*	*2.2*	*1.8*
RSG + Sulfonylurea	14.4	*-0.7*	*1.5*	*1.8*
Sulfonylurea	14.4	*-0.2*	*0.6*	*1.0*
RSG + Insulin	**14.1**	***-1.0***	***10.8***	***2.8***
Insulin	**14.1**	***-0.2***	***3.4***	***1.1***

* Includes all doses and regimens

** Mean change from baseline at the day 91 - 196 window. return to text in Label return to Safety Summary Anemia

*** % of patients with an on-therapy hemoglobin value >2gm/dL below the lower limit of the reference range.

Table 1.9: Incidence of Edema in the Rosiglitazone Clinical Program (Double-Blind Population)*

	Edema (%)	
	Control	**RSG**
RSG monotherapy	1.3	4.8
RSG + Metformin	2.2	4.4
RSG + Sulfonylurea	1.0	3.0
RSG + Insulin	**5.4**	**14.7**

*Includes all doses and regimens return to text return to Safety Summary

Table 1.10: Rate of Heart Failure in the Rosiglitazone Phase 3 Program				
	Double-blind Controlled Trials % of pts	Including OL, Uncontrolled Extensions % of pts	Rate/100 pt years (95% CI)	
Placebo	0.2	-	0.6	(0.01-3.30)
Metformin	0.0	-	0.0	(n/a-3.76)
Sulfonylureas	0.4	-	0.6	(0.11-1.62)
Insulin	1.0	-	2.2	(0.27–7.94)
RSG Monotherapy	0.2	0.5	0.7	(0.40-1.09)
RSG + Metformin	0.3	0.5	0.7	(0.15-2.18)
RSG + Sulfonylureas	0.7	0.5	0.6	(0.21-1.51)
RSG + Insulin	2.5	4.4	7.4	(4.79-11.12)
return to text 9)precautions return to text 14)Adverse Reactions				

Table 1.3: Incidence of Selected Presenting Conditions Related to Macrovascular Disease in the Rosiglitazone Double Blind Population

	Monotherapy Studies	*Metformin Combination Studies*	*SU Combination Studies*	*Insulin Combination Studies*
	(%)	*(%)*	*(%)*	*(%)*
Congestive Heart Failure	*1.0*	*0.7*	*1.3*	*2.5*
Ischemic Heart Disease	*4.2*	*3.4*	*8.0*	*14.1*
Vascular Disease	*2.6*	*3.0*	*3.4*	*9.2*

Table 1.4: Incidence of Selected Presenting Conditions Related to Microvascular Disease in the Rosiglitazone Double Blind Population

	Monotherapy Studies	*Metformin Combination Studies*	*SU Combination Studies*	*Insulin Combination Studies*
	(%)	*(%)*	*(%)*	*(%)*
retinopathy	*1.5*	*5.2*	*4.4*	*19.1*
Peripheral neuropathy	*8.9*	*14.0*	*7.4*	*33.9*

return to Safety Review Cardiac Events

Table 8.H.4.9: On-therapy Reports of Cardiovascular Events* - Rosiglitazone in Combination with Insulin, Double-blind and Open-label

	Population RSG + INS N = 541		INS N = 203	
Preferred Term **	**n**	**%**	**n**	**%**
Cardiac failure†	24††	4.4	2	1.0
Dyspnea	23	4.3	2	1.0
Cerebrovascular disorder	9	1.7	2	1.0
Coronary artery disorder	9	1.7	1	0.5
Peripheral ischemia	7	1.3	2	1.0
Angina pectoris	6	1.1	2	1.0
Myocardial infarction	6	1.1	0	0.0
Myocardial ischemia	5	0.9	0	0.0
Angina pectoris aggravated	3	0.6	1	0.5
Cardiomegaly	2	0.4	1	0.5
Cardiac arrest	2	0.4	0	0.0
Claudication intermittent	1	0.2	0	0.0
Total Patients‡ w/Cardiovascular AEs	77	14.2	10	4.9

* A patient could have more than one cardiovascular event.
** Sorted by descending order of preferred term frequency, RSG+INS.
† One patient with cardiac failure is represented in both treatment groups because the onset day was both the last day of the acute study and first day of the extension study.
†† One patient (082.027.13978) also had an on-therapy AE of pulmonary edema which began 22 days after the onset of the on-therapy cardiac failure.
‡ Patients counted only once, regardless of number of preferred terms.

Data Source: ISS Table 4.2.4.1.a and 4.2.4.1.b; Appendix 4.0a return to Safety Summary Cardiac events

Table 8.H.8.18: Rates of ALT Levels >3X ULRR* in the Rosiglitazone Clinical Program

n (%) patients with ALT >3X ULRR based on the entire rosiglitazone clinical program

Rosiglitazone	Placebo	SU, Metformin and Insulin
13/4948 (0.26%)	1/561 (0.18%)	5/1238 (0.40%)
0.33 per 100 patient years of exposure (3998.5 patient years)	0.59 per 100 patient years of exposure (169.5 patient years)	0.70 per 100 patients years of exposure (731.6 patient years)

*ULRR = upper limit of the reference range return to Safety Summary Hepatic

Data Source: Original NDA 21-071; 120-Day Safety Update, 24-March-1999; ISS Table 8.3.4.1.4.a

Table 23 Mean Change From Baseline in HbA1c and FPG at Week 26 by Subgroups - Intent-to-Treat Patients study 082

Change from Baseline	HbA1c			FPG		
	Insulin + Placebo	Insulin + RSG 2mg bd	Insulin + RSG 4mg bd	Insulin + Placebo	Insulin + RSG 2mg bd	Insulin + RSG 4mg bd
Age <65 yrs						
n	83	82	79	83	82	79
mean ± SD	0.09 ± 0.984	-0.64 ± 1.104	-1.24 ± 1.139	9.4 ± 71.79	-39.2 ± 73.45	-50.0 ± 62.27
median	0.10	-0.60	-1.20	-2.0	-30.5	-55.0
Age ≥65 yrs						
n	20	24	24	21	24	24
mean ± SD	0.25 ± 0.961	-0.66 ± 0.971	-1.04 ± 0.720	13.5 ± 52.51	-49.3 ± 61.38	-26.0 ± 49.40
median	0.15	-0.65	-1.05	22.0	-58.0	-28.5
Males						
n	58	60	56	58	60	56
mean ± SD	0.07 ± 0.838	-0.49 ± 1.133	-0.98 ± 0.930	8.8 ± 67.68	-28.2 ± 72.5	-45.2 ± 62.43
median	0.00	-0.50	-1.00	5.0	-27.5	-37.0
Females						
n	45	46	47	46	46	47
mean ± SD	0.19 ± 1.137	-0.84 ± 0.961	-1.45 ± 1.149	12.1 ± 69.39	-58.8 ± 65.13	-43.5 ± 58.01
median	0.20	-0.60	-1.50	3.5	-57.5	-53.0
Baseline BMI <27kg/m^2						
n	10	11	17	11	11	17
mean ± SD	0.17 ± 1.275	-0.34 ± 0.555	-1.08 ± 0.750	-20.9±67.33	-37.9 ± 67.37	-42.5 ± 62.47
median	0.05	-0.50	-1.00	-5.0	-34.0	-48.0
Baseline BMI ≥27kg/m^2						
n	92	95	86	92	95	86
mean ± SD	0.12 ± 0.954	-0.68 ± 1.112	-1.22 ± 1.109	13.5 ± 67.87	-41.9 ± 71.45	-44.8 ± 60.07
median	0.20	-0.60	-1.20	9.0	-35.0	-45.5
Baseline HbA1c <9%						
n	64	54	51	65	54	51
mean ± SD	0.29 ± 0.897	-0.40 ± 0.915	-0.86 ± 0.842	-0.5 ± 55.57	-38.8 ± 59.73	-32.5 ± 54.51
median	0.20	-0.50	-0.90	-7.0	-33.5	-37.0
Baseline HbA1c ≥9%						
n	39	52	52	39	52	52
mean ± SD	-0.16 ± 1.049	-0.90 ± 1.168	-1.52 ± 1.149	28.2 ± 82.80	-44.2 ± 81.12	-56.1 ± 63.62
median	-0.10	-0.85	-1.70	39.0	-38.5	-57.0
Baseline FPG <200mg/dL						
n	65	46	51	66	46	51
mean ± SD	0.8 ± 1.005	-0.28 ± 0.935	-1.24 ± 0.980	28.6 ± 61.83	-5.5 ± 51.42	-23.7 ± 49.30
median	0.00	-0.25	-1.20	19.5	-16.5	-26.0
Baseline FPG ≥200mg/dL						
n	38	60	52	38	60	52
mean ± SD	0.21 ± 0.935	-0.92 ± 1.096	-1.15 ± 1.135	-21.6±67.5	-69.1 ± 71.45	-64.7 ± 63.34
median	0.20	-0.80	-1.20	-28.0	-70.0	-66.5

Data Source: Section 14, Tables 14.5.1A, 14.5.2A, 14.5.3A, 14.5.4A and 14.5.5A; Appendix C, Listing C.L1.

Return to Subgroup Analysis Efficacy Review 082

Table 23 Mean Change From Baseline in HbA1c and FPG at Week 26 by Subgroups - Intent-to-Treat Patients study 095

Change from Baseline	HbA1c			FPG		
	Insulin + Placebo	Insulin + RSG 4mg od	Insulin + RSG 8mg od	Insulin + Placebo	Insulin + RSG 4mg od	Insulin + RSG 8mg od
Age <65 yrs						
N	63	66	71	63	66	71
Mean ± SD	0.3 ± 0.99	-0.5 ± 1.00	-0.8 ± 0.98	12.1± 62.92	-22.5 ± 68.80	-30.2±66.48
Median	0.20	-0.40	-0.70	6.0	-19.0	-13.0
Age ≥65 yrs						
N	32	31	24	32	31	24
Mean ± SD	-0.1 ± 0.80	-0.3 ± 0.87	-0.6 ± 0.90	-5.9 ± 68.00	-30.7 ± 60.36	-46.2 ± 61.59
Median	0.05	-0.10	-0.55	-17.5	-35.0	-47.5
Males						
N	43	62	56	43	62	56
Mean ± SD	0.0 ± 0.90	-0. 5 ± 0.92	-0.6 ± 1.03	10.5± 63.61	-27.8 ± 58.99	-25.2 ± 65.04
Median	0.10	-0.40	-0.55	-5.0	-27.0	-15.0
Females						
N	52	35	39	52	35	39
Mean ± SD	0.2 ± 0.99	-0.4 ± 1.04	-0.9 ± 0.83	2.3 ± 65.71	-20.2 ±77.62	-47.2 ± 64.37
Median	0.20	-0.30	-0.80	1.5	-24.0	-38.0
Baseline BMI <27kg/m^2						
N	16	15	14	16	15	14
Mean ± SD	0.1 ± 1.39	-0.1 ± 1.04	-0.3 ± 0.81	11.1 ± 71.92	-16.6 ± 58.33	-33.9 ± 50.28
Median	0.00	-0.10	-0.25	10.5	-29.0	-31.5
Baseline BMI ≥27kg/m^2						
N	79	82	81	79	82	81
Mean ± SD	0.2 ± 0.84	-0.5 ± 0.94	-0.8 ± 0.97	5.0 ± 63.42	-26.6 ± 67.54	-34.3 ± 67.85
Median	0.20	-0.45	-0.70	-5.0	-24.5	-17.0
Baseline HbA1c <9%						
N	47	55	42	47	55	42
Mean ± SD	0.3 ± 0.77	-0.2 ± 0.81	-0.4 ± 0.80	5.5 ± 47.92	-19.1 ± 55.31	-29.6 ± 70.68
Median	0.20	-0.10	-0.40	-2.0	-25.0	-26.0
Baseline HbA1c ≥9%						
N	48	42	53	48	42	53
Mean ± SD	-0.0 ± 1.08	-0.7 ± 1.07	-1.0 ± 0.98	6.5 ± 78.03	-32.9 ± 77.87	-37.9 ± 61.20
Median	0.00	-0.6	-0.8	-13.5	-26.5	-16.0
Baseline FPG <200mg/dL						
N	47	56	55	47	56	55
Mean ± SD	0.3 ± 0.71	-0.3 ± 0.98	-0.6 ± 0.92	30.7 ± 62.66	6.9 ± 51.34	-8.7 ± 52.94
Median	0.20	-0.10	-0.50	19.0	10.5	-6.0
Baseline FPG ≥200mg/dL						
N	48	41	40	48	41	40
Mean ± SD	0.0 ± 1.13	-0.6 ± 0.91	-0.9 ± 0.98	-18.2 ± 57.30	-68.8 ±58.70	-69.3 ± 64.98
Median	0.00	-0.60	-0.80	-19.5	-68.0	-79.0

Data Source: Section 14, Tables 14.5.1A, 14.5.2A, 14.5.3A, 14.5.4A and 14.5.5A; Appendix C, Listing C.L1.

Return to Subgroup Analysis Efficacy Review study 095

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-071/S-004

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

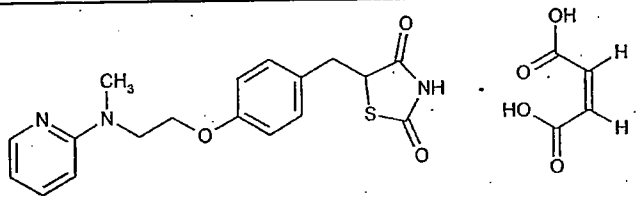
Organization CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**NDA # 21-071** Approved: 25-MAY-1999
Name and Address of Applicant: SmithKline Beecham Pharmaceuticals	**Supplement** SEI-004 Doc. 07-FEB-2000 Rec. 08-FEB-2000
	Name Of The Drug Avandia® Tablets
	Nonproprietary Name Rosiglitazone maleate Tablets
Supplement provides the information to support the use of Avandia® (Rosiglitazone maleate) Tablets in combination with insulin for the treatment of patients with Type 2 diabetes mellitus.	**New Correspondence** --

Pharmacological Category Hypoglycemic Agent. Adjunct to diet to improve glycemic control in patients with NIDDM whose hyperglycemia cannot be managed by diet alone.	**How Dispensed** Oral Rx	**Supporting Documents** --
Dosage Form Tablets	**Potencies** 1.0-, 2.0-, 4.0- and 8.0-mg	

Chemical Name and Structure

Rosiglitazone maleate

$C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$
MW = 357.4 + 116.1 = 473.5



(±)-5[[4-[2-Methyl-2-(pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (Z)-2-butenedioate (1:1)

Comments: Avandia was approved for the treatment of Type 2 diabetes mellitus on May 25, 1999 as monotherapy and in combination with metformin. This [efficacy] Supplement, SEI-004, details the information to support the use of Avandia® (Rosiglitazone maleate) Tablets in combination with insulin for the treatment of patients with Type 2 diabetes mellitus. The drug substance and drug product remain unchanged. The appropriateness of the data to support the proposed therapeutical use will be evaluated by other disciplines. Avandia tablets will be manufactured at the NDA 21-071 approved facilities, no additional manufacturing sites are proposed. A claim for categorical exclusion from environmental assessment information is provided. Categorical exclusion from environmental assessment information is granted.

Conclusions and Recommendations There are no changes regarding Chemistry, Manufacture and Controls of neither the drug substance nor the drug product submitted under this efficacy supplement. Consequently, from the chemistry point of view, this supplement can be approved.

Reviewer Name (and signature) Xavier Ysern, PhD — **Date Completed:** 17-APR-2000

R/D Init.

filename: /nda/21071s04.doc

DISTRIBUTION: Original: NDA 21-071 cc: HFD-510 Division File/ JWeber / SMoore/ XYsern

AP

Stephen Moore 4/17/2000

Confidential

SmithKline Beecham

Avandia

BRL-49653

Categorical Exclusion Claim for the sNDA

ERL Report Number 1999-135

P. Scott Ziegenfuss, M.S.*

*Environmental Research Laboratory

Signatory: Robert Hannah
Affiliation: Associate Director, Environmental Research Laboratory

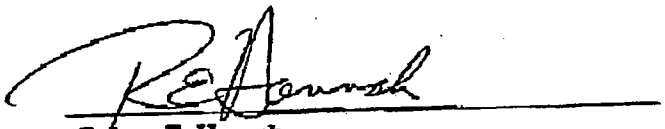
SB Document Number: BRL-049653/RSD-10168T/1

Issue Date: 6 December 1999

Endorsements

Document No.: BRL-049653/RSD-10168T/I

Title: Categorical Exclusion Claim for the sNDA

Approved by: 

Robert E. Hannah

Position: Associate Director

Address: Environmental Research Laboratory, US

Date: 6 December 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-071/S-004

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-071	**Supplement #:**	004
Brand Name:	Avandia®	**Generic Name:**	rosiglitazone maleate
Strength(s):	2 mg, 4 mg, and 8 mg oral tablets		
Sponsor:	SmithKline Beecham Pharmaceuticals One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101		
Submission Date:	07-FEB-00	**Review Date:**	09-MAR-00
Submission Type:	New Drug Application		
Reviewer:	Steven B. Johnson, B.Pharm, Pharm.D.		

Application 21-071/S-004 has been submitted by SmithKline Beecham Pharmaceuticals to support the use of Avandia® (rosiglitazone maleate) Tablets in combination with insulin for the treatment of patients with Type 2 diabetes mellitus.

No new pharmacokinetic data has been submitted with this application. All of the human pharmacokinetics and bioavailability information referenced within this document is available by cross-referencing the original application, NDA 21-071, which was approved 25-MAY-99.

Steven B. Johnson, B.Pharm, Pharm.D.
Division of Pharmaceutical Evaluation-II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader: 09-MAR-00

FT initialed by Hae-Young Ahn, Ph.D., Team Leader: 3/17/00

CC: NDA 21-137 (orig., 1 copy), HFD-510 (WeberJ), HFD-870 (AhnH, HuangS, JohnsonST), ~~HFD-850 (Lesko, ChenML)~~, CDR

Code: AP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-071/S-004

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA #: 21-071 SE1-004

OCT 18 2000

Drug: Avandia (rosiglitazone maleate)

Sponsor: SmithKline Beecham

Indication: Treatment of NIDDM

Date of Submission: February 7, 2000

Statistical Reviewer: Joy Mele, M.S. (HFD-715)

Volume Numbers in Statistical Section: Volumes 1-30, 42-45

Medical Input: William Lubas, M.D. (HFD-510)

Introduction

The sponsor has submitted the results of 2 randomized, double-blind, multicenter controlled clinical trials (Table 1) designed to assess the efficacy and safety of the combined administration of rosiglitazone (RSG) with insulin (INS) in patients inadequately treated with insulin alone.

Table 1. Controlled Clinical Trials

Study (Sites)	Design	Treatment (ITT N)	Duration of Treatment
082 (38 USA)	Add-on to Insulin	Insulin twice daily (104) RSG 2 mg twice daily + INS (106) RSG 4 mg twice daily + INS (103)	26 weeks
095 (35 USA)	Add-on to Insulin	Insulin twice daily (95) RSG 4 mg once daily + INS (97) RSG 8 mg once daily + INS (95)	26 weeks

Reviewer's Statistical Methods

The sponsor's protocol-defined analysis for the primary efficacy variable (HbA1c at Week 26 LOCF) is an analysis of covariance of the change from baseline with baseline as a covariate and including terms for region and treatment. This reviewer performed analyses using the sponsor's model and also alternate models including various covariates to establish the robustness of the results. Unless noted otherwise, this reviewer's results were in agreement with the sponsor's results. In addition, this reviewer has presented the results for fasting plasma glucose (FPG), a secondary efficacy variable. Hochberg's procedure was used to adjust for multiple comparisons (each combination to insulin alone).

This reviewer only reviewed the efficacy data; for a review of safety, see the medical review.

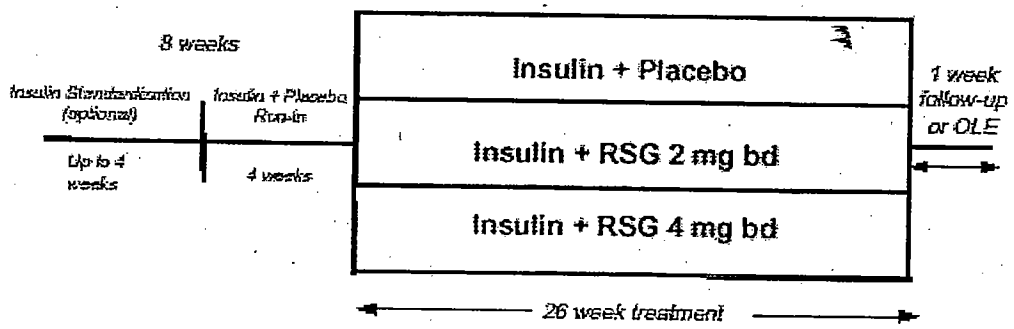
Study 082 (conducted 7/97 to 8/98)

Study 082 was a randomized, double-blind multicenter study designed to assess the efficacy and safety of rosiglitazone (RSG) as add-on therapy for patients inadequately controlled (FPG≥140, HbA1c≥7.5%) on insulin (twice daily injections).

After screening for inclusion/exclusion criteria, patients were given placebo with insulin single-blind for 4 weeks (run-in). Patients with FPG≥140 after 2 weeks of the run-in and with variation in weight of <10% were randomized to placebo, RSG 2mg twice daily or RSG 4mg twice daily (Figure 1) plus insulin. The insulin dose was to be kept constant throughout the study. Patients were treated for 26 weeks with visits at Weeks 0, 2, 4, 8,12, 18 and 26.

The primary objective of this trial was to show that combination therapy was superior to the insulin monotherapy arm; the trial was powered with 71 patients per treatment group to find a treatment effect of 0.75% or greater for HbA1c at endpoint (Week 26 LOCF).

Figure 1. Sponsor's schematic of 082 trial design



Patient Disposition

A total of 370 patients were screened for this study, 367 entered the placebo run-in period. Of 367 patients, 319 (87%) were randomized (Table 2, 107 to INS, 107 to RSG 2mg + INS and 105 to RSG 4mg+ INS). About 80% of the patients completed the study with the lowest completion rate in the RSG 4mg + INS group. Most dropouts occurred during the first 3 months of the study. Only 6 patients are not included in the intent-to-treat (ITT) population.

Table 2. Study 082 Number (%) of patients on study by treatment group and week

	INS	RSG 2 mg twice + INS	RSG 4 mg twice + INS
Randomized	107 (100%)	107 (100%)	105 (100%)
Week 4	100 (93%)	100 (93%)	97 (92%)
Week 8	97 (91%)	99 (92%)	97 (92%)
Week 12	89 (83%)	93 (87%)	84 (80%)
Week 18	84 (79%)	87 (81%)	81 (77%)
Week 26	84 (79%)	87 (81%)	81 (77%)
Sponsor's ITT	**104 (97%)**	**106 (99%)**	**103 (98%)**

In the combination therapy groups, the major reason for discontinuation is an adverse event (Table 3). The type of ADE varied widely; most occurred during the first 3 months of study.

Table 3. Study 082 Reasons for withdrawal from double-blind treatment post-randomization

	INS	RSG 2 mg twice + INS	RSG 4 mg twice + INS
ADE	2 (2%)	9 (8%)	8 (8%)
Lack of Efficacy	5 (5%)	0 (0%)	1 (1%)
Protocol Deviation	7 (6.5%)	3 (3%)	6 (6%)
Lost-to-Follow-up	5 (5%)	2 (2%)	4 (4%)
Other	4 (4%)	6 (6%)	5 (5%)

Patient Demographics and Baseline Characteristics

The treatment groups were well-balanced regarding baseline characteristics. The mean age of patients was 57 years (range of 26 to 80); about 22% were over 65 years (Table 4). About 56% were male. About 70% were white. Oral anti-diabetic use was not allowed for the 3 months prior to the study and on study.

Table 4. Study 082 Baseline Characteristics

	INS (n=104)	RSG 2 mg twice + INS (n=106)	RSG 4 mg twice + INS (n=103)
Age ≥65 years	20%	23%	23%
Race			
White	68%	72%	71%
Black	18%	19%	16%
Other	14%	9%	14%
# of Years of Diabetes			
Mean (SD)	12 (6)	13 (7)	13 (8)
Median	11	12	10
Range	1 to 26	0 to 33	1 to 40
Baseline daily insulin dose (units)			
Mean (SD)	70 (30)	71 (44)	78 (36)
Median	66	62	72

Efficacy Results

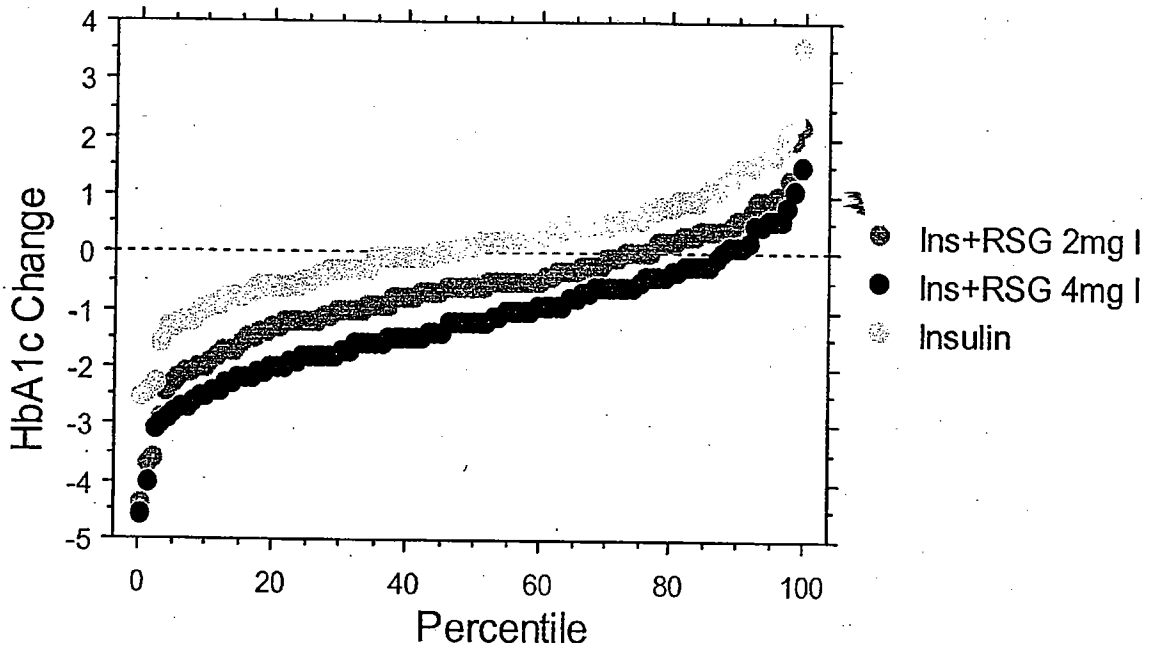
The HbA1c changes at Week 26 for both LOCF (ITT) and for observed cases showed highly significant (P<.0003) treatment differences for each combination compared to insulin alone (Table 5).

Table 5. Study 082 Mean HbA1c (%)

	INS (n=104)	RSG 2 mg twice + INS (n=106)	RSG 4 mg twice + INS (n=103)
Baseline	8.9 (1.1)	9.1 (1.3)	9.0 (1.3)
Change from Baseline			
Week 26 LOCF	+0.12 (1.0)	-0.64 (1.1)	-1.2 (1.1)
Week 26 Completers	+0.15 (1.0) (n=87)	-0.68 (1.1) (n=88)	-1.3 (1.1) (n=79)

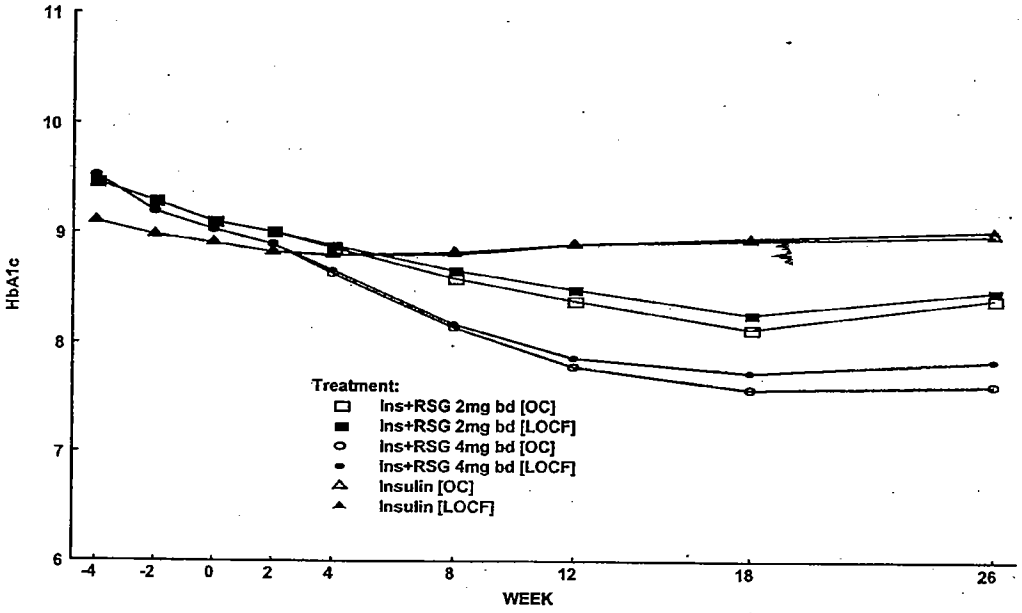
The distributions of the responses (Figure 2) show a clear demarcation of the groups. Nearly 90% of the patients show some improvement at endpoint in the INS+RSG 4mg twice daily group; about 40% of the insulin treated patients have an endpoint reduction in HbA1c.

Figure 2. Study 082 Cumulative Distribution Plot of Change from Baseline of HbA1c Week 26 LOCF (endpoint)



The longitudinal results for HbA1c (Figure 3) show a maximum mean response at Week 18 for both combination groups; the response to insulin remains essentially unchanged for the duration of the trial. Completers on INS+rosiglitazone 4 mg twice a day (open circles in Figure 3) show the best response of all groups.

Figure 3. Study 082 HbA1c by week on study and treatment for last-observation-carried-forward (LOCF) and observed cases (OC) data



The results for fasting plasma glucose, a secondary endpoint, showed statistically significant differences between insulin alone and each combination (P<.0003, Table 6)

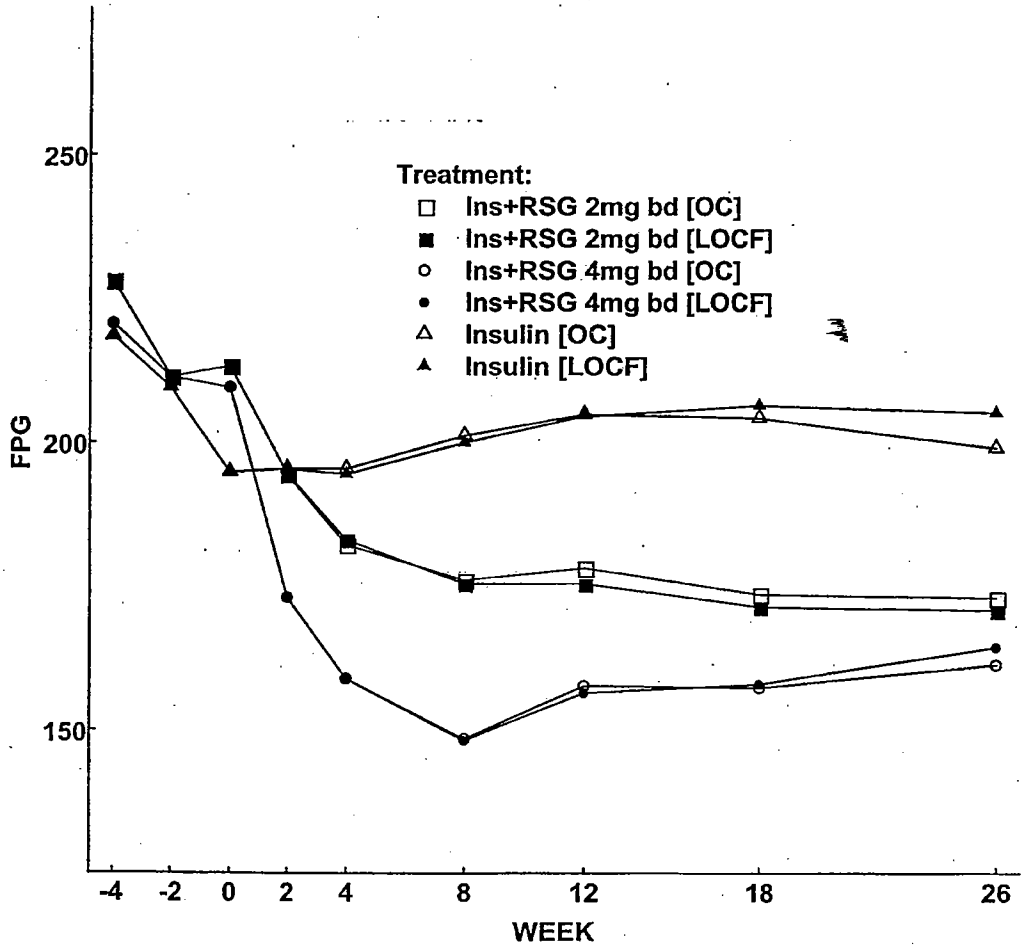
Table 6. Study 082 Fasting Plasma Glucose (mg/dL) Mean (SD)

	INS (n=104)	RSG 2 mg twice + INS (n=106)	RSG 4 mg twice + INS (n=103)
Baseline	195 (53)	212 (58)	209 (58)
Change from Baseline Week 26 LOCF	+10.3 (68)	-41.5 (71)	-44.4 (60)
Week 26 Completers	+8.0 (67) (n=85)	-44.3 (74) (n=87)	-43.3 (61) (n=78)

The results over time for FPG are shown in Figure 4. In the highest dose, it appears that the response is maximized at Week 8 followed by a small increase in FPG. The results for both

LOCF and OC are the same suggesting that carrying forward the data for the ~20% dropouts does not bias the LOCF results.

Figure 4. Study 082 FPG by week on study and treatment for last-observation-carried-forward (LOCF) and observed cases (OC) data



Overall, the results for Study 082 show that the addition of rosiglitazone to insulin in patients inadequately treated with insulin alone significantly reduces HbA1c and FPG.

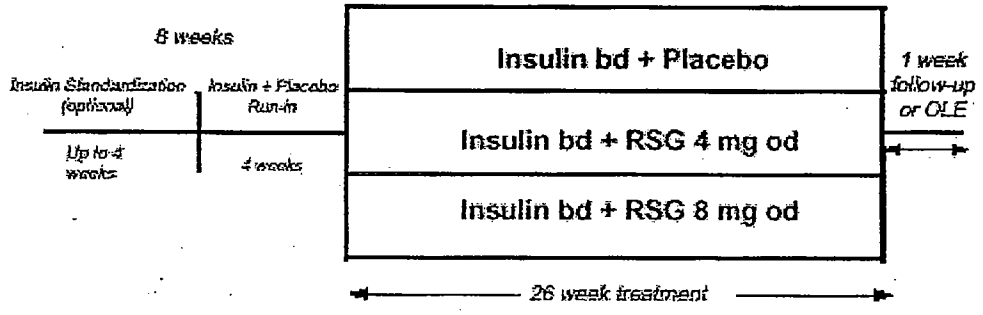
Study 095 (conducted 8/97 to 12/98)

Like Study 082, Study 095 was a randomized, double-blind multicenter study designed to assess the efficacy and safety of rosiglitazone (RSG) as add-on therapy for patients inadequately controlled (FPG≥140, HbA1c≥7.5%) on insulin (twice daily injections). The difference between this study and Study 082 is the dosing regimen; daily doses are the same but rosiglitazone was given once a day in Study 095.

After screening for inclusion/exclusion criteria, patients were given placebo with insulin single-blind for 4 weeks (run-in). Patients with FPG≥140 after 2 weeks of the run-in and with variation in weight of <10% were randomized to placebo, RSG 4 mg **once daily** or RSG 8 mg once daily (Figure 5) plus insulin. The insulin dose was to be kept constant throughout the study. Patients were treated for 26 weeks with visits at Weeks 0, 2, 4, 8,12, 18 and 26.

The primary objective of this trial was to show that combination therapy was superior to the insulin monotherapy arm; the trial was powered with 71 patients per treatment group to find a treatment effect of 0.75% or greater for HbA1c at endpoint (Week 26 LOCF).

Figure 5. Sponsor's schematic of 095 trial design



Patient Disposition

A total of 344 patients passed screening and entered the placebo run-in period. Of those patients, 292 (85%) were randomized (Table 7, 96 to INS, 99 to RSG 4 mg daily+INS and 97 to RSG 8 mg daily + INS). The completion rate was slightly higher in the insulin alone group than the combination groups (+4-9%). No patients withdrew during the last 2 months of the study. The intent-to-treat (ITT) population is comprised of about 98% of the randomized patients.

Table 7. Study 082 Number (%) of patients on study by treatment group and week

	INS	RSG 4 mg daily + INS	RSG 8 mg daily + INS
Randomized	96 (100%)	99 (100%)	97 (100%)
Week 4	86 (90%)	93 (94%)	88 (91%)
Week 8	84 (88%)	87 (88%)	84 (87%)
Week 12	82 (85%)	83 (84%)	79 (81%)
Week 18	80 (83%)	78 (79%)	72 (74%)
Week 26	80 (83%)	78 (79%)	72 (74%)
Sponsor's ITT	**95 (99%)**	**97 (98%)**	**95 (98%)**

An adverse event was a major reason for withdrawal in all treatment groups (Table 8).

These events occurred throughout the trial. Of the 19 patients listed as other, 15 discontinued due to withdrawal of consent.

Table 8. Study 095 Reasons for withdrawal from double-blind treatment post-randomization

	INS (n=95)	RSG 4 mg daily + INS (n=97)	RSG 8 mg daily + INS (n=95)
ADE	4 (4%)	6 (6%)	10 (10%)
Lack of Efficacy	4 (4%)	0 (0%)	0 (0%)
Protocol Deviation	2 (2%)	3 (3%)	2 (2%)
Lost-to-Follow-up	3 (3%)	6 (6%)	3 (3%)
Other	3 (3%)	6 (6%)	10 (10%)

Patient Demographics and Baseline Characteristics

The treatment groups were well-balanced on most baseline characteristics. The mean age of patients was 58 years (range of 24-84); about 70% were under 65 years (Table 9). About 70% were Caucasian; 16% were Black and 14% were listed as other races. There were small imbalances in gender (more males in combinations) and insulin dose (highest in the 8 mg+INS group).

Table 9. Study 095 Baseline Characteristics

	INS (n=95)	RSG 4 mg daily + INS (n=97)	RSG 8 mg daily + INS (n=95)
Age ≥65 years	34%	32%	25%
Female (%)	55%	36%	41%
Race			
White	73%	68%	73%
Black	16%	16%	15%
Other	12%	17%	13%
# of Years of Diabetes			
Mean (SD)	13 (8)	13 (8)	13 (7)
Median	12	12	11
Range	0 to 42	1 to 46	1 to 33
Baseline daily insulin dose (units)			
Mean (SD)	65 (29)	76 (45)	74 (29)
Median	60	60	70

Efficacy Results

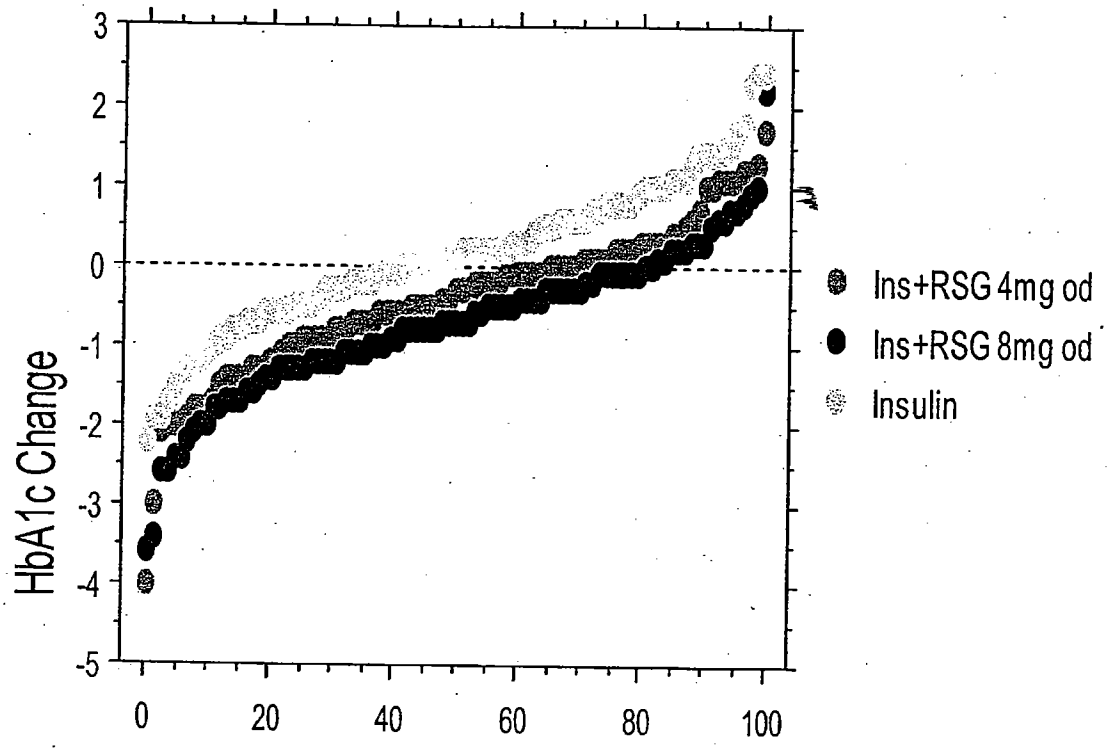
Both the completer and LOCF (ITT) results showed a significant treatment effect for each combination compared to insulin alone ($p<.0001$, Table 10).

Table 10. Study 095 Mean HbA1c

	INS (n=95)	RSG 4 mg daily + INS (n=97)	RSG 8 mg daily + INS (n=95)
Baseline	9.1 (1.2)	8.8 (1.1)	9.1 (1.0)
Change from Baseline			
Week 26 LOCF	+0.13 (0.9)	-0.43 (1.0)	-0.74 (1.0)
Week 26 Completers	+0.10 (1.0) (n=81)	-0.47 (1.0) (n=77)	-0.74 (1.0) (n=72)

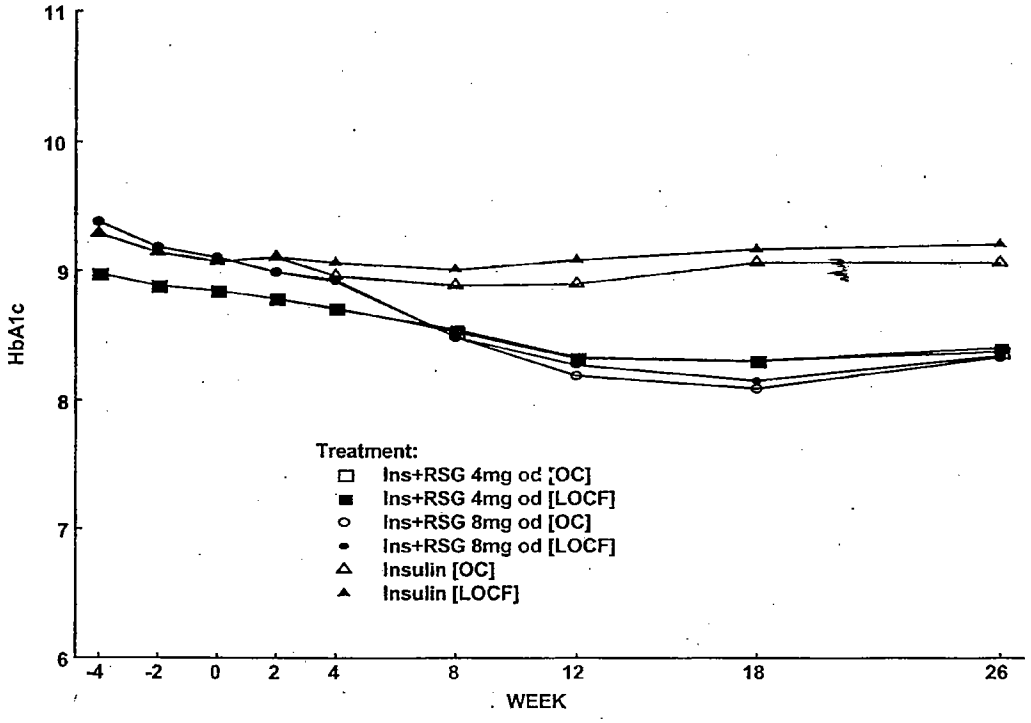
Figure 6, a cumulative distribution plot, shows that about 80% of the patients administered insulin plus rosiglitazone 8mg once-a-day had a decrease in HbA1c at endpoint; about half that many insulin-treated patients had some improvement. The combination curves are shifted to the left of what was seen for twice-a-day dosing (Figure 2) as expected given the differences in the mean responses between the two dosing regimens.

Figure 6. Study 095 Cumulative Distribution Plot of Change from Baseline of HbA1c Week 26 LOCF (endpoint)



The data by week on study (Figure 7) shows a small difference at baseline between the 4 mg combination group and the other two groups which needs to taken into consideration when examining the results at endpoint. The pattern of response is similar to what was seen in Study 082.

Figure 7. Study 095 HbA1c by week on study and treatment for last-observation-carried-forward (LOCF) and observed cases (OC) data



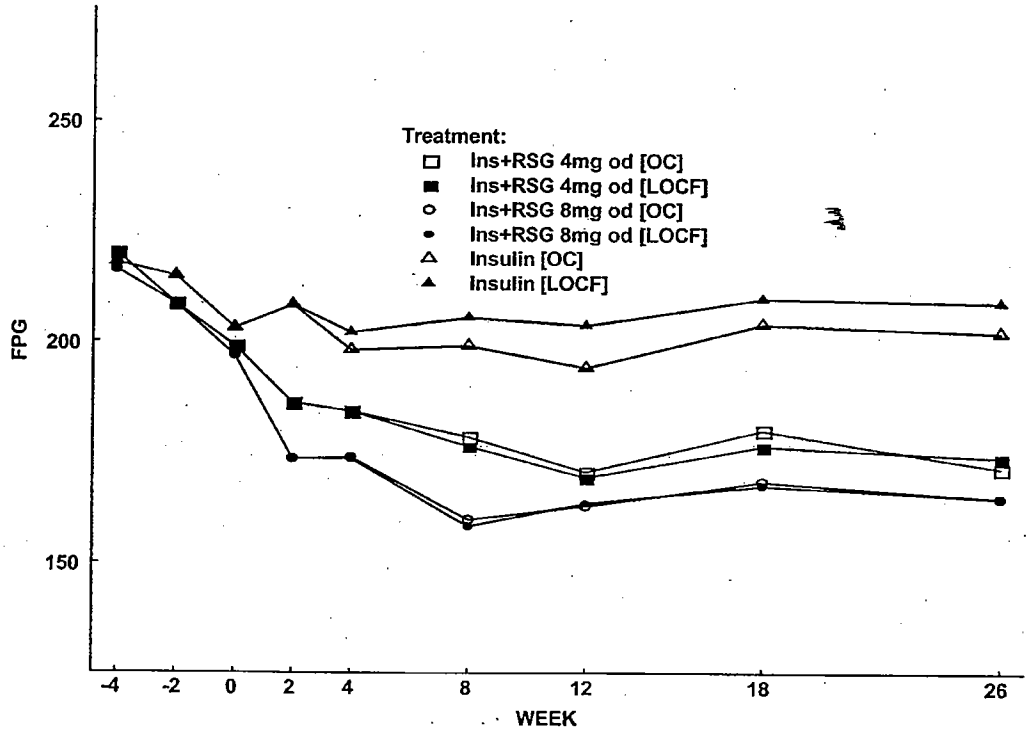
The FPG results revealed highly significant differences between each combination group and insulin alone (p<.0001).

Table 6. Study 095 Fasting Plasma Glucose

	INS (n=95)	RSG 4 mg daily + INS (n=97)	RSG 8 mg daily + INS (n=95)
Baseline	203 (57)	199 (66)	199 (61)
Change from Baseline Week 26 LOCF	+6.0 (65)	-25 (66)	-34 (65)
Week 26 Completers	+5.1 (61) (n=81)	-25 (63) (n=76)	-30 (60) (n=71)

FPG results over time show some visit to visit variability in response (Figure 8). It is interesting to note in the insulin only group that FPG decreases during the run-in but then appears to remain stable during the treatment period; this suggests that the run-in was sufficiently long to obtain a reasonable assessment of FPG on insulin alone before adding rosiglitazone. The maximum response for combination therapy appears to be attained after about 2 months of therapy.

Figure 8. Study 095 FPG by week on study and treatment for last-observation-carried-forward (LOCF) and observed cases (OC) data



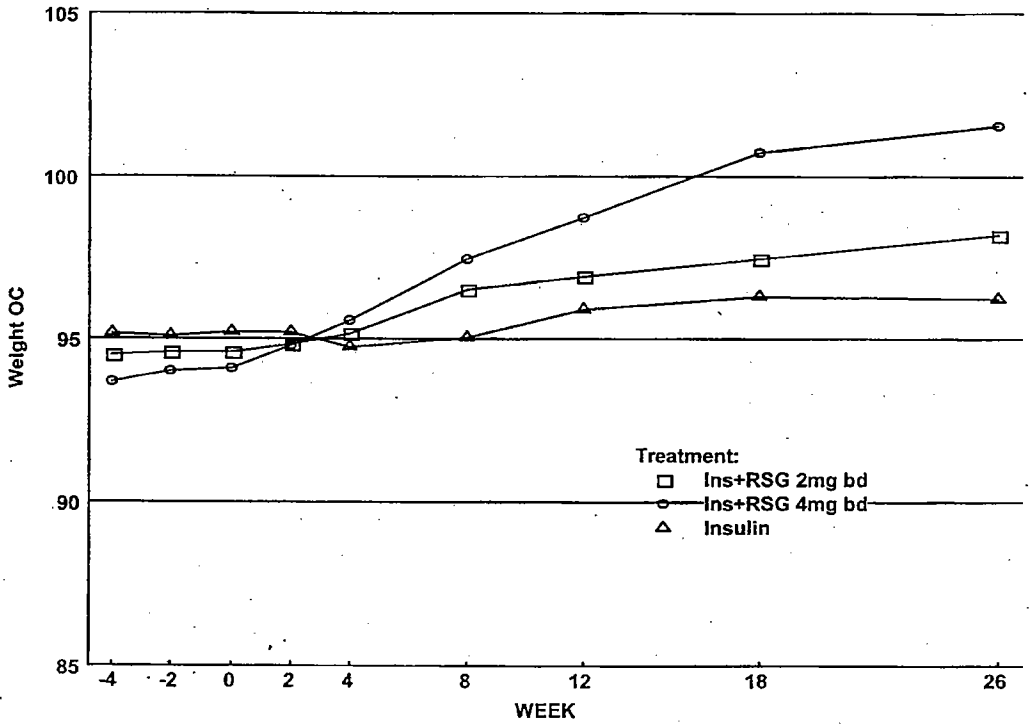
Subgroup Analyses

This reviewer examined subgroups based on age (<65 versus ≥65), BMI, gender, baseline HbA1c, baseline FPG and duration of disease for both studies. The subgroup results were consistent with what has been observed for rosiglitazone monotherapy; larger treatment effects are seen for females and for heavier patients (BMI>30), no differences were observed for the other subgroups. BMI, however, is not a good predictor of response; the correlation between BMI and HbA1c change from baseline is only about -0.1 so variations in HbA1c response cannot be explained by differences in BMI.

Weight Gain

As for rosiglitazone monotherapy, significant weight gains are seen with rosiglitazone treatment. Figure 9 shows weight for the patients on study by treatment group and week in Study 082.

Figure 9. Mean Weight (kg) by treatment group and week for Study 082 observed cases.



Median gains of about 4-5 kg at endpoint were seen in the high dose combination group for once and twice a day, respectively, compared to <1 kg in the insulin group (Table 7 and Appendix 1).

Table 7. Weight median changes from baseline at Week 26 OC

	Insulin	INS+RSG 4mg daily	INS+RSG 8mg daily
Study 082/**twice** daily	0.85	4.1	5.4
Study 095/**once** daily	0.4	2.65	4.4

Labeling Comments

The sponsor's proposed labeling to describe the two trials reviewed here is presented below followed by this reviewer's comments.

Combination with Insulin

[redacted] two 26-week randomized, double-blind [redacted] designed to assess the efficacy and safety of *Avandia* in combination with insulin [redacted] patients inadequately controlled on insulin (65 [redacted] The mean duration of disease for these patients (12-13 years) [redacted]

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%). [redacted]

1. [redacted]

2. [redacted]

3. The numbers reported in the second paragraph are treatment differences (control-subtracted means). The sponsor's use of the term "mean reduction" is misleading. [redacted]

4. [redacted]

Overall Comments

The sponsor has presented the results of two studies to support an indication for treatment of Type 2 diabetes with insulin plus rosiglitazone. The designs of these studies were nearly identical with the exception of the dosing regimen for rosiglitazone; in Study 082, rosiglitazone was dosed twice a day and in Study 095, once a day. In each study, patients shown to be insufficiently treated with insulin alone (FPG≥140, HbA1c≥7.5%) were randomized to insulin, insulin plus RSG 4mg daily or insulin plus RSG 8mg daily and treated up to 26 weeks. There were about 100 patients in each arm and about 80% completed the study. Patients in both studies were predominately Caucasian (>70%) and <65 years old (70-80%). The median years of diabetes was approximately 12 years in both studies. Baseline HbA1c was about 9% and baseline FPG was about 200.

The addition of rosiglitazone to insulin results in statistically significant decreases in HbA1c and FPG. The means in Table 8 below suggest that twice-a-day dosing is more effective than once-a-day dosing; this is consistent with results for rosiglitazone monotherapy. Head-to-head comparisons would need to be done to confirm this; however, the comparability of the study designs and patient populations along with previous monotherapy results suggest that the difference is credible.

Table 8. HbA1c and FPG mean changes from baseline

	Insulin	INS+RSG 4mg daily	INS+RSG 8mg daily
Study 082/**twice** daily			
HbA1c change	+0.1	-0.6	-1.2
FPG change	+10	-42	-44
Study 095/**once** daily			
HbA1c change	+0.1	-0.4	-0.7
FPG change	+6	-25	-34

Differential treatment effects were seen for subgroups based on gender and BMI with larger effects seen for women and heavier patients (BMI>~30). Significant dose-related weight gains were observed after 26 weeks of therapy; 4-5 kg in the INS+RSG 8mg daily group, 3-4 kg in the INS+RSG 4mg daily group and <1kg in the insulin group.

From a statistical perspective, the sponsor has provided sufficient efficacy data to support an indication for insulin plus rosiglitazone therapy in patients insufficiently treated with insulin alone.

Joy D. Mele, M.S.
Mathematical Statistician

Concur:

Todd Sahlroot, Ph.D.
Team Leader

JTS 11/13/00

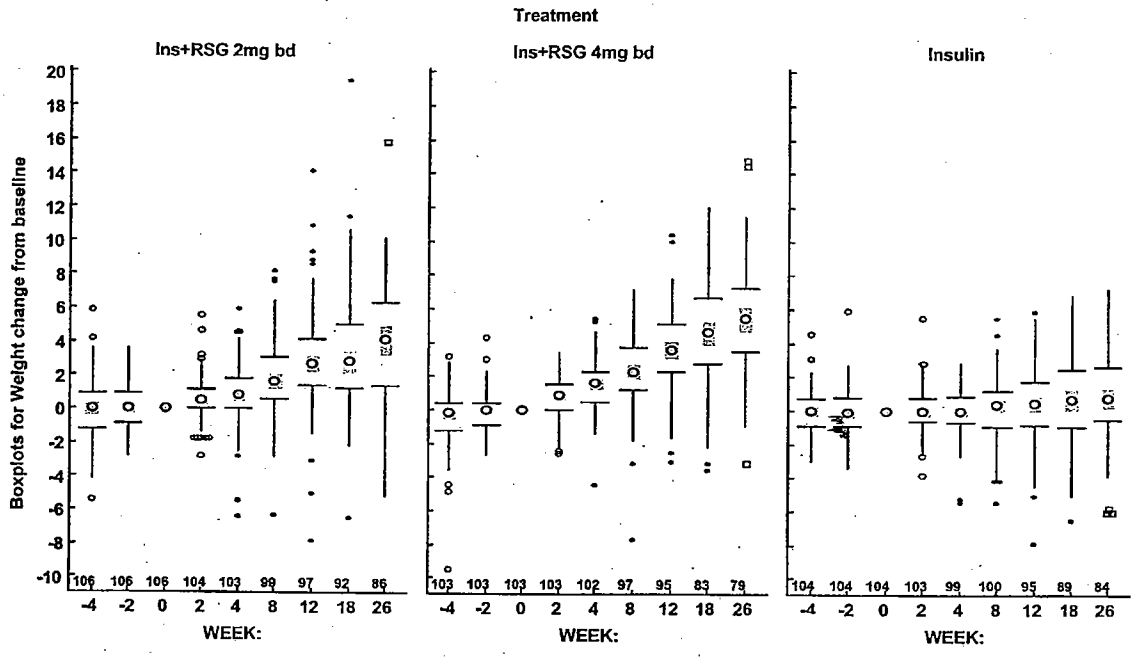
Ed Nevius, Ph.D.
Director of DOB2

EN 11/18/00

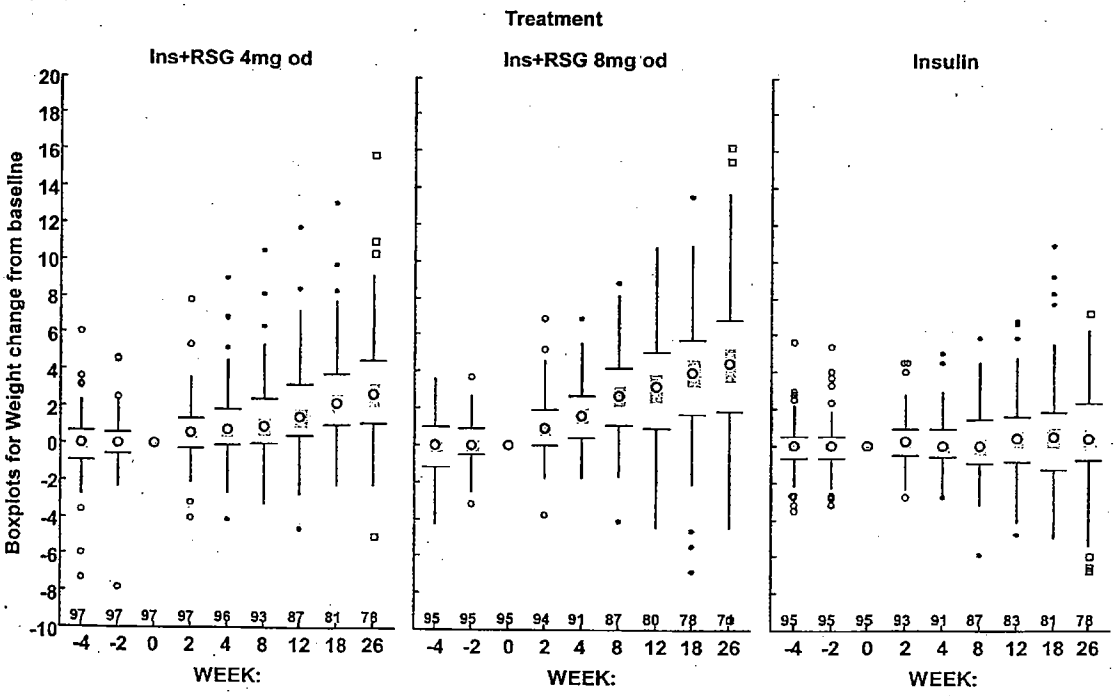
cc:
Archival NDA# 21-071 SE1-004
HFD-510
HFD-510/Weber, Lubas, Malozowski,
HFD-715/Division 2 File, Chron, JMele, TSahlroot
Mele/x76376/DOB2/Word-rosi_s4.rev.doc/November 3

Appendix 1. Mean weight changes by treatment group and week

Study 082



Study 095



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-071/S-004

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Item 14: Patent Certification

SmithKline Beecham
Pharmaceuticals

January 21, 2000

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg. rm. 2-14
12420 Parklawn Dr.
Rockville, MD 20857

Re: NDA No. 21-071 Patent Information

Dear Sirs:

In accordance with 21 C.F.R. 314.53(d)(4), SB submits the following patent information relating to the subject NDA application.

Pat. No.	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
5,741,803	April 21, 2015	drug/drug product composition method of use	SmithKline Beecham Corporation	Charles M. Kinzig, Corporate Intellectual Property - UW2220, SmithKline Beecham Corporation 709 Swedeland Road King of Prussia, PA 19406

The undersigned declares that U.S. Patent Number 5,741,803 covers the composition and method of use of *Avandia* (rosiglitazone maleate). This product is the subject of this application for which approval is being sought.

This letter is being submitted in duplicate.

Very truly yours,

for Sharon W. Shapowal

One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101. Telephone (215) 751-4000 Fax (215) 751-3950

SmithKline Beecham
Pharmaceuticals

January 21, 2000

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg. rm. 2-14
12420 Parklawn Dr.
Rockville, MD 20857

Re: NDA 21-071 Patent Information

Dear Sirs:

In accordance with 21 C.F.R. 314.53(d)(4), SB submits the following patent information relating to the subject NDA application.

Pat. No.	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
5,002,953	August 30, 2008	drug/drug product composition method of use	SmithKline Beecham Corporation	Charles M. Kinzig, Corporate Intellectual Property - UW2220, SmithKline Beecham Corporation 709 Swedeland Road King of Prussia, PA 19406

The undersigned declares that U.S. Patent Number 5,002,953 covers the composition and method of use of *Avandia* (rosiglitazone maleate). This product is the subject of this application for which approval is being sought.

This letter is being submitted in duplicate.

Very truly yours,

for Sharon W. Shapowal

Item 13: Patent Information

Patent 1

Pat. No.	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
5,002,953	August 30, 2008	drug/drug product composition method of use	SmithKline Beecham Corporation	Charles M. Kinzig, Corporate Intellectual Property - UW2220, SmithKline Beecham Corporation 709 Swedeland Road King of Prussia, PA 19406

Patent 2

Pat. No.	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
5,741,803	April 21, 2015	drug/drug product composition method of use	SmithKline Beecham Corporation	Charles M. Kinzig, Corporate Intellectual Property - UW2220, SmithKline Beecham Corporation 709 Swedeland Road King of Prussia, PA 19406

EXCLUSIVITY SUMMARY for NDA # 21-071 SUPPL: 004

Trade Name: Avandia Tablets Generic Name: Rosiglitazone Maleate

Applicant Name: GlaxoSmithKline HFD-510

Approval Date: February 27, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_/ NO /✔/

   b) Is it an effectiveness supplement? YES /✔/NO /_/

      If yes, what type(SE1, SE2, etc.)? SE-1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_✔__/ NO /__/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

      YES /___/ NO /_✔_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Applicant will be granted 3 years exclusivity.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /✔_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /✔_/ NO /___/

If yes, NDA # 21-071 Drug Name: Avandia

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_✔__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_✔_/ NO /_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA 21-071 Avandia (rosiglitazone maleate)

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /__/ NO /__✔_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_✔_/ NO /__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_✔_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_✔/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_✔_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/NO /_✔_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 085

Investigation #2, Study # 136

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an

already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / / NO /✔/

Investigation #2 YES / / NO /✔/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA 21-071/S-004 Study # 085
NDA 21-071/S-004 Study # 136

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✔/

Investigation #2 YES /___/ NO /✔/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1 , Study # 085

Investigation # 2 , Study # 136

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

YES /✔/ NO /___/ Explain:

Investigation #2

YES /✔/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Jena Weber
Signature of Preparer Date: 9/25/02
Title: PM

Signature of Office or Division Director Date

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
2/27/03 07:07:12 PM

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21071	**Trade Name:**	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T
Supplement Number:	4	**Generic Name:**	ROSIGLITAZONE
Supplement Type:	SE1	**Dosage Form:**	TAB
Regulatory Action:	PN	**Proposed Indication:**	For use in combination with insulin for the treatment of patients with type 2 diabetes mellitus.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

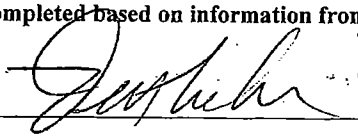
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JENA WEBER



Signature

4/6/00

Date

Item 16: Debarment Certification

Pursuant to section 306(K)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that the applicant did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

4 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-071
S004

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2 (a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CRF 54.2(f).

Clinical Investigators		
	Please see attached list	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 542(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David E. Wheadon, M.D.	**V.P. & Director, Regulatory Affairs-N.A. and Product Professional Services**
FIRM/ORGANIZATION: **SmithKline Beecham Pharmaceuticals**	
SIGNATURE: David E. Wheadon, MD	DATE: **24 January 2000**

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by Electronic Document Services/USDHHS: (301) 433-2454 EF

20 Page(s) Withheld

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-071/5004

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: June 30, 2002
2/20/03

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David E. Wheaden, M.D.	Senior Vice President, U.S. Regulatory Affairs
FIRM / ORGANIZATION	
GlaxoSmithKline Pharmaceuticals	
SIGNATURE	**DATE**
David E Wheaden, MD	Feb 20, 2003

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (6/02)

Created by: PSC Media Arts Branch (301) 443-2454 EF

Certification of Absence of Clinical Investigator Financial Interests/Arrangements as to a GlaxoSmithKline-Sponsored Study

List (A) Supporting Item (1) of Form FDA 3454

List of Investigators with No Disclosable Financial Interests/Arrangements

Study ID	Protocol Title
49653/136	A 26-week randomised, double-blind, multicentre, placebo-controlled study to evaluate the efficacy, safety and tolerability of rosiglitazone with concurrent insulin therapy and/or a sulphonylurea in type 2 diabetic patients with chronic renal failure (not on dialysis).
Study Sponsor: GlaxoSmithKline	

Austria

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 104	Name
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 105	Name:
	Subinvestigator(s) *Indicate last name, first*

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 106	Name:
	Subinvestigator(s) *Indicate last name, first*

Germany

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 402	Name:
	Subinvestigator(s) *Indicate last name, first*
	Name:
	Name:
	Name:
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 403	Name:
	Subinvestigator(s) *Indicate last name, first*
	Name:
	Name:
	Name:
	Name:
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 406	Name:
	Subinvestigator(s) *Indicate last name, first*
	Name:
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 407	Name:
	Subinvestigator(s) *Indicate last name, first*

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 410	Name:
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 411	Name:
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 412	Name
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 413	Name
	Subinvestigator(s) *Indicate last name, first*

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 414	Name:
	Subinvestigator(s) *Indicate last name, first*
	Name: /
Clinical Site Address (Site ID)	**Principal Investigator** ***Indicate last name, first***
Site 415	Name:
	Subinvestigator(s) ***Indicate last name, first***
Clinical Site Address (Site ID)	**Principal Investigator** ***Indicate last name, first***
Site 420	Name:
	Subinvestigator(s) ***Indicate last name, first***
Clinical Site Address (Site ID)	**Principal Investigator** ***Indicate last name, first***
Site 421	Name:
	Subinvestigator(s) ***Indicate last name, first***

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 422	Name:
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 423	Name:
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
	Name:
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
	Name:
	Subinvestigator(s) *Indicate last name, first*

Italy

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 501	Name:
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	**Principal Investigator** ***Indicate last name, first***
Site 502	Name:
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	**Principal Investigator** ***Indicate last name, first***
Site 503	Name:
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	**Principal Investigator** ***Indicate last name, first***
Site 505	Name:
	Subinvestigator(s) *Indicate last name, first*

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 506	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	**Principal Investigator** *Indicate last name, first*
Site 507	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	**Principal Investigator** *Indicate last name, first*
Site 508	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	**Principal Investigator** *Indicate last name, first*
Site 510	
	Subinvestigator(s) *Indicate last name, first*

Sweden

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 701	Name:
	Subinvestigator(s) *Indicate last name, first*

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 702	Name:
	Subinvestigator(s) *Indicate last name, first*

Denmark

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 726	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 727	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 728	Name:
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 729	Name:
	Subinvestigator(s) *Indicate last name, first*

Norway

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 760	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Siet 763	
	Subinvestigator(s) *Indicate last name, first*

Finland

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 778	[redacted]
[redacted]	
	Subinvestigator(s) *Indicate last name, first*
	[redacted]

UK

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 901	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 902	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 903	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 904	
	Subinvestigator(s) *Indicate last name, first*

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first (Inv. ID)*
Site 906	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	**Principal Investigator** *Indicate last name, first*
Site 907	
	Subinvestigator(s) *Indicate last name, first*

Ireland

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 951	
	Subinvestigator(s) *Indicate last name, first*

2 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-071
S004

Certification of Absence of Clinical Investigator Financial Interests/Arrangements as to a GlaxoSmithKline-Sponsored Study

List (A) Supporting Item (1) of Form FDA 3454

List of Investigators with No Disclosable Financial Interests/Arrangements

Study ID	Protocol Title
49653/085	A 26 week randomised, double-blind, multicentre study to investigate the effects of rosiglitazone on insulin requirements in insulin-treated type 2 diabetic patients.
Study Sponsor: GlaxoSmithKline	

Germany

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 450	
	Subinvestigator(s) *Indicate last name, first*

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 452	
	Subinvestigator(s) *Indicate last name, first*

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 453	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 454	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 458	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 459	
	Subinvestigator(s) *Indicate last name, first*

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 460	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 463	
	Subinvestigator(s) *Indicate last name, first*

Italy

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 501	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 503	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 504	
	Subinvestigator(s) *Indicate last name, first*

Netherlands

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 601	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	**Principal Investigator** *Indicate last name, first*
Site 602	
	Subinvestigator(s) *Indicate last name, first*

Sweden

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 703	
	Subinvestigator(s) *Indicate last name, first*

Norway

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 751	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 753	
	Subinvestigator(s) *Indicate last name, first*

Finland

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 776	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 777	
	Subinvestigator(s) *Indicate last name, first*

Spain

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 801	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 802	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 803	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 804	
	Subinvestigator(s) *Indicate last name, first*

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 805	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 811	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 812	
	Subinvestigator(s) *Indicate last name, first*
Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 813	
	Subinvestigator(s) *Indicate last name, first*

UK

Clinical Site Address (Site ID)	Principal Investigator *Indicate last name, first*
Site 924	
	Subinvestigator(s) *Indicate last name, first*

3 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-671
5004

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concern [redacted], who participated as a clinical investigator in the submitted study, Study 49653/085: *"A 26 week randomised, double-blind, multicentre study to investigate the effects of rosiglitazone on insulin requirements in insulin-treated type 2 diabetic patients."*

Name of clinical investigator

Name of clinical study

is submitted in accordance with 21 CFR part

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Significant payments of other sorts (including payments to spouse and dependent children, and payments to an affiliated institution directly supporting, or made on behalf of, the investigator) >$25,000.

Please mark the applicable checkbox.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
David E. Wheadon, M.D.	Senior Vice President, U.S. Regulatory Affairs
FIRM/ORGANIZATION: GlaxoSmithKline Pharmaceuticals	
SIGNATURE: David E Wheadon, MD	DATE: Feb 20, 2003

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3455 (3/99)

Created by Electronic Document Services/USCHHS: (301) 433-2454 EF

1 Page(s) Withheld

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-_____

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

PROJECT MANAGER LABELING REVIEW

Application Number: 21-071/S-004

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

Sponsor: GlaxoSmithKline

Material Reviewed: Package insert

Submission Date: August 26, 2002

Receipt Date: August 27, 2002

Background and Summary: Avandia was approved by the Agency on May 25, 1999. It is indicated as an adjunct to diet and exercise in the treatment of patients with Type 2 Diabetes Mellitus. This supplemental new drug application proposes a new indication for the use of Avandia in combination with insulin for the treatment of patients with Type 2 diabetes mellitus.

Review: The current label (AV:L8, date of issuance May 2000), was compared to the accepted final draft labeling (AV:LX). The new identifier for the PI (package insert) is AV:L9; Date of Issuance March 2003. Changes to the PI appear below.

- Under **DESCRIPTION:** Remove hydroxypropyl methylcellulose as an inactive ingredient, add Hypromellose 2910.
  Comment: This is acceptable.

- Under the **CLINICAL STUDIES,** add:
  The addition of *Avandia* to either metformin, a sulfonylurea or insulin resulted in significant reductions in hyperglycemia compared to any of these agents alone
  Comment: This is acceptable.

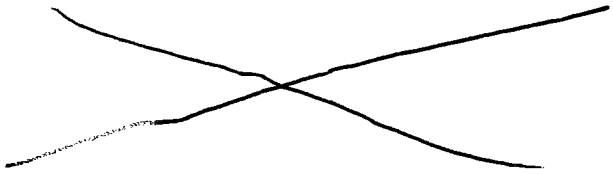
- Under the **CLINICAL STUDIES, Combination With Insulin,** add:

  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 67 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.
Comment: This is acceptable.

- **INDICATIONS AND USAGE:**
  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.
  Comment: This is acceptable.

- **WARNINGS, Cardiac Failure and Other Cardiac Effects**: Patients should be observed for signs and symptoms of heart failure.



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).
Comment: This is acceptable.

- **ADVERSE REACTIONS, Trials of AVANDIA as Monotherapy and in Combination With Other Hypoglycemic Agents:**

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.
Comment: This is acceptable.

- **DOSAGE AND ADMINISTRATION, 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.
  Comment: This is acceptable.

- **DOSAGE AND ADMINISTRATION, 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.
  Comment: This is acceptable.

- **STORAGE,** revise to appear:
  DATE OF ISSUANCE Mar. 2003 ©2003, GlaxoSmithKline
  AV:L9
  Comment: This is acceptable.

In addition, numerous editorial changes have been made; these are acceptable.

Conclusion: Issue AP letter, request FPL.

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

/s/

Jena Weber
5/13/03 10:34:40 AM
CSO

Jena Weber
5/13/03 10:37:11 AM
CSO

19 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

1 § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-071
5004

Memorandum of Meeting Minutes

Meeting Date: Thursday October 5, 2000

Time: 3:30pm Location: Conf. Room 13B45

Type of Meeting: Reference NDA 21-071 - Avandia (SKB); discussion of labeling revisions [redacted] (found under Hepatic Effects of PREACAUTIONS section).

Meeting Chair: David Orloff, M.D. Meeting Recorder: Jena Weber, RHPM

FDA Attendees:

John Jenkins, M.D.	Office Director
David Orloff, M.D.	Division Director, DMEDP
Robert Perlstein, M.D.	Medical Officer
Lahn Green, R.Ph.	Epidemiology
Zili Li, M.D.	Medical Officer, Epidemiology
Evelyn Rodriguez, M.D.	Team Leader, Epidemiology
Jena Weber, RHPM	Regulatory Health Project Manager

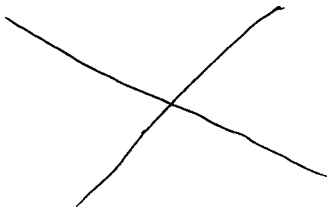
SmithKline Beecham Attendees:

David Wheadon, M.D.	North American Regulatory Affairs
Clare Kahn, Ph.D.	North American Regulatory Affairs
David Krause, M.D.	Clinical R&D, Medical Affairs
Sharon Shapowal, R.Ph.	North American Regulatory Affairs
Martin Freed, M.D.	Clinical R&D; Medical Affairs
Jeffrey Fried, M.D.	Worldwide Clinical Safety

The meeting began at 3:30 p.m. with self-introductions of all attendees. The following is a summary of the important points raised and agreed to at the meeting.

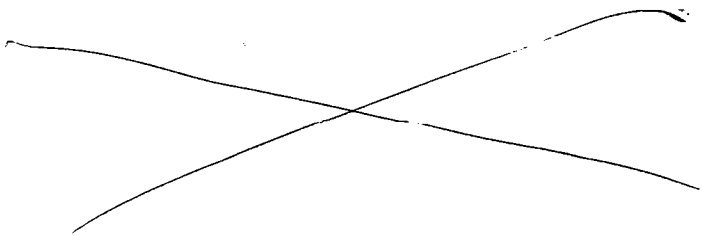
- Avandia labeling discussion; current package insert reads as follows:
  PRECAUTIONS – Information for Patients
  It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. Patients should be advised that it can take 2 weeks to see a reduction 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 every 2 months for the first 12 months, and periodically thereafter.

Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician.



- The company will provide data on elevated hepatic event rates in Type 2 DM subjects.
- 
- 3 cases of liver failure from postmarkekting surveillance have been identified by FDA; SKB confirms and acknowledges the same cases. However, they believe that 2 of the 3 cases had additional factors that led to death.

Discussion following company presentation:



General Conclusions:

- SKB will investigate CHF data further for prior CHF or NYHA Class I/II status.

David G. Orloff, M.D.

Jena Weber, RHPM

Avandia10-5doc
DGO 1/22/&2/1RP 1/22/01

gsk GlaxoSmithKline

FAX TRANSMITTAL SHEET

TO: Jena Weber FROM: Sharon Shapowal

FAX NO: 301-443-9282 DATE: 27 FEB 03

TOTAL NO. OF PAGES (INC COVER): 5

SENDER'S PHONE NO: 215-751-3099 FAX: 215-751-4096

SUBJECT: 21-071/S-004

Edits to label sections discussed

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-071
5009

GlaxoSmithKline
U.S. Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA
19101-7929
USA

Telephone: 215 751 3868
Fax: 215 751 4926
www.gsk.com

February 28, 2003

David G. Orloff, M.D., Division Director
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
HFD-510, Fishers Document Room, 14B19
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-071; AVANDIA® (rosiglitazone maleate) Tablets
Amendment to Approved sNDA 21-071/S004

Dear Dr. Orloff:

Reference is made to our approved New Drug Application 21-071 for Avandia® (rosiglitazone maleate, and to supplement sNDA 21-071/S-004 submitted on February 7, 2000. Reference is also made to the FDA approved letter for S-004 dated February 27, 2003.

At this time, we are submitting documents to the approved NDA, officially, that were transmitted by secure e-mail on February 26, 2003 (Clean label, and annotated label – draft, and summary table) and February 27, 2003 (Clean label and annotated label – final) to Ms. Jena Weber.

If you have any questions or requests regarding this submission, please do not hesitate to contact me at (215) 751-3434.

Sincerely,

Clare Kahn for:

Sharon Shapowal, R.Ph.
Director
U.S. Regulatory Affairs

February 20, 2003

GlaxoSmithKline
U.S. Regulatory Affairs
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19101-7929
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Fax: 215 751 4926
www.gsk.com

David G. Orloff, M.D., Division Director
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
HFD-510, Fishers Document Room, 14B19
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-071; AVANDIA® (rosiglitazone maleate) Tablets
Amendment to Pending Supplement (S-004)
FDA Request for Information - Financial Disclosure

Dear Dr. Orloff:

Reference is made to our approved New Drug Application 21-071 for Avandia® (rosiglitazone maleate, and to supplement sNDA 21-071/S-004 submitted on February 7, 2000. Also, reference is made to the FDA approvable letter for S-004, dated February 8, 2001, and to our complete response to the approvable action, dated August 26, 2002.

Finally, reference is made to our teleconference with Ms. Jena Weber and Dr. Joanna Zawadzki on February 7, 2003, During the conference call, GSK and FDA participants discussed the financial disclosure information needed for Protocols 085 and 136. At this time, we are amending the supplement to provide the financial disclosure information requested during the teleconference.

If you have any questions or requests regarding this submission, please do not hesitate to contact me at (215) 751-3434.

Sincerely,

Sharon W Shapowal

Sharon Shapowal, R.Ph.
Director
U.S. Regulatory Affairs

February 19, 2003

GlaxoSmithKline
U.S. Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA
19101-7929
USA

Telephone: 215 751 3868
Fax: 215 751 4926
www.gsk.com

David G. Orloff, M.D., Division Director
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
HFD-510, Fishers Document Room, 14B19
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-071; AVANDIA® (rosiglitazone maleate) Tablets
Amendment to Pending Supplement (S-004)
FDA Request for Information

Dear Dr. Orloff:

Reference is made to our approved New Drug Application 21-071 for Avandia® (rosiglitazone maleate, and to supplement sNDA 21-071/S-004 submitted on February 7, 2000. Also, reference is made to the FDA approvable letter for S-004, dated February 8, 2001, and to our complete response to the approvable action, dated August 26, 2002.

Finally, reference is made to our teleconference with Ms. Jena Weber and Dr. Joanna Zawadzki on February 7, 2003, during which GSK and FDA participants agreed the content and format of new data analyses/presentations with specific focus on updated pooled information and specific safety information. At this time, we are amending the supplement to provide the new data analyses. The data were submitted via secure e-mail on February 14, 2003 to the attention of Ms. Weber.

Also discussed during the teleconference was financial disclosure information needed for Protocols 085 and 136. These data are compiled with final reviews ongoing at the local (country) level. Thank you for your continued patience.

If you have any questions or requests regarding this submission, please do not hesitate to contact me at (215) 751-3434.

Sincerely,

Sharon W. Shapowal

Sharon Shapowal, R.Ph.
Director
U.S. Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-071/S-004

GlaxoSmithKline
Attention: Sharon Shapowal, R.Ph.
Director, U.S. Regulatory Affairs
One Franklin Plaza; P.O. Box 7929
Philadelphia, PA 19101

8/29/02

Dear Ms. Shapowal:

We acknowledge receipt on August 27, 2002, of your August 26, 2002, resubmission to your supplemental new drug application for Avandia® (rosiglitazone maleate) Tablets, 2 mg, 4 mg, and 8 mg.

With this amendment, we have received a complete response to our action letter dated February 8, 2001.

If you have any questions, please contact 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
Center for Drug Evaluation and Research

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

/s/

Jena Weber
8/29/02 09:49:59 AM

GlaxoSmithKline
U.S. Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA
19101-7929

Tel. 215 751 3868
Fax. 215 751 4926

August 26, 2002

David G. Orloff, M.D., Director
Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
Document Room, 14-B-19
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
AUG 2 7 2002
CDR/ODER

Re: NDA 21-071/S-004: Combination of AVANDIA® (rosiglitazone maleate) with Insulin Complete Response to the Approvable Action

Dear Dr. Orloff:

Reference is made to our approved New Drug Application 21-071 for Avandia® (rosiglitazone maleate), and to supplement sNDA 21-071/S-004 submitted on February 7, 2000. Reference is also made to the FDA approvable letter for S-004, dated February 8, 2001, and to our correspondence reflecting intent to amend, pursuant to 21 CFR 314.110(a)(1), dated February 15, 2001. Finally, reference is made to our correspondence of March 5, 2002 (Ref. Serial No ~~—~~ IND 43,468), Status of Major Amendment (S-004). At that time, we notified the review team that the major amendment for S-004 would be submitted shortly with information sufficient to justify an approval for insulin combination use.

At this time, we are amending the supplement to provide the complete response to the approvable letter of February 8, 2001. Similar action is being taken, as well, in other countries where regulatory authorities have likewise requested additional information before the combination of *Avandia* and insulin might be approved.

Literature references cited in Items 2 thru 8 are contained under each individual item folder (i.e., hpbio\pubs, clinstat\pubs and summary\pubs.) Any publication citation not contained in individual item folders is available upon request.

If you have any questions or requests regarding this submission, please do not hesitate to contact me at (215) 751-3434.

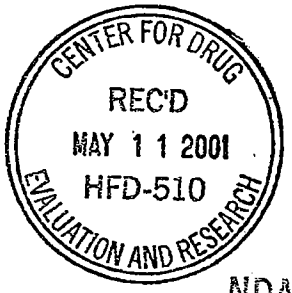
Sincerely,

Sharon W. Shapowal

Sharon Shapowal, R.Ph.
Director
U.S. Regulatory Affairs

Complete Desk Copy: Ms. J. Weber

ORIGIN.



GlaxoSmithKline

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Fax. 215 751 3400
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May 11, 2001

NDA ORIG AMENDMENT
SE1-004-BM

NDA 21-071/S-004
Avandia® (rosiglitazone maleate) Tablets
Amendment to a Pending sNDA

David Orloff, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Amendment to a Pending Supplement:
Response to FDA Request for Information

Dear Dr. Orloff:

Reference is made to our New Drug Application for the anti-diabetic compound, *Avandia* (rosiglitazone maleate), NDA 21-071, and to our supplement NDA 21-071/S-004 (*Avandia* in combination with insulin for the treatment of type 2 diabetes mellitus) submitted on February 7, 2000. Reference is also made to the FDA approvable letter to S-004, dated February 8, 2001. Further reference is made to a fax from DMEDP, dated January 10, 2001, requesting additional information (Attachment 1).

At this time, we are submitting, in duplicate, the requested data (Attachment 2). As agreed during our teleconference call of January 18, 2001, because this request for information was not time sensitive, it could be prioritized after activities directed toward closure on labeling and safety supplement 21-071/S-006. We apologize for any delay in delivering this response, and hope that it is still within an acceptable time frame for your purposes.

Please do not hesitate to contact me at (215) 751-3434 (phone) or (215) 751-4096 (fax) with any question(s) regarding these data.

Sincerely yours,

Sharon W. Shapowal, R.Ph.
Director, Avandia®
U.S. Regulatory Affairs

Desk copy: J. Weber (cover letter)
W. Lubas (full copy)

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

ORIGINAL

GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA
19101-7929

Tel. 215 751 4000
Fax. 215 751 3400
www.gsk.com

February 15, 2001

Avandia® (rosiglitazone maleate) Tablets
NDA 21-071/S-004

SE1 004 BL
NDA SUPP AMEND

David G. Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control 14B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

2/21/1
Hand
Copy given to
Dr. W. Labes

Other: **Notification of intent to file an amendment to pending supplement**
Partial reply to the approvable action

Dear Dr. Orloff:

Reference is made to the approved New Drug Application for Avandia® (rosiglitazone maleate) Tablets, NDA 21-071, and to our supplement of February 7, 2000 (sNDA 21-071/S-004), which provides for the combination of *Avandia* with insulin for the treatment of patients with Type 2 diabetes mellitus. Reference is also made to the FDA approvable letter to S-004, dated February 8, 2001.

At this time, we are notifying the FDA of our intent to file an amendment to this pending application.

2/26/01

In addition, we are enclosing a copy of revised, highlighted (marked-up) labeling for *Avandia*, as a partial response to this approvable action. (See Attachment 1.) This label supercedes all previous copies of draft labeling submitted to 21-071/S-004. The label is revised in accord with our discussions related to approved supplement 21-071/S-006 (Ref. action letter dated February 8, 2001) and our agreement related to 21-071/S-004. Except for minor technical editing changes, it is identical to the label submitted on February 8, 2001 to S-006. Safety data from the insulin combination studies of supplement S-004 have been included in the following sections: **WARNINGS, PRECAUTIONS (Edema, Weight gain)**, and **ADVERSE REACTIONS.**

As agreed, these changes will become effective prior to approval of S-004, concurrent with label changes being implemented with the approval of S-006. When the complete response to the approvable action of S-004 is submitted, and full approval of the insulin combination indication becomes possible, additional labeling changes may be required.

Please do not hesitate to contact me by phone at (215) 751-3434 or by fax at (215) 751-4096, if you have any questions regarding these documents.

Sincerely,

Sharon W. Shapowal, R.Ph.
Director, *Avandia*
U.S. Regulatory Affairs

Desk copy: Ms. J. Weber

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

MESSAGE CONFIRMATION

12/21/00 12:26
ID=DMEDP-CDER-FDA

NO.	MODE	BUD	GROUP
750	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
12/21 12:24	02'00"	215 751 4096	006/006	OK		0000

Avandia 004 LBL

TELEFAX

TO: SKB - att. Thomas Shepperd

Ref NDA 21-071/S-004

FAX: 215-751-4096

PHONE: --

FROM: Jena M. Weber, RHPM

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS

DEC 21

SmithKline Beecham Pharmaceuticals
One Franklin Plaza, PO Box 7929
Philadelphia, PA 19101

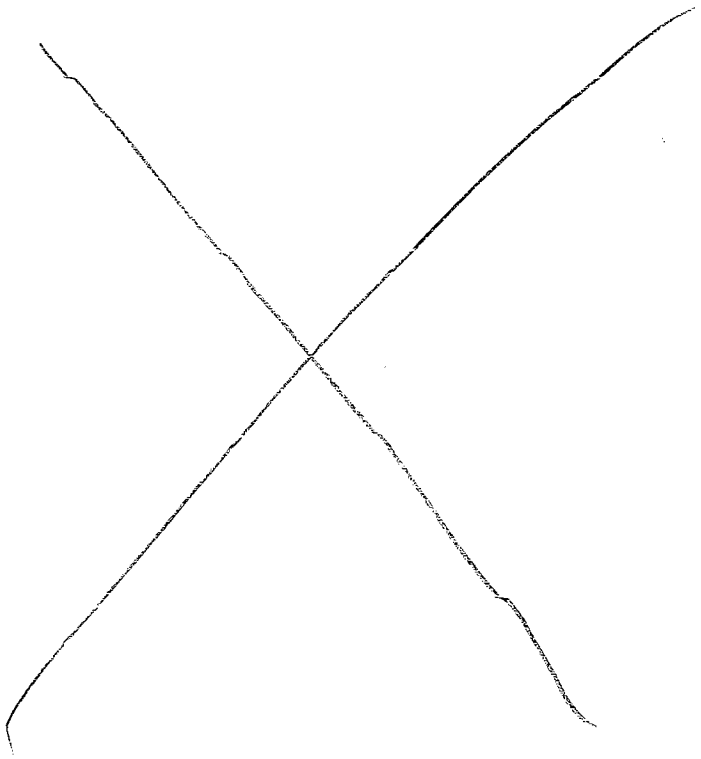
Attention: Sharon Shapowal, R.Ph.
Director, US Regulatory Affairs

Fax: 215-751-4096.

Ref: NDA 21-071/S-004, (Rosiglitazone) submission dated February 7, 2000; combination of Avandia plus insulin for the treatment of patients with Type 2 diabetes mellitus.

As per our telephone conference on December 7, 2000, we are proposing the following changes to the **PRECAUTIONS** section of the Avandia package insert. Your response should be in writing to your NDA.

PRECAUTIONS



4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-071/5004

SmithKline Beecham
Pharmaceuticals

DESK COPY

November 8, 2000

NDA 21-071/S-004
Avandia® (rosiglitazone maleate) Tablets
Amendment to a Pending sNDA

David Orloff, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Amendment to a Pending Supplement:
Response to FDA Request for Information

Dear Dr. Orloff:

Reference is made to our New Drug Application for the anti-diabetic compound, *Avandia* (rosiglitazone maleate), NDA 21-071, and to the pending supplement, NDA 21-071/S-004 (*Avandia* in combination with insulin for the treatment of type 2 diabetes mellitus) submitted on February 7, 2000. Further, reference is made to 2 requests by medical officer Dr. William Lubas for additional information: the first request was to clarify data contained in the November 1, 2000 amendment (Ref. Attachment 1); and the second request was to supply additional displays of select adverse events by responder status and maximum weight change for the double blind trials (Ref. Attachment 2). The requests were made on November 2, 2000 and these data were submitted electronically through secure e-mail on November 7 and November 8, 2000, respectively.

One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101. Telephone (215) 751 4000. Fax (215) 751 3400.

The data herein submitted, in duplicate, serve to officially amend the file for 21-071/S-004. Please do not hesitate to contact me at (215) 751-3434 (phone) or (215) 751-4096 (fax) with any question(s) regarding these data.

Sincerely yours,

Sharon W. Shapowal, R.Ph.
Director, Avandia®
U.S. Regulatory Affairs

Desk copy: J. Weber (cover letter)

SmithKline Beecham
Pharmaceuticals

November 1, 2000

NDA 21-071/S-004
Avandia® (rosiglitazone maleate) Tablets
Amendment to a Pending sNDA

David Orloff, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Amendment to a Pending Supplement:
Complete Response to FDA Request for Information

Dear Dr. Orloff:

Reference is made to our New Drug Application for the anti-diabetic compound, *Avandia* (rosiglitazone maleate), NDA 21-071, and to the pending supplement, NDA 21-071/S-004 (*Avandia* in combination with insulin for the treatment of type 2 diabetes mellitus) submitted on February 7, 2000. Further reference is made to a fax from DMEDP, dated October 3, 2000, requesting additional information. In addition, reference is made to a brief clarifying teleconference between representatives of SB and Dr. Lubas on October 3, 2000. Finally, reference is made to a partial response to the October 3, 2000 request for information, which was submitted October 6, 2000 and included a copy of the August 20, 1999 submission to IND 43,468 (Serial No. 217).

At this time, we are submitting, in duplicate, the requested information on weight (**Attachment 1**), as well as the October 3, 2000 meeting minutes of the telephone conversation between Dr. Lubas and the SB team (**Attachment 2** for reference) as

One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101. Telephone (215) 751 4000. Fax (215) 751 3400

October 3, 2000 FDA request for additional information. Attachments 1 & 2 were transmitted via secure e-mail to Dr. Lubas on October 31, 2000.

In addition, given the subject of our discussion with DMEDP at the October 5, 2000 meeting in Rockville, and given the areas of interest delineated in the FDA fax of October 3, 2000, SB is attaching to this response a safety update recently completed by SB (**Attachment 3**). The document is similar to the safety update submitted just prior to approval of the sulfonylurea combination sNDA, and is being made available to the FDA for information purposes.

Finally, the original fax from DMEDP, sent to SB on October 3, 2000, has also been attached (**Attachment 4**).

We believe that the information included in this amendment satisfactorily answer all questions raised by DMEDP, and look forward to labeling discussions and approval of the insulin combination sNDA. Please do not hesitate to contact me at (215) 751-3434 (phone) or (215) 751-4096 (fax) with any question(s) regarding these data.

Sincerely yours,

Sharon W. Shapowal, R.Ph.
Director, Avandia®
U.S. Regulatory Affairs

Desk copy: J. Weber (cover letter)
W. Lubas (full copy)

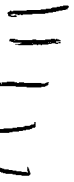
OCT 3 2000

Dear Jena,

Please forward the following questions to SmithKline Beecham in reference to NDA 21-071/S-004.

1) Please provide the missing financial disclosure information for the following investigators

Protocol 095 Center 21



Protocol 095 Center 22

2) Please replot the weight gain data for each of the studies 082, 095 and 114 as a bar graph showing the distribution of the weight change in individual patients on insulin alone, insulin and 4mg of Avandia and insulin and 8mg of Avandia.

   Please plot a similar graph for the patients in study 114 showing their total weight gain (including the weight change from studies 082 or 095).

   If there are any significant outliers please mention any adverse events they may have had including anemia, edema and cardiac events also include any pertinent medical history in these patients.

3) Make tables showing the incidence of adverse events of anemia, edema and cardiac failure (number and %) seen with weight gain. You may use a table similar to the one shown here for anemia.

Incidence of Anemia in double blind and open labile population						
Weight Gain (kg)	Insulin + Placebo N=		Insulin + 4mg RSG N=		Insulin + 8mg RSG N=	
	N	%	N	%	N	%
0 to 1						
>1 to ≤ 2						

>2 to ≤ 3						
>3 to ≤ 4						
>4 to ≤ 5						
>5 to ≤ 6						
>6						
Total pts with wt gain						

4) Please reanalyze your data on the patients who developed anemia during combination therapy to see if it is possible to determine if it was primarily normocytic or hypochromic, and discuss your findings.

5) Please supply the information used to support the following underlined labeling change in the " " section.

OCT 3 2000

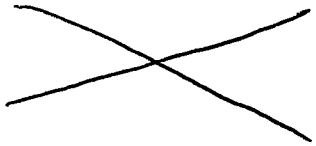
SmithKline Beecham Pharmaceuticals
1250 South Collegeville Road
Mail Code UP4340, PO Box 5089
Collegeville, PA 10426-0989

Attention: Sharon Shapowal, R.Ph.

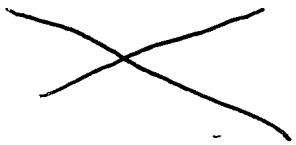
Fax: 215-751-4096

Ref: NDA 21-071/S-004, Avandia (rosiglitazone) submission dated February 7, 2000. Please provide the following additional information in reference to supplement 004 of your NDA 21-071.

Please provide the missing financial disclosure information for the following investigators, Protocol 095 Center 21;



Protocol 095 Center 22;



Please replot the weight gain data for each of the studies (082, 095 and 114), as a bar graph showing the distribution of the weight change in individual patients on insulin alone, insulin and 4mg of Avandia, and insulin and 8mg of Avandia.

Please plot a similar graph for the patients in study 114 showing their total weight gain (including the weight change from studies 082 or 095).

If there are any significant outliers, please mention any adverse events patients may have had including anemia, edema and cardiac events. Please also include any pertinent medical history for these patients.

Please create tables showing the incidence of adverse events of anemia, edema and cardiac failure (number and %) seen with weight gain. You may use a table similar to the one shown here for anemia.

Incidence of Anemia in double blind and open labile population						
Weight Gain (kg)	Insulin + Placebo N=		Insulin + 4mg RSG N=		Insulin + 8mg RSG N=	
	N	%	N	%	N	%
0 to 1						
>1 to ≤ 2						
>2 to ≤ 3						
>3 to ≤ 4						
>4 to ≤ 5						
>5 to ≤ 6						
>6						
Total pts with wt gain						

Please re-analyze your data on the patients who developed anemia during combination therapy to see if it is possible to determine if it was primarily normocytic or hypochromic, and discuss your findings.

Please supply the information used to support the following underlined labeling change in the ' ' section.

This information was faxed to Sharon Shapowal on October 3, 2000.

CLEARED FOR FAXING

10/2/00

William Lubas, M.D.

10/2/00

Saul Malozowski, M.D.

10/2/00

David Orloff, M.D.

10/2/00

Jena Weber, RHPM

SmithKline Beecham
Pharmaceuticals

DESK COPY
J. Weber

October 6, 2000

NDA 21-071/S-004
Avandia® (rosiglitazone maleate) Tablets
Amendment to a Pending sNDA

David Orloff, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Amendment to a Pending Supplement:
Partial Response to FDA Request for Information

Dear Dr. Orloff:

Reference is made to our New Drug Application for the anti-diabetic compound, *Avandia* (rosiglitazone maleate), NDA 21-071, and to the supplement submitted to this application on February 7, 2000 (i.e. S-004). The subject of the supplement is *Avandia* in combination with insulin for the treatment of type 2 diabetes mellitus. Further reference is made to a fax from the division, dated October 3, 2000, requesting additional information for medical officer Dr. William Lubas. In addition, reference is made to a brief clarifying teleconference between representatives of SB and Dr. Lubas on October 3, 2000.

At this time, we are amending the supplement with several of the items specified in the October 3rd facsimile. Also included, as promised during the teleconference, is a copy of the August 20, 1999 submission to IND 43,468 (Serial No 14 which contains an assessment report that we believe will be of interest to Dr. Lubas during his review. The remainder of the information requested in the fax, which requires additional programming and data collection, is being compiled and will be submitted to the NDA shortly.

A table of contents for this submission is included on Page 000006. You will note that a full copy of the annotated label has been included (starting on page 000010), given the question on labeling raised by Dr. Lubas.

000001

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However, please be aware that the annotations are pasted into a very early version of the *Avandia* label. At the time of approval action, we will need to transfer the "insulin" annotations into the most recent *Avandia* label, which now includes, for example, the sulfonylurea indication and data. Please do not hesitate to contact me at (215) 751-3434 (phone) or (215) 751-4096 (fax) with comments or questions on this amendment.

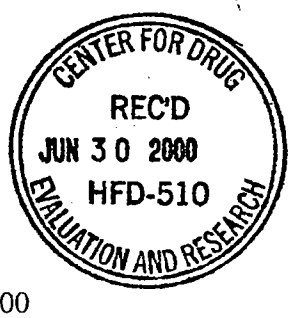
Sincerely yours,

Sharon W. Shapowal, R.Ph.
Director, Avandia®
U.S. Regulatory Affairs

Desk copy: J. Weber (cover letter)
W. Lubas (full copy)

NDA SUPP AMEND
S-004
6M

SmithKline Beecham
Pharmaceuticals



June 29, 2000

Avandia® (rosiglitazone maleate) Tablets
NDA 21-071/S-004

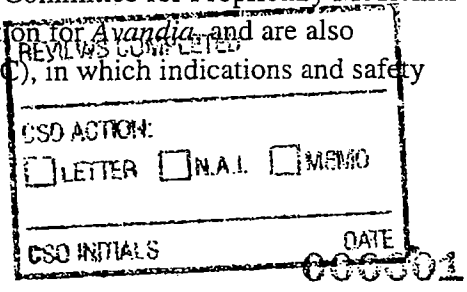
John K. Jenkins, M.D., Acting Director
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products (HFD-510)
Document Control 14B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Amendment to Pending Efficacy Supplement – 21-071/S-004
Update of Foreign Marketing History

Dear Dr. Jenkins:

Reference is made to our approved New Drug Application for Avandia® (rosiglitazone maleate) Tablets, NDA 21-071, and to our submission of February 7, 2000 (sNDA 21-071/S-004), the subject of which is *Avandia* in combination with insulin for the treatment of patients with Type 2 diabetes mellitus.

At this time, we are updating the information regarding foreign marketing history as it applies to approval of rosiglitazone in the European Union (EU), in general, and also as it applies to the insulin combination indication (S-004) in particular. While the information provided is broader in scope than generally included in the foreign market history, we are supplying these documents for context. We are enclosing both the final opinion of the Committee for Proprietary Medicinal Products (CPMP) on the granting of a marketing authorization for *Avandia*, and are also enclosing a sample summary of product characteristics (SPC), in which indications and safety information are described.



One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101. Telephone (215) 751 4000. Fax (215) 751 3400.

We had expected these documents to be posted on the web site of the European Agency for the Evaluation of Medicinal Products (EMEA) on May 29, 2000 as discussed with Dr. Malozowski on May 30, 2000. However, we now expect the documents to be posted on July 3, 2000. As noted in a conversation this past Monday with Ms. Weber, the site address is: www.eudra.org/en_home.htm.

Please do not hesitate to contact me by phone at (215) 751-3434 or by fax at (215) 751-4096, if you have any questions regarding these documents.

Sincerely,

Sharon W. Shapowal, R.Ph.
Director, *Avandia*
U.S. Regulatory Affairs

Desk copy: Ms. J. Weber

000002

SmithKline Beecham
Pharmaceuticals

DESK COPY

May 26, 2000

Avandia® (rosiglitazone maleate) Tablets
NDA 21-071/S-004

John K. Jenkins, M.D., Acting Director
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products (HFD-510)
Document Control 14B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Amendment to Pending Efficacy Supplement – 21-071/S-004
Follow up to request for expedited review – Label changes proposed

Dear Dr. Jenkins:

Reference is made to our approved New Drug Application for Avandia® (rosiglitazone maleate) Tablets, NDA 21-071, and to our submission of February 7, 2000 (sNDA 21-071/S-004), the subject of which is *Avandia* in combination with insulin for the treatment of patients with Type 2 diabetes mellitus. Reference is also made to our letter of May 11, 2000, wherein we urged the FDA to expedite review of this efficacy supplement, given recent events in the U.S. market.

The purpose of this letter is to follow our request for expedited review with proposed changes to the *Avandia* label – changes we wish to implement immediately while awaiting full approval of the insulin combination efficacy supplement. The changes which we propose for immediate inclusion in the *Avandia* label are **not** intended to encourage off-label use in combination with insulin, but rather, to provide additional information regarding the use of our product, should physicians combine *Avandia* with insulin in the treatment of their type 2 diabetes patients, during the period when such use is "off label".

000001

One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101. Telephone (215) 751 4000. Fax (215) 751 3400.

The main reason for our request for immediate label change is that a number of former Rezulin® (troglitazone) users, some of whom are concurrent insulin users, have likely switched to *Avandia* and are likely continuing to use insulin with their *Avandia*. With only two TZDs now on the U.S. market after the withdrawal of *Rezulin*, the number of patients receiving *Avandia* for use in combination with insulin may continue to grow. The best way to provide physicians with information on such use is to accelerate approval of S-004 and the associated labeling for *Avandia*+insulin combination indication. We have included a copy of the submitted draft label of S-004. (See Attachment 1.) However, we recognize that even with added efforts by the Agency to accelerate review of the supplement, that review could take months to complete. Attached is *Avandia* labeling that reflects changes SB would like to include immediately in the U.S. P.I., during the possible intervening months, while the full *Avandia*+insulin combination labeling is awaiting approval. (See Attachment 2.) You will note that the text is mostly excerpted from the pending draft label currently under review as part of S-004.

Our team would like to discuss with the Agency the label changes directed to the off-label use of *Avandia* in combination with insulin. The proposed labeling includes a number of changes designed to address the potential development of hypoglycemia in the combination use with insulin. For example, the proposed labeling includes language in the DOSAGE AND ADMINISTRATION section recommending that, if a patient reports hypoglycemia or if the patient's fasting plasma glucose level drops below [redacted] mg/dL, the insulin dosage be reduced by 10-25%. We would also propose to include in the labeling in the ADVERSE REACTIONS section the rates of serious hypoglycemia observed in our trials and to revise the PRECAUTIONS section to highlight this possible event, as well. While, based on our current labeling and physicians' own experience with insulin and oral hypoglycemic agents, we believe that physicians treating patients on insulin understand the potential for those patients to develop hypoglycemia, we also believe that this information, particularly the recommendation for a reduction in the dosage of insulin if hypoglycemia develops, would be useful to physicians in managing their diabetic patients.

Another example of a change that SB proposes for the interim period would be inclusion of edema and congestive heart failure rates from the combination clinical trials in the label. [redacted] At that time, [redacted] That proposal and subsequent discussions with the FDA resulted in the inclusion in the *Avandia* label of the precaution regarding heart failure. [redacted] we recognize that FDA may not view the inclusion of the rates as necessary in light of the precaution already in the *Avandia* label. However, since we have proposed to include the hypoglycemia rates from the insulin studies, we suggest that the heart failure rates and edema rates also be included in the ADVERSE REACTIONS section at this time. Additionally, so that prescribers can better understand the rates in the context of the patient population and the [redacted]

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We are sensitive to the FDA's concern that changes in labeling addressing off-label uses not be used as a vehicle for off-label promotion. SmithKline Beecham does not intend to promote *Avandia* off-label in combination with insulin. Nevertheless, so that the efficacy and other data relating to such combination use can be made available to prescribers, we again feel the need to request that the review of the full label be expedited.

In our letter to you dated May 11, 2000, we cited public health need as a reason to expedite review of the efficacy supplement, 21-071/S-004, and its labeling. We recognize that the "public health need" described and cited by FDA as one criterion for expedited review does not fit with the *Avandia* situation by the strict definition of this term, which is: "Events that affect the availability of a drug for which there is no alternative." (Ref. MAPP 5240.1, Requests for expedited review of supplements to approved ANDA's and AADA's, November 1999). There is an alternative to *Rezulin* in the U.S., namely pioglitazone, which is available, approved, and labeled for use in combination with insulin. However, it is always in the best interest of the public health to assure that there are alternatives for patients intolerant of or unable to use the single approved agent for whatever reason. In that context, there is an urgent need for *Avandia* to be labeled for such use and for the review to be expedited.

We believe that the label changes, herein proposed for immediate implementation, would provide physicians additional information upon which to base informed decisions should off-label use in combination with insulin be under consideration. We would like to discuss with the FDA review division our proposal to expedite the review of S-004 and also to discuss the potential labeling changes that could be implemented immediately in the interim period prior to what we believe will be final approval of this supplement. We will call to schedule a meeting or teleconference after you have had an opportunity to review this request

Thank you for considering this request. Please do not hesitate to contact me by phone at (215) 751-3434 or by fax at (215) 751-4096.

Sincerely,

Sharon W. Shapowal, R.Ph.
Director, *Avandia*
U.S. Regulatory Affairs

Desk copy: Ms. J. Weber

000003

SmithKline Beecham
Pharmaceuticals

May 11, 2000

Avandia® (rosiglitazone maleate) Tablets
NDA 21-071/S-004

John K. Jenkins, M.D., Acting Director
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products (HFD-510)
Document Control 14B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Amendment to Pending Efficacy Supplement – 21-071/S-004
Expedited Review Requested

Dear Dr. Jenkins:

Reference is made to our approved New Drug Application for Avandia® (rosiglitazone maleate) Tablets, NDA 21-071, and to our submission of February 7, 2000 (sNDA 21-071/S-004), the subject of which is *Avandia* in combination with insulin for the treatment of patients with Type 2 diabetes mellitus. Further, reference is made to the Agency's acknowledgement letter of February 25, 2000, identifying the primary user fee goal date of the prior approval supplement as December 8, 2000 and the secondary user fee goal date as February 8, 2001.

SmithKline Beecham believes that circumstances have arisen which necessitate an expedited review of the file and revision of the user fee goal date.

Shortly after submission of the supplement on February 7, 2000, there was a significant event that suddenly changed the therapeutic options available to U.S. citizens for the treatment of Type 2 diabetes. Rezulin® (troglitazone) was withdrawn from the U.S. market. This occurred on March 21, 2000. At the time of withdrawal, it is estimated that as many as 500,000 patients were receiving troglitazone in combination with other agents, one of which was insulin. The NDC

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Patient Tracking Study data indicate that in February 2000, 37.5% of patients receiving troglitazone were using the thiazolidinedione in combination with insulin. At the same timepoint, insulin combination with pioglitazone was an estimated 28.9% of use and with *Avandia*, an estimated 27.2% of use (though off label and not promoted). A significant number of former troglitazone users have been switched to *Avandia*. One can expect that many of these patients were receiving insulin at time of switch and that many are continuing on such therapy. SmithKline Beecham urges the Agency to expedite approval of the pending supplement, or at a minimum, to move up the primary goal date from December 8, 2000.

The label of *Avandia* contains a precaution regarding heart failure – a precaution directed particularly to the off-label use of rosiglitazone in combination with insulin. SB and FDA representatives discussed this label change soon after the launch of *Avandia* in the U.S., given that significant off-label use was estimated to be occurring even then. However, other important information (e.g. dosing recommendations, adverse event rates) are unavailable in the prescribing information to support this indication of use. There is a *public health need* to assure that all patients who require thiazolidinedione plus insulin therapy, and all prescribers who elect to treat their patients with this therapeutic option, are supplied with the appropriate information required to make informed decisions on usage. Without a change in the *Avandia* label, SB cannot broadly disseminate such information.

We urge the Agency to consider the magnitude of current, potential off-label use of *Avandia* in combination with insulin. We urge the Agency to consider the public health need. The team at SmithKline Beecham stands ready to assist the FDA team in whatever way necessary to expedite the review, which we are confident will conclude with approval.

Thank you for considering this important issue. Please do not hesitate to contact me by phone at (215) 751-3434 or by fax at (215) 751-4096.

Sincerely,

Sharon W. Shapowal

Sharon W. Shapowal, R.Ph.
Director, *Avandia*
U.S. Regulatory Affairs

Desk copy: Ms. J. Weber

NDA SUPP AMEND
SE1

SmithKline Beecham
Pharmaceuticals

CENTER FOR DRUG
REC'D.
MAY - 8 2000
HFD-510
EVALUATION AND RESEARCH

DUPLICATE May 5, 2000

NDA 21-071/S-004
Avandia® (rosiglitazone maleate) Tablets

COPY

John Jenkins, MD, Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Amendment to Pending sNDA
Missing Reference and Data Source Tables

Dear Dr. Jenkins:

Reference is made to our supplemental New Drug Application for the anti-diabetic compound, Avandia® (rosiglitazone maleate), sNDA 21-071/S-004 (*Avandia* in combination with insulin), submitted February 7, 2000 .

Submitted herewith, in duplicate, are one reference and four data source tables, which were inadvertently omitted from the submission. The reference (#17) should have been electronically linked to the Item 3 Summary (Volume 5.1.001, Item 3.H, page 000098) and the Overall Benefit to Risk Assessment and Conclusion (Volume 5.8.001 Item 8.J, page 000033). The data source tables (HOMA.2 for studies 011, 015, 020 and 094) should have been electronically linked to the Annotated Labeling (Volume 5.1.001, Item 3.A, page 000004) the Item 3 Summary (Volume 5.1.001, Item 3.H, pages 000074-75) and the Overall Benefit to Risk Assessment and Conclusion (Volume 5.8.001 Item 8.J, pages 000009-10).

One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101. Telephone (215) 751 4000. Fax (215) 751 3400.

We sincerely apologize for any inconvenience that this may have caused. Please do not hesitate to contact me at 215-751-3434 (phone) or 215-751-4096 (fax) with comments or questions on this matter.

Sincerely,

Sharon W. Shapowal

Sharon W. Shapowal, RPh
Director, *Avandia*®
U.S. Regulatory Affairs

Desk copy: Ms. J. Weber

MEMORANDUM

See attached e-mail dated April 5, 2000.

Reference: NDA 21-071/S-004, Avandia Tablets (rosiglitazone)
Supplement provides for use of Avandia in combination with insulin for the treatment of patients with type 2 diabetes.

Conclusions:

1. Application is filable.
2. Application will be reviewed under the standard review clock (USER FEE GOAL DATE: December 8, 2000).
3. No Advisory Committee will be assembled.

Concur:

Robert Misbin,M.D.

4/18/00
Saul Malozowski, M.D.

18-APR-2000
Xavier Ysern, Ph.D.

4/18/2000
Stephen Moore, Ph.D.

4/25/00
Joy Mele, M.S.

4/18/00
Todd Sahlroot, Ph.D.

4/26/00
Herman Rhee, Ph.D.

4/24/00
Ronald Steigerwalt, Ph.D.

Steven Johnson, PhamD.

5/2/00
Hae-Young Ahn, Ph.D.

4/17/00
Jena Weber, RHPM

E L E C T R O N I C M A I L M E S S A G E

Date: 05-Apr-2000 09:45am EDT
From: Jena Weber
WEBERJ
Dept: HFD-510 PKLN 14B04
Tel No: 301-827-6422 FAX 301-443-9282

TO: Robert Misbin (MISBINR)
TO: Saul Malozowski (MALOZOWSKIS)
TO: Xavier Ysern (YSERNX)
TO: Stephen Moore (MOOREST)
TO: Joy Mele (MELE)
TO: Todd Sahlroot (SAHLROOTT)
TO: Herman Rhee (RHEEH)
TO: Ronald Steigerwalt (STEIGERWALTR)

CC: Steve Johnson (JOHNSONST)
CC: Hae Young Ahn (AHNH)

Subject: Avandia S/004

All,

This e-mail and your responses will serve as our filing meeting for NDA 21-071/S-004; Avandia - used in combination with insulin for the treatment of type 2 DM. As you are aware, we just approved supplement 001 that called for the combination use of Avandia w a SU.

We decided at admin rouonds last week that this new supplement will be a STANDARD review, so we are looking at a 12/8/00 due date with ALL reviews due around Thanksgiving of this year. Like supplement 001, PCL, BPH and CHM all refer to and cross-reference the original NDA approved on May 25, 1999. Regardless, I will need the following from you:

MOR: Bob, like supplement 001, the contents for S-004 are just about all clinical, so the usual review by you is needed. Please be sure to reference financial disclosure/information. A clinical update will be provided later on.

BPH: Steve, thanks, I already have your review indicating that no new PK data/info was submitted, and I assume, none are needed. (?).

CHM: Xavier, need the usual mini-review and whether EA/EER's are needed. If not, a statement saying so.

PCL: Herman, information is cross-referenced, but please provide a statment that no new data/info are needed.

EVERYONE SHOULD TAKE A LOOK AT THE PROPOSED LABELING CHANGES PRN.

Thanks,
Jena

FEB 25 2000

NDA 21-071/S-004

PRIOR APPROVAL SUPPLEMENT

SmithKline Beecham Corporation
Attention: Sharon Shapowal, R.Ph.,
Director, NARA
One Franklin Plaza
200 N. 16th Street
Philadelphia, PA 19102

Dear Ms. Shapowal:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Avandia (rosglitazone maleate) Tablets
NDA Number:	21-071
Supplement Number:	S-004
Therapeutic Classification:	Standard (S)
Date of Supplement:	February 7, 2000
Date of Receipt:	February 8, 2000

This supplement proposes to support the use of Avandia Tablets in combination with insulin for the treatment of patients with Type 2 diabetes mellitus.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 8, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 8, 2000, and the secondary user fee goal date will be February 8, 2001.

Be advised that; as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Jena Weber, Regulatory Management Officer, at (301) 827-6422.

Sincerely,

eng 2.24.02

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-071
HFD-510/Div. Files
HFD-510/~~M. Simoneau~~ Weber
HFD-510/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: ddk/February 23, 2000
Initialed by: Galliers 2.23.00
final: ddk/February 24, 2000
filename: 21071004

PRIOR APPROVAL SUPPLEMENT ACKNOWLEDGEMENT (AC)

SmithKline Beecham
Pharmaceuticals

February 7, 2000

NDA 21-071/S-004
Avandia® (rosiglitazone maleate) Tablets

Volumes 5.1.001, 5.8.001 - 5.8.038

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852

Avandia® (rosiglitazone maleate) Tablets: NDA 21-071/S-004

Dear Dr. Jenkins:

Submitted herewith, in duplicate, in accordance with Section 314.50 of Title 21 of the Code of Federal Regulations is a supplemental New Drug Application to support the use of **Avandia® (rosiglitazone maleate) Tablets in combination with insulin for the treatment of patients with Type 2 diabetes mellitus.**

Avandia is a thiazolidinedione, a class of drugs, which activate PPARγ receptors and directly target insulin resistance, a fundamental defect in the pathophysiology of type 2 diabetes. The initial NDA 21-071 for *Avandia* as monotherapy and in combination with metformin was approved by FDA on May 25, 1999. A supplemental application to support the use of *Avandia* in combination with sulfonylurea was submitted on June 3, 1999 and is currently under review in the Division of Metabolic and Endocrine Drug Products (DMEDP).

This supplemental New Drug Application specifically details the efficacy of *Avandia* in combination with insulin. Safety and efficacy data up to the clinical cut-off of 18 December 1998 is being submitted for patients receiving rosiglitazone in combination with insulin. Results of two pivotal studies have provided evidence that *Avandia* used in combination with insulin is effective in improving glycemic control at doses of 4mg/day ——— along with a decrease in the mean total daily dose of insulin.

One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101. Telephone (215) 751 4000. Fax (215) 751 3400

The safety and efficacy of *Avandia* has been investigated in an extensive clinical development program. The integrated safety database is substantial, both in terms of patient numbers and by duration of exposure, with more than 5100 patients exposed to *Avandia* (as monotherapy or in combination with metformin, sulfonylureas, or insulin); more than 3700 patients were exposed for at least 6 months and 2179 patients exposed for 12 months or longer.

As discussed on March 3, 1999 in a telephone conversation between Enid Galliers of FDA and Clare Kahn of SB, we are incorporating extensive sections of NDA 21-071 by cross-reference only. These sections are indicated in the Item 1 NDA Index and also parenthetically in text where appropriate. A tabular listing of the volumes included with this supplement is provided following this letter. The proposed draft labeling has been highlighted by bold, colored, underlined text to indicate where additions/changes are being proposed to the currently approved labeling for *Avandia*.

The entire NDA efficacy supplement is being made available in electronic copy to fully support the reviewers. Sections which are included by cross-reference to the initial NDA have been previously loaded onto the FDA network and remain available electronically to reviewers. The electronic efficacy files will be loaded on the FDA network as soon as the necessary arrangements can be made. A description of the electronic submission (contents of media, number/format, file descriptions, size of submission) are contained in the "**Guide to the Electronic Submission**" that appears in Volume 5.1.001, immediately following the NDA Index.

In accordance with the Prescription Drug User Fee Act of 1997, a check in the amount of $142,870.00 (the full fee for an NDA supplement containing clinical data) has been sent via wire transmittal to the FDA on January 31, 2000 (User Fee ID: —— . A copy of the wire transfer receipt showing the submitted User Fee is enclosed on page 000165 of this volume. Financial disclosure information has been provided for investigators who participated in the two controlled pivotal clinical trials (082 & 095)of *Avandia* in combination with insulin.

Avandia was approved for the treatment of Type 2 diabetes mellitus in the United States on May 25, 1999 as monotherapy and in combination with metformin. It has also been approved in numerous other countries for these indications and in combination with sulfonylureas as outlined in Item 3.C. *Avandia* has not been approved for use in combination with insulin in any country. *Avandia* has also not been refused marketing authorization or withdrawn from marketing in any country on safety grounds.

SmithKline Beecham commits to providing all necessary support for the review of this NDA including full technical support in the use of the electronic documentation.

Should you have any questions regarding this supplemental New Drug Application, please do not hesitate to contact me by phone at (215) 751-3868 or by fax at (215) 751-4096.

Sincerely,

Sharon W. Shapowal

Sharon W. Shapowal, R.Ph.
Director
U.S. Regulatory Affairs

Division of Metabolic and Endocrine Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: 21-071/S-004

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

Sponsor: GlaxoSmithKline

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Combination

Submission Date: August 26, 2002.

Receipt Date: August 27, 2002.

Filing Date: October 27, 2002.

User-fee Goal Date: February 27, 2003.

Proposed Indication: To add Avandia in combination with insulin for the treatment of patients with Type 2 Diabetes Mellitus.

Other Background Information: This submission is in response to our AE letter dated 2/8/01.

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	✔		Vol. 1.1
2. Form FDA 356h (original signature)	✔		Vol. 1.1
a. Establishment information		✔	NN

(facilities ready for inspection?)			
b. Reference to DMF(s) & Other Applications			NN
3. User Fee FDA Form 3397 4. Patent information & certification	✔		Vol. 1.1
5. Debarment certification (Note: Must have a definitive statement)	✔		Vol. 1.1
6. Field Copy Certification			NN
7. Financial Disclosure	✔		Vol. 1.1
8. Comprehensive Index	✔		Vol. 1.1
9. Pagination	✔		Vol. 1.1
10. Summary Volume	✔		Vol. 1.1
11. Review Volumes	✔		
12. Labeling (PI, container, & carton labels)	✔		Vol. 1.1
a. unannotated PI			
b. annotated PI	✔		Vol. 1.1
c. immediate container			N/A
d. carton			N/A
e. patient package insert (PPI)			N/A
f. foreign labeling (English translation)		✔	N/A
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	✔		Electronic
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	✔		Electronic

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	✔		Electronic
2. Foreign Marketing History		✔	
3. Summary of Each Technical Section	✔		Vol. 1.1
a. Chemistry, Manufacturing, & Controls (CMC)		✔	N/A – Cross Reference
b. Nonclinical Pharmacology/Toxicology		✔	N/A – Cross Reference
c. Human Pharmacokinetic & Bioavailability		✔	N/A – Cross Reference
d. Microbiology			N/A
e. Clinical Data & Results of Statistical Analysis	✔		Electronic (2 studies)
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	✔		Vol. 1.1
5. Summary of Safety	✔		Electronic
6. Summary of Efficacy	✔		Electronic

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	✔		Electronic
2. Controlled Clinical Studies	✔		Electronic

a. Table of all studies			
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	✔		Electronic
c. Optional overall summary & evaluation of data from controlled clinical studies	✔		Electronic
3. Integrated Summary of Efficacy (ISE)		✔	
4. Integrated Summary of Safety (ISS)		✔	
5. Drug Abuse & Overdosage Information		✔	N/A
6. Integrated Summary of Benefits & Risks of the Drug	✔		Electronic
7. Gender/Race/Age Safety & Efficacy Analysis of Studies		✔	

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		✔	N/A
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)		✔	N/A
a. Proposed unannotated labeling in	✔		1.1

c. Efficacy data in SAS data set format (only if paper submission)		✔	N/A
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		✔	N/A
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)			N/A
3. Exclusivity Statement (optional)		✔	Qualifies for 3 yr. exclusivity

Y=Yes (Present), N=No (Absent)

Conclusions: AP may be approved.

Jena Weber
Regulatory Project Manager

ADMINISTRATIVE REVIEW

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

/s/

Jena Weber
2/27/03 06:07:41 PM
CSO

Jena Weber
2/27/03 06:10:07 PM
CSO

NDA REGULATORY FILING REVIEW

NDA 21-073/S-004 SE-1
Avandia (rosiglitazone maleate) Tablets 2 mg, 4 mg & 8 mg.

Applicant: GlaxoSmithKline

Date of Application: August 26, 2002
Date of Receipt: August 27, 2002
Date of Filing Meeting: N/A
Filing Date: N/A

Indication(s) requested: To add insulin in combination to Avandia for the treatment of patients with Type 2 Diabetes Mellitus.

Type of Application: Full NDA _____ Supplement _✔_
(b)(1) __✔__ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classifications: S__✔__ P_____
Resubmission after a withdrawal or refuse to file: No, response to AE letter dated 2/8/01.
Chemical Classification: (1,2,3 etc.)_1
Other (orphan, OTC, etc.) N/A

User Fee Status: Paid ___
Form 3397 (User Fee Cover Sheet) submitted: YES
User Fee ID# —
Clinical data? YES
Date clock started after UN: N/A

User Fee Goal date: **2/27/03**

Action Goal Date (optional) _____

Note: If an electronic NDA: all certifications require a signature and must be in paper.

- Does the submission contain an accurate comprehensive index? YES
- Form 356h included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.
- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:

- If electronic NDA, does it follow the Guidance? YES

- Patent information included with authorized signature? YES
- Exclusivity requested? NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement. **3 years exclusivity to be granted.**

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

- Pediatric Rule appears to be addressed for all indications? NO

- Pediatric assessment of all ages? NO
  (If multiple indications, answer for each indication.)
  If NO, for what ages was a waiver requested? _____
  For what ages was a deferral requested? _____

- Field Copy Certification (that it is a true copy of the CMC technical section)? NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in DSS YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in DSS? YES

List referenced IND numbers: IND 43,468

End-of-Phase 2 Meeting? NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC?	NO
Trade name and labeling (PI) sent to ODS?	NO
Advisory Committee Meeting needed?	NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

• Did sponsor request categorical exclusion for environmental assessment?	YES
If no, did sponsor submit a complete environmental assessment?	NO
• EA consulted to Nancy Sager (HFD-357)?	NO
• Establishment Evaluation Request (EER) package submitted?	NO
• Parenteral Applications Consulted to Sterile Products (HFD-805)?	N/A

505(b)(2) **NA**

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?
Yes ____ No _____
(Normally, FDA will refuse-to-file such applications.)

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
Yes _____ No _____
If yes, the application must be refused for filing under 314.54(b)(1)

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
Yes _____ No _____
If yes, the application must be refused for filing under 314.54(b)(2)

For a 505(b)(2) application, which of the following does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

- Submit a statement as to whether the listed drug(s) identified have received a period of marketing exclusivity?

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

If the application is a 505(b)(2), has the Director, Div. of Regulatory Policy II, HFD-007 been notified? YES _____ NO _____

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

/s/

Jena Weber
2/27/03 06:00:48 PM
CSO

Filing Rev. s-4

Jena Weber
2/27/03 06:02:41 PM
CSO

ROUTING AND TRANSMITTAL SLIP

Date 12/19

TO: (Name, office symbol, room number, building, Agency/Post)	Initials	Date
W. Rubas	WJ	12/20
S Malozowski	SM	12/20
3. D Orloff	DO	12/19
4. Okebu		
5. T Zawalski		12/20

Action	File	Note and Return
Approval	For Clearance	Per Conversation
As Requested	For Correction	Prepare Reply
Circulate	For Your Information	See Me
Comment DRK	Investigate	Signature
Coordination	Justify	

REMARKS

For NDA 21-071/S-006 Avandia

Revised LBL (FPA)

*please return to Jena

12/21 - need to E-cap

DO NOT use this form as a RECORD of approvals, concurrences, disposals, clearances, and similar actions

FROM: (Name, org. symbol, Agency/Post)	Room No.—Bldg.
	Phone No.

5041-103

*U.S. GPO: 1998-404-763/40011

OPTIONAL FORM 41 (Rev. 1-94)
Prescribed by GSA

MEMORANDUM

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

DATE: June 10, 2004

TO:
NDA 20-261/S-033, Lescol (fluvastatin) Tablets
NDA 21-102/S-005, Lescol (fluvastatin) Extended Release Tablets
NDA 20-182/S-006, Carnitor (levocarnitine) Injection
NDA 21-116, Thyro-tabs (levothyroxine)
NDA 19-643/S-067, Mevacor (lovastatin) Tablets
NDA 21-316/S-001, Altocor (lovastatin) Extended Release Tablets
NDA 21-204/S-006, Starlix (nateglinide) Tablets
NDA 21-249, Advicor (niacin/lovastatin) Tablets
NDA 20-381/S-013, Niaspan (niacin extended releast)
NDA 21-071/S-004, Avandia (rosiglitazone) Tablets
NDA 20-926/s-006, Renagel (sevelamer) Tablets
NDA 21-179/S-002, Renagel (sevelamer) Capsules
NDA 20-280/s-031, Genotropin (somatropin)
NDA 21-318, Forteo (teriparatide)

FROM: Kati Johnson, CPMS

SUBJECT: **Applications where "Rule Not Addressed" letter did not issue**

The Pediatric Research Equity Act (PREA) was enacted on December 3, 2003. Prior to that time, we were enjoined from enforcing the Pediatric Rule for a period of 411 days. PREA includes mandates to ensure that the need for pediatric studies, including those applications submitted during the period of enjoinment, are addressed.

At the CPMS meeting on 5/13/04, we were requested to issue "Rule not addressed" letters to the sponsors of applications which did not address the Pediatric Rule in the timeframe between the suspension of the Pediatric Rule and the enaction of PREA. On the list of 13 applications on the list distributed for HFD-510, only 1 application required a letter be sent to the firm [redacted]. This letter was issued 6/2/04. This memo was drafted to provide a brief explanation as to why letters were not issued for the remaining 12 applications.

Application Number	Drug Name	Type	Submission Date	Approval Date	Reason Rule Not Addressed, letter didn't issue
NDA 20-261/S-033 NDA 21-192/S-005	Lescol (fluvastatin) Lescol XL	SE1 SE1	7/31/02 7/31/02	5/27/03 5/27/03	Indication not seen in peds (patients with coronary ht. disease to decrease risk of undergoing coronary revascularization)
NDA 20-182/S-006	Carnitor (levocarnitine) Injection	SE1	1/29/99	12/15/99	Orphan indication (carnitine deficiency in ESRD patients)
NDA 21-116	Thyro-Tabs (levothyroxine)	NDA	8/19/99	10/24/02	Contains pediatric information
NDA 19-643/S-067	Mevacor (lovastatin)	SE5	4/16/01	2/14/02	Supplement submitted in response to Written Request
NDA 21-316/S-001	Altocor (lovastatin) Extended Release Tablets	SE1	3/30/01	9/11/02	Indication not seen in peds (prevention of coronary heart disease)
NDA 21-204/S-006	Starlix (nateglinide) Tablets	SE1	12/19/02	10/20/03	Disease is the same in peds and adults (combination treatment with thiazolidinediones)
NDA 21-249	Advicor (niacin/lovastatin)	NDA	9/21/00	12/17/01	Limited patient population
NDA 20-381/S-013	Niaspan (niacin extended release)	SE1	3/29/02	1/31/03	Adult-only indication (combination treatment with lovastatin for treatment of adult dylipidemia)
NDA 21-071/S-004	Avandia (rosiglitazone)	SE1	2/7/00	2/27/03	Disease is the same in peds and adults (type 2 diabetes)
NDA 20-926/S-006 NDA 21-179/S-002	Renagel (sevelamer)Tablets Renagel (sevelamer) Capsules	SE8 SE8	3/3/02 5/20/02	2/6/04 2/6/04	PREA doesn't apply (not a new indication, route of administration, dosage form,
NDA 20-280/S-031	Genotropin (somatropin)	SE1	6/30/02	7/25/01	Pediatric indication (treatment of small for gestational age pts).
NDA 21-318	Forteo (teriparatide)	NDA	11/29/00	11/26/02	Potential for osteosarcoma

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

/s/

Kati Johnson
6/10/04 07:15:33 AM
CSO

Weber, Jena M

From: Zawadzki, Joanna K
Sent: Monday, April 28, 2003 7:56 PM
To: Orloff, David G
Cc: Weber, Jena M; Zawadzki, Joanna K
Subject: NDA 21-071/S-004 (8/26/02)

David,

Attached is the review of this supplement for combination rosiglitazone and insulin use. As we discussed, it has not been placed in DFS. Please let me know if it should be placed in DFS.

Thank you.

Joanna

N27071S004-in srosi review.doc

Weber, Jena M

From: Sharon.W.Shapowal@sbphrd.com
Sent: Monday, March 03, 2003 11:37 AM
To: weberj@cder.fda.gov
Subject: The Pink Sheet

Jena: This is the article to which I was referring. GSK corporate communications did not distribute the approval letter or the new label. I do not know how the reporter obtained these items, but must have, given the quotations.

Thanks, Sharon

March 3, 2003 | Volume 65 | Number 009 | page 12

GSK Avandia/Insulin Use Based On 220-Patient Study Showing No Cardio Risk

GlaxoSmithKline's long-awaited approval of ***Avandia*** in combination with insulin is based on a 220-patient study showing no cardiovascular safety signal in type 2 diabetes patients.

The Feb. 27 approval comes two years after GSK received a new label warning about the use of Avandia with insulin. Clinical studies designed to support the indication showed an increased risk of heart failure in diabetes patients taking both products.

Revised Avandia (rosiglitazone) labeling retains the clinical observational data indicating an increased cardiovascular risk but adds information from a controlled study contradicting that finding.

"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 patients received insulin control), there was no difference in cardiovascular adverse events with Avandia in combination with insulin compared to insulin control," the revised warnings section of labeling says.

Avandia labeling continues with a cautionary statement about concomitant use with insulin and recommends a revised administration schedule for the combination.

"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," the clinical trials section says.

Avandia labeling also recommends 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." When used with insulin, Avandia doses greater than 4 mg daily are not indicated, labeling states.

In promoting the new indication, GSK will be challenged to reverse clinicians' current impressions about combination Avandia/insulin use.

GSK has been working to clarify Avandia's safety profile since FDA cited the company in July 2001 for its presentation of risk information in Avandia DTC ads and promotions during a medical conference (1"The Pink Sheet" Aug. 6, 2001, p. 3).

FDA said GSK downplayed heart failure warnings added to labeling in February 2001. A bolded warning, which was removed with the insulin approval, stated that "the use of Avandia in combination therapy with insulin is not indicated."

Avandia labeling retains the clinical trial data on which the bolded warning was based. In a 611-patient study, cardiac failure was reported in 10 Avandia/insulin patients, three of whom had no prior incidence of CHF or cardiac failure.

After receiving the Avandia/insulin warning in 2001, GSK lobbied FDA to require similar revisions to Lilly/Takeda's ***Actos*** (pioglitazone) labeling and establish a "level playing field."

Actos labeling was updated in January 2002 with a warning against concomitant use with insulin, in addition to clinical data showing a potential increased risk of heart failure ([2]"The Pink Sheet" Feb. 25, 2002, p. 12). Prior to the Avandia sNDA approval, Actos was the only thiazolidinedione indicated for use with insulin.

GlaxoSmithKline CEO J.P. Garnier boasted about the company's involvement in the Actos labeling change during a 2002 investor presentation. Referring to Actos' approved use with insulin, Garnier declared: "In practice, it's a very bad use of a TZD, any TZD."

GSK conducted four 26-week trials in 1,100 patients to support the insulin approval. Revised Avandia labeling cites results from two studies in which 206 patients received Avandia plus insulin and 203 received placebo plus insulin. The mean duration of disease in the patients was 12 to 13 years.

"Single or divided doses of Avandia 4 mg daily plus insulin significantly reduced FPG (mean reduction of 32 to 40 40 mg/dL) and HbA1c (mean reduction of .6% to .7%). Approximately 40% of all patients treated with Avandia reduced their insulin dose."

The indication has been "approvable" at FDA since February 2001; GSK submitted a response on Aug. 26, 2002. FDA approved the sNDA (21-071/S-004) within six months. Avandia is also indicated for combination use with metformin and a sulfonylurea.

Weber, Jena M

From: Weber, Jena M
Sent: Thursday, February 27, 2003 5:44 PM
To: CDER-DDR510
Subject: Pick-up information for action package to be copied.

Hi,

The following action package will be ready for copying **on Tues/March 4, 2003.**

NDA 21-071/S-004
Division of Metabolic and Endocrine Drug Products, HFD-510
PM is Jena Weber at x76422
1 volume

Thanks,
[redacted] ENA

Weber, Jena M

From: Weber, Jena M
Sent: Thursday, February 27, 2003 5:40 PM
To: CDER-APPROVALS
Cc: Orloff, David G; Zawadzki, Joanna K; Johnson, Kati
Subject: NDA 21-071/S-004

Reference supplement 004 for Avandia, NDA 21-071:

Supplement approved 2/27/03
NDA 21-071/S-004
Avandia (rosiglitazone maleate) Oral Tablets, 2 mg, 4 mg
GlaxoSmithKline
New indication for the use of Avandia in combination with insulin for the treatment of patients with Type 2 Diabetes Mellitus.
Rx only.
Oral hypoglycemic agent
Standard 6-month review clock (User Fee Goal Date = 2/27/03).

Thanks,
Jena

Weber, Jena M

From: Orloff, David G
Sent: Tuesday, February 25, 2003 3:10 PM
To: Weber, Jena M; Zawadzki, Joanna K
Subject: RE: follow-up note

Joanna,
I need you to advise on this, as I do not know what specific issues you feel need discussion. I also need a final review, today, before you leave.

DGO

-----Original Message-----
From: Weber, Jena M
Sent: Tuesday, February 25, 2003 2:24 PM
To: Orloff, David G; Zawadzki, Joanna K
Subject: FW: follow-up note

Ref. Avandia/S-004
FYI
Jena

[WEBERJ]

-----Original Message-----
From: Sharon.W.Shapowal@sbphrd.com [mailto:Sharon.W.Shapowal@sbphrd.com]
Sent: Tuesday, February 25, 2003 2:17 PM
To: weberj@cder.fda.gov
Subject: follow-up note

Jena: My management (Dr. Wheadon) has offered to make a team available for face-to-face labeling discussions, tomorrow in Rockville. He noted that something similar (exchange of diskettes?) was done in the case of the original approval.

Let me know if this is a possibility. Thanks, Sharon

Weber, Jena M

From: Orloff, David G
Sent: Friday, February 21, 2003 11:48 AM
To: Zawadzki, Joanna K
Cc: Weber, Jena M
Subject: Avandia-insulin supplement

Joanna,
We are down to the deadline, next week Thursday, and I have a meeting Tuesday and one to prepare for Friday. Please finalize your review, including labeling, and prepare a redline-strikeout version of the electronic label for discussion internally, all ASAP. There is no reason that we should be down to the wire on this. In all likelihood,

DGO

David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn 14B-45, HFD-510
5600 Fishers Lane
Rockville, MD 20857

Weber, Jena M

From: Zawadzki, Joanna K
Sent: Friday, February 07, 2003 10:34 AM
To: Orloff, David G
Cc: Weber, Jena M; Zawadzki, Joanna K
Subject: review

David,

Attached is my review. I am still writing the risk benefit section and have not yet included labeling comments.

N27071S004-in
osi 203 respon

Joanna

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 09-Feb-2001 10:08am EST
From: David Orloff
ORLOFFD
Dept: HFD-510 PKLN 14B45
Tel No: 301-827-6430 FAX 301-443-9282

TO: 65 addressees

CC: John Jenkins (JENKINSJ)

Subject: Congratulations Avandia team!

To the Division:
Yesterday we issued simultaneous actions on two pending supplement for Avandia (rosiglitazone maleate), and I want to congratulate and thank the contributing team for all their efforts. The label for Avandia has been considerably strengthened through a process of careful data review and successful negotiation, the way it is supposed to work.

These are the team members. I hope that I have not left anyone out. If so, please forgive me.

MO: Malozowski, Lubas, Misbin, Zawadzki
STT: Mele, Sahlroot
CHM: Ysern, Moore
BPH: SJohnson, Ahn
PM: Weber, Galliers, KJohnson

To summarize:
S-004 was an efficacy supplement proposing a new indication for the combined use of Avandia and insulin in Type 2 diabetes based on the data from two 26-week RCTs. S-006 was a labeling supplement to add safety information arising out of post-marketing reports related to liver, and heart/volume overload.

Of note, [redacted] Bill Lubas' probing review of the safety data from the two trials led to a similar recommendation. In these trials of older diabetics with longstanding disease, addition of Avandia 4 or 8 mg daily to a stable insulin regimen was associated with modest improvement overall in glycemic control as measured by HbA1c but at the cost of a 3-fold increase in the incidence of cardiovascular adverse events, including congestive heart failure, shortness of breath, edema, and fatal and non-fatal cardiac ischemic events relative to insulin alone. Notably, these events occurred in patients with and without prior history of heart disease and thus the data do not suggest that we can, as yet, predict those at risk. As such, we took an approvable action, pending

the sponsor's addressing in further studies the mechanism(s) by which the drug contributes to these adverse events, prospective identification of those at risk, strategies for prevention, and algorithms for treatment.

Nevertheless, in not approving the proposed use of Avandia with insulin based on safety concerns, we and the sponsor agreed that addditional information should be added to labeling to warn of the potential hazards of the combination, and, as such, the Warnings and Precautions section have been significantly bolstered with regard to cardiovascular risks associated with Avandia use. This labeling was approved as part of supplement 006.

Finally, we have also amended the labeling regarding hepatic effects based on post-marketing reports of serious liver disease. Although it still appears that Avandia (as well as Actos) use carries little in the way of hepatic risk, nevertheless, there have been reports and this is now disclosed in labeling. Similar labeling is under negotiation for Actos.

And so again I want to offer my thanks to the team for a job well done. Special recognition goes to Bill Lubas for taking on the insulin combination supplement late last year, for doggedly studying the safety data, and for an excellent review, and to Joanna Zawadzki for her work on S-006 and for her collaboration with Bill in putting us on track to the major, important labeling changes that will be effected shortly.

DGO