CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-071/001

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Food and Drug Administration

Memorandum

Date: 3/19/00 /S/

From: Saul Malozowski
Medical Team Leader

Subject: Avandia, rosiglitazone (NDA 21071-S001). Team leader recommendations: Avandia in combination with sulfonilureas.

To: John Jenkins
Acting Division Director, DMEDP

This is to support the medical officer recommendation for approval of this product-labeling modification to allow Avandia's use in combination with sulfonilureas.

The supportive studies indicate that this product can be used effectively and safely in combination with sulfonilureas. No additional safety issues emerged during these studies.

The sponsor request should be granted following the MO recommendations for labeling changes.

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NDA 21-071s

Rosiglitazone (Avandia) in Combination with Sulfonylureas

Submitted by Smithkline Beecham June 3, 1999

Robert I Misbin MD
March 14, 2000
Revised March 27, 2000

Introduction:

Rosiglitazone (RSG, Avandia) was approved in May 1999 for the treatment of type 2 diabetes mellitus, both as monotherapy and in combination with metformin. In June 1999 SKB resubmitted efficacy data from three trials of RSG plus sulfonylureas. Safety data from these trials were in the original application and have been reviewed previously. I note the July 14, 1999 fax from SKB indicating that all pivotal data were submitted prior to the February 2, 1999 final rule date for financial disclosure. In this document, I review the efficacy data from the three trials and safety update submitted February 25, 2000. The current status of the hepatotoxicity issue is also discussed.

Study 079 – RSG in patients on maximal dose glyburide

This was a 26-week randomized, double-dummy, three arm trial of Glyburide (Gly) monotherapy vs RSG monotherapy vs combination therapy of Glyburide+RSG in patients whose hyperglycemia was inadequately controlled on 20 mg/day of Gly. The study population were patients with type 2 diabetes with FPG between 140 and 300 mg/dl after having been on maximal dose Gly (20 mg/day non-micronized or 12 mg per day micronized), for at least 30 days. Patients could either have been on Gly monotherapy or combination therapy with an antidiabetic drug other than a thiazolidinedione. The 26-week treatment period was preceded by a 4-week run-in during which time patients were treated with 10 mg Gly bid. Other antidiabetic drugs were stopped during the run-in period and were not permitted during the study. Patients were randomized to one of three treatment groups: Glyburide 10 mg bid + RSG placebo, RSG 2 mg bid + Gly placebo, or RSG 2 mg bid + Gly 10 mg bid. Patients with two consecutive FPG > 350 mg/dl were withdrawn for lack of efficacy.

In addition to the ITT analysis, an efficacy evaluable (EE) population was also analyzed. These were patients who did not have a major protocol violation such as taking a prohibited antidiabetic drug. The ITT population was about 99 patients in each group and the EE population was about 80 in each group. 58/104 patients withdrew from the RSG monotherapy arm compared to 45/106 in the Gly monotherapy arm, and 21/99 in the combination arm. Withdrawal due to lack of efficacy occurred in 20% of patients on RSG monotherapy compared to 9% on Gly monotherapy and 7% on combination therapy. Withdrawal due to lack of efficacy tended to occur earlier with RSG monotherapy than with Gly monotherapy.

The mean patient age was about 58 years. There were about 66% male, 72% with BMI of 27 or above. Approximately 70% were white. Approximately 60% had previously been on Gly monotherapy and 40% had been on combination therapy. The most common concomitant antidiabetic medication was metformin, which had been taken by 31-37 % of patients in each arm. Mean HbA1c at baseline was about 9.2% and FPG 222 mg/dl. Median duration of diabetes was 7 years in all groups. Compliance with study medications was about the same in all three groups. The protocol violation of taking

metformin during the blinded trial occurred in 13% of RSG monotherapy patients, 8% of Gly monotherapy and 5% of RSG+ Gly.

Change in HbA1c for the ITT population is shown in the table (5.2 table 16). The mean HbA1c at baseline was about 9.2%. This rose 0.9 and 1.9 % units in the Gly and RSG monotherapy arms respectively but fell 0.5 % units in the Gly+ RSG combination arm. The changes from baseline were also statistically significant. The superiority of Gly+ RSG to either drug alone was highly significant ($p<0.0001$)

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Study 079 – Section 5.2 Table 16; Section 5.3.2 Figure 6 and Section 5.4 Figure 8.

Table 16 Change in HbA1c at Week 26 Compared to Baseline and Monotherapy Groups

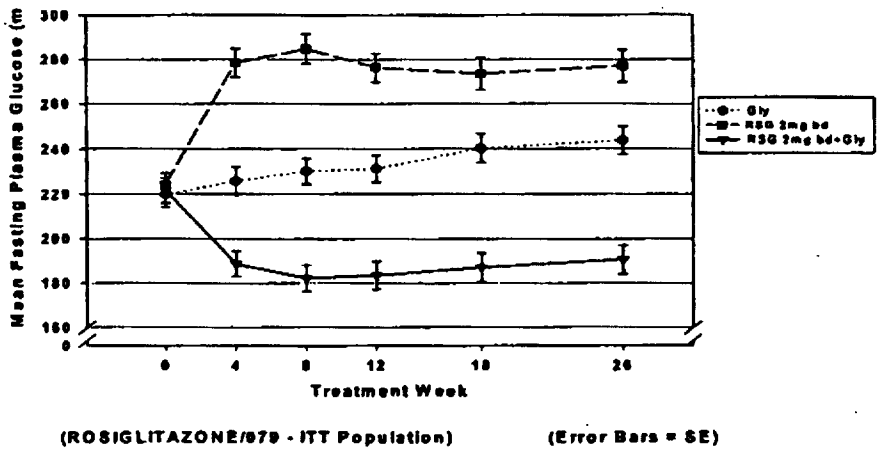
(Intent-to-Treat Population)

	Treatment Group		
HbA1c (%) Reference range: <6.5	Gly	RSG 2mg bd	RSG 2mg bd + Gly
N	99	99	98
Baseline (mean ± SD)	9.3 ± 1.43	9.1 ± 1.14	9.2 ± 1.34
Median	9.2	9.0	9.1
Week 26 (mean ± SD)	10.1 ± 1.76	11.0 ± 1.95	8.7 ± 1.60
Median	10.1	11.2	8.5
Change from Baseline (mean ± SD)	0.9 ± 1.17	1.9 ± 1.71	-0.5 ± 1.14
95% CI	(0.6, 1.1)	(1.5, 2.2)	(-0.7, -0.3)
p-value *	<0.0001	<0.0001	<0.0001
Comparison with RSG 2mg bd + Gly (adjusted mean)	-1.4	-2.4	—
95% CI **	(-1.7, -1.1)	(-2.8, -2.0)	—
Significance Level **	0.0500	0.0500	
p-value †	<0.0001	<0.0001	—

N = Those patients who had both a baseline and a week 26 value (using LOCF).
* From paired t-test.
** From Hochberg's procedure using standard error from ESTIMATE statements within GLM model
† From comparisons of LS means within GLM model
SAS output is presented in Section 14, Tables 14.8.1A and 14.8.2A
Data Source: Section 14, Tables 14.3A and 14.4A; Appendix C, Listings C.L1 and C.L2, and Appendix F, Listing F.L1

Analysis of secondary efficacy parameters confirmed the change in HbA1c. A time course of the change in FPG is shown in the figure below. FPG rose rapidly in patients transferred to RSG monotherapy but fell in patients on combination RSG + Gly.

Figure 6 Mean Fasting Plasma Glucose (FPG) over Time

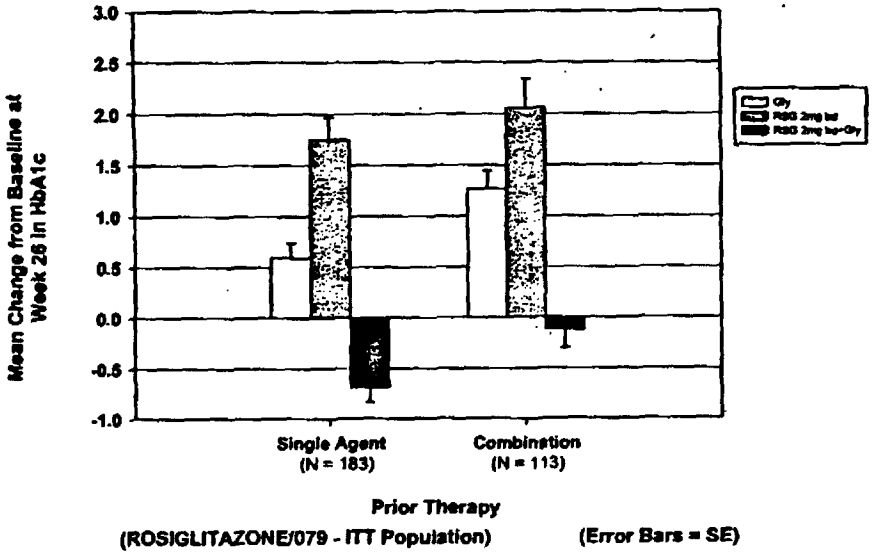


Data Source: Section 14, Table 14.2A

Plasma insulin levels changed little in the patients on Gly or Gly+ RSG but fell significantly in patients on RSG monotherapy. All cholesterol values rose from baseline in all groups. The greatest rise was seen with RSG monotherapy and the least rise with Gly monotherapy. LDL cholesterol rose 22, 13 and 0.3 mg/dl in RSG, RSG+Gly and Gly respectively from the mean baseline of about 125 mg/dl. The rise from baseline was not significant for Gly monotherapy but was significant for both RSG groups. LDL/HDL and total chol/HDL rose significantly in patients on RSG monotherapy, but not in patients on Gly monotherapy. There was an increase from baseline with RSG+Gly for chol/HDL. Mean VLDL and triglycerides rose in all groups but the rise was greatest in patients on RSG monotherapy. Mean body weight rose 3.8 kg ($p<0.0001$) from baseline in patients on combination Gly+ RSG and fell 1.53 kg ($p=0.002$) in patients on RSG monotherapy. Weight was little changed in patients on GLY monotherapy.

Interpretation of the efficacy data is complicated by the fact that 40% of patients had been taking antidiabetic agents (mostly metformin) other than just glyburide before entering the study. Continuation of glyburide alone represented a step down in the intensity of treatment in these patients. The exacerbation of hyperglycemia observed in this subset is not at all surprising (see figure).

Figure 8 Change from Baseline at Week 26 in Mean HbA1c by Prior Therapy



Data Source: Section 14, Table 14.5.6A

For patients previously on glyburide alone, continuation of glyburide resulting in a rise in HbAc of about 0.6% units. Addition of RSG resulted in a fall of about 0.7% units from baseline for a net treatment effect of about – 1.3 % units attributable to RSG. The treatment effect for RSG was also about –1.3% units in patients previously on combination therapy, but in this case the bulk of the effect was made up of the rise in HbA1c in patients switched from the glyburide combination to glyburide alone. Patients switched from glyburide combination (mostly metformin) to glyburide + RSG showed little mean change in HbA1c (about –0.1 % units). It would have been of interest to examine the changes in body weight and serum lipids based on previous therapy (combination vs glyburide alone). With respect to the primary measure of efficacy, HbA1c, it is clear that the combination of RSG+ Gly is better than either monotherapy alone. Also, glyburide monotherapy (20 mg/d) is more efficacious than RSG alone (2-mg bid). RSG added to glyburide was effective in both men and women, but it appeared to be somewhat more effective in women.

Safety:

There were two cardiac deaths, one on RSG monotherapy and one on Gly monotherapy. 1.9% of patients on RSG monotherapy and 7.1% of patients on combination reported edema. Hypoglycemia requiring the assistance of a third party was reported one patient each on Gly alone and Gly+ RSG. Hypoglycemia was reported by 6/106 (5.7%) of patients on Gly and 8/99(8.1%) of patients on RSG+ Gly. No hypoglycemia was reported by patients on RSG monotherapy. Lipid related AE's (hyperlipidemia) was

reported in 1.9% of patients on Gly, 12.5% on RSG and 17.2% on RSG+ Gly. A clinically insignificant reduction in hemoglobin of 0.3 g/dl (p=0.005) was reported for RSG+ Gly vs Gly alone.

- Summary:

RSG is effective when used in combination with a maximal dose of glyburide.

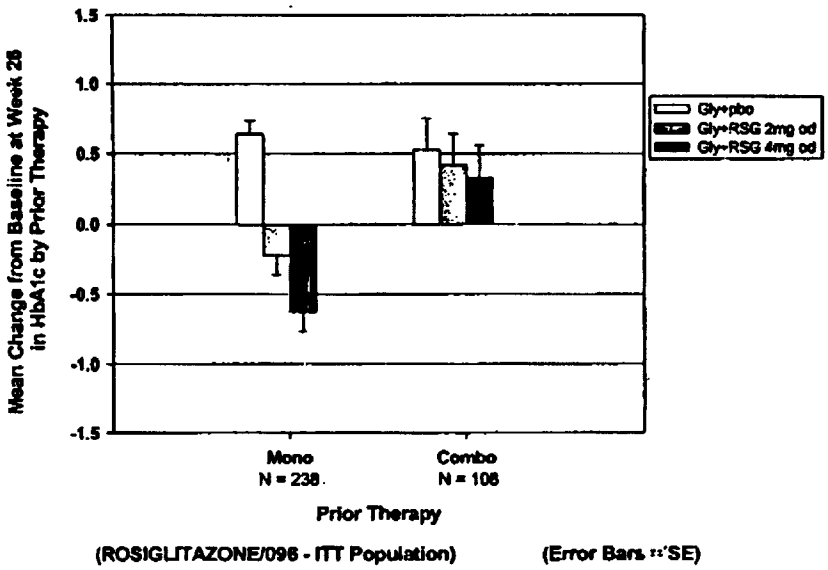
Study 096

This was a 26 week placebo-controlled study of RSG in patients with type 2 diabetes inadequately controlled on at least half maximal dose (10 mg/d) of glyburide. Patients continued to receive their previous dose of glyburide and were randomized to placebo vs RSG 2 mg od or RSG 4 mg od. The NDA also did not provide information about the actual dose of glyburide. But this was faxed to E&M on 2/24/00. At my request, the data were expressed as percent maximal approved dose, to normalize for the fact that the maximal approved dose of standard glyburide is 20mg and the maximal approved dose of micronized glyburide is 12 mg. The median and minimum doses were 75% and 50% in all three groups. The mean ranged from 75.6-78.3%. Thus, most patients were taking about 15 mg of glyburide or 9 mg of micronized glyburide, 75% of the maximal dose for both preparations.

Placebo controlled treatment lasted for 26 weeks and was preceded by a four week placebo run-in. Inclusion criteria were type 2 diabetes, 40-80 years of age, fasting C peptide > 0.8 ng/ml . FPG between 140-300 mg/dl at visits 2 and 3 of the four week run-in while taking 10 mg or more of glyburide (or 6 mg or more of micronized glyburide) for at least 14 days. The use of other antidiabetic agents was prohibited during the run-in and during the study. Withdrawal criteria for lack of efficacy included FPG > 350 mg/dl on two consecutive clinic visits. 9/115 placebo patients (7.8%) were withdrawn because of lack of efficacy compared to 5/116 (4.3%) and 3/116 (2.6%) patients on 2 and 4 mg RSG respectively. The ITT groups had 115-116 patients each and were well matched for demographic factors. The mean age was 60 years, 78% male, 88% with BMI at least 27, 90% white. Approximately 30 % had been other antidiabebetic medications before study in addition to glyburide. Mean baseline HbA1c was about 9.1%, mean FPG was about 215 mg/dl. 9 patients were excluded from the ITT population in the placebo group because of major protocol violations compared to 3 patients each in the RSG groups.

HbA1c rose 0.55 in patients on placebo and fell 0.30 in patients on RSG 4 mg. There was no change in patients on RSG 2 mg. The placebo subtracted treatment effect at endpoint was –0.60 and –0.80 for RSG 2 and 4 mg respectively and was significant in both groups (p=0.0001). It is important to note that RSG was primarily effective in patients who had previously been on glyburide monotherapy. It was not effective in patients previously on glyburide combination (see figure below)

Figure 10 Change from Baseline at Week 26 for HbA1c by Prior Therapy (ITT Population)



Data Source: Section 14, Table 14.5.6A

Mean FPG rose 23 mg/dl in placebo patients and fell 11 and 25 mg/dl in the RSG 2mg and 4mg groups respectively. The placebo-subtracted treatment effect was 29 and 47 mg/dl for RSG 2 and 4 mg respectively. Time courses for the ITT and EE populations are shown below in figures 6 and 7.

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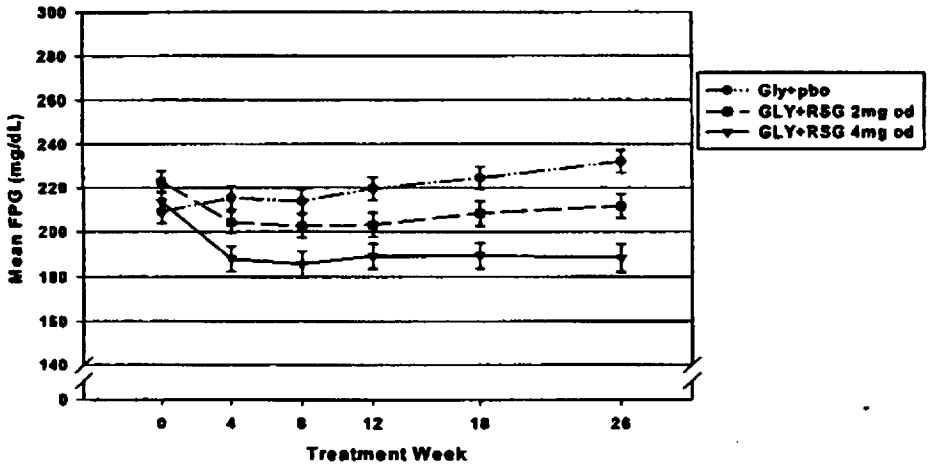
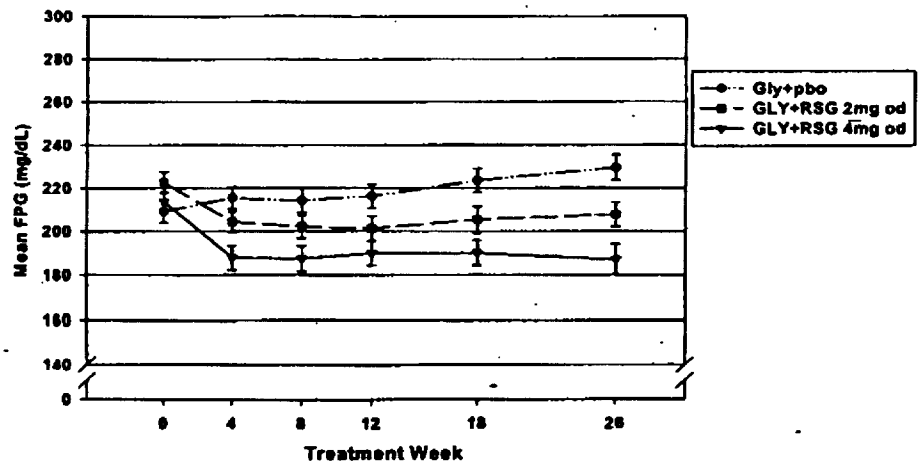
Figure 6 Mean FPG Over Time (ITT Population)



(ROSIGLITAZONE/096 - ITT Population) (Error Bars = SE)

Data Source: Section 14, Table 14.2A

Figure 7 Mean FPG Over Time (EE Population)



(ROSIGLITAZONE/096 - EE Population) (Error Bars = SE)

Data Source: Section 14, Table 14.2B

There were no consistent changes in insulin or C peptide levels. Total cholesterol rose in all groups. Placebo subtracted increases were 15 and 22 mg/dl for RSG 2 and 4 mg respectively which were both statistically significant. Mean LDL chol was about 122 mg/dl at baseline. It rose significantly on RSG 2-mg (12 mg/dl) and 4 mg (18 mg/dl)

groups but there was a small rise of 3 mg/dl (NS) on placebo. The placebo-subtracted rise in LDL chol was 9.1 (p=0.015) and 14.8mg /dl (p=0.0001) for RSG 2 and 4 mg. LDL/HDL was unchanged with placebo but rose in both RSG groups. At 4 mg the baseline value was 2.796 and rose by 0.324 at endpoint (p=0.0004). The difference from placebo was 0.295 (p=0.0042). VLDL rose significantly in all three groups but the rise was significantly greater on RSG. Change in triglyceride was variable. The only group with a significant rise from baseline (214 to 262) was RSG 2 mg. However this was not significantly different from placebo. There was significant weight gain from baseline, 1.88 and 2.64 kg for RSG 2 and 4-mg groups and small gain of 0.22kg (NS) on placebo. The placebo-subtracted weight gain was 1.66 kg (p= 0.012) at 2 mg and 2.42 kg (p=0.0002) at 4 mg. Subgroup analysis showed that RSG appeared more effective in female patients, in patients 65 years old and older and patients whose BMI was 27 or over.

The protocol design had two major defects that make the results difficult to interpret. Approximately one third of patients had been on combination therapy before the placebo run-in. Four weeks is barely enough time for equilibration of changes in FPG and not enough time for equilibration in changes in HbA1c. We do not know if the types of antidiabetic medications other than glyburide were equally distributed among the three arms. Also, patients were required to be taking half-maximal glyburide for at least 14 days, which is a clearly inadequate amount of time to establish a baseline with respect to HbA1c.

It may be worthy of note that there was a mean decrease in HbA1c of 0.15, 0.10 and 0.17 during the 4 week placebo run-in for groups later randomized to placebo, RSG 2mg and 4 mg respectively, although there was a rise in placebo patients during the 26-week blinded period. During the placebo run- in period, FPG decreased 7.3 mg/dl in placebo group but rose 10.3 and 6.9 mg/dl in the RSG 2 and 4 mg groups. As already noted, this instability of baseline measurements can probably be attributed recent increases in glyburide dose before screening and to withdrawal of non-sulfonylureas during the placebo run-in.

Safety:

There were no deaths in this study. Hypoglycemia was reported by 2 /115 (1.7%) of patients on placebo, 7/116 (6%) of patients on RSG 2 mg and 3/115 (2.6%) of patients on RSG 4 mg. The few patients who developed elevated ALT levels, edema or anemia have been covered in the review of the original NDA. Mean QTc interval fell slightly in patients on placebo and rose slightly in patients on RSG but the difference was not statistically significant. As shown in the table, there was no difference between RSG and placebo for on-therapy ECG values of potential clinical concern.

	Gly + placebo	Gly + 2 mg RSG	Gly + 4 mg RSG
QTc>500 msec	3 (2.6%)	2 (1.7%)	4 (3.4%)
Increase > 30% with Baseline QTc < 440	1(0.9%)	0	0
Increase > 15% with baseline QTc>440	1 (0.9%)	0	0
New LVH	0	2 (1.8%)	1(0.9%)

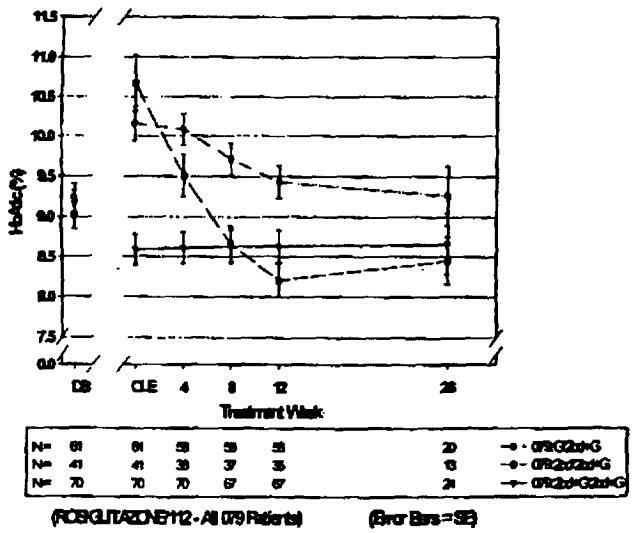
Summary:

One can conclude that RSG is effective when added to glyburide monotherapy. But it does not appear to differ from placebo when patients on glyburide used in combination with other oral agents are discontinued from those other oral agents. As was seen in the trials in the original NDA, RSG causes weight gains and adversely affects lipid levels.

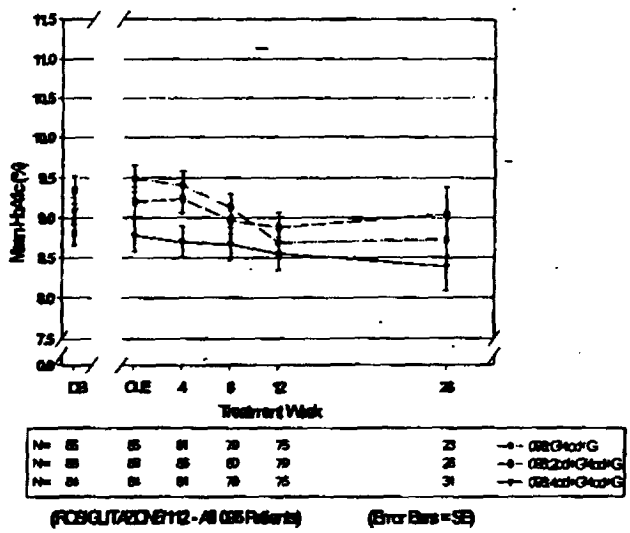
Extension studies for 096 and 079

Patients who satisfactorily completed the blinded portions of studies 079 or 096 were eligible to enter an open-label extension study. For 079 all patients were treated with 10 mg of glyburide plus RSG 2 mg bid. For 096 patients were treated with their usual dose of glyburide plus RSG 4 mg od. Criteria for lack of efficacy were FPG.>350 mg/dl on two occasions. A time course of the change in HbA1c is shown below

Figure 2 Mean HbA1c Over Time



Break between DB and OLE = 26 weeks
Data Source: Section 14, Tables 14.2Aa and 14.2Ba; Section 17, Figure 3.1a



Break between DB and OLE = 26 weeks
Data Source: Section 14, Tables 14.2Ab and 14.2Bb; Section 17, Figure 3.1b.

HbA1c levels changed little in patients who received the same treatment during the extension as during the blinded portion of the trial. At six months, the change was +0.06 in trial 079 and +0.12 in trial 096. For patients who received intensification of therapy during the extension study, there was generally additional reduction in HbA1c. In 079, patients who had been on RSG 2-mg bid showed a reduction of 2.38 at six months when glyburide was added in the extension. Addition of RSG 2-mg bid to glyburide background resulted in reduction of 0.69%. In 096 going form RSG 2 mg od to 4 mg resulted in mean reduction of 0.1% compared to a mean rise of 0.12% in patients previously on 4 mg od and continued on 4mg od. Another may to evaluate long-term efficacy is to examine the rate of withdrawal due to lack of efficacy. In 079, 3/70(4%) of patients who were continued on Gly+ RSG 2 mg bid dropped out due to lack of efficacy. In 096, 7/84(8%) of patients continued on Gly + 4 mg RSG od dropped out due to lack of efficacy. In both trials, dropouts during the extension were even less frequent in patients who were given intensification of treatment during the extension.

Summary:

The efficacy of RSG when added to glyburide appears to be maintained for one year.

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Study 015

European study of RSG plus concurrent sulfonylureas therapy

This double-blind placebo controlled study was carried out in 60 centers in Europe. Inclusion criteria were patients with type 2 diabetes 30-80 years old who had been on a stable dose of glyburide, glipizide, or gliclazide for at least 2 months before screening. Patients were required to have HbA1c > 7.5% and FPG< 15 mM(270 mg/dl) with fasting C peptide > 0.8 ng/dl. Following a 2-4 week placebo run-in, patients were randomized to one of three arms, RSG 1 mg bid, RSG 2 mg bid or matching placebo. Patients were instructed to continue their previous dose of SFU. Other antidiabetic medications were not allowed.

Among the ITT population, 57% was < 65 years old, 58% were male, 42% had BMI < 27 and 97% were white. 42% were taking glyburide (median dose 15 mg) 48% on gliclazide (median 160 mg) and 9.4% were taking Glipizide (median dose 15 mg). One patient had had been taking an additional oral agent, metformin. Approximately 5% of patients decreased the dose of SFU during the study, but these were randomly distributed among the three treatment arms. 36 % of patients on placebo withdrew compared to 28% and 24% of patients on RSG 1 and 2 mg bid respectively.

Mean HbA1c at baseline was 9.2% in all groups. It rose 0.2 in placebo patients and fell 0.5 and 0.9 in patients on RSG 1 and 2 mg bid respectively. The placebo subtracted mean treatment effect at 26-week endpoint was 0.6% units and 1.0% units for 1 and 2 mg respectively. Both were significant with $p<0.0001$. Mean FPG rose 6 mg/dl on placebo and fell 24 and 45 mg/dl on RSG 1 and 2 mg bid. The placebo subtracted treatment effect was a reduction of 24 mg/dl at 1 mg bid and 44 mg/dl at 2 mg bid (both $p<0.0001$). The reduction in FPG reached a plateau at 8 weeks at 2 mg bid and at 12 weeks at 1 mg bid. These changes in HbA1c and FPG occurred in patients on any of the three sulfonylureas background treatments.

There were small reductions in serum insulin levels in the RSG groups but these were not statistically significant. C peptide fell from 0.9 to 0.8 nM in all three groups. The reduction from baseline was statistically significant at $p<0.0001$ but the differences between groups were not. There were small but statistically significant increases in total cholesterol and HDL chol from baseline in both RSG groups. In the RSG 2 mg bid group, LDL rose from 140 to147 mg/dl ($p=0.0006$). The difference from placebo was 7.3 mg/dl ($p=0.003$). Triglyceride levels rose significantly from baseline in both RSG groups, but the difference from placebo of +32 mg/dl ($p=0.002$) was only signficant in the 1 mg bid group. However, the rise in VLDL from baseline and the difference from placebo was significant in both groups. The rise at 1 mg bid was 4 mg/dl ($p<.001$) at 1 mg bid was 2 mg/dl ($p=0.02$). There was no change for placebo. LDL/HDL was unchanged.

Hypoglycemia was reported by 2% of patients on placebo compared to 3.4% and 5.3% of patients on 1 and 2 mg bid of RSG. None were reported with blood glucose documented to be less than 50 mg/dl. Hypercholesterolemia was reported in 1% of patients on placebo and 1.5% and 4.7% of patients on RSG. Mean weight gain was 0.07 kg in patients on placebo compared to 0.8 kg and 1.77 kg in patients on RSG 1 mg and 2 mg bid. Both the changes from baseline and the difference from placebo were highly significant.

There were four deaths. One placebo patient died of a subarachnoid hemorrhage and three RSG patients died of acute MI's. Mean hemoglobin was unchanged at 14.5 g/dL in patients on placebo but fell 0.40($p<0.001$) and 0.66 g/dL ($p<0.001$) in patients on RSG 1 mg and 2 mg bid.

PK data are as follows:

RSG plasma concentration, ng/mL

Predose	Week 4	Week 12	Week 26
1mg	11	12	12
2mg	24	21	25
Postdose			
1mg	66	66	62
2mg	126	132	127

Summary:

RSG is effective as add-on therapy in patients on sulfonylureas. The adverse events profile, primarily weight gain, is similar to what has been found in other studies. Blood levels of RSG remain constant over time and are proportional to the dose.

Safety:

A safety update was submitted February 28, 2000. Total exposure to RSG either as monotherapy or in combination with oral antidiabetic agents was 4696 patients with 2549 exposed for 12 months or greater and 997 expose for 24 months or longer. No new safety issues were identified.

Liver toxicity:

The safety update identified the following patients who could be classified as having drug associated hepatitis during open-label extension trials:

009.610.00936 – 50 year old male patients treated with SFU plus RSG 1 mg bid during the controlled portion of the trial and 2 mg bid during the extension. A brief rise in ALT to about 100 was observed at month six. ALT rise again to "1 at month 15 and was 211 U/L at month 18 at which time RSG was withdrawn. AST was 228 . The investigator attributed the enzyme elevations to alcohol consumption.

112.008.71427 - 50 year old male patient on RSG 2 mg bid plus SFU experienced transient ALT of 312 at month 15 AST was 222 . He was continued on RSG and repeat ALT at month 18 was normal . ALT was normal at month 21.

114.024.14234 – 77 year old male on RSG 4 mg bid plus insulin. Two consecutive ALT elevations 218 and 282 noted after about 12 and 13 months of treatment. RSG was withdrawn.

Marketing of Avandia began in the USA in June 1999 and approximately 400,000 patients have been given prescriptions through Dec 31, 1999. Through March 1, 2000 FDA has received two reports of death due to liver failure and no reports of transplants. One patient who died had a previous history of liver failure (with elevated ammonia levels) several years earlier due to alcoholic hepatitis. The pattern of enzyme abnormalities during both episodes (very high AST out of proportion to the elevation in ALT) was much more consistent with alcoholic hepatitis than with glitazones hepatitis. The second case was a 46 year old women from [redacted] who died of hepatic failure with a picture of cholestatic jaundice (direct bilirubin 10.3 mg/dl indirect bilirubin 1.1 mg/dl). Her ALT was 1185 and AST 1939. The patients had a history of "abnormally high" liver enzymes in 1990. In 1993, her ALT and AST were normal but her alkaline phosphatase and gamma GT were both elevated.

I published a review of irreversible hepatic failure associated with troglitazone (Annals Internal Medicine February 16, 1999) that included cases reported to FDA through June 5, 1998. There were 21 deaths due to liver failure and 3 transplants for a total of 24 cases of irreversible liver failure. There were 14 other additional deaths that I did not believe should be attributed to troglitazone hepatotoxicity because of the presence of other causes of liver failure (metastatic cancer, severe heart failure or preexisting liver disease) or inadequate documentation. Applying the same criteria to the two fatal Avandia cases described above, I would probably have attributed both cases to preexisting liver disease.

In trying to understand the significance of these cases, it is important to bear in mind that liver abnormalities occur in diabetic patients who are not taking glitazones. Jick et al published results from a study of 44,406 type 2 diabetic patients in the UK and identified 605(1.5%) in which a liver disorder was identified within 90 days of receiving a first prescription for an oral antidiabetic medication between 1989-1996 (Diabetes Care 22, 2067, 2999).. One patient was a debilitated 86 year old women who developed jaundice shortly after receiving metformin and glyburide, and died of "liver failure" one month later. Given the patient's advanced age and debilitation, I would probably have attribute her death to multiple organ failure and not to drug-associated hepatitis. A second patient presented with "ascites" and subsequently died with a diagnosis of "non-specific hepatitis". A third patient presented with jaundice which led to a liver transplant. From these last two cases, I believe a reasonable estimate for the risk of developing unexplained and irreversible liver failure within 90 days of receiving a first prescription for an oral antidiabetic agent is 2/44,406 or about 4 per 100,000. Approximately 400,000 patients have received Avandia through December 31, 1999. Based on my estimate from the Jick paper, one would expect about 16 cases of irreversible liver failure even in the absence of Avandia. Assuming that only 10% of the cases are reported, 1-2 patients with irreversible liver failure would be reported as due to Avandia, even if Avandia had no liver toxicity whatever (10% x 16 cases/400,000).

Anemia:

A small fall in hemoglobin and hemoglobin has been observed with all thiazolidine-diones and has been attributed to dilution from expansion of the intravascular space. As shown in the table below, there appears to be a small but progressive fall in hemoglobin during long-term treatment with RSG, either as monotherapy or in combination with other oral agents. The fact that hemoglobin continues to fall with prolonged treatment seems inconsistent with the idea that it may be related to expansion of the intrascular space.

Change in Hemoglobin (g/dl) During Prolonged Treatment

Days on RSG	# of patients	monoRx	+ metformin	+SFU
31-60	3821	-0.6	-0.7	-0.4
91-196	3667	-1.0	-1.0	-0.7
379-560	2180	-1.2	-1.2	-0.8
>560	1419	-1.3	-1.3	-1.0

Congestive Heart Failure:

Edema has been consistently reported as an adverse event in trials of RSG and other thiazolidinediones. Increased reporting of congestive heart failure in RSG trials of insulin-treated patients but not patients treated with oral agents was the subject of a previous review and label change (reprinted below in its original form).

NDA 21071 – Avandia – Smithkline Beecham
Labeling Revision for congestive heart failure
Submitted to IND —— August 20, 1999

This submission contains preliminary data from a phase 3 placebo-controlled trial of rosiglitazone in type 2 diabetic patients on insulin. The submission was prompted by the observation of increased reporting of congestive heart failure in patients treated with rosiglitazone. Reporting of CHF during the 26 week double blind period was 1% for insulin (n=203), 1.9% for insulin + 4 mg RSG (n=206) and 3.0% for insulin + 8 mg RSG (n=202). CHF was described as a serious adverse event for 4 patients (1.0%) on RSG + insulin and 1 patients (0.5%) on insulin monotherapy. All patients who entered the open label extension received 8 mg RSG plus insulin. 3.6% of these patients reported CHF. To correct for exposure, the data expressed per 100 patient years was 7.4 cases/100 pt years for insulin + RSG, and 2.2 for insulin monotherapy. (See table).

	Double blind controlled trials, %	*Rate/100 pt years (95% conf)*
Placebo	*0.2*	*0.6 (0.01-3.30)*
Metformin	*0.0*	*0.0 (n/a-3.76)*
Sulfonylurea	*0.4*	*0.6 (0.11-1.62)*
Insulin	*1.0*	*2.2 (0.27-7.94)*
RSG	*0.2*	*0.7 (0.4-1.09)*
RSG +metformin	*0.3*	*0.7 (0.2-2.2)*
RSG + sulfonylurea	*0.7*	*0.6 (0.2-1.5)*
RSG + insulin	*2.5*	*7.4 (4.79-11.12)*

It should be noted that CHF on RSG monotherapy was the same as for other oral agents and placebo.
It should also be noted that among patients on insulin monotherapy was greater than for RSG or any other monotherapy. This probably reflects the fact that insulin is generally reserved for patients who do not respond or who no longer respond to other forms of therapy. Patients with type 2 diabetes who receive insulin can be expected to have more advanced disease so it is not surprising that reporting of CHF would be greater in this group than in other patients. Although not reflected in the table above, RSG and the other drugs of this class are associated with fluid retention and edema. Although overlap of the confidence intervals does not completely exclude a chance association, I think the more likely explanation is that RSG can unmask CHF in susceptible patients and that

insulin-requiring patients are more susceptible than others are. That the finding was dose-dependent supports this explanation.

RSG was effective in lowering HbA1c levels. Baseline values were about 9%. At week 26, the reduction was 0.7 and 1.3% for 4 and 8 mg RSG respectively. Patients who developed CHF were on average about 8 years older than patients who did not develop CHF and had a mean duration of diabetes, which was about five years longer. However, there did not appear to be any imbalance with respect to these factors between patients who received RSG plus insulin and those who received insulin plus placebo. The majority of patients who developed CHF had a risk factor such as prior history of CHF, previous myocardial infarction or LVH. 200/408 (49%) RSG patients were said to have a risk factor compared to 72/203 (35%) placebo patients. Although this small baseline imbalance may not completely explain increase in CHF in RSG patients, it is important to point out that proportion of patients at risk of CHF was high and that CHF developed in only a few.

[ ]

" Since thiazolidinediones can cause fluid retention, which can exacerbate congestive heart failure, patients at risk for congestive heart failure (particularly those on insulin) should be monitored for signs and symptoms of heart failure."

Robert I Misbin MD
IND ——NDA 21071
October 21, 1999

There have also been several post-marketing reports of congestive failure in patients treated with RSG. This is presently under investigation by OPDRA. The CHF warning in the current label is probably adequate provided that the label is updated to reflect the postmarking reports of CHF.

Labeling Issues to be communicated to SKB

PD: change "[redacted]" to "additive".

Indications: The language for metformin and SFU are similar. It would be preferable to combine the indications as follows:

[redacted]

Dosage and Administration: [redacted]. A sentence should be added to warn physicians to lower the dose of SFU in case of hypoglycemia. This appears in the Actos label and should be in the Avandia label as well.

Liver toxicity and congestive heart failure: the text should be updated to reflect post-marketing reports.

Summary:

The results of the three studies in this application support the efficacy of RSG when used in combination with sulfonylureas. The magnitude of the effect varies in the three studies because of differences in study design. Studies 079 and 096 had serious flaws in design. Discontinuation of other antidiabetic therapy during the run-in led to instability in the baseline measures of hyperglycemia. The minimal duration of treatment with sulfonylurea prior to randomization was also inadequate. But when results of the three trials are taken together, there is little doubt that RSG is effective in treating hyperglycemia when used in combination with sulfonylureas. These trials disclose no new information about adverse events. The weight gain and lipid changes are similar to what was observed in the monotherapy trials. Anemia and edema continue to be problems. Congestive heart failure may also develop in certain patients.

Recommendation:

Pending appropriate changes in the label, Avandia should be approved to be used in combination with sulfonylureas.

/S/

Robert I Misbin MD
HFD 510
March 14, 2000,
revised March 27, 2000

/S/

3/24/00

APPEARS THIS WAY
ON ORIGINAL

NDA 21-071/S-001
Avandia (rosiglitazone maleate) Tablets
SmithKline Beecham

The safety update review was submitted on February 28, 2000, and comments pertaining to this submission are included in the medical officer's review on page 13.

/S/
Jena Weber, RHMP