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Application Number NDA 21-178/s-004

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

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

APPLICATION #:	NDA 21178.....	APPLICATION TYPE:	sNDA.....
SPONSOR:	Bristol-Myers Squibb..... Antidiabetic	PROPRIETARY NAME:	GLUCOVANCE..... Metformin/Glyburide.....
CATEGORY OF DRUG:		USAN / Established Name:	Oral.....
MEDICAL REVIEWER:	Robert I Misbin.	ROUTE:	September 11, 2002.....
		REVIEW DATE:	

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
Nov 30, 2001	Nov 30, 2001	Supplement to NDA	

Addendum: Pediatric studies
Labeling for Hypoglycemia

Recommendations:

The request for waiver of pediatric studies should be granted.

The dosage and administration section should provide guidance about how to deal with hypoglycemia in patients on triple therapy

Signed: Medical Reviewer: Robert I Misbin MD Date: Sep 11, 2002

Medical Team Leader: _____ Date: _____

21178 - addendum

Issues relating to NDA 21178 (addition of a thiazolidinedione to Glucovance) not covered in the review of August 2, 2002.

Pediatric studies:

This NDA establishes the safety and efficacy of triple therapy (rosiglitazone plus metformin plus a sulfonylurea) in patients who were inadequately treated with metformin plus a sulfonylurea. For patients in the study, the mean duration of diabetes was about nine years. This reflects the natural history of type 2 diabetes. Patients are typically responsive to single agents initially, but eventually require multiple treatments. Given that type 2 diabetes is rarely seen before the age of 12, pediatric patients with diabetes will be adults before they are likely to require triple therapy. It should also be noted that the long-term safety (beyond 1-2 years) of thiazolidinediones has not been established and that these drugs have not been studied in children. For these reasons, it seems impractical and unnecessary to perform a trial of triple therapy in pediatric patients.

Recommendation: The request for waiver of pediatric studies should be granted.

Labeling:

The dosage and administration section should provide guidance about how to deal with hypoglycemia in patients on triple therapy. The following language is a suggestion of what should be added:

[]

Robert I Misbin MD
September 11, 2002

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

/s/

Robert Misbin
9/11/02 04:55:09 PM
MEDICAL OFFICER

David Orloff
9/11/02 07:20:33 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEDICAL OFFICER REVIEW

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

APPLICATION #: NDA 21178..... APPLICATION TYPE: sNDA.....
SPONSOR: Bristol-Myers PROPRIETARY NAME: GLUCOVANCE.....
Squibb..... Antidiabetic Metformin/Glyburide.....
CATEGORY OF DRUG: USAN / Established Name: Oral.....
ROUTE: Robert I Misbin. REVIEW DATE: August 2, 2002.....
MEDICAL REVIEWER:

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
Nov 30, 2001	Nov 30, 2001	Supplement to NDA	
May 9, 2002	May 10, 2002	Safety Update	
May 9, 2002	May 10, 2002	Information requested	

The application contains results of a trial of rosiglitazone (RSG) vs placebo in patients whose hyperglycemia was inadequately treated with Metformin/Glyburide (Glucovance). Mean HbA1c was about 8% at baseline. The mean placebo-subtracted change was a reduction in HbA1c of 1.02% units at 24 weeks. No serious or unexpected safety issues emerged.

Recommendation – Approval

Signed: Medical Reviewer: Robert I Misbin MD Date: August 2, 2002

Medical Team Leader: _____ Date: _____

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**APPEARS THIS WAY
ON ORIGINAL**

Executive Summary:

1. Recommendations:

The addition of rosiglitazone (RSG) to Glucovance (Metformin/Glyburide) resulted in a clinically significant reduction in HbA1c. No new adverse events were observed. The adverse event profile and other physiological changes associated with rosiglitazone in this study are similar to what has been observed in previous studies of rosiglitazone

Pending minor changes in the label, I recommend that this sNDA be approved.

2. Summary of Clinical Findings

Addition of RSG to Metformin/Glyburide 2000mg/10mg resulted in clinically significant reduction in HbA1c and other measures of hyperglycemia. The fall in serum insulin levels, rise in body weight, and changes in lipid classes observed with RSG are similar to what has been observed in studies of Avandia submitted by Smithkline-Beecham in their NDA approved May 1999. Addition of RSG to Met/Gly was associated with increased reporting of hypoglycemia. These were generally reported to be mild-moderate and none required medical intervention. The hypoglycemia was managed by reduction in the dose of Metformin/Glyburide. One patient (on RSG during the double blind period) withdrew because of hypoglycemia.

Addition of RSG to Met/Gly was associated with increased reporting of edema, which was mild to moderate in intensity and responded to diuretics and sometimes resolved spontaneously. Clinically significant decreases in hemogram (> 3 g/dl) was observed in 9 patients on RSG, 3/181 during the 24 week double-blind phase and six during the extension. A clinically significant rise in ALT (approximately 6 x ULN) was observed in three patients on RSG, 1/181 during the double-blind period, and two during the extension. RSG was withdrawn in two of these patients. The ALT level fell to normal in the third patient despite being continued on RSG. The adverse event findings observed in patients on RSG in this study are similar to what has been reported in studies submitted by SmithKline Beecham in the NDA for Avandia.

Note: The Sponsor refers to their product as Glucovance (Metformin/Glyburide) but lists the dose for individual tablets with the glyburide component first.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Review

1 Introduction and Background:

Metformin(Met) and glyburide(Gly) are mainstays of the treatment of type 2 diabetes. Although it was not available in the United States until 1995, metformin had been widely used in Europe for many years before. The primary glucose lowering activity of metformin is to inhibit glucose production by the liver. Glyburide is one member of the sulfonylurea (SFU) class of compounds. These agents lower glucose levels by stimulating insulin secretion by the pancreatic beta cells.

Because they have different mechanisms of action, metformin and glyburide are often used in combination. GLUCOVANCE is fixed dose combination of metformin and glyburide. It can be used as first-line therapy for patients not previously treated with pharmacological agents. But its purpose initially was to provide the convenience of a single tablet for patients who were taking metformin in combination with a sulfonylurea.

Thiazolidinediones (TZD's) improve insulin resistance. They have a different mechanism of action from metformin or sulfonylureas (SFU) and can therefore be used in combination with these agents. The use of metformin with a SFU and a TZD is called "triple therapy". The TZD, troglitazone, had been approved for use as part of a triple therapy regimen. However, troglitazone was removed from the market in March 2000 because of liver toxicity. The remaining TZD's are rosiglitazone (RSG) and pioglitazone. Both RSG and pioglitazone are approved to be used in combination with metformin and in combination with SFU's. But they are not approved to be used as part of a triple therapy regimen.

This sNDA was submitted by Bristol-Myers Squibb (BMS) to allow addition of a TZD to Glucovance. If approved, this sNDA would support a statement in the Glucovance label for the addition of a TZD for patients on Glucovance. The trial consisted of the addition of RSG vs placebo in patients who were taking Glucovance as background therapy. The trial was not designed to provide new information about Glucovance. It is unusual for a Sponsor to perform a trial that does not provide new information about its own product. But this is understandable when one considers that the addition of a TZD to Glucovance would allow patients to continue longer on Glucovance. Patients whose hyperglycemia could not be adequately controlled on Glucovance alone would otherwise be switched to injections with insulin.

2 **Clinically relevant findings from Chemistry, Toxicology, Biopharmaceuticals, statistics and other consultants:** No additional comments

3 **Human Pharmacokinetics and Pharmacodynamics:** No additional comments

4 **Clinical data and Sources:** The results of one phase 3 trial (138-055) was submitted. This is described in detail in section 6, "Review of Efficacy". Reference to postmarketing data is made in section 7, "Review of safety".

5 **Clinical Review Methods:** The review was conducted of the hard copy of the NDA. No routine inspections of the sites were performed. Although the consent document was not reviewed, the trial appears to have been conducted in accordance with acceptable ethical standards. The escape criteria for lack of efficacy are praiseworthy. The financial disclosure documentation appears adequate. Regulatory statements regarding documents reviewed

NDA 21-178 supplement, submitted November 30, 2001

Safety update submitted May 9, 2002

Response to request for information submitted May 09, 2002

The Sponsor, Bristol-Myers Squibb (BMS), submitted debarment and financial disclosure documents November 30, 2001. I have examined these documents and found them to be acceptable. The debarment statement indicated that no investigator who had been debarred as of October 3, 2000 had data in the submission.

The following financial disclosure information has been submitted:

1 Form OMB No. 0910-0396. The applicant certifies that BMS has not entered into any financial arrangement with the clinical investigators named in the lists included in the NDA whereby the value of compensation to the investigator could be affected by the outcome of the study.

2 The applicant further certifies that none of the listed clinical investigators disclosed a proprietary interest in the product or an equity interest in BMS.

3 The applicant certifies that no listed investigator was the recipient of other payments such as honoraria, consultation fees, research grants, or compensation in the form of equipment from BMS.

4 List of investigators from whom completed financial disclosure forms were received.

5 Certification pursuant to 21 CFR 54.5(c) that the applicant acted with due diligence to obtain financial disclosure information from a list of investigators from whom completed forms were never received.

6 List of investigators not submitting financial disclosure information and the studies to which they contributed data.

7 The investigators listed as not submitting financial disclosure forms each contributed data from single sites in large, multicenter trials. Analyses of efficacy data in this NDA did not reveal any significant effect of center on outcomes. Furthermore, the data on both safety and effectiveness were consistent across the multiple trials submitted

to the NDA. In sum, the absence of financial disclosure information from the investigators listed does not call into question the overall integrity of the data submitted.

Inspections: DSI inspected one site for cause. The investigator for the site was Mark De Bruin, D.O. Several deficiencies were reported. This information is contained in a report from Antoine El-Hage of DSI dated June 7, 2002.

6 Review of Efficacy

Study:138-055

This was a randomized, two arm, double blind, controlled trial of rosiglitazone (RSG) vs placebo in patients with type 2 diabetes who were inadequately controlled on a 2000mg/10mg dose of Metformin/Glyburide.

Run-in phase: Patients with type 2 diabetes whose HbA1c level was between 7 and 10% at screening while taking at least 2000 mg of Metformin combined with at least half the maximal dose of a sulfonylurea (SFU) were enrolled into a 2-week run-in of Metformin/Glyburide 2000 mg/10mg. Patients who were on monotherapy or patients taking lower doses of combination therapy were enrolled into a 12-week run-in in which Metformin/Glyburide was titrated to control. Those patients whose HbA1c remained between 7 and 10% after the 2 or 12 week run-in phase were eligible to be enrolled into the double-blind portion. Metformin/Glyburide was administered as 500mg/2.5 mg tablets. The maximal dose was 2000 mg/10 mg (two tablets bid). At the end of the run-in >98% of patients were taking 2000 mg/10 mg. The dose was 1500/7.5 mg in six patients (1.7%), three of whom were randomized to RSG and three to placebo.

Double-blind phase: The purpose of this study was to compare rosiglitazone to placebo in patients with HbA1c between 7 and 10% while taking Metformin/Glyburide in a dose of at least 1500/7.5 mg after the 2 or 12 week run-in described above. The double-blind phase lasted 24 weeks. The maximal allowed dose was 2000mg/10mg. All tablets were taken before the morning or evening meals. Randomized patients were asked to take a 4 mg RSG tablet or matching placebo each morning. The dose of RSG was doubled (4 mg in the morning and 4 mg in the evening) after 8 weeks for patients whose HbA1c was > 7% or mean daily glucose (MDG) was > 126 mg/dl. For patients with documented hypoglycemia (BG<50), downward titration of Metformin/Glyburide was allowed at the discretion of the investigator.

Inclusion/exclusion, withdrawal criteria: In addition to the criteria listed above, patients were between 20 and 78 years old and had BMI values between 23 and 40 kg/m². Patients with childbearing potential were excluded unless they were practicing contraception. Other exclusion characteristics were included as per the labels of Glucovance and Avandia.

Subjects were discontinued from double blind therapy due to lack of glycemic control according to the criteria listed below. These patients were then eligible to enter an open label triple-therapy extension.

Week 12: MDG>240 mg/dl

Week 16: MDG>200 AND reduction of MDG from baseline< 20 mg/dl

Week 20 MDG> 200 mg/dl

Triple Combination (Open-label) extension:

This optional 20-week extension study of Glucovance plus rosiglitazone was designed to provide additional data in patients who completed the double blind period. It also provided rescue therapy with rosiglitazone for patients who failed to achieve adequate glycemic control during the double blind period.

Disposition of Subjects:

181 subjects were randomized to Met/Gly+RSG and 184 to Met/Gly + placebo. They had a mean age of 57 years, 8.8 years with diabetes. 8.5% had been on monotherapy, 28% on submaximal combination therapy and 63% on maximal combination therapy*. The combination of Glyburide + Metformin was used by 45%, Glipizide + Metformin by 32% and Glimepiride + Metformin by 10%. Mean lab values at baseline were HbA1c 8.1%, FPG 175 mg/dl, MDG 181 mg/dl., insulin 19.9 uU/ml. Mean body weight was 93kg and mean BMI was 31.7 mg/m². They were 60% male, 40% female, 74% white, 16% Latino and 8% black. The two arms were well matched except that 4.4% of the RSG patients were black compared to 10.9% of the placebo patients. The disposition of patients is as follows:

37% of patients in the placebo arm discontinued compared to 20% in the RSG arm. This difference is largely due to lack of efficacy in the placebo arm. 25% discontinued because of lack of efficacy in the placebo arm compared to 8.8% in the RSG arm. 2.7% discontinued because of an AE on placebo compared to 5% on RSG. An additional patient on RSG discontinued because of hypoglycemia.

* at least 2000 mg of metformin plus 10 mg or greater of Glyburide (or equivalent dose of another SFU).

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ON ORIGINAL**

Dosing

The final doses of medication are shown in the following table.

By and large, most patients received near maximal doses of study medications. That some patients in the RSG arm were receiving a lower dose of Met/Gly at endpoint than at baseline reflects back-titration to prevent hypoglycemia.

From Table 9.1D

	% of patients	
Met/Gly+RSG	Met/Gly + RSG	Met/Gly+Placebo
500/2.5 +4	0.6	0
1000/5 +4	1.1	0
1000/5 +8	1.7	0
1500/7.5 +4	2.2	1.6
1500/7.5 +8	7.7	0
2000/10 +4	11.6	8.7
2000/10 +8	75.1	89.7
Mean	1914/9.6 +7.4	1992/10 +7.6

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Efficacy Results:**HbA1c**

	RSG+Met/Gly	Placebo+Met/Gly
Baseline	8.14	8.09
Last	7.23	8.21
ANCOVA adj chg	-0.91	+0.11
Treatment effect	-1.02	
P value	<0.001	

Analysis by subset suggested that the addition of RSG was more effective in females than in males. In females the mean change in HbA1c was -1.22 compared to -0.90 in males. This difference is small and may not be statistically significant, but greater efficacy in females was also observed in the RSG trials performed by SmithKline Beech for AVANDIA. Addition of RSG to Met/Gly was equally effective in patients over and under the age of 60. Not surprisingly, the mean absolute reduction HbA1c was greater in patients with higher baseline levels of HbA1c. The mean placebo subtracted reduction was -0.83 in patients with baseline HbA1c <8% compared to -1.31 in patients with HbA1c of 9% or over. Addition of RSG also appeared somewhat less effective in black patients (-0.65) than in white patients (-1.06) or Latinos (-1.19).

The mean changes in FPG and fructosamine shown in the table s below are consistent with the changes in HbA1c

Mean FPG

	RSG+Met/Gly	Placebo+Met/Gly
Baseline	178	173
Last	136	184
ANCOVA adj chg	-0.41	+7.4.
Treatment effect	- 48.5	
P value	<0.001	

Mean fructosamine (micromol/L)

	RSG+Met/Gly	Placebo+Met/Gly
Baseline	325	324
Last	299	335
ANCOVA adj chg	-25.6	+11.6.
Treatment effect	- 37.3	
P value	<0.001	

Mean levels of free fatty rose at baseline was 0.55 mEq/L. Mean levels rose slightly (0.08) in patients on placebo but fell slightly(0.06) in patients on RSG. The difference between RSG and placebo was -0.13 mEq/L (p<0.001). Insulin levels fell slightly in

both groups. The reduction was somewhat greater in patients on RSG but the difference was not statistically significant. C-peptide levels rose slightly in both groups. At endpoint mean C-peptide levels were 4.43 ng/ml in patients on RSG and 5.00 in patients on placebo. The placebo subtracted difference of -0.49 was statistically significant ($p < 0.001$), indicating that the rise in C peptide was less in RSG-treated patients. Because unstimulated levels of insulin and C peptide are low and difficult to measure, it should not be surprising that the results are not definitive. I cannot explain why insulin levels fell slightly but C-peptide levels rose slightly, unless there was some technical problem in the assay. However, the data do show that RSG appears to lower insulin and C peptide relative to placebo. Taken together, the changes in free fatty acids, insulin and C peptide are consistent with the notion that RSG lowers glucose levels by increasing insulin sensitivity.

* insulin is stable in plasma stored at -20C but C peptide is not. If baseline and endpoint samples were measured in the same assay, the C peptide levels would appear higher at endpoint than at baseline because of loss of C peptide that occurred during storage.

Body weight and Lipids:

Mean body weight at baseline was about 93 kg. There was a gain of 3.03 kg in the RSG group compared to a gain of 0.03 kg in the placebo group. The weight gain attributable to RSG was 3.01 kg (95% cf 2.37-3.64). Changes in lipids are shown in the table below. The major finding is a fall in LDL cholesterol in patients on placebo compared to a rise in LDL cholesterol in patients on RSG. This was partially offset by the rise in HDL cholesterol in patients on RSG. Although not calculated by the Sponsor, the mean LDL/HDL ratio changed from 2.58 to 2.14 (-0.44) in patients on RSG compared to a change of 2.71 to 2.18 (-0.52) in patients on placebo.

Mean Values of Total, HDL, and LDL Cholesterol and triglyceride, mg/dl;

		Baseline	Final	Change	RSG effect
Total chol	RSG	191	210	19*	+15*
	Placebo	191	196	4.4	
HDL chol	RSG	43	54	11*	+4*
	Placebo	42	49	7.3*	
LDL chol	RSG	111	116	5.4*	+13*
	Placebo	114	107	-7.1*	
Triglyceride	RSG	202	212	10	-15
	Placebo	196	221	25*	

From table 10.8.1

- 95% cf limits do not overlap for differences or include zero for change

Efficacy summary: Addition of RSG to Metformin/Glyburide 2000mg/10mg resulted in clinically significant reduction in HbA1c and other measures of hyperglycemia. The rise in body weight and LDL cholesterol observed with RSG are similar to what has been observed in studies of Avandia submitted by SKB.

Open-Label Triple Combination Extension (TCE)

There were 313 patients who entered the open-label extension trial of triple therapy. 254 patients had completed the double blind portion and 59 patients were rolled over from the double-blind portion because of “lack of glycemic control”. Of these 59 patients, 44 had received placebo during the double-blind portion and 15 had received RSG. Of the 44 patients who had previously received placebo, 6 patients withdrew from triple therapy because of lack of glycemic control. Of the 15 who had previously received RSG, 5 patients withdrew from open-label triple therapy because of lack of glycemic control.

Patients were allowed a titration up to 8 mg of RSG. The mean doses of study medications at endpoint were the same regardless of whether patients had been on RSG or placebo during the double-blind portion. These were Glucovance 1923/9.6 + RSG 7.1 mg. Approximately 71% took Glucovance 2000/10 plus RSG 8 mg.

The efficacy data, change in HbA1c, for the patients who entered the TCE are shown in the table below. It should be noted that RSG given during the double blind period was associated with a reduction of HbA1c of 0.94% units compared to a rise of 0.07% units with placebo. There was a small further reduction in HbA1c with RSG during the TCE for patients who received RSG initially. Although the exact reduction cannot be calculated directly from the data shown because not all patients entered the extension phase (TCE). For patients who received placebo initially, the reduction in HbA1c during the TCE was about 1.3% units. It is worth noting that the mean HbA1c values at baseline and last visit are about the same in both groups (8.1 at baseline and 6.8 at last visit). Thus the final result of triple therapy was about the same regardless of whether patients received RSG or placebo during the initial double blind phase.

Change in HbA1c

Double Blind Arm:	Glucovance + RSG	Glucovance +Placebo
Baseline	8.12 (n=155)	8.10 (n=158)
Double blind week 24/ TCE week 0	7.18 (n=155)	8.17 (n=158)
TCE week 8	7.26 (n=141)	7.77 (n=150)
TCE week 20	6.85 (n=140)	6.80 (n=135)

Another way of looking at the efficacy data is to display the proportion of patients who achieved HbA1c < 7%.

Proportion of patients with HbA1c<7%

Double Blind Arm:	Glucovance + RSG	Glucovance +Placebo
Baseline	3.9% (n=155)	2.5% (n=158)
Double blind week 24/ TCE week 0	43.2% (n=155)	13.3% (n=158)
TCE week 8	42.6% (n=141)	24.0% (n=150)
TCE week 20	62.9% (n=140)	62.5% (n=135)

The fall in FPG (-43 mg/dl) that occurred with RSG during the double blind phase was duplicated (-45 mg/dl) when RSG was given during the TCE to patients who had received placebo previously.

The fall in insulin (-5.6 uU/ml) that occurred with RSG during the double blind phase was duplicated (-4.2 uU.ml) when RSG was given during the TCE to patients who had received placebo previously. But the increase in C peptide (0.25 ng/dl) that occurred with RSG during the double blind phase did **not** occur when RSG was given during the TCE. Instead there was a decrease of 0.35 ng/ml. Also, C peptide levels fell somewhat during the TCE (from 4.36 ng/ml to 4.33 ng/ml) in patients who had had RSG during the double-blind period.

The rise in body weight (3.0 kg) that occurred with RSG during the double blind phase was duplicated (2.6 kg) when RSG was given during the TCE to patients who had received placebo previously.

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ON ORIGINAL**

7 Safety Review:

Double-blind phase:

1/184 patients died on placebo and 0/181 patients on RSG. The death in the placebo patients was a cardiac arrest following a pneumonectomy for newly diagnosed lung cancer. Serious adverse events occurred in 8/184 (4.3%) of patients on placebo compared to 3/181(1.7%) on RSG. With respect to cardiovascular serious AE's, there were two patients on RSG (one report of myocardial infarct and one of coronary artery disease), and four patients on placebo (The fatal cardiac arrest, one invasive cardiac procedure, one chest pain, and one coronary artery disease). Two of the patients with serious cardiovascular AE's on RSG withdrew from the trial. Other than the death, there was one placebo patient who also withdrew because of coronary artery disease. None of these adverse events can reasonably be attributed to study drug in my judgment. There were no reports of congestive heart failure.

Edema occurred in 4/184 (2.2%) placebo patients and 14/181 (7.7%) on RSG. The edema was described as mild or moderate in intensity and resolved in 2 of the placebo patients and 7 of the RSG patients. Diuretics were used in 1 of the placebo patients and 7 of the RSG patients. Hematological events occurred in 1.1% of patients on placebo compared to 3.3% of patients on RSG. In three of the RSG patients the fall in hgb exceeded 3g/dl. One patient on RSG developed a rise in ALT from 33 U/L (0-40) to 270 U/L after 57 days of treatment. ALT levels fell to 67, three days after RSG was discontinued.

Hypoglycemia occurred more frequently in patients treated with RSG than in patients treated with placebo. 95/181(53%) of patients on RSG reported a total of 519 events, whereas 45/184 (25%) of patients on placebo reported a total of 86 events. All events were described as mild-moderate except 9 events (7 on RSG and 2 on placebo) that were described as severe. These "severe" events occurred in 3 patients on RSG and 2 patients on placebo. No events were described as "very severe" and none required medical assistance. Hypoglycemia documented by finger stick glucose < 50 mg/dl occurred in 40/181(22%) of patients on RSG and in 6/184 (3%) of patients on placebo. There was a total 97 events documented by glucose< 50 mg/dl in patients on RSG compared to 9 events in patients on placebo. There were 18 subjects in the RSG group and 1 in the placebo group who reduced their dose of Metformin/Glyburide because of hypoglycemia. One subject in the RSG group withdrew from the study because of hypoglycemia. At the time he withdrew, his HbA1c was 6.1% (down from 7.3 at baseline) and his finger stick glucose was 55mg/dl.

To some extent the increased reporting of hypoglycemia is expected given those patients on RSG had lower HbA1c levels. However, the table below demonstrates that there was more hypoglycemia with RSG at all levels of HbA1c.

Hypoglycemia during double-blind period

Final HbA1c	Rosiglitazone			Placebo		
	N	Subjects	Events/ subject	N	Subjects	Events/ subject
<6.5	39	13(33%)	3.5	10	1 (10%)	1.0
6.6-7.0	44	14(32%)	2.1	17	1 (5.9%)	1.0
7.1-8.0	61	12(20%)	1.8	60	3 (5.0%)	1.0
>8.0	33	1 (3.0%)	1.0	91	1 (1.1%)	1.0
Not stated	4	0		6	0	
Total	181	4(22%)	2.4	184	6 (3.3%)	1.5

Triple Combination Extension

No deaths occurred. Edema was reported in about 6 % of patients. Two patients, previously on placebo, were discontinued because of AE's related to the liver. There were a total of three patients, previously on placebo, in whom ALT elevations were observed during ACE. One patient discontinued because of a ALT of 228 (ULN=-40) on day 135. A second patient had ALT of 228 on day 113 which fell to 112 on day 117. On the last treatment day his (her) ALT was 29. In the third patient, the ALT of 58 on day 89 fell to 16 on the last treatment day.

Reductions in hemoglobin of > 3 g/dl were observed six patients. Three of these had been on placebo during the double blind period and three on RSG. The worst case of anemia had hemoglobin of 8.4 g/dl with hematocrit of 26%.

Hypoglycemia with dipstick glucose < 50 mg/dl was reported in 1.9% of subjects. There were no episodes of hypoglycemia that required medical assistance.

Postmarketing reports:

Hypoglycemia in patients on Glucovance

Through March 31, 2002, _____ tablets have been sold. BMS estimates that cumulative market exposure in the US the breakdown by dosage strength is:

1.25mg/250mg - []
 2.5mg/500mg - []
 5mg/500mg - []

(data provided by BMS in submission of May 15, 2002)

According to BMS there have been 15 reports of "hypoglycemia" or "decreased blood glucose", through March 31, 2002. BMS submitted copies of the MedWatch reports. There are six reports confirmed by glucose values. In addition, there are seven cases reported by a physician named: _____ None of his reports contain any clinical information. I attempted to contact this physician by calling the telephone listed on the report form, but received a recorded message saying that the telephone had been disconnected. Details of the six documented cases are as follows:

10783967 – 79 year old female hospitalized for three days after receiving two doses of Glucovance 5/500. Blood glucose values were in the 50's. The patient is now on Glucophage and readings are within normal limits – reported by patient

10788701 – 84 year old women on Glucovance 1.25/250 (bid) plus Glucophage XR (1000 mg hs). Blood glucose values 50-60. Glucovance was discontinued and the patient is recovering - reported by MD

10873867 – 65 year old female experienced blood sugar of "30" associated with syncope and pain in arms and shoulders. Given Glucovance 5/500 tid one day earlier. Reported by patient.

10885267 – patient admitted to ICU unresponsive with glucose of zero while taking Glucovance 5/500. Reported by nurse, no other details.

10591014 – 53 year old male patient taking Glucovance 1.25/250 for eight days and reports glucose in the 20's associated with feeling faint and shaky – reported by patient.

10850501 – 81 year old female passed out in a mall . Paramedics revived her with glucose after noting her BG was 36. Dose of Glucovance unknown – reported by patient.

Joslyn Swann, in the Office of Drug safety, has conducted a postmarketing safety review of hypoglycemia. Through June 12, 2002 she found 22 reports of "hypoglycemia" or "blood glucose decreased" in the AERS data base (raw numbers not corrected for possible duplication). This finding is largely consistent with the 15 distinct reports through March 31, 2002 submitted by BMS.

Based on the postmarketing reports, it appears that the risk of hypoglycemia with Glucovance is very small. It is worth noting that three of the six patients with documented hypoglycemia described above were aged 79-84. The risk of hypoglycemia in elderly patients is well described in the label for products that contain glyburide and other sulfonylureas.

The one troubling finding is that there were two cases in which patients developed severe hypoglycemia after just 2-3 doses of the maximal strength Glucovance tablet. The current label already contains a bolded warning that the maximal strength tablet should not be used as initial therapy because of the risk of hypoglycemia. The current label also states

that patients already taking the combination of metformin plus a SFU should be started on the equivalent dose of Glucovance.

Congestive heart failure in patients on TZD's

The incidence and prevalence of CHF is greater in patients with diabetes compared to patients without diabetes (Nichols et al, Diabetes Care 24, 1614-1619, 2001).

The risk of CHF with diabetes seems primarily related to patients' underlying cardiac status, but insulin use also appears to be a risk factor.

The labels for both RSG (Avandia) and PIO (Actos) contain statements that TZD's cause fluid retention and can cause/exacerbate CHF in some patients. The risk appears greatest for patients who were taking insulin at the time the TZD's were started. Insulin use can be regarded as a marker for duration/severity of diabetes. Thus the greater risk of CHF in patients on insulin (with and without TZD's) probably reflects poor cardiac function from long-standing diabetes.

The use of insulin is generally reserved for patients who have failed oral therapy. But the effectiveness of triple therapy (RSG plus Metformin/Glyburide) described in this sNDA may change that. It seems likely that patients failing a Metformin/SFU combination will be started on a TZD in lieu of insulin. This means that one needs to consider the risk that addition of the TZD may precipitate CHF in some of these patients. Although there were no reports of CHF in this sNDA, the risk of edema appeared to be increased 3 fold (7.7% to 2.2%). In considering the potential problem of CHF in patients on "triple therapy", it is appropriate to have a brief review of post-marketing results related to CHF in patients on TZD's:

1 Post-marketing reports through August 6, 2001 of congestive heart failure leading to hospitalization for patients on RSG or PIO was reviewed by Lanh Green, HFD 430 (July 16, 2002). She found 47 domestic cases (25 on RSG and 22 on PIO). There was one fatality (one patient on 16 mg of RSG). Half the patients had been taking insulin. The mean dose was 6.7 mg for RSG and 29 mg for PIO. The mean time to hospitalization was 89 days. In 26 of 47 (55%) cases, the CHF was considered to be new onset.

2 Delea and coworkers used an insurance claims data base with information on 17 million patients annually to investigate insurance claims for congestive heart failure from 1/95 through 3/01 for patients on TZD's. They concluded that patients on TZD's were more likely to have CHF (hazard ratio=1.7, p<.001). The CHF risk at 36 months was 8.2% for patients on TZD's and 5.3% for controls. (abst 385, American Diabetes Association annual meeting, June 2002)

3 A postmarketing study on the effect of 600 mg troglitazone (TRZ) on the echocardiogram parameters, left ventricular mass index (LVMI) and stroke volume index (SVI), in patients with class 3 and 4 heart failure was reported March 12, 2002. The

patients had poor glycemic control on pharmacological therapy. Most patients were taking sulfonylureas; about half were taking insulin.

The study was double-blind, placebo controlled and was preceded by a four week run-in during which an attempt was made to bring the patients to “dry weight” by optimizing diuretic therapy. Although planned for 24 week, the study was terminated in March 2000. 77 patients (40 placebo and 37 TRZ) were randomized but only 39 patients (20 placebo and 19 on TRZ) completed the 24 weeks. There were seven deaths, 5 in the placebo-treated group (heart arrest, peritonitis, myocardial infarction, heart arrest, urosepsis) and 2 in TRZ-treated patients (myocardial infarction, retroperitoneal hemorrhage with renal failure). Of the four cardiac deaths, three were on placebo and one on troglitazone. Excluding the deaths, there were five placebo patients who withdrew for reasons related to cardiac/CHF status (two with new myocardial infarcts, and three said to have worsening CHF) and four troglitazone-patients (one with a pleural effusion and three said to have worsening CHF).

There was little change in measurements related to CHF and small differences between the two groups between baseline and final visit. 17% had worsening of pulmonary rales on TRZ and none on placebo. Diuretic therapy remained unchanged in 28 placebo-treated patients and 25 TRZ-treated patients. The dose of diuretics increased in 5 placebo-treated patients and 9 TRZ-treated patients. Three in each group reduced their doses of diuretics. Mean (SE) left ventricular ejection fraction was 40.5(2.5)% in placebo patients and 32.4(2.7)% in TRZ-treated patients. The change from baseline to last observation was -0.9 (2.5)% for placebo patients and 2(1.9)% for TRZ patients.

Of the patients who completed 24 week, 16% of patients on TRZ had worsening ankle edema compared to 5% on placebo. 26% of patients on troglitazone had improvement in ankle edema compared to 41% on placebo. Change from baseline to 24 weeks for the primary echocardiographic parameters are shown in the table.

	LVMI	SVI
Baseline mean	123.2 gr/m ²	29.2 mL/m ²
TRZ: adjusted mean change from baseline (n)	-12.9 (19)	-0.1 (16)
Placebo: adjusted mean change from baseline (n)	-11.3 (20)	0.4 (19)
Treatment effect	-1.6	-0.5
90% confidence interval	-10.5, 7.3	-5.1, 4.1

An ANCOVA based on general linear model incorporating the effects of treatment, center, and baseline (as covariant) was used

Change from baseline to 24 weeks for metabolic parameters are as follows. Mean HbA1c was 7.8 and 8.4% for patients on placebo and TRZ respectively. The change at 24 weeks was +0.2 for placebo patients and -1.2 for TRZ-treated patients. Mean FPG was 161 mg/dl and 189 mg/dl for patients on placebo and TRZ respectively. The change at 24

weeks was +13 mg/dl for placebo patients and -51 mg/dl for TRZ-treated patients. Patients on placebo had a mean weight loss of 2.7kg compared to a mean weight gain of 3.2kg in patients of TRZ (p=0.045). Mean triglycerides at baseline were 288 mg/dl and 361 mg/dl for patients on placebo and TRZ respectively. The change at 24 weeks was -50 mg/dl for placebo patients and -94 mg/dl for TRZ-treated patients. Because of the wide range in baseline values and responses, this difference in the fall in triglycerides was not statistically significant.

Given the small number of patients in this study, one must be cautious about drawing firm conclusions. It appears that TRZ caused fluid retention in a few patients, as manifested by worsening of ankle edema, pulmonary rales, and increased use of diuretics. But the frequency and magnitude of these changes were surprisingly small when one considers the baseline characteristics. Echocardiographic parameters showed little change. There were fewer deaths on TRZ than on placebo (2 vs 5), fewer cardiac deaths (1 vs 3), and fewer withdrawals because of cardiac events in patients who did not die (4 vs 5). Glycemic control was unquestionably improved by TRZ.

Summary of safety issues related to edema and heart failure with TZD's

TZD treatment leads to edema in some patients and to congestive heart failure in a few. In the controlled trials of RSG and PIO, insulin-treated patients had more reports of CHF, probably because they had had diabetes longer and/or had been more difficult to control. Addition of RSG or PIO appeared to increase the risk of CHF still further.

Although there were no reports of CHF in this sNDA, patients who received RSG appeared more likely to develop edema than those who received placebo. For this reason, I would expect that patients who are taking Glucovance with a TZD, would be at greater risk of developing CHF than patients taking the TZD, metformin or glyburide alone. But even when one considers the problem of CHF in insulin-treated patients, the absolute risk from the TZD is small. Furthermore, CHF in patients taking TZD's appears to be reversible, and may be offset by improvement in metabolism. If one considers all serious cardiac events (including death), there is no evidence that use of a TZD is harmful, even in high risk patients.

**APPEARS THIS WAY
ON ORIGINAL**

8 Dosage and administration –Dosing Regimen and Administrative Issues Labeling issues

It should be clear in the text and the data display (table 4), that the safety and efficacy of Glucovance itself were not studied. Looking at table 4, one could get the false impression that the data pertained to patients started on triple therapy vs patients started on Glucovance alone. The table should be revised to make it clear that Glucovance was given as background.

The text says that a TZD is

_____ This does not follow directly from the trial design. The maximum labeled dose of Glucovance is 20mg/2000mg (four 5/500 tablets) but the maximum dose in the trial was 10/2000 (four 2.5/500 tablets). The problem here is that the maximum labeled dose is 20/2000 but the maximum effective dose appears to be 10/2000. (Table 3 of the current label shows that 20/2000 given as 5/ 500 tablets was no more effective than 10/2000 given as 2.5/500 tablets). One solution would be to withdraw the 5mg/500mg tablet. Otherwise, I would suggest the following wording:

[_____]

This new wording reflects my belief that the labeling should not require a clinician to push the dose of Glucovance to its maximum before adding a TZD. Requiring a study design in which one drug is added to a maximum dose of the other is important to establish the principle that improved glycemic control with the combination was not simply due to a shared mechanism (as would be expected to occur, for example, if a repaglinide were added to a subtherapeutic dose of a SFU). But clinicians should not be so constrained. Metformin, SFU's and TZD work by different mechanisms. Physicians should be able to use them in any combinations that appear appropriate.

It should also be noted that the proposed label would allow addition of **any** TZD (rosiglitazone and pioglitazone are currently marketed) to Glucovance, even though only rosiglitazone was studied. I do not object to this wording because there is ample reason to believe that pioglitazone would be effective also if used in combination with Glucovance. Prior to its removal because of liver toxicity, troglitazone had been approved to be used in triple therapy along with metformin and a sulfonylurea. In addition, there is an application presently under review that shows that all three TZD's are effective when added to repaglinide. Repaglinide is a non-SFU insulin secretagog which has previously been shown to be effective when used in combination with metformin. In short, I believe that triple therapy can consist of metformin with **any** TZD and **any** insulin secretagog.

9. Special Populations : Already adequately covered in existing label

10. Conclusions, Recommendations and Labeling: Addition of RSG to Metformin/Glyburide 2000mg/10mg resulted in clinically significant reduction in HbA1c and other measures of hyperglycemia. The fall in serum insulin levels, rise in body weight, and changes in lipid classes observed with RSG in this study are similar to what appears in the Avandia label. Addition of RSG to Met/Gly was associated with increased reporting of hypoglycemia. These were generally reported to be mild-moderate and none required medical intervention. The hypoglycemia was managed by reduction in the dose of Metformin/Glyburide. One patient (on RSG during the double blind period) withdrew because of hypoglycemia. Addition of RSG to Met/Gly was associated with increased reporting of edema, which was mild to moderate in intensity, responded to diuretics and sometimes resolved spontaneously. Clinically significant decreases in hemogram was observed in nine patients on RSG. A clinically significant rise in ALT was observed in three patients on RSG. RSG was withdrawn in two of these patients. The adverse event findings observed in patients on RSG in this study are similar to what has been reported in studies submitted by SmithKline Beecham in the NDA for Avandia.

In summary, the addition of RSG to metformin/glyburide resulted in clinically significant reduction on HbA1c. No new adverse events were observed. The adverse event profile and other physiological changes associated with RSG in this study are similar to what has been observed in previous studies of Avandia.

Recommendations: Pending minor changes in the label (see below), I recommend that this sNDA be approved.

Robert I Misbin MD
August 2, 2002

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ON ORIGINAL**

Labeling – For transmission to BMS

Table 4 –It should be indicated in the table that the dose of Glucovance was given as 2.5/500mg tablets. The title should be changed to make it clear that the trial compared RSG vs placebo and that Glucovance was background.

Table 6 – The only important information in this table is the three-fold increase in edema in patients on rosiglitazone. The problem of edema (and potentially CHF in some patients) with RSG should be added to the *Precautions* section and this table can be omitted.

Dosage and administration – The proposed label says that a TZD can be added ~~_____~~ This does not follow directly from the trial design. The maximum dose of Glucovance is 20mg/2000mg (four 5mg/500mg tablets) but the maximum dose in the trial was 10/2000 (four 2.5mg/500mg tablets). The text could be left as it is if the 5mg/500mg tablet were withdrawn. (It was noted in the original NDA that 20mg/2000 mg was no more effective than 10mg/2000mg.. Thus, it is not clear why BMS chose to market the 5mg/500mg dose.) Otherwise, the text should be reworded so as not to conflict with the trial design.

The text also states ~~_____~~

What actually needs to be reduced to avoid hypoglycemia is the glyburide component of Glucovance. If patients develop hypoglycemia on 5/500 tablets, the simplest course of action would be to switch them to an equal number of 2.5/500 tablets. The statement quoted above would be acceptable if the 5/500mg tablet were discontinued. Otherwise, the text needs to be modified. One additional possibility would be to discontinue Glucovance in favor of metformin alone. This was the solution employed in two post-marketing reports.

Robert I Misbin MD
August 2, 2002

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ON ORIGINAL**

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

/s/

Robert Misbin
8/2/02 04:01:06 PM
MEDICAL OFFICER

David Orloff
9/12/02 05:48:30 PM
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**APPEARS THIS WAY
ON ORIGINAL**