CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-178

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.....	PROPRIETARY NAME:	GLUCOVANCE.....
CATEGORY OF DRUG:	Antidiabetic	USAN / Established Name:	Metformin/Glyburide.....
		ROUTE:	Oral.....
MEDICAL REVIEWER:	Robert I Misbin.	REVIEW DATE:	September 11, 2002.....

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. Patient 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

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

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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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 unusal 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 marched 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 equvalent dose of another SFU).

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

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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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

	Rosiglitazone				Placebo		
Final HbA1c	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 assistence.

Postmarketing reports:

Hypoglycemia in patients on Glucovance

Through March 31, 2002, 831 million tablets have been sold. BMS estimates that cumulative market exposure in the US the breakdown by dosage strength is:

[ ] (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 [redacted] 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 Glucopahge 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/m2	29.2 mL/m2
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.

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 "for patients not adequately controlled on a maximum dose of Glucovance." 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

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. [redacted]

Dosage and administration – The proposed label says that a TZD can be added [redacted] 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 [redacted]

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

NDA 21178
Glucovance Tablets: Metformin/Glyburide
250mg/1.25 mg
500mg/2.5 mg
500mg/5 mg

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Robert I Misbin MD
HFD 510
July 3, 2000, revised July 7
Finalized July 10, 2000 supplementary review July 27

Introduction:

Sulfonylureas and biguanides have been the mainstay of treatment for type 2 diabetes since the 1950's. Tolbutamide and phenformin were used either alone or in combination until the early 1970's when the UGDP study cast doubt on their safety. Later studies, particularly UKPDS have totally refuted (in my opinion) the safety concerns raised by UGDP. It now seems clear that treatment of hyperglycemia with metformin or glyburide does not increase the risk of cardiovascular death as one might have suspected from UGDP. In addition, UKPDS demonstrated that long-term treatment of hyperglycemia will frequently require the use of both agents in combination. Phenformin was removed from the market in 1977 because of lactic acidosis and no other biguanide was marketed in the United States until metformin in 1995.

Glucovance is a fixed dose combination of glyburide and metformin. The Sponsor, BMS, had initially proposed that Glucovance be developed to be used in lieu of its individual components. Their initial study proposal (which became study 011) was modeled after the study in the original NDA in which metformin was added to patients inadequately controlled on sulfonylureas. However, E& M requested that a study be performed as first-line therapy in naive patients also. This became study 039.

The design of Study 039 had to take into account the fact that the individual components were well established to be safe and effective for the treatment of hyperglycemia. For this reason, we did not think it would be ethical to allow patients' hyperglycemia to go untreated. Despite a history of "failing diet alone", there are always some patients who are likely to improve on placebo because of the regimentation of a study. But patients, whose glucose did not fall, were removed from the study and treated with Glucovance open-label. In addition, patients with moderately severe hyperglycemia at screening were also allowed to be treated with Glucovance open label. Although this study design may seem somewhat unorthodox, it reproduced the kind of conditions that physicians encounter in routine practice.

Regulatory statements regarding documents reviewed

NDA 21-178 submitted September 30, 1999
Safety update submitted January 18, 2000
Revised labeling submitted June 12, 2000

The Sponsor, Bristol-Myers Squibb (BMS), submitted debarrment and financial disclosure documents on September 30, 1999. I have examined these documents and found them to be acceptable:
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 three sites. One site had patients in study 039. The second site had patients in study 011. The third site had patients in both studies. All inspections found that the data were acceptable. This information is contained in a report from Roy Blay of DSI dated June 16, 2000.

PK issues:

(Comments based on review by Steven Johnson)

The metformin component of Glucovance is bioequivalent to Glucophage. The glyburide component of Glucovance is not bioequivalent to Micronase, but the deviation from bioequivalence is very small. The 90% CF for Glucovance 500/2.5 for C max is ——— and for AUC is ——— The point estimates of C max and AUC of glyburide in Glucovance are 10% and 18% higher, respectively, than for Micronase. This may appear to present a problem for patients already on Glucophage plus Micronase who are switched to Glucovance. But I would not expect a small increase in glyburide dosing to have a major adverse effect. The different marketed preparations of glyburide are not bioequivalent. Also, PK data from different lots of Micronase itself would not necessarily pass a bioequivalency test. No data were submitted comparing the bioavailability of glyburide in Glucovance to that of Diabeta or Glynase. A statement should be included in the dosing section of the label to warn physicians that some patients may be at risk of hypoglycemia if switched to Glucovance (see labeling issues).

Protocol 039 – First line therapy

This was a double blind study to evaluate the efficacy and safety of Glucovance therapy in comparison to placebo, and to glyburide and metformin monotherapy in previously untreated patients with type 2 diabetes. The primary comparison was Glucovance vs placebo after 20 weeks of blinded therapy. The blinded therapy was continued to 32 weeks and the effects of Glucovance vs placebo and vs monotherapy with metformin and glyburide were also assessed at the end.

Following a two week single-blind placebo run-in, patients were randomized to one of five treatment arms: placebo, glyburide 2.5 mg, metformin 500 mg, Glucovance 250/1.25 or Glucovance 500/2.5. Patients received these treatments double blind, once daily with breakfast for four weeks. This was followed by a 28 weeks double-blind treatment phase. The initial four-week titration was allowed by 24 weeks of treatment at stable dose. Dose titration was aimed at attempting to achieve FPG of 126 mg/dl (7 mM) without hypoglycemia. The initial treatment of one tablet per day with breakfast was increased to one tablet at breakfast plus one at supper in the evening. This could be increased to two tablets with breakfast and one with supper and finally to two tablets each with breakfast and supper. The maximum dose was two tablets blinded medication twice per day (four tablets total). Patients were removed from blinded medication because of "lack of efficacy" according to the criteria defined below. Patients removed for lack of efficacy were eligible to enter open-label treatment with Glucovance.

Patients were eligible to participate who had type 2 diabetes for at least one month but not longer than ten years. Patients were not eligible if they had been treated with an antidiabetic agent within eight weeks of screening. Patients entered the single blind placebo lead-in if FPG was 240 mg/dl or less and HbA1c was between 7-11%. Patients with HbA1c 11-12 were not eligible for inclusion into the double-blind treatment phase but were eligible for direct enrollment into open label therapy phase. Patients whose FPG was > 240 and whose HbA1c was 12 or less were also eligible for direct enrollment into open-label treatment phase. Patients, who were withdrawn from the blinded study for "lack of efficacy" described below, were also eligible for enrollment into the open-label treatment phase directly.

Glucose criteria for withdrawal of patients because of lack of efficacy:

Weeks 4-8	FPG>200 AND less than 20 mg/dl fall from baseline
Weeks 12-20	FPG>200
Weeks 20-28	HbA1c > 8%

806 patients were randomized and 533 completed double-blind therapy. Of these 533 patients, 515 (97%) were rolled over into the open label therapy phase. There were six patients lost to follow-up and lacking post-baseline data and 267 who prematurely

discontinued double-blind therapy. Of these 267, 138 were rolled over into open-label therapy. The study population was 54% man and 46% women. There was a small gender imbalance because the placebo group had 47% men and 53% women. There were about 78% white, 8% black, and 11% Hispanic. The mean BMI was 30.1. The mean age was 56.6 years. The mean duration of diabetes was about 3 years.

Failure to complete the double blind portion was largely related to glycemic control. Among placebo patients, 40% withdrew because of hyperglycemia compared to 5% and 6% on low and medium dose Glucovance respectively. By contrast 11% of patients on Glucovance 500/2.5 withdraw because of an AE, mostly hypoglycemia (see below), compared to 2% of placebo patients who withdrew because of an AE.

Mean HbA1c at baseline was about 8.2%. This fell slightly in the placebo group. There was a significant reduction from baseline in all active treatment arms and all were different from placebo. Both formulations of Glucovance were significantly better than either metformin or glyburide monotherapy but the two preparations were not different from each other. The results with Glucovance 250/1.25 are particularly impressive because it resulted in equal reduction in HbA1c as Glucovance 500/2.5 with a lower final dose of drug. Mean data are shown in the tables below.

20 week: First –Line Therapy

	Placebo	Metformin	Glyburide	Glucovance 250/1.25	Glucovance 500/2.5
Final Dose		1307	5.3	557/2.78	818/4.1
HbA1c (change)	8.14 (-.21)	8.23 (-1.03)	8.14 (-1.24)	8.22 (-1.48)	8.20 (-1.53)
Diff from placebo		-0.82	-1.02	-1.26	-1.31
Diff from Gly				-0.24	-0.29
Diff from Metf				-0.44	-0.49

Final Dose of Glyburide(Gly) and /or Metformin(M), % of Patients

	Placebo	Metformin	Glyburide	250/1.25	500/2.5
> 5mg Gly	NA	NA	36%	0	20%
>1000mg M	NA	56%	NA	0	20%

As shown in the following table, the superiority of Glucovance to either monotherapy component is primarily due to increased efficacy in patients whose initial HbA1c was 9% or over. Indeed, for patients whose initial HbA1c was 10 or greater, the reduction in HbA1c achieved with low dose Glucovance was approximately the same as the sum of the reduction achieved with glyburide and metformin alone. No other demographic factors seemed to affect response.

Baseline HbA1c	placebo	Glyburide	Metformin	Glucovance 250/1.25	Glucovance 500/2.5
<8%	-0.10 n=75	-0.93 n=77	-0.73 n=68	-0.90 n=71	-0.92 n=74
8-8.9%	-0.31 n=40	-1.27 n=34	-1.26 n=39	-1.31 n=35	-1.75 n=39
9.0-9.9%	-0.46 n=25	-1.89 n=22	-1.50 n=23	-2.40 n=30	-2.37 n=28
>9.9%	0.09 n=7	-1.87 n=9	-1.28 n=11	-3.21 n=13	-2.78 n=11

(from table 10.1.2),

Mean data for other efficacy variables are shown in the table below. With respect to fasting glucose, both doses of Glucovance are statistically better than metformin but not than glyburide. With respect to 2 hr pp glucose and fructosamine both formulations of Glucovance are statistically better than both monotherapies. Fasting insulin levels were higher with both formulations of Glucovance than with metformin but marginally lower than with Glyburide monotherapy. However, postprandial insulin levels were higher with Glucovance than with Glyburide monotherapy.

Mean data - Secondary Efficacy Variables at 20 weeks

		Placebo	Glyburide	Metformin	Glucovance 250/1.25	Glucovance 500/2.5
FPG	Baseline	177	189	175	178	177
	Change	+5	-38	-21	-42	-40
2hr PPG	Baseline	205	221	214	220	221
	Change	+5	-42	-40	-61	-59
Fruct'min	Baseline	252	250	249	248	248
	Change	-9	-40	-33	-45	-50
Insulin	Baseline	19	17	17	17	15
	Change	+1	+7	0	+4	+5
Ins 2 hr	Baseline	60	61	52	55	52
	Change	+1	+15	+4	+30	+25

A maximum fall in fasting plasma glucose was observed at six weeks with glyburide and at about eight weeks with the other active treatments. Because the drug dosages were titrated for four weeks, these results should not be taken as the time required to achieve the maximal effect of the initial dose. As shown later, the time required for a maximal glucose lowering effect of the initial dose of Glucovance is about four weeks.

Durability of activity was assessed by change in HbA1c from weeks 20 to 32. The data, shown in the table below, indicate that there was a small rise in HbA1c in all groups without statistically significant differences among treatment arms. It should be noted that these data are for patients continuing beyond 20 weeks. Patients who did not respond adequately had already been withdrawn.

	Placebo	Glyburide 2.5 mg	Metformin 500 mg	Glucovance 250/1.25	Glucovance 500/2.5
Number	N=76	N=105	N=104	N=116	N=122
HbA1c at week 20	7.33	6.64	6.79	6.68	6.44
Change at 32 weeks	0.22	0.14	0.17	0.19	0.24

Discontinuation due to lack of efficacy was 5-6 % for Glucovance, 16% each for glyburide and metformin and 40% for placebo during the 32 week blinded comparison. Among placebo and metformin patients, most of the dropouts occurred during the first 20 weeks. In the other arms, the dropouts were equally distributed between the first 20 weeks and the last 12 weeks. These data are presented in the table below. It should be noted that had discontinuation due to lack of efficacy been the primary outcome variable, instead of HbA1c, the results of the study would have been the same. Glucovance was better than metformin and glyburide monotherapy; and metformin and glyburide monotherapy were better than placebo.

Discontinuation due to lack of glycemic control, % of patients (n = 158-165)

	Placebo	Metformin 500 mg	Glyburide 2.5 mg	Glucovance 250/1.25	Glucovance 500/250
Total, %	40	16	16	5	6
Week 0- 20	29	11	8	2.5	3
P vs gly	NA	NA	NA	0.043	0.054
P vs metf	NA	NA	NA	0.003	0.005
P vs placebo	NA	<0.001	<0.001	<0.001	<0.001
Week 20- 32	11	5	8	2.5	3

Body weight:

The mean body weight at baseline was about 88 kg. The mean change in body weight at 20 weeks for patients on placebo and metformin were –0.7 kg and –0.6kg which were not statistically different from zero. As expected, patients on glyburide monotherapy had a small but statistically significant mean increase in body weight of 1.7 kg. The mean increases in body weight on Glucovance 250/1.25 and 500/2.5 were 1.4 and 1.9 kg respectively. The weight increase in patients on Glucovance was the same as that in patients on glyburide monotherapy. Thus, the metformin component of Glucovance does not appear to prevent glyburide-related weight gain.

Lipids:

There was little change in lipid levels. Mean total cholesterol at baseline was about 205 mg/dl. There was a mean rise of 6 mg/dl in placebo patients while levels in patients on active treatment were unchanged or lower. The placebo subtracted differences were –9 for glyburide, -8 for metformin and –6 and –7 mg/dl for the two Glucovance groups. Differences in LDL cholesterol and HDL cholesterol were not statistically significant. There was a statistically significant decrease in triglycerides both from baseline (-30 mg/dl) and placebo (-27 mg/dl) in patients on glyburide. But the changes in patients on metformin monotherapy and both formulations of Glucovance were not different from placebo or from glyburide monotherapy. It should be noted that the glyburide group had the highest mean value (250 mg/dl) at baseline and Glucovance 500/2.5 had the lowest (193 mg/dl) at baseline. Since reduction in triglyceride is often related to a high baseline value, the possible superiority of glyburide should be viewed with some skepticism.

Safety

There was one death due to a motor vehicle accident, which occurred in a patient on metformin. Discontinuation due to AE's was usually related to hypoglycemia for patients on glyburide and gastrointestinal complaints for patients on metformin. Two patients on Glucovance 500/2.5 also discontinued because of gastrointestinal complaints.

Hypoglycemia was reported in 3% of patients on placebo and metformin, 21% of patients on glyburide, 11% of patients on Glucovance 250/1.25 and 38% of patients on Glucovance 500/2.5. Glucovance 250/1.25 was statistically better than glyburide, but Glucovance 500/2.5 was statistically worse. As shown below, this apparent anomaly persisted if one looks at subjects with documented (BG<50 mg/dl) hypoglycemia, and subjects who discontinued therapy because of hypoglycemia. Because only one placebo subject and no metformin-treated subject had hypoglycemia documented with BG< 50 mg/dl, and no drop-outs because of hypoglycemia, data from the metformin and placebo arms are not included in the tables below.

	Glyburide	Glucovance	
		250/1.25	500/2.5
	N=160	N=158	N=162
Subjects with FPG < 50 mg/dl	10(6%)	8(5%)	26(16%)
Subjects discontinuing Due to hypoglycemia	5(3.1%)	4(2.5%)	9(5.6%)

For the patients shown above with hypoglycemia documented by BG< 50 mg/dl, mean baseline HbA1c values were 7.6% for glyburide monotherapy, 7.4% for Glucovance 125/250 and 8.0% for Glucovance 500/2.5. For patients discontinuing because of hypoglycemia, mean baseline HbA1c values were 7.2% for glyburide, 7.0% for Glucovance 125/2.5 and 7.5% for Glucovance 500/2.5. The distribution of subjects reporting hypoglycemia according to baseline HbA1c is shown below.

Baseline HbA1c	Subjects Reporting Treatment- Emergent Hypoglycemia		
	Glyburide	Glucovance	
		250/1.25	500/2.5
<7	7(47%) n=15	4 (29%) n=14	10(39%) n=26
7-8	23(34%) n=68	14(24%) n=59	23(43%)n=53
8-9	4(11%) n=38	1(3%) n=37	15(35%)n=43
>9	2(5%) n=39	2(4%) n=48	13(33%)n=40

One would normally expect a greater proportion of the patients reporting hypoglycemia to have lower HbA1c values. This was true for patients on glyburide monotherapy and Glucovance 250/1.25. However, for patients on Glucovance 500/2.5, a substantial proportion of patients at higher HbA1c values also reported hypoglycemia. The same relationship was true if one looks at end of study HbA1c also. Five subjects on Glucovance 500/2.5 with end of study HbA1c values over 7.1% had documented hypoglycemia (BG<50 mg/dl). There were no such subjects either on glyburide monotherapy or Glucovance 125/250.

The difference in subjects reporting hypoglycemia between the two formulations of Glucovance is particularly striking when one considers that reduction of HbA1c was virtually identical. Taking just patients with baseline HbA1c over 8% from the table above, 3/85 (4 %) subjects on Glucovance 250/125 reported hypoglycemia compared to 28/83 (34%) subjects of Glucovance 500/2.5. Remembering that the titrated dose of glyburide was 2.78 mg with Glucovance 250/1.25 compared to 4.41 mg with Glucovance 500/2.5, it is clear that the lower dose preparation allows for finer tuning of the glyburide dose so that better glycemic control can be achieved.

The frequency of gastrointestinal AE's were 43.4% with metformin monotherapy, 38.3 with Glucovance 500/2.5, 31.6% with Glucovance 250/1.25 and 24% each with glyburide and placebo. The frequency of gastrointestinal events was related to the dose of

metformin. The final dose of metformin was 1307 mg for patients on metformin monotherapy, 818 mg for patients on Glucovance 500/2.5 and 557 mg for patients on Glucovance 250/1.25. The difference in frequency of gastrointestinal events between metformin and Glucovance 250/1.25 was significant (p=0.037), but the difference between metformin and Glucovance 500/2.5 was not significant.

Fasting lactate levels at baseline and week 32 are shown in the table below. None of the differences were statistically significant. The metformin group showed the largest increase from baseline, +1.6 mg/dl (SD=5.4 n=91), but this was also not significant. It should also be noted that the normal reference range of 3-12 mg/dl is inappropriately low.

Fasting Lactate Levels (mg/dl)

	Placebo	Metformin	Glyburide	Glucovance 250/1.25	Glucovance 500/2.5.
Basal	13.3	13.2	13.7	12.4	12.7
Week 32	12.7*	14.0	13.2	12.9	12.5
Mean diff	+ 0.6	1.6	-0.2	0.9	0
SD	5.7	5.4	5.5	5.1	4.9

Laboratory normal ref range 3-12 mg/dL (0.3-1.3 mM).

* although mean values appear to go down, the mean difference was +0.6 (SD 5.7 n=57). The apparent discrepancy is because there were baseline data in 142 patients.

Open-label Period

Patients who completed the double-blind treatment were eligible for enrollment into an open-label extension. In addition, patients who withdrew from the double-blind treatment because of lack of adequate glycemic control were also eligible to enter open label treatment with Glucovance. Finally, patients who were excluded from entering the placebo controlled double blind treatment period because of inadequate glycemic control were allowed to enter open label treatment with Glucovance directly.

Patients whose HbA1c was <9% were treated initially with Glucovance 250/ 1.25 bid with meals. Those with HbA1c > 9% were treated with Glucovance 500/2.5 bid with meals. The dose was titrated to attempt to achieve HbA1c of 7%. Patients whose HbA1c remained 8% after 12 weeks at metformin/glyburide 2500mg/12.5 mg were discontinued.

The study was planned for 52 weeks of open-label treatment. The data presented in the NDA represents an interim report on patients enrolled into open-label therapy as of May 21, 1999. There is a reasonably large cohort of patients, whose glucose levels were too high for enrollment into the placebo-double blind treatment phase, who completed 26

weeks of open label treatment. Changes in HbA1c and FPG for these patients are shown below. These results show that a maximal glucose lowering effect of Glucovance is seen in 4 weeks and persists for at least 26 weeks.

Direct Enrollment of Patients in Poor Glycemic Control
(HbA1c 11 -12 or FPG>240 with HbA1c no greater than 12)

	HbA1c	Change from baseline
Baseline	10.6 n=160	
13 weeks	7.15 n=158	-3.44
26	7.09 n=144	-3.54
	Fasting Plasma Glucose	
Baseline	283 n=170	
2 weeks	168 n=156	-115
4	151 n=153	-132
13	152 n=154	-130
26	161 n=130	-122

Final dose: 1569/7.85 (metformin/glyburide)

Efficacy data for patients who rolled over from the double-blind treatment phase are limited. Since the duration of double blind treatment and open label Glucovance treatment were variable, it would be misleading to present mean HbA1c data for the patients who rolled over. However, data from these patients may provide a valuable insight into the relative efficacy of the two components in individual patients.

There were 22 patients who failed to respond to glyburide and were rolled over to Glucovance. One of these patients failed to respond to Glucovance as well. However, seven showed a good response to Glucovance. In 14 patients, it was not possible to make a clear distinction between the response to Glucovance and the initial treatment with glyburide. There were 24 patients who failed to respond to metformin and were rolled over to Glucovance. Three failed to respond to Glucovance. Ten showed a good response and in 11 patients the distinction was unclear.

Poor response to monotherapy	Response to Glucovance: good response	poor response	unclear
Glyburide (n=22)	7	1	14
Metformin (n=24)	10	3	11

In the four patients who failed to respond to Glucovance, the mean last FPG at the end of monotherapy was 211mg/dl and was 219 mg/dl at the end of Glucovance treatment. Mean FPG values for the patients who responded to Glucovance but failed to respond initially to monotherapy are shown below.

Last FPG on Glyburide	Last FPG on Glucovance	reduction	N
229	138	91(39-156)	7

Last FPG on Metformin	Last FPG on Glucovance	reduction	N
231	141	90(50-216)	10

Given that there were 160 patients in each monotherapy arm, it appears that there are about 5% of patients who did not respond initially to glyburide monotherapy but did respond to combination therapy and 7% who did not respond initially to metformin monotherapy but did respond to combination therapy.

The study is not definitive and there may be several ways of interpreting the results. But I believe the most straightforward explanation is as follows:

Most patients with type 2 diabetes (80-90%) appear to respond to either metformin or glyburide. When the two treatments are used together as Glucovance, the result is roughly the sum of what would be seen with each individual component. However, there are about 5% of patients who do not respond to glyburide but do respond to the metformin component of Glucovance, and about 7% of patients who do not respond to metformin but do respond to the glyburide component of Glucovance.

Safety:

Data are available on 826 patients, 500 on Glucovance 250/1.25 and 326 on 500/2.5. One patient died due to multiple injuries in a plane accident. There were 19 hospitalizations for surgery or ischemic heart disease. 19 patients discontinued because of an AE , 7 due to hypoglycemia (no event required medical assistance) and 8 due to a gastrointestinal complaint. An additional patient withdrew from the open-label period because of elevated lactate levels.* Other causes for discontinuation seem unrelated to treatment. The one trauma-related death has already been noted.

*(This patient had a baseline fasting lactate of 14.7 mg/dl before randomization to glyburide. On the final day of double blind glyburide her fasting lactate was 15.2. Repeat determinations during open-label treatment with Glucovance were 21.4, 16.7, and 18.6. The patient was withdrawn because these values were interpreted as being elevated. However, the change from baseline is not abnormal. Also, the maximal value on Glucovance treatment of 21.4 mg/dL is not outside the 95% confidence limits seen in otherwise normal patients with diabetes.)

Summary

Glucovance 250/1.25 is better than either of its components, glyburide or metformin, alone as first line therapy in patients whose starting HbA1c is 9% or greater. Use of the glyburide and metformin together as initial therapy allows for better glycemic control to be achieved with lower doses of each component, thus minimizing adverse events.

APPEARS THIS WAY
ON ORIGINAL

Second line therapy – 138-011

Patients were studied who had inadequate control of hyperglycemia (FPG 126 mg/dl – 300 mg/dl and HbA1c at least 7.4% at screening) while on at least half-maximal dose of sulfonylureas for at least 1 month. There was a two week single-blind glyburide run-in (5 mg bid for one week and 10 mg bid for one week) followed by 16 weeks of double blind

treatment. There were 4 treatment arms: Glyburide 20 mg fixed dose as 5 mg tablets, metformin 500 mg, Glucovance 500/2.5 and Glucovance 500/5 with appropriate placebo tablets for triple dummy blinding. The titration of metformin or Glucovance was done at the discretion of the investigator for FPG >140. Titration continued until either FPG was < 140 or the maximal dose (two tablets twice daily) was achieved.

717 patients were enrolled and 639 received randomized therapy, approximately 160 in each group. Mean age was approximately 60 years, mean duration of diabetes 7.4 years, and mean BMI about 30.6. There were 59.6% male, 68% white. Mean HbA1c at baseline was about 9.5% with FPG about 213 mg/dl. There were no baseline imbalances.

Changes in HbA1c are shown in the following table.

	Metformin	Glyburide	Glucovance 500/2.5	Glucovance 500/5
Final Dose	1840	20	1760/8.8	1740/17
HbA1c: baseline	9.51	9.63	9.43	9.44
Final	9.82	9.61	7.92	7.91
Diff from Gly			-1.69	-1.70
Diff from Metf			-1.90	-1.91

As expected, there was no mean change (-0.02) in HbA1c in the glyburide group and a small increase (0.31) in the metformin group. Mean reduction in HbA1c was 1.51 and 1.53 for Glucovance 500/2.5 and 500/5 respectively. This was superior to either of the monotherapies ($p<0.001$). Changes in HbA1c were little different whether patients had previously been on submaximal or maximal dose SFU. Indeed, patients who had been on submaximal SFU experienced a small mean rise in HbA1c (0.10) after treatment with 20 mg glyburide while those previously on maximal dose showed a small mean fall (-0.11).

From mean baseline FPG values of about 213 mg/dl, there was a mean rise of 3 mg/dl and 20 mg/dl in the glyburide and metformin monotherapy groups respectively as opposed to mean reductions of 43 and 49 mg/dl in the Glucovance 500/2.5 and 500/5 respectively. Both Glucovance groups were superior to both monotherapy groups ($p<0.0001$). The maximal reduction in FPG was achieved at 8 weeks in both Glucovance arms. A summary of results for HbA1c and FPG are shown below

	Glyburide	Metformin	500/2.5	500/5
HbA1c				
Final	9.61	9.82	7.92	7.91
Change from baseline	-0.02	0.31	-1.51	-1.53
FPG				
Final	221	234	169	161

Change from baseline	3	20	-43	-49

From tables 10.1.1 and 10.2.1

Final doses of study medications are shown in the tables below. It is striking that the large disparity in final glyburide dose between the two Glucovance preparations is not reflected in differences in control of hyperglycemia.

Final Metformin dose, % of patients

Dose mg/d	Metformin monotherapy	Glucovance 500/2.5	500/5
500	2.6	3.8	2.5
1000	5.2	9.4	12.3
1500	13.7	18.1	19.1
2000	78.4	68.8	66

Final Glyburide dose, % of patients

	Glyburide	500/2.5	500/5
2.5-5	0	13.2	2.5
7.5	0	18.1	0
10	0	68.8	12.3
15-20	100 (all at 20 mg)	0	84.9

118/630 randomized patients discontinued randomized treatment, 42 because of hyperglycemia and 8 withdrew consent because of hyperglycemia. Combining these two groups there were 50 patients who discontinued the trial because of inadequate hyperglycemia control. There were 17/164 (10.4%) patients on glyburide, 27/153 (17.6%) patients on metformin, 4/160(2.5%) patients on Glucovance 500.2.5 and 2/162 (1.2%) patients on Glucovance 500/5.

Body weight:

Mean body weight fell 2.8 kg in the metformin group but rose 0.4 kg in the glyburide group. The weight gain on Glucovance 500/2.5 and 500/5 was 0.8 and 0.5 kg respectively.

Lipids:

Mean cholesterol at baseline was about 214 mg/dl. It was unchanged at endpoint in the glyburide group but fell about 10 mg/dl in the other three groups. Mean LDL cholesterol fell 14 mg/dl on metformin monotherapy and 8 and 0.4 mg/dl in each of the Glucovance groups. Based on 95% CF the reduction in LDL chol on metformin monotherapy was greater than the reduction with Glucovance 500/5. Mean HDL was little changed in any

group. Triglyceride on glyburide was essentially unchanged. There were small reductions in triglyceride on Glucovance compared to a small rise on metformin. There were no statistically significant differences.

Safety

There were four deaths due to myocardial infarction, equally distributed among the two monotherapies and Glucovance. Gastrointestinal AE's occurred in 21% of glyburide patients, 39% of metformin patients and 35% of Glucovance patients. A gastrointestinal AE led to discontinuation of double blind therapy in 1/164 (0.6%) patient on glyburide, 6/153 (3.9%) patients on metformin and 7/322 (2.1) patients on Glucovance (both formulations combined). There were no reports of severe hypoglycemia and no patients discontinued treatment because of hypoglycemia. There were 26 (4.1%) patients who reported symptoms of hypoglycemia, 3 on glyburide, 1 on metformin and 22 on Glucovance. One glyburide patient had a finger stick value of " < 40mg/dl". The lowest documented finger stick value on Glucovance was 51 mg/dl. The highest was 101 mg/dl. Baseline fasting lactate was about 11 mg/dl. There was a mean rise of 0.86 mg/dl (SD 6.29) in patients on metformin and a mean fall of 0.6 mg/dl (SD 5.74) in glyburide patients. The patients on Glucovance changes of 0.54 mg/dl for Glucovance 500/2.5 and –0.16 mg/dl for Glucovance 500/5.

Summary:

Glucovance is safe and effective for treatment of hyperglycemia in patients inadequately treated with sulfonylureas. There is no difference between the 500mg/2.5mg and 500mg/5 mg preparations except that final titrated dose of glyburide. There seems to be no rational for treatment regimens that exceed 10 mg of glyburide.

Integrated Summary of Safety:

Safety issues during the double blind periods in studies 019 and 011 were discussed under the individual studies. On January 18, 2000, the Sponsor submitted a four-month safety update, which covered all data through September 30, 1999 for events in patients enrolled in long-term open label studies. There were data on 1303 patients with a mean duration of

exposure of 210 days. Numbers of patients on low, medium and high dose Glucovance were 501, 518 and 284 respectively. Their mean age was 56years, 58% male, and 77% white.

There were no deaths. 33 patients (2.5%) had serious adverse events. Two of these were hospitalizations for congestive heart failure due to ischemic heart disease which led to discontinuation of study drug. A total of 15(1.2%) patients discontinued because of an adverse event. In addition to the two heart patients already noted, there were three with diarrhea and four with hypoglycemia, two with rashes and four patients with other conditions.

APPEARS THIS WAY
ON ORIGINAL

Labeling Issues:

Description – change '———— to ————

Mechanism – delete ———————————— The text should be the same as in the Glucophage label.

Clinical studies -

[ ]

Hypoglycemia – the text above table 6 says that hypoglycemia in patients on Glucovance 250/1.25 occurred primarily in patients with HbA1c <8 but fails to mention that hypoglycemia was reported in several patients on 500/2.5 whose HbA1c was above 8. This omission should be corrected.

Dosage and Administration - The text for initial therapy and second line therapy follow directly from the clinical trials and is acceptable.

[ ]

From their press release of Jan 28, 2000, it appears that BMS hopes that patients on combination therapy will be switched to Glucovance

" A significant number of people with type 2 diabetes require more than one medication to manage their condition. It is our hope that our novel oral antidiabetic will provide an improved and simplified treatment alternative for these patients."

In a revised label submitted June 12, BMS has deleted this indication. However, I am recommending we grant this indication based on the PK data and the results of the clinical trials of first line and second line therapy.

I suggest the following wording:

[ ]

The Sponsor should also add a statement cautioning about the greater bioavailability of glyburide in Glucovance vs Micronase and the lack of comparative data to other formulations of glyburide.

Although the dose of 2000/20 (four 500 mg/5 mg tablets) was studied, it was no more effective than 2000/10 (four 500 mg/2.5 mg tablets). The maximal effective dose of glyburide seems to be 10 mg. Giving larger doses of glyburide promotes hypoglycemia without lowering HbA1c levels. Therefore, it is not clear which patients, if any, should be given the 500/5mg formulation.

[ ]

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ON ORIGINAL

Discussion

Glucovance is safe and effective for the treatment of hyperglycemia in previously untreated patients and patients previously on monotherapy with sulfonylureas. Although no studies were done in patients previously on the combination of a glyburide plus metformin, I would be willing to extend the Glucovance indication to these patients as well based on the PK data and results of the other clinical trials(see labeling comments

above). The use of Glucovance as initial treatment in naïve patients will break new ground and requires additional comments

For patients whose HbA1c is 9% or above, the use of Glucovance as initial therapy leads to better control than when either glyburide or metformin is used alone. Since control of hyperglycemia is achieved using a lower titrated dose than when either component is used as monotherapy, the adverse events (hypoglycemia for glyburide and gastrointestinal complaints for metformin) of the individual components are minimized. The results are particularly impressive with the lowest dose combination Glucovance 250mg/1.25mg. For patients with milder hyperglycemia, the potential advantage of starting with Glucovance is less apparent. Even for patients with severe hyperglycemia who are successfully treated with Glucovance, it is not clear that long-term treatment with Glucovance would be better than use of the individual components as monotherapy.

UKPDS has shown that patients generally fail monotherapy after a period of several years. Based on these data, one could argue that patients who respond well to Glucovance should remain on this product indefinitely. On the other hand, there are possible disadvantages of this course of action. The weight-sparing effect of metformin is lost when given with glyburide as Glucovance. Particularly for patients who are obese, long-term treatment with metformin alone might be preferable to Glucovance. Patients who are likely to develop azotemia would be better off on glyburide than on Glucovance because of the risk of lactic acidosis. The metformin label also cautions against its use in patients over 80 and in patients with congestive heart failure. Thus, elderly patients on Glucovance should probably be taken off Glucovance at some point in order to be consistent with the precautions and contraindications in the metformin label.

The question of the relative efficacy of Glucovance versus its individual components is more complicated than it may seem. Although glyburide and metformin treat different aspects of diabetes, it is now recognized that lowering glucose levels by any mechanism can affect all aspects of diabetes. Metformin, for example, does not stimulate insulin secretion directly. But lowering glucose levels with metformin would be expected to improve beta cell function in some patients, indirectly, by alleviation of "glucose toxicity". After initial treatment with Glucovance, one might expect these patients to do perfectly well if switched to glyburide alone. Obese patients, however, would probably be better off on metformin alone.

The problem of investigating relative efficacy is made very difficult by fact that the criteria for diagnosis of type 2 diabetes are non-specific. It is generally recognized that type 1 diabetes is an autoimmune disease of the beta cells. In addition to hyperglycemia, patients with type 1 diabetes generally have immune markers at some point in the disease process. No pathogenesis-based diagnostic criteria are recognized for type 2 diabetes.
Other than satsifying safety criteria, patients are generally recruited for clinical trials of new drugs to treat type 2 diabetes, if they have diabetes by glucose criteria and do NOT have type 1 diabetes. I have little doubt that there are several defects that contribute to the

phenotype of what we call type 2 diabetes. It stands to reason that patients with certain defects will be responsive to one class of drugs while patients with other defects will be responsive to a different class of drugs. Most studies of patients with type 2 diabetes shave shown a combination of insulin resistance in liver and muscle plus reduced beta cell reserve, but the extent of each defect varies in different patients. One might expect that patients whose beta cell defect predominates might respond best to sulfonylureas, those with insulin resistance to respond best to "glitazones" and those with excess hepatic glucose output to respond best to metformin. These distinctions are impossible to make with the designs of clinical trials that have previously been used, but should be made before patients are committed to lifetime combination therapy.

This problem applies to the use of Glucovance as first line treatment for patients with HbA1c>9. When taken as a group, we know that these patients will have an excellent response to low dose Glucovance within a few weeks. Very few patients will fail therapy because of lack of efficacy or adverse events. But once having removed the "toxic" effect of severe hyperglycemia, it is entirely possible that certain patients would do equally as well on glyburide monotherapy while others would do well metformin monotherapy. Preliminary analysis suggests that one of the two components may be unnecessary in about 5-7% of patients who respond well to Glucovance (p 12). This question is particularly important for young adults and children. Should a favorable response to four weeks of Glucovance mean that a patient with type 2 diabetes should be on combination therapy for life? My hunch is that most of children and obese non-elderly adults would be better off on metformin alone because of its favorable effect on weight. To answer this question would require a study in which patients were randomized to Glucovance vs monotherapy with each component AFTER an initial period of treatment with Glucovance.

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ON ORIGINAL

Phase 4

Phase 4 commitments are generally made to resolve safety issues that came to light during the review and had not been resolved at the time of approval. Glyburide and metformin have both been used to treat type 2 diabetes for many years. No new safety issues emerged from this study. Therefore I do not see any strong reason for requiring any phase 4 studies before Glucovance is marketed.

The long term effects of combination therapy with Glucovance vs monotherapy with the individual components have not been demonstrated. Although UKPDS suggested that obese patients on metformin monotherapy may have improved survival, this benefit was not observed in glyburide-treated patients for whom metformin was added. A study comparing the long-term effects of the combination of glyburide plus metformin vs monotherapy with glyburide and metformin would be of interest. But the scope of such a study is beyond what I believe FDA can reasonably request of BMS. A generic metformin will probably be available within two years which is well before such a study can be completed. Although Glucovance will likely be a successful product, cost considerations will probably lead many physicians to use generic glyburide and metformin instead of Glucovance. BMS may complain that they will have difficulty recouping the cost of a large long-term outcomes study and argue against being compelled to make such an extensive phase 4 commitment. In this context, it is worth noting that BMS is about to complete a very large phase 4 study for Glucophage (the COSMIC trial), the results of which will benefit manufacturers of all future metformin products.

Recommendations:

Pending revisions in labeling the Glucovance 250/1.25 and 500/2.5 tablets should be approved. The 500/5 mg tablets are not necessary and should not be approved

Robert I Misbin MD

Medical Officer
HFD 510
July 3, 2000
Revised July 7, 2000
Finalized July 10, 2000

21178 a

Supplementary medical officer review

The safety update submitted January 18, 2000 is adequate for approval. The requirement of a safety update within 120 days of approval should be waived. The reason for this recommendation is as follows:

The blinded trials have ended. Follow-up of safety issues during open-label treatment is not likely to yield any new information because there is already a very large safety base for glyburide and metformin. Both drugs were used long-term in the UKPDS. With respect to metformin specifically, the COSMIC trial of over 8000 patients has not yielded any new safety issues. Neither has the 2000 patient year experience of metformin treatment of impaired glucose tolerance in the NIH Diabetes Prevention Trial.

Recommendations for label:

BMS has sent additional analysis regarding patients in the open-label trail. Based on Dr Jenkin's request that the data be presented in the text rather than as a table, I suggest the following wording to replace table 2:

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I continue to oppose approval of the 5.0mg/500mg dosage form. If this dosage form is approved anyway, the Dosage and Administration section of the label should have the following statement:

[

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Robert I Misbin MD