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/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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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:

[redacted]

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:

[redacted]

/S/

Robert I Misbin MD
July 27, 2000

[redacted]

/S/

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

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

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 debarment 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 98-125 and for AUC is 1.08-1.29. 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	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	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

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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.

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	Glucovance 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.

Labeling Issues:

Description – change [redacted] to [redacted]

Mechanism – delete [redacted] The text should be the same as in the Glucophage label.

Clinical studies - delete [redacted]

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. [redacted] 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:

[redacted]

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.

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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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.

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

[/S/]

Robert I Misbin MD
Medical Officer
HFD 510
July 3, 2000
Revised July 7, 2000
Finalized July 10, 2000

Concur
[/S/] 7/10/00

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

APPEARS THIS WAY
ON ORIGINAL

Robert I Misbin MD
HFD 510

July 3, 2000
Revised July 6, 2000

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 submitted Disbarrment and financial disclosure documents on September 30, 1999. I have examined these documents and found them to be acceptable.

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 98-125 and for AUC is 1.08-1.29. 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.

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	Glucovance 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.

Labeling Issues:

Description – change [redacted] to [redacted]

Mechanism – delete [redacted] The text should be the same as in the Glucophage label.

Clinical studies - delete [redacted]

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:

[redacted]

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.

APPEARS THIS WAY
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.

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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.

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

/S/

Robert I Misbin MD
Medical Officer
HFD 510
July 3, 2000
Revised July 5, 2000

/S/ 7/6/00

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ON ORIGINAL