APPLICATION #:	**NDA 21-178**	**APPLICATION TYPE:**	
SPONSOR:	**Bristol Myers Squibb**	**PROPRIETARY NAME:**	**Glyburide/Metformin tablets……**
CATEGORY OF DRUG:		**USAN / Established Name:**	**Glucovance…….**
		ROUTE:	**Oral…….**
MEDICAL REVIEWER:	**Robert I Misbin**	**REVIEW DATE:**	**Jan 12, 2004……..**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
July 21, 2003	Electronic Submission		

Overview of Application/Review-

Use of Glucovance in pediatric patients with type 2 diabetes:

Recommended Regulatory Action - The label should be revised to state:

"The safety and efficacy of GLUCOVANCE were evaluated in an active-controlled, double-blind, 26-week trial involving a total of 167 pediatric patients (ranging from 9 to 16 years of age) with type 2 diabetes. The mean HbA1c at baseline in these patients was about 7.8%. GLUCOVANCE was not shown statistically to be superior to either metformin or glyburide with respect to reducing Hb_{A1c} from baseline . No unexpected safety findings were associated with GLUCOVANCE in this trial."

Signed: Medical Reviewer: Robert I Misbin_____ Date: January 12, 2004

Medical Team Leader: _____ Date: _____

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Executive Summary

I. Recommendations:

The Glucovance label currently says

Under Pediatric use:

"Safety and effectiveness of GLUCOVANCE in pediatric patients have not been established."

The Sponsor proposes to change this to:

"The safety and efficacy of GLUCOVANCE were evaluated in an active-controlled, double-blind, 26-week trial involving a total of 167 pediatric patients (ranging from 9 to 16 years of age) with type 2 diabetes. (b) (4) *No unexpected safety findings were associated with GLUCOVANCE in this trial."*

This should be revised to read:

"The safety and efficacy of GLUCOVANCE were evaluated in an active-controlled, double-blind, 26-week trial involving a total of 167 pediatric patients (ranging from 9 to 16 years of age) with type 2 diabetes. The mean HbA1c at baseline in these patients was about 7.8%. GLUCOVANCE was not shown statistically to be superior to either metformin or glyburide with respect to reducing Hb_{A1c} from baseline . No unexpected safety findings were associated with GLUCOVANCE in this trial."

The following statement, presently in the Dosage and Administration Section,

"GLUCOVANCE is not recommended for use during pregnancy or for use in pediatric patients"

can be modified to read:

"GLUCOVANCE is not recommended for use during pregnancy."

II Summary of Clinical Findings

The Sponsor submitted the results of one 26 week, three-arm, active-controlled double-blind trial. The three arms were Glucovance, metformin alone, and glyburide alone.

167 patients with type 2 diabetes, ages 9-16, were randomized and received double-blind medication. 87 (52%) patients had never previously received antidiabetic medications. The mean age was 13.7 years. They were 35% male and 65% female. Distribution by ethnicity was 62% white, 21% black, 13% Hispanic, 4% Asian, 1% other.
Patients were > 50th percentile for weight and did not have adequate glycemic control on exercise/diet with or without a single oral hypoglycemic drug. Inadequate glycemic control was defined as HbA1c > 6.4% and mean fasting glucose (MFG)< 350 mg/dl.

Drug-naïve patients had to have HbA1c between 6.4% and 14% at screening. After a one week lead-in, drug-naïve patients with MFG<350 mg/dl were randomized. Non-naive patients (on a single oral hypoglycemic agent) had to have HbA1c between 6.4% and 9% at screening. They underwent a variable 2 – 4 week washout period. During the washout, subjects were eligible for randomization if the MFG was 200-350 mg/dl.

The primary efficacy variable was change in HbA1c. The study was designed to test the superiority of Glucovance to each of the monotherapies. The ITT population consisted of the 160 subjects who had HbA1c measurements at baseline and endpoint.

Efficacy:

The major efficacy findings are shown in the table below. Glucovance (Metformin/Glyburide) was not superior to metformin or glyburide monotherapy with respect to reduction in HbA1c.

	MET/GLY	MET	GLY
HbA1c	N=57	N=54	N=49
Baseline	7.85	7.99	7.70
Week 26/last	7.05	7.46	6.80
Adj mean change*	**-0.80**	**-0.48**	**-0.96**
FPG			
Baseline	154	176	154
Week 26/last	135	143	135
Adj mean change*	**-23**	**-25**	**-23**
Body weight			
Baseline	80.1	79.7	78.9
Week 26/last	81.3	79.7	81
Adj mean change*	**+1.24**	**0.00**	**+2.08**
Mean Final Dose	**623mg/3.1mg**	**1500 mg**	**6.5 mg**

* There were no statistically significant differences between Glucovance and the monotherpies.

These results appear to be at variance to the results found in the original NDA in trials conducted in adult patients with type 2 diabetes. These data are summarized* in the tables below for the purpose of comparison to data from the pediatric trial shown above.

Studies in Adults:

	Mean Change In HbA1c		
	Met/Gly	Met	Gly
HbA1c, baseline	8.22 n=149	8.23 n=141	8.14 n=142
HbA1c, change	-1.48	-1.03	-1.24
Final dose, mg	577/2.78	1307	5.3

* To facilitate comparison to the pediatric study, only data from the Metformin/Glyburide 250/1.25 mg, metformin monotherapy and glyburide monotherapy arms are shown. The adult study also had a placebo arm, and a Metformin/Glyburide 500 mg/2.5 mg arm. Data from these arms are not included in this table but are shown in later tables.

In the original NDA, Glucovance was found to be superior to metformin and glyburide, and was therefore approved for initial therapy in adults with type 2 diabetes. However, the superiority of Glucovance was largely driven by data from patients with HbA1c of 9% and above (see table below).

Studies in Adults: Change in HbA1c according to Baseline HbA1c

HbA1c, baseline	Met/Gly		Met		Gly	
<8	-0.90	n=71	-0.73	n=68	-0.93	n=77
8-8.9	-1.31	n=35	-1.26	n=39	-1.27	n=34
9.0-9.9	-2.40	n=30	-1.50	n=23	-1.89	n=22
>9.9	-3.21	n=13	-1.28	n=11	-1.87	n=9

For patients with HbA1c under 9% there was no advantage of Glucovance over the individual monotherapies. That very few pediatric patients had this degree of hyperglycemia may well account for the difference between the results of the pediatric trial and the original trial in adults. As shown in an earlier table, the mean HbA1c values at baseline in the pediatric study were about 7.7 – 8%.

A second difference between the pediatric trial and the adult trial was that the adult trial allowed only treatment-naïve patients to be randomized. In her review, the FDA statistical reviewer makes the point that Glucovance appeared better than the monotherapies in naïve but not in non-naïve pediatric patients.

	Met/Gly	Met	Gly
Naïve	-1.35	-0.92	-1.23
Non-naïve	-0.09	-0.20	-0.68

That all three treatments appeared less effective in the non-naïve patients may mean that these patients did not receive adequate doses of study medications.

Safety:

No unexpected safety issues emerged during the study. There were only small differences in the spectrum and frequency of adverse events among the three treatment arms. Due to dose-sparing of metformin, patients on Glucovance appeared to have somewhat fewer gastrointestinal complaints than patients on metformin monotherapy. Patients on metformin monotherapy gained less weight. As expected, hypoglycemia appeared related to glyburide.

Conclusions:

Little if any new or unexpected information about the use of Glucovance in children was learned from this trial. Although there may appear to be differences in efficacy between children and adults, these apparent differences likely reflect differences in trial design.

In adult patients, an important use of Glucovance is first line therapy for moderately severe hyperglycemia. The results with Glucovance in this setting are probably better than what could be obtained with insulin, although FDA has reviewed no direct comparison of Glucovance to insulin. Patients with moderately severe hyperglycemia were not studied in the pediatric trial. Based on the experience with adults, it is likely that Glucovance would have been effective in pediatric patients with moderately severe hyperglycemia, and this combination therapy might save children with type 2 diabetes from being started on injections of insulin. The revised label should not preclude physicians from considering this possibility. It is therefore important to indicate that the negative results in this trial pertain to patients whose HbA1c levels at baseline were about 7.8%.

Clinical Review:

I Introduction and Background

Glucovance (metformin/glyburide) is a fixed dose combination product containing metformin and glyburide. It was originally developed as a convenience for patients who were taking metformin and glyburide as individual medications. However, it is also useful as initial therapy. Particularly in patients with moderately severe hyperglycemia, initial therapy with Glucovance, is more effective than either metformin or Glyburide alone.

The following two tables are taken from the original NDA and show the results of a double blind, placebo-controlled study. When the entire patient population is viewed as a whole, Glucovance is seen to be more effective than either Metformin monotherapy or Glyburide monotherapy. But the major advantage to Glucovance is in patients with baseline HbA1c > 9%. In patients whose HbA1c at baseline was < 8%, all active treatment arms gave the same result.

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

Baseline HbA1c	placebo	Glyburide	Metformin	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

A special feature of the Glucovance development program was direct enrollment into an open-label study of patients who failed to respond during double-blind treatment or whose hyperglycemia at screening was too severe to allow them to be randomized into a placebo-controlled trial. Results from this study are shown in the table below. Particularly impressive is that the reduction in fasting plasma glucose occurred over 2-4 weeks and

was not associated with hypoglycemia. These results support the use of Glucovance as first line therapy in patients with moderately severe hyperglycemia, a situation in which many patients would ordinarily have been treated with insulin.

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)

Type 2 diabetes has recently been recognized to be an important problem in obese adolescents, particularly in Latinos and African Americans. Given the fact that children with type 1 diabetes invariably require insulin, it is understandable that many pediatricians start children with type 2 diabetes on insulin also, even though most of these children could probably be treated effectively with an oral agent. Particularly in children with moderately severe hyperglycemia (FPG about 300 mg/dl), Glucovance as initial treatment might preclude the need for injections of insulin.

But should a favorable initial response to Glucovance mean that a child with type 2 diabetes should be on a combination of drugs for life? My hunch is that most of patients, even those with moderately severe hyperglycemia, could be controlled with monotherapy once the "toxic" of hyperglycemia itself were removed. To answer this question, I proposed in my review of the original NDA (July 10, 2000) that in order to obtain pediatric exclusivity, BMS should perform a study in which patients are randomized to either Glucovance or to monotherapy with metformin or glyburide AFTER their hyperglycemia had been stabilized with Glucovance. In lieu of this proposal, FDA issued a written request for a standard three-arm study comparing Glucovance to each of the monotherapies in patients with HbA1c > 6.4%. The study population included treatment-naive children as well as children already on oral anitidiabetic therapy.

II Clinically relevant findings from review from other disciplines: No additional information

III Pharmocokinetic and Pharmacodynamics:

The report by the Biopharm reviewer SM Chung states:

"It seems that glyburide and metformin pharmacokinetics of Glucovance® are not associated with age and body surface area in the pediatric type 2 diabetes though the interpretations are limited by small number of pediatric patients in this study."

IV Description of Clinical Sources The results of one phase 3 trial (138-055) was submitted. This is described in detail in section V1, "Review of Efficacy".

V Clinical Review Methods

The review was conducted from an electronic submission. No routine inspections of the sites were performed. The financial disclosure and debarment documentation appear adequate

The Sponsor, Bristol-Myers Squibb (BMS), submitted debarment and financial disclosure documents on July 23, 2003. I have examined these documents and found them to be acceptable. The debarment statement indicated that BMD had not and will not use any data from an investigator who had been debarred. This statement was dated July 3 , 2003.

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 Two sites were listed as having completed the financial disclosure forms incorrectly but neither of these sites randomized any patients.No additional comments

V1 Review of Efficacy

The Sponsor submitted the results of one multicenter, randomized, three-arm, parallel-group, active controlled double blind trial. The duration of the study was 26 weeks. The three arms were Glucovance, metformin alone, and glyburide alone.

167 patients with type 2 diabetes, ages 9-16, were randomized and received double-blind medication. The mean age was 13.7 years. They were 35% male and 65% female. Distribution by ethnicity was 62% white, 21% black, 13% Hispanic, 4% Asian, 1% other. Patients with type 2 diabetes > 50th percentile for weight, who did not have adequate glycemic control on exercise/diet alone or exercise/diet with a single oral hypoglycemic drug. Inadequate glycemic control was defined as HbA1c > 6.4% and mean fasting glucose (MFG)< 350 mg/dl.

Drug-naïve patients had to have HbA1c between 6.4% and 14% at screening. After a one week lead-in, drug-naïve patients with MFG<350 mg/dl were randomized. Non-naive patients (on a single oral hypoglycemic agent) had to have HbA1c between 6.4% and 9% at screening. They underwent a variable 2 – 4 week washout period. During the washout, these subjects were eligible for randomization if the MFG was 200-350 mg/dl. Subjects with MFG> 350 mg/dl at any point were eligible for direct entry into open-label treatment. An interim safety report for the extension study was submitted but no efficacy data. (b) (4)

Demographic characteristics at baseline are shown in the following tables.

Characteristic	Metformin HCl/Glyburide N = 59	Metformin HCl N = 55	Glyburide N = 53	Total N = 167
Body Weight (kg), n (%)				
< 50	8 (13.6)	7 (12.7)	11 (20.8)	26 (15.6)
50 - < 70	17 (28.8)	16 (29.1)	14 (26.4)	47 (28.1)
70 - < 90	16 (27.1)	13 (23.6)	13 (24.5)	42 (25.1)
90 - < 110	9 (15.3)	11 (20.0)	8 (15.1)	28 (16.8)
≥ 110	9 (15.3)	8 (14.5)	7 (13.2)	24 (14.4)
n	59	55	53	167
Mean (SD)	80.09 (27.70)	79.92 (27.54)	77.65 (30.32)	79.26 (28.36)
Median	74.20	73.20	74.00	74.00
Range	36.5 - 146.8	27.0 - 151.0	29.6 - 158.1	27.0 - 158.1
Waist Circumference (cm)				
n	59	55	53	167
Mean (SD)	93.10 (22.06)	93.88 (20.77)	90.08 (24.04)	92.40 (22.23)
White	36 (61.0)	29 (52.7)	38 (71.7)	103 (61.7)
Black	14 (23.7)	13 (23.6)	8 (15.1)	35 (21.0)
Asian/Pacific Islander	2 (3.4)	3 (5.5)	1 (1.9)	6 (3.6)
Hispanic/Latino	7 (11.9)	10 (18.2)	5 (9.4)	22 (13.2)
Other	0	0	1 (1.9)	1 (0.6)
Body Mass Index (kg/m^2), n (%)				
< 20	4 (6.8)	6 (10.9)	9 (17.0)	19 (11.4)
20 - < 25	17 (28.8)	13 (23.6)	16 (30.2)	46 (27.5)
25 - < 30	13 (22.0)	9 (16.4)	8 (15.1)	30 (18.0)
30 - < 35	9 (15.3)	11 (20.0)	9 (17.0)	29 (17.4)
≥ 35	16 (27.1)	16 (29.1)	11 (20.8)	43 (25.7)
n	59	55	53	167
Mean (SD)	30.31 (9.65)	29.74 (8.42)	28.67 (9.45)	29.60 (9.17)
Median	27.10	29.90	25.40	27.60
Range	18.4 - 58.1	15.5 - 50.5	16.4 - 53.0	15.5 - 58.1

To cover the cost of study participation, patients received $26 for each completed study visit ($50 for those traveling fifty miles or greater). A bookstore gift certificate of $25 was given at visits weeks 0,2,4,6,10,14,18,22, and 26 of the double blind treatment phase and visit weeks 2,4,6,10,14,18,22, and 26 of the open-label treatment phase.

Table 8.5 presents the number of randomized subjects who received antihyperglycemic medications prior to screening.

Table 8.5: Number (Percent) of Subjects Who Received Antihyperglycemic Medications Prior to Screening

	Number (%) of Subjects		
Drug Name	**Metformin HCl/Glyburide N = 59**	**Metformin HCl N = 55**	**Glyburide N = 53**
Total Number of Subjects Who Received Prior Antihyperglycemic Medications	26 (44.1)	30 (54.5)	24 (45.3)
Total Number of Prior Antihyperglycemic Medications	36	39	28
Diabetes Therapy	26 (44.1)	30 (54.5)	24 (45.3)
Acarbose	0	1 (1.8)	2 (3.8)
Gliclazide	1 (1.7)	3 (5.5)	2 (3.8)
Glimepiride	1 (1.7)	0	0
Glipizide	0	1 (1.8)	2 (3.8)
Glyburide	4 (6.8)	2 (3.6)	1 (1.9)
Insulin	8 (13.6)	8 (14.5)	4 (7.5)
Lispro Insulin	3 (5.1)	1 (1.8)	0
Metformin	18 (30.5)	22 (40.0)	16 (30.2)
Pioglitazone	1 (1.7)	1 (1.8)	1 (1.9)

The primary efficacy outcome was change in HbA1c. Secondary outcomes were change in fructosamine, fasting plasma glucose, 2-hour postprandial glucose, fasting and 2-hour postprandial insulin and C peptide levels, body weight.

The study medications were Metformin/Glyburide 250/1.25 mg, metformin 500 mg and Glyburide 1.25mg. Matching placebos (triple dummy) were used to insure blinding. Dosing began once daily in the morning. The dose was titrated at weeks 2,4,6,10, and 14 as needed if MFG>126 mg/dL and kept constant thereafter.

Discontinuations due to lack of glycemic control were 10.2% for Glucovance, 20% for metformin and 11.3% Glyburide. One patient on Glucovance withdrew because of hypoglycemia.

The final doses of study medications are shown in the following tables:

Table 9.1B: Final Dose of Metformin HCl/Glyburide Received During the Double-Blind Phase

Dose (in mg per day)	Number (%) of Subjects Metformin HCl/Glyburide N = 59
250/1.25	16 (27.1)
500/2.50	14 (23.7)
750/3.75	13 (22.0)
1000/5.00	16 (27.1)
Mean	622.9/3.114

CV138059

Table 9.1C: Final Dose of Metformin HCl Received During the Double-Blind Phase

Dose (in mg per day)	Number (%) of Subjects Metformin HCl N = 55
500	11 (20.0)
1000	7 (12.7)
1500	8 (14.5)
2000	29 (52.7)
Mean	1500.0

CV138059

Table 9.1D: Final Dose of Glyburide Received During the Double-Blind Phase

Dose (in mg per day)	Number (%) of Subjects Glyburide N = 52
2.5	16 (30.8)
5.0	9 (17.3)
7.5	6 (11.5)
10.0	21 (40.4)
Mean	6.54

Efficacy results:

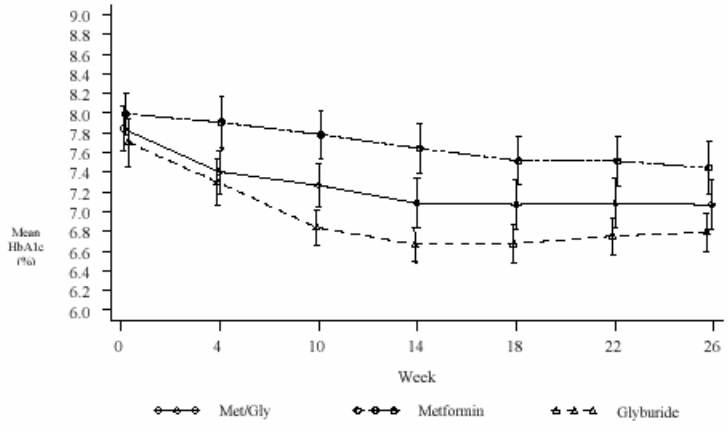
Mean HbA1c fell from baseline in all three groups. Although the reduction in HbA1c appeared somewhat less with metformin, the differences between metformin monotherapy and the other two arms were not statistically different.

Table 10.1.1: Summary of HbA_{1c} Changes from Baseline

	Metformin HCl/Glyburide N = 57	Metformin HCl N = 54	Glyburide N = 49
Baseline Mean (SD)	7.85 (1.74)	7.99 (1.59)	7.70 (1.69)
Week 26/Last Mean (SD)	7.05 (1.88)	7.46 (1.98)	6.80 (1.40)
Adjusted[a] Mean Change from Baseline (SE[b])	-0.80 (0.19)	-0.48 (0.20)	-0.96 (0.21)
Difference[c] Between Metformin HCl/Glyburide vs. (SE[b])		-0.32 (0.27)	0.16 (0.28)
Overall p-value[b]: 0.239			

Furthermore, the time course shown below suggests that the reduction in HbA1c in the metformin arm may not have been complete even at endpoint.

Figure 10.1.1: Mean HBA_{1c} Level (Percent) Over Time



Subset analysis by the Sponsor, shown in the table below, indicates that there was no subset in which Metformin/Glyburide was clearly better than the individual monotherapies.

Table 10.1.3: Mean Change in HbA_{1c} Level (Percent) from Baseline to Week 26 of the Double-Blind Phase or the Last Prior Visit in Subpopulations

	Metformin HCl/Glyburide N = 57		Metformin HCl N = 54		Glyburide N = 49	
Subgroup	**n**	**Mean Change (SE)**	**n**	**Mean Change (SE)**	**n**	**Mean Change (SE)**
Gender						
Male	21	-0.88 (0.28)	16	-0.85 (0.42)	21	-0.68 (0.21)
Female	36	-0.75 (0.35)	38	-0.41 (0.18)	28	-1.07 (0.35)
Race						
White	35	-0.70 (0.18)	28	-0.55 (0.17)	34	-0.78 (0.19)
Black	13	-0.26 (0.54)	13	-0.53 (0.29)	8	-0.85 (1.00)
Hispanic/Latino	7	-1.79 (1.33)	10	-0.84 (0.67)	5	-1.58 (0.30)
Other	2	-2.50 (1.90)	3	0.57 (1.24)	2	-1.55 (2.25)
Age						
9 - 13years	22	-0.61 (0.50)	20	-0.56 (0.20)	19	-1.44 (0.37)
14 - 16 years	35	-0.91 (0.24)	34	-0.53 (0.26)	30	-0.56 (0.25)
Baseline HbA_{1c}						
< 7.0%	20	-0.09 (0.19)	17	-0.44 (0.14)	22	-0.40 (0.11)
7.0% – < 8.0%	16	-0.63 (0.39)	15	-0.48 (0.26)	12	-0.53 (0.37)
≥ 8.0%	21	-1.60 (0.51)	22	-0.65 (0.39)	15	-1.93 (0.55)

In her review, FDA statistician Lee Pian makes the point that Glucovance appeared better than the monotherapies in naïve patients but not in non naïve patients. That all three treatments appeared less effective in the non-naïve patients probably means that these patients may have been under-dosed. In this regard it should be noted that the current label recommends that previously treated patients be started on 2.5g/500mg or 5mg/500mg **twice daily.** The recommended starting dose for naïve patients, 1.25mg/250mg **once daily,** was used uniformly in this trial. I also suspect that the greater efficacy of Glyburide monotherapy in the non-naïve patients (-0.68) relative to the other two arms) may be an overestimate due to a baseline imbalance related to previous use of insulin. Four of the 53 patients (7.5%) randomized to glyburide monotherapy had a history of insulin use (> 45 days before randomization). By contrast, 11 of the 59 patients (19%) randomized to Glucovance had a history of insulin use and 9 of the 55 (16%) patients randomized to metformin had a history of insulin use. One might expect that it would be more difficult to control hyperglycemia with an oral agent in patients who had a history of insulin use.

	Met/Gly	Met	Gly
Naïve	-1.35	-0.92	-1.23
Non-naïve	-0.09	-0.20	-0.68

(From statistical review by Lee Pian Table 8)

Final doses of study medications in naive and non-naïve patients are given in the following table. A small discrepancy exists between the FDA analysis by Lee Pian and what the Sponsor reported.

Final mean dose by treatment (ITT):

	Metformin/Glyburide 250/1.25 mg	Metformin 500 mg	Glyburide 2.5 mg
Naïve	586/2.9 mg	1300 mg	6.4 mg
Non Naïve	700/3.5 mg	1707 mg	6.9 mg
All patients	636/3.2 mg	1519	6.6 mg
Sponsor's	623/3.1 mg	1500 mg	6.5 mg

Mean changes in secondary variables are shown in the next several tables. There were no statistically significant differences between Metformin/Glyburide and the individual monotherapies. As was expected, metformin monotherapy was associated with less weight gain and less postprandial hyperinsulinemia than were the glyburide-containing treatments, but the differences were not statistically different.

Table 10.2.1: Mean Change in Fasting Plasma Glucose Level (mg/dL) from Baseline to Week 26 of the Double-Blind Phase or the Last Prior Visit

	Metformin HCl/ Glyburide N = 53	Metformin HCl N = 50	Glyburide N = 46
Baseline Mean (SD)	154.3 (56.9)	175.7 (68.4)	154.2 (54.8)
Week 26/Last Mean (SD)	134.9 (57.0)	143.1 (61.5)	135.3 (47.5)
Adjusted[a] Mean Change from Baseline (SE[b])	-23.4 (6.8)	-24.5 (7.1)	-22.9 (7.3)
Difference[c] Between Metformin HCl/Glyburide vs. (SE[b])		1.1 (9.8)	-0.5 (10.0)
Overall p-value[b]: 0.988			

Table 10.4.1: Mean Change in Fasting Insulin Level (microIU/mL) from Baseline to Week 26 of the Double-Blind Phase or the Last Prior Visit

	Metformin HCl/ Glyburide N = 45	Metformin HCl N = 42	Glyburide N = 41
Baseline Mean (SD)	30.52 (59.52)	24.72 (24.81)	18.64 (23.92)
Week 26/Last Mean (SD)	25.00 (25.51)	23.44 (26.50)	21.63 (25.72)
Adjusted[a] Mean Change from Baseline (SE[b])	-1.05 (3.66)	-1.35 (3.78)	-1.85 (3.84)
Difference[cc] Between Metformin HCl/Glyburide vs. (SE[b])		0.30 (5.26)	0.80 (5.31)
Overall p-value[b]: 0.989			

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Table 10.4.2: Mean Change in 120-Minute Postprandial Insulin Level (microIU/mL) from Baseline to Week 26 of the Double-Blind Phase or the Last Prior Visit

	Metformin HCl/Glyburide N = 32	Metformin HCl N = 29	Glyburide N = 34
Baseline Mean (SD)	58.38 (55.96)	72.32 (92.75)	39.07 (38.89)
Week 26/Last Mean (SD)	68.21 (62.94)	66.73 (90.81)	44.56 (41.74)
Mean Change from Baseline (SE)	9.83 (8.33)	-5.59 (8.06)	5.49 (4.22)
95% CI	(-7.16, 26.83)	(-22.09, 10.91)	(-3.10, 14.07)

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Table 10.6.1: Mean Changes in Body Weight (kg) from Baseline to Week 26 of the Double-Blind Phase or the Last Prior Visit

	Metformin HCl/ Glyburide N = 59	Metformin HCl N = 54	Glyburide N = 51
Baseline Mean (SD)	80.09 (27.70)	79.71 (27.76)	78.91 (30.05)
Week 26/Last Mean (SD)	81.33 (28.82)	79.70 (28.13)	80.99 (29.65)
Adjusted[a] Mean Change from Baseline (SE[b])	1.24 (0.59)	-0.01 (0.62)	2.08 (0.64)
Difference[cc] Between Metformin HCl/Glyburide vs. (SE[b])		1.25 (0.86)	-0.84 (0.87)
Overall p-value[b]: 0.062			

Table 10.7.1: Means and Mean Changes from Baseline in Serum Lipids Over Time During Double-Blind Phase

	Treatment Group	N	Baseline Mean (SE)	On-Therapy Mean (SE)	Change from Baseline Mean (SE)	Mean Change from Baseline 95% CI
CHOL	Metformin HCl/Glyburide	44	176.3 (6.6)	178.0 (5.8)	1.7 (3.0)	(-4.3, 7.7)
	Metformin HCl	37	180.3 (7.0)	171.1 (4.4)	-9.2 (5.4)	(-20.1, 1.8)
	Glyburide	38	168.5 (5.8)	159.6 (5.0)	-8.9 (3.6)	(-16.2, -1.7)
HDL-C	Metformin HCl/Glyburide	44	45.9 (2.0)	48.2 (1.6)	2.3 (1.3)	(-0.4, 5.0)
	Metformin HCl	36	47.4 (2.5)	50.2 (2.5)	2.8 (1.1)	(0.5, 5.1)
	Glyburide	37	46.5 (1.7)	48.4 (2.1)	1.9 (1.4)	(-0.9, 4.6)
LDL-C	Metformin HCl/Glyburide	42	104.8 (4.9)	106.1 (4.7)	1.3 (3.2)	(-5.1, 7.8)
	Metformin HCl	36	108.1 (5.0)	101.3 (3.6)	-6.7 (3.4)	(-13.6, 0.2)
	Glyburide	37	99.3 (5.3)	89.5 (4.6)	-9.8 (2.9)	(-15.7, -4.0)

	Treatment Group	N	Baseline Mean (SE)	On-Therapy Mean (SE)	Change from Baseline Mean (SE)	Mean Change from Baseline 95% CI
TRIG	Metformin HCl/Glyburide	43	132.3 (23.4)	114.7 (13.6)	-17.6 (16.1)	(-50.1, 14.9)
	Metformin HCl	36	162.4 (55.1)	94.1 (9.7)	-68.3 (54.0)	(-177.9, 41.3)
	Glyburide	34	113.0 (12.3)	114.5 (15.5)	1.6 (13.3)	(-25.5, 28.6)

VII Review of Safety

There were no deaths. One patient on Metformin/Glyburide discontinued because of hypoglycemia. One patient on Glyburide discontinued because of a skin infection. As shown in the table below, there were few serious adverse events, and they seemed unrelated to study medications.

Table 12.3: Summary of Subjects Who Experienced Serious Adverse Events During Double-Blind Therapy

Subject ID Age (years)/ Gender/Race	Treatment Dose at SAE Onset (mg)	Days From First DB Dose to SAE Onset	SAE by Primary Term	Relationship to Study Drug
Metformin HCl/Glyburide				
0083/001 15/M/White	MG3	101	Abdominal pain	Not Likely
0093/002 16/M/White	MG2	175	Fracture bone	Unrelated
Metformin HCl				
0019/003 11/F/Hispanic/Latino	PSTM2	72	Pancreatitis	Unrelated
0031/001 13/F/Hispanic/Latino	M4	56	Pharyngitis	Unrelated
0038/001 14/F/Black	M2	22	Behavior change	Unrelated
Glyburide				
0038/005 16/F/Black	G4	42	Infect skin bacteria	Not Likely
0093/001 16/F/White	G1 G1[a]	48 67	Nausea/vomiting Nausea/vomiting	Not Likely Unrelated
0141/001 13/F/White	G1	114	Abnormality ovary	Not Likely

Hypoglycemic events were few and not severe. As expected, hypoglycemia was largely related to the final dose of Glyburide.

Table 12.5.2: Hypoglycemia During Double-Blind Therapy by Treatment Group and Treatment Required

Treatment Required	Metformin HCl/Glyburide N = 59		Metformin HCl N = 55		Glyburide N = 52	
	Events n (%)[a]	Subjects n (%)[b]	Events n (%)[a]	Subjects n (%)[b]	Events n (%)[a]	Subjects n (%)[b]
None	0	0	1 (33.3)	1 (1.8)	0	0
Easily Managed by Subject	6 (100.0)	5 (8.5)	2 (66.7)	2 (3.6)	16 (94.1)	3 (5.8)
Required Nonmedical Assistance	0	0	0	0	1 (5.9)	1 (1.9)
Required Medical Assistance	0	0	0	0	0	0
Total	6	5 (8.5)	3	2 (3.6)	17	3 (5.8)

As expected, gastrointestinal events were largely related to metformin.
This result is shown in the following table. It may be noteworthy that only 20% of patients on metformin monotherapy reported gastrointestinal events. This is less than the 32% reported in the trial of metformin monotherapy done by BMS previously for [redacted] (b) (4). Part of the difference may be due to a somewhat lower final dose of metformin in the current study. However, it should also be noted that 40% of the patients entering the metformin monotherapy arm in the current study had been taking metformin previously. These patients had probably become tolerant to metformin and may therefore not have reported the gastrointestinal complaints after randomization.

Table 12.5.3: Gastrointestinal Adverse Events of Nausea, Vomiting, Diarrhea, or Abdominal Pain During Double-Blind Therapy by Treatment Group

Primary Term	Number (%) of Subjects		
	Metformin HCl/Glyburide N = 59	Metformin HCl N = 55	Glyburide N = 52
Abdominal Pain	6 (10.2)	4 (7.3)	3 (5.8)
Diarrhea	4 (6.8)	7 (12.7)	1 (1.9)
Nausea/Vomiting	4 (6.8)	4 (7.3)	1 (1.9)
Total Number of Events	17	24	6
Total Number of Subjects	9 (15.3)	11 (20.0)	5 (9.6)

The open-label extension provided no unexpected safety findings.

Table 13.3: Open-Label Phase Safety Summary

	Number (%) of Subjects				
		Previous Double-Blind Treatment Group			
Event	Direct Enrollees MFG ≥ 350 mg/dL) N = 7	Metformin HCl/ Glyburide N = 36	Metformin HCl N = 36	Glyburide N = 27	Total N = 106
AE[a,b,c] Total Subjects	3 (42.9)	6 (16.7)	5 (13.9)	9 (33.3)	23 (21.7)
ADE[a,b,c]	0	1 (2.8)	2 (5.6)	2 (7.4)	5 (4.7)
SAE[c]	1 (14.3)	2 (5.6)	1 (2.8)	1 (3.7)	5 (4.7)
Death[c]	0	0	0	0	0
Discontinuations Due to AE (Includes clinical and laboratory AEs)	0	0	0	0	0

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VIII Dosing and Administration Issues – Pediatric Labeling

The Glucovance label currently says

Under Pediatric use:

"Safety and effectiveness of GLUCOVANCE in pediatric patients have not been established."

The Sponsor proposes to change this to:

"The safety and efficacy of GLUCOVANCE were evaluated in an active-controlled, double-blind, 26-week trial involving a total of 167 pediatric patients (ranging from 9 to 16 years of age) with type 2 diabetes. (b) (4) *No unexpected safety findings were associated with GLUCOVANCE in this trial."*

This should be revised to read:

"The safety and efficacy of GLUCOVANCE were evaluated in an active-controlled, double-blind, 26-week trial involving a total of 167 pediatric patients (ranging from 9 to 16 years of age) with type 2 diabetes. The mean HbA1c at baseline in these patients was about 7.8%. GLUCOVANCE was not shown to be superior to either metformin or glyburide with respect to reducing Hb_{A1c} from baseline . No unexpected safety findings were associated with GLUCOVANCE in this trial."

IX Use in Special Populations

The following statement, presently in the Dosage and Administration Section,

“GLUCOVANCE is not recommended for use during pregnancy or for use in pediatric patients”

can be modified to read:

“GLUCOVANCE is not recommended for use during pregnancy.”

X Conclusions and Recommendations

Little if any new or unexpected information about the use of Glucovance in children was learned from this trial. Although there may appear to be differences in efficacy between children and adults, these apparent differences reflect inconsistencies in trial design. In recognition of this situation, the Sponsor has requested minimal changes in the label regarding pediatric use. They do not propose to present the data, but simply state:

"The safety and efficacy of GLUCOVANCE were evaluated in an active-controlled, double-blind, 26-week trial involving a total of 167 pediatric patients (ranging from 9 to 16 years of age) with type 2 diabetes. (b) (4) *No unexpected safety findings were associated with GLUCOVANCE in this trial."*

In adult patients, an important use of Glucovance is first line therapy for moderately severe hyperglycemia. The results with Glucovance in this setting are probably better than what could be obtained even with insulin. Patients with moderately severe hyperglycemia were not studied in the pediatric trial. My strong suspicion is that Glucovance would have been effective in these patients, and might save children with type 2 diabetes from being started on injections of insulin. The revised label should not preclude physicians from considering this possibility. It is therefore important to indicate that the negative results in this trial pertain to patients whose HbA1c levels at baseline were about 7.8%.

The revised label should state the following:

"The safety and efficacy of GLUCOVANCE were evaluated in an active-controlled, double-blind, 26-week trial involving a total of 167 pediatric patients (ranging from 9 to 16 years of age) with type 2 diabetes. The mean HbA1c at baseline in these patients was about 7.8%. GLUCOVANCE was not shown statistically to be superior to either metformin or glyburide with respect to reducing Hb_{A1c} from baseline . No unexpected safety findings were associated with GLUCOVANCE in this trial."

The following statement, presently in the Dosage and Administration Section,

"GLUCOVANCE is not recommended for use during pregnancy or for use in pediatric patients"

can be modified to read:

"GLUCOVANCE is not recommended for use during pregnancy."

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
1/12/04 11:43:15 AM
MEDICAL OFFICER

David Orloff
1/12/04 05:41:53 PM
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