CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-178

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-178	**Relevant IND**:	52,837
Brand Name:	Glucovance® **Generic Name**:	Metformin Hydrochloride / Glyburide	
Strength(s):	250 mg/1.25 mg, 500 mg/2.5 mg, and 500 mg/5 mg Tablets		
Sponsor:	Bristol-Myers Squibb Pharmaceutical Research Institute PO Box 4000, Princeton, NJ 08543-4000		
Submission Date:	30-SEP-99		
Submission Type:	New Drug Application		
Reviewer:	Steven B. Johnson, B.S.Pharm, Pharm.D.		

Terms and Abbreviations

Agency	Food and Drug Administration
AUC	Area under the plasma-concentration-time curve
BA	Bioavailability
BCS	Biopharmaceutical Classification System
BE	Bioequivalence
BMS	Bristol-Myers Squibb
C_{max}	Maximum drug concentration
DMEDP	Division of Metabolic and Endocrine Drug Products
OCPB	Office of Clinical Pharmacology and Biopharmaceutics
NDA	New Drug Application
T_{max}	Time of maximum drug concentration
$t_{1/2}$	Drug elimination half-life

Synopsis

The sponsor, Bristol-Myers Squibb (BMS), has submitted NDA 21-178 for a fixed combination product, Glucovance®, which contains glyburide, a sulfonylurea, and metformin hydrochloride, a biguanide. Both of these drug substances have been reviewed and approved by the Agency for marketing and sales in the United States as drug products and used for the treatment of type 2 diabetes mellitus. The maximum recommended daily dose of Glucovance® is 2000 mg metformin hydrochloride and 20 mg glyburide, amounts equivalent to four times the highest proposed Glucovance® strength (500 mg/5 mg).

As the components of Glucovance® have been previously marketed, and their combined use previously approved by the Agency, in depth assessment of Glucovance® was not needed. However, certain assurances needed to be met with regard to the bioequivalence of each of the components of Glucovance® to currently marketed products. This point presents a potential problem in that there are more than one marketed glyburide products. In fact, three brand name glyburide products are currently marketed and none have been shown to be bioequivalent to each other: Micronase® (non-micronized), DiaBeta® (non-micronized), and Glynase® (micronized). This is not an issue when Glucovance® is used for first and second line treatments, as defined in the label. However, it does pose a problem when patients switch from Glucovance® component products to Glucovance®, because bioequivalence between

marketed glyburide products has not been established. Switchability issues were not studied and were not addressed in the product label.

Included in this submission were two clinical studies and five pharmacokinetic (PK) studies. Of the five PK studies, only three had direct relevance. The first study was a definitive BE study that compared two different formulations of Glucovance®, 500 mg/2.5 mg and 500 mg/5 mg tablets, with coadministered Glucophage® and Micronase®. Results demonstrated bioequivalence of the metformin component and bioinequivalence of the glyburide component. In fact, the glyburide component was consistently bioinequivalent to Micronase® in each of the relevant PK studies. It should also be noted that different lots of Micronase®, with different particle sizes, were also found to be bioinequivalent to each other. These two results suggest that glyburide is subject to significant formulation variability. Another point for consideration is that none of the three marketed glyburide containing products have been shown to be bioequivalent.

In an attempt to control for the glyburide variability, the second study was conducted to evaluate the effect of particle size on BE. The outcome of this study made obvious the necessity of maintaining consistency of glyburide particle size, and the sponsor proposed a three-tiered distribution specification. This specification was found to be acceptable with minor modifications.

The third study involved appraisal of the potential for food effect on the two Glucovance® components. Results of this two-way crossover study showed that a high fat meal had no effect on the metformin component, but significantly reduced the T_{max} of the glyburide component, and AUC and C_{max} were not affected. This finding will not be clinically important, as Glucovance® is labeled to be given with meals and this practice was followed during the two clinical studies included in the application.

The metformin results, however, were not expected. In previous experience with metformin, it was shown that food reduced Glucophage's C_{max} by 40%, lowered AUC by 25%, and increased the T_{max} by approximately 35 minutes. Although the T_{max} was again increased by about 30 minutes, C_{max} and AUC remained unchanged between the fed and fasting states. The most plausible explanation for this finding is that in both study periods, subjects were given a 20% glucose solution to overcome the hypoglycemic properties of the glyburide component, which, in turn, produced a "semi-fasted" state, and not a "true" fasted state. In addition, metformin has relatively high solubility and low permeability. In other studies, glucose has been shown to alter membrane permeability. The combination of altered membrane permeability and a low permeability drug appears to have been sufficient to overcome the expected food effect. However, this outcome may not be clinically significant.

In addition to the PK studies, dissolution studies were conducted and profiles were generated for the clinical and commercial lots. The dissolution methods were both found to be acceptable. When dissolution profiles of clinical and commercial lots from the ——————— manufacturing site were compared, there was adequate similarity. This site manufactured all of the tablets used in the PK and clinical studies. The similarity calculations generated when the ——— commercial lots were compared with the Humacao (Puerto Rico) commercial lots were also acceptable.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-178 submitted 30-OCT-99. The overall Human Pharmacokinetic Section is acceptable to OCPB. Please convey ***Comments to Firm*** and ***Labeling Comments*** to the sponsor as appropriate.

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Background

Glucovance® is indicated for the treatment of type 2 diabetes mellitus. This product is a combination of two previously marketed drug substances, metformin, a biquanide, and glyburide, a sulfonylurea. The combined use of these agents has also been previously approved, as indicated in the Glucophage® and Micronase® labels.

Metformin acts as an insulin sensitizer to improve glucose tolerance by lowering both basal and postprandial plasma glucose. Metformin causes this plasma glucose lowering by reducing hepatic glucose production, decreasing intestinal absorption of glucose, and increases peripheral glucose uptake and utilization (to a limited extent).

Glyburide, in contrast, is a second generation insulin secretogogue and is dependent upon functioning pancreatic beta cells for clinical effect. As an insulin secretogogue, glyburide lowers plasma glucose acutely by stimulating the release of insulin from the pancreas. This stimulated increase in insulin release is sufficient, in many cases, to overcome the insulin resistance in type 2 diabetes mellitus.

The combined use of these agents, as shown in the clinical studies included in this application and data from previous studies, clearly shows the superior clinical benefit of Glucovance® as compared with either agent taken by itself.

Drug Formulation
Is the composition of each strength tablet similar?

[redacted]

Components and Composition				
Component	250 mg / 1.25 mg Amount Per Tablet	500 mg / 2.5 mg Amount Per Tablet	500 mg / 5 mg Amount Per Tablet	Function
Metformin Hydrochloride / Magnesium Stearate	[redacted]	[redacted]	[redacted]	[redacted]
Glyburide[2]				
Croscarmellose Sodium				
Povidone				
Microcrystalline Cellulose	[redacted]	[redacted]	[redacted]	[redacted]
Magnesium Stearate				
Total Weight Uncoated[4]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Weight Coated				

[redacted]

Dissolution
Has the sponsor proposed appropriate dissolution methods and specifications?
Was sufficient data submitted for evaluation of the dissolution methods and specifications?
Were the dissolution results, comparing different manufacturing sites, acceptable?

Two dissolution methods have been proposed for this submission, one for each component of Glucovance®. The metformin hydrochloride and the glyburide dissolution methods were found to be acceptable. The metformin hydrochloride method is identical to the method previously accepted by the Agency for Glucophage®. The glyburide method is per the Office of Generic Drugs "Glyburide *In Vivo* Bioequivalence and *In Vitro* Dissolution Testing" guidance for industry.

Dissolution Methods		
	Metformin Component	Glyburide Component
Apparatus:	2 (paddles)	2 (paddles)
Speed:	50 RPM	75 RPM
Medium:	pH 6.8 phosphate buffer	pH 9.5 Borate Buffer
Volume:	1000 mL	500 mL
Units Tested:	12	12
Time Points:	5, 10, 15, & 30 minutes	5, 10, 15, & 30 minutes
Specifications:	NLT — (Q) @ 30 minutes	NLT — (Q) @ 30 minutes

Dissolution data from clinical and commercial batches were submitted for analysis; which included data from the two commercial manufacturing facilities. Dissolution samples were analyzed by a validated [redacted] method. The resultant data are presented in the following table:

Dissolution Results									
Study:	Clinical	Clinical	Clinical	Stability	BA	BA	Stability	Stability	Stability
Type:	Clinical			Commercial			Commercial		
Site:							Squibb-Humacao (Puerto Rico)		
Lot #:	9127	9134	9111	9120	9117	9114	4801 SNCC	4801 SNCC1	4806 SNCC
Strength:	250/1.25	500/2.5	500/5	250/1.25	500/2.5	500/5	250/1.25	500/2.5	500/5
Component:	Metformin Hydrochloride			Metformin Hydrochloride			Metformin Hydrochloride		
5 min									
10 min									
15 min									
30 min									
Component:	Glyburide			Glyburide			Glyburide		
5 min									
10 min									
15 min									
30 min									
Mean (SD)									

——— facilities will be manufacturing Glucovance® tablets: ——————— Squibb Manufacturing – Humacao Facility (Puerto Rico). In a 04-DEC-98 meeting between Bristol Myers Squibb and the Agency, it was agreed that dissolution testing, to compare the commercial formulations manufactured at each facility, was acceptable. Results of these comparisons are presented in the following table:

f_2 Similarity Calculations			
		Metformin Hydrochloride	Glyburide
Reference	Test	f_2	f_2
9127 ——— 9134 ——— 9111 ———	9120 ——— 9117 ——— 9114 ———	76.0	81.5
9120 ——— 9117 ——— 9114 ———	4801SNCC ——— 4801SNCC1 ——— 4806SNCC ———	50.3	57.5
Lot # (Batch Size); Similarity = $f_2 \geq 50$ – Absence of Similarity = $f_2 < 50$.			

Results of the similarity (f_2) analyses show that the equivalent strength clinical and commercial lots from the ——————— facility have similar dissolution profiles for both the metformin and glyburide components. Similar profiles were also seen when the ——————— commercial and Humacao commercial batches were compared. These results are acceptable.

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Note: Values (f_2) presented in the above table have been recalculated using only three of the four time points as appropriate: 5, 10, and 15 minutes – not 30 minutes. Use of more than one value above 85% results in a falsely elevated f_2. Similarity values were overestimated by the sponsor because of their inclusion of more than one time point above 85% dissolution.

Analytical Methodology

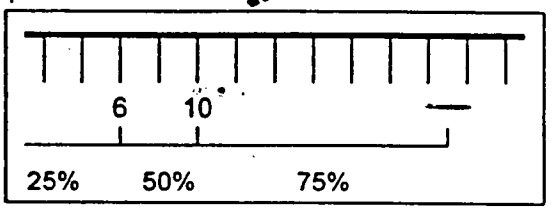
Have the analytical methods been sufficiently validated?

Human plasma samples were analyzed for the metformin hydrochloride and glyburide components using validated ——————— methods, respectively, and were found to be acceptable. Results of the assay validation reports are provided in the following table:

Statistical Analysis of Study CV138-042				90% CI*		
Component	Treatment	Parameter	Mean (SD)	PE	Low	High
Glyburide	Lot 9101	C_{max}	90.2 (34.7)	0.74	0.65	0.84
		AUC_{0-t}	633 (277)	0.84	0.78	0.90
	Lot 9118	C_{max}	125 (69.9)	0.99	0.87	1.12
		AUC_{0-t}	689 (247)	0.91	0.86	0.97
	Lot 9117	C_{max}	121 (47.4)	ref	ref	ref
		AUC_{0-t}	757 (308)	ref	ref	ref
* Relative to lot 9117 based on adjusted means derived from ANOVA. Dose = 2 x 500 mg/2.5 mg tablets						

In order to maintain rigorous particle size distribution of the glyburide component of Glucovance®, the sponsor has proposed the following three-tiered particle size specification:

- **25% undersize value not more than 6 μm**
- **50% undersize value 7 – 10 μm**
- **75% undersize value not more than ___μm**



These specifications are based on the particle size distribution of the glyburide component in Glucovance® lots 9117 and 9118, which were bioequivalent. These specifications are not acceptable as stated. The 75% undersize value should be designated, "75% undersize value not more than 21 μm."

The particle size distribution is measured by a validated _____ method (SM248533), in which volume is measured and results are presented in terms of equivalent spheres. This volume measurement method is similar to a mass distribution and considered acceptable by the chemistry reviewer.

– Biowaivers –

Can the biowaiver request be granted for the 250 mg/1.25 mg strength tablet not used in the PK biostudies?

In order to grant a biowaiver for a drug product, three criteria must be met:

1. **Are the individual strength tablets proportional?**
2. **Has dosage form equivalence been established between Glucovance® and its marketed components, Glucophage® and Micronase®?**
3. **Does each strength tablet exhibit a similar dissolution profile?**

As discussed under the section ***Drug Formulation***, the 250 mg/1.25 mg tablet is one-half of the 500 mg/2.5 mg tablet and is therefore directly proportional. Dosage form equivalence was established for the metformin component through its comparison with Glucophage®. However, the glyburide component was not found to be equivalent to Micronase®, but was similar (see ***Single-Dose Bioequivalence***).

The following table presents full multi-point dissolution with f_2 calculations, under different media conditions, for the 500 mg/2.5 mg (lot #: 9117 – reference) and 250 mg/1.25 mg (lot #: 9120) strength tablets. Results confirm that a similar dissolution profile exists between these two strengths.

Demonstration of Drug Release Equivalence				
	Metformin Hydrochloride		Glyburide	
	Reference	Test	Reference	Test
Lot #:	9117	9120	9117	9120
Media Type:	pH 6.8 Buffer		pH 9.5 Buffer	
5 minutes	24.2	28.4	32.6	32.6
10 minutes	52.4	59.4	65.3	64.1
15 minutes	75.0	85.8	87.3	89.5
30 minutes	100.6	103.0	100.9	100.5
f_2	57.9		87.7	
Media Type:	pH 0.1 M		pH 6.4	
5 minutes	23.1	26.5	11.4	12.7
10 minutes	47.0	53.3	35.6	39.7
15 minutes	68.8	79.8	56.3	62.8
30 minutes	103.5	104.2	82.8	85.3
f_2	58.9		68.8	
Media Type:	pH 4.5 Buffer		pH 8.0 Buffer	
5 minutes	19.9	22.0	10.6	12.9
10 minutes	42.5	46.3	31.5	38.1
15 minutes	63.1	71.9	51.2	61.3
30 minutes	101.1	101.6	81.4	88.5
f_2	65.0		57.2	
Mean (SD)				

Therefore, since the previously mentioned biowaiver criteria were adequately met, a biowaiver for the Glucovance® 250 mg/1.25 mg strength tablet can be granted.

– Food Effect –

What effect does food have on the two components of Glucovance®?

Previous experience with Glucophage® suggests that food decreases the extent and delays the absorption of metformin – as evidenced by a 40% lower C_{max}, 25% lower AUC, and an increase in T_{max} by approximately 35 minutes. However, Glucophage® is labeled to be taken with food to minimize gastrointestinal side effects and the reduction in rate and extent of absorption does not appear to manifest clinically. No data is available on the effect of food on Micronase®.

Study CV138-032, "Evaluation of Effect of Food on the PK of Metformin and Glyburide Combination Tablet," examined food effect in 24 normal healthy subjects administered a single 500 mg/5mg tablet in a two-way crossover design. Analyzed data, as presented in the following table, provide interesting results. The effect of food on the metformin component was subtle, but not significant when compared with Glucophage®. As mentioned previously, due to the hypoglycemic effects of glyburide a 20% glucose solution was administered to each subject in both the "fed and fasted" states. The presence of the glucose appears to have created a "semi-fed" state and so the expected differences in PK parameters were not observed.

The effect of a high fat meal on the glyburide component significantly reduces the T_{max} from 7.5 hours (fasting) to 2.75 hours (fed), and reduces the extent of absorption (fed/fasting = 0.88; 90% CI = 0.74-1.03). The clinical relevance of this is not known.

Statistical Analysis of Study CV138-032				90% CI*		
Component	Treatment	Parameter	Mean (SD) or Mean [range]	PE	Low	High
Metformin	Fasted	C_{max}	733 (209)	ref	ref	ref
		$AUC_{0-\infty}$	5461 (1129)	ref	ref	ref
		T_{max}	2.5 [1.0, 4.0]	—	—	—
	Fed – High Fat	C_{max}	644 (262)	0.85	0.75	0.95
		$AUC_{0-\infty}$	5340 (1357)	0.96	0.88	1.05
		T_{max}	3.0 [1.0, 7.0]	—	—	—
Glyburide	Fasted	C_{max}	139 (33.4)	ref	ref	ref
		$AUC_{0-\infty}$	1077 (325)	ref	ref	ref
		T_{max}	7.5 [.5, 12.0]	—	—	—
	Fed – High Fat	C_{max}	167 (59.0)	1.11	0.88	1.41
		$AUC_{0-\infty}$	991 (342)	0.88	0.74	1.03
		T_{max}	2.75 [2.0, 12.0]	—	—	—
* Relative to fasted treatment based on adjusted means derived from ANOVA. Dose = 1 x 500 mg/5 mg tablets						

Comments to Medical Officer

There does not appear to be any significant PK abnormalities with this drug product. However, the variability issue surrounding glyburide is of some concern. The extreme variability can be accounted for by the particle size distribution, in part, but does not account for all of the observed inconsistency.

In the clinical study, CV138-011, the 500 mg/2.5 mg tablets (lot #s: 9101 and 9135) were used. Lot # 9101 has a larger particle size than the to-be-marketed product and is less bioavailable. The particle size of lot # 9135 was similar to the reference lot (lot #: 9117) used in study CV138-042, and the to-be-marketed formulation.

Comments to Chemistry Reviewer

In a telephone conference held on 20-JUN-00, between BMS – US, BMS – Moreton, UK, and myself, particle size distribution specifications and particle size measurement technique was discussed. The distribution specifications and technique were explained in detail. The measurement technique was considered acceptable by OCPB, however, the specifications at the 75% undersize value were not (see ***Human PK Studies*** – **Particle Size**). No data was provided comparing different measurement techniques.

Labeling Comments

(Where applicable, ~~strikeout~~ text should be removed from labeling. Double <u>underlined</u> text should be added to labeling. ◆ Indicates an explanation only and is not intended to be included in the labeling).

Page 1:

Page 5: ***Pharmacokinetics / Absorption and Bioavailability***

Clinical Pharmacology and Biopharmaceutics Review
Addendum A - Dissolution Tolerance Specifications

NDA:	21-178	**Relevant IND:**	[redacted]
Brand Name:	Glucovance®	**Generic Name:**	Metformin Hydrochloride / Glyburide
Strength(s):	250 mg/1.25 mg, 500 mg/2.5 mg, and 500 mg/5 mg Tablets		
Sponsor:	Bristol-Myers Squibb Pharmaceutical Research Institute PO Box 4000, Princeton, NJ 08543-4000		
Submission Date:	30-SEP-99		
Submission Type:	New Drug Application		
Reviewer:	Steven B. Johnson, B.S.Pharm, Pharm.D.		

Upon further review of the dissolution data results submitted in NDA 21-178, it has been determined that the specifications set by the sponsor were not reflective of the individual components of Glucovance®. The recommended dissolution method and tolerances are presented in table 1, and those proposed by BMS are shown in table 2.

Table 1 – Dissolution Methods – FDA Recommendation		
	Metformin Component	**Glyburide Component**
Apparatus:	2 (paddles)	2 (paddles)
Speed:	50 RPM	75 RPM
Medium:	pH 6.8 phosphate buffer	pH 9.5 Borate Buffer
Volume:	1000 mL	500 mL
Units Tested:	12	12
Time Points:	5, 10, 15, & 30 minutes	5, 10, 15, & 30 minutes
Specifications:	[redacted] (Q) [redacted]	[redacted] (Q) [redacted]

Table 2 – Dissolution Methods – Proposed by BMS		
	Metformin Component	**Glyburide Component**
Apparatus:	2 (paddles)	2 (paddles)
Speed:	50 RPM	75 RPM
Medium:	pH 6.8 phosphate buffer	pH 9.5 Borate Buffer
Volume:	1000 mL	500 mL
Units Tested:	12	12
Time Points:	5, 10, 15, & 30 minutes	5, 10, 15, & 30 minutes
Specifications:	[redacted] (Q) [redacted]	[redacted] (Q) [redacted]

Note to Sponsor

Based on the dissolution data results submitted for Glucovance®, the Agency recommends the following tolerance specifications: Metformin hydrochloride component - NLT [redacted] (Q) [redacted] ; Glyburide Component - NLT [redacted] (Q) [redacted]

Steven B. Johnson, B.S.Pharm, Pharm.D. [/S]
Division of Pharmaceutical Evaluation-II
Office of Clinical Pharmacology and Biopharmaceutics

FT initialed by Hae-Young Ahn, Ph.D., Team Leader: 25-JUL-00 [/S]

CC: NDA 21-178 (orig., 1 copy), HFD-510 (KochW), HFD-870 (AhnH, HuangS, JohnsonST), CDR

NDA 21-178
Glucovance (metformin and glyburide) Tablets

We refer to your submission dated September 30,1999. The following comment was submitted by Dr. Steven Johnson on July 10, 2000:

Particle Size

The three-tiered particle size distribution specifications is generally sound. However, the 75% particle size distribution of NMT — is not acceptable. The 75% undersize value should be designated a value NMT which is supported by the PK data presented in this application.

/S/

CLEARED FOR FAXING: 7/10/00

Hae-Young Ahn, Ph.D. Date
Biopharmaceutics Team Leader

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

CLINICAL REPORT SYNOPSIS

TITLE OF STUDY: Evaluation of the effect of food on the pharmacokinetics of metformin and glyburide combination tablet

INVESTIGATOR: [redacted]

STUDY CENTER: [redacted]

PUBLICATIONS: None

STUDY PERIOD: November 7, 1998 to December 7, 1998

CLINICAL PHASE: I

OBJECTIVES:
The objective of this study was to determine the effect of food on the pharmacokinetics of a metformin and glyburide combination tablet.

METHODOLOGY:
This was an open-label, randomized, single-dose, two-treatment, two-period, crossover study in 24 healthy men/women. Subjects who fulfilled the inclusion and exclusion criteria were admitted to the clinic and randomized to one of 2 sequences. The two treatments were:

Treatment 1 1x Metformin/Glyburide (500/5) tablet after an overnight fast
Treatment 2 1x Metformin/Glyburide (500/5) tablet 5 min after a high fat meal (breakfast)

Serial plasma samples were obtained for 48 hours following dosing and were analyzed for metformin and glyburide using a validated [redacted] method, respectively.

NUMBER OF SUBJECTS:
A total of 26 subjects were enrolled and 24 completed the study. Two subjects were discontinued due to poor compliance.

MAIN CRITERIA FOR INCLUSION:
Healthy young men and women between 18 and 40 years of age, within ±15% of their ideal body weight. If the female subjects were not post-menopausal, they were required to not be nursing, pregnant, capable of becoming pregnant or, if of childbearing potential, were practicing an effective method of contraception. Good health was determined by medical history, physical examination and clinical laboratory tests. The subjects agreed to prohibitions and restrictions of the study protocol and gave written informed consent.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
Metformin/Glyburide combination tablets containing 500 mg metformin HCl and 5 mg glyburide (Lot # 9111) were supplied by Bristol-Myers Squibb. The total dose was 500 mg metformin and 5 mg glyburide (1 tablet) administered orally in each of the two treatments.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
Not applicable.

DURATION OF TREATMENT: Two single doses were administered, with at least one week washout between doses.

Glyburide Pharmacokinetic Parameters

Treatment	CMAX (ng/ml)	TMAX* (h)	TAUC(0-T) (ng.h/ml)	Point Estimate (90% CI)*	
				Cmax	AUC
Fasted	139(33.4)	7.5(2.5,12)	1077(325)		
High fat meal	167(59.0)	2.75(2.0,12.0)	991(342)	1.11(0.88,1.41)	0.88(0.74,1.03)

As indicated in the table above, there was no food effect on metformin. The median difference in TMAX was also not statistically significant. The criterion for no food effect was met for CMAX of glyburide but for AUC(0-T), the food effect was indeterminate. The estimated median difference in TMAX was statistically significant.

SAFETY AND TOLERABILITY RESULTS:

There were no serious or severe adverse events (AEs). All AEs were mild or moderate. A total of 50 treatment emergent AEs were reported in this study. The most frequently reported AEs were nausea/vomiting, diarrhea, headache and dizziness. The number of total AEs reported was similar between the fed and fasted treatments. No clinically relevant abnormalities were found in the vital signs and ECG recordings during or post treatment. There were 5 marked abnormalities in the laboratory tests observed at discharge. These included one subject with low hemoglobin, low hematocrit and low erythrocyte count, one subject with low inorganic phosphate and one subject with high creatine kinase. None of these marked abnormalities were considered clinically significant and were not reported as AEs by the investigator.

CONCLUSIONS:

There was no effect of the high fat meal on the bioavailability of metformin from the metformin-glyburide combination tablet. For the glyburide component, no food effect was concluded for CMAX, however, the effect of food was indeterminate for AUC. The TMAX of glyburide was significantly shortened when the combination tablet was administered after a high fat meal. In clinical practice, the combination tablet will be taken with food. Therefore, an earlier TMAX after a high fat meal is not expected to be clinically relevant.

DATE OF REPORT: May 6, 1999.

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE
CLINICAL REPORT SYNOPSIS

TITLE OF STUDY: Assessment of Pharmacokinetics and Bioavailability of Metformin and Glyburide combination tablets relative to coadministered Glucophage® and Micronase®.

INVESTIGATOR: [redacted]

STUDY CENTER: [redacted]

PUBLICATIONS: None

STUDY PERIOD: June 24, 1997 to July 17, 1997.

CLINICAL PHASE: I

OBJECTIVES:
The objective of this study was to assess the pharmacokinetics and bioavailability of metformin and glyburide from combination tablets 3, 4, and 5 relative to the two agents co-administered as Glucophage® and Micronase®.

METHODOLOGY:
A single site, randomized, four-treatment, four-period complete crossover, open-label, single oral dose study was conducted to evaluate the pharmacokinetics and bioavailability of metformin and glyburide from combination tablets 3, 4, and 5 (referred to as combination tablets A, B, and C in the study protocol) relative to the two agents co-administrered as Glucophage® and Micronase®. Twenty four subjects who fulfilled the inclusion and exclusion criteria were admitted to the clinic and randomized to one of 4 sequences. A brief description of the four treatments is provided below. Serial plasma samples were obtained for 48 hours following dosing. Plasma samples were analyzed for metformin and glyburide using validated [redacted] methods respectively.

Treatment	Formulations
TCA	2 x metformin HCl/glyburide 500/2.5 mg Combination tablet 3
TCB	2 x metformin HCl/glyburide 500/2.5 mg Combination tablet 4
TCC	2 x metformin HCl/glyburide 500/2.5 mg Combination tablet 5
TCD	2 x 500 mg Glucophage® tablets and 1 x 5 mg Micronase® tablet

NUMBER OF SUBJECTS:
A total of 24 subjects were enrolled. 23 subjects completed all four periods of the study. One subject completed only three periods. He did not complete the study due to personal reasons.

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE
CLINICAL REPORT SYNOPSIS

MAIN CRITERIA FOR INCLUSION:
Healthy young men and women between 18 and 40 years of age, within ±15% of their ideal body weight. If the female subjects were not post-menopausal, they were required to not be nursing, pregnant, capable of becoming pregnant or, if of childbearing potential, were practicing an effective method of contraception. Good health was determined by medical history, physical examination and clinical laboratory tests. The subjects agreed to prohibitions and restrictions of the study protocol and gave written informed consent.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
Combination tablet 3 (Batch # 970418A), Combination tablet 4 (Batch # 970419A), and Combination tablet 5 (Batch # M97023) were provided by Bristol-Myers Squibb. Subjects were dosed 2 tablets of the appropriate combination treatment during three study periods. Each tablet contained 500 mg of metformin HCl and 2.5 mg of glyburide.

DURATION OF TREATMENT: Four single doses of metformin HCl and glyburide, as individual agents or combination tablets, were administered with at least one week washout between each dose.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
Glucophage® 500 mg tablets (Batch# ADL) and Micronase® 5 mg tablets (Batch# 376JU) were supplied by Bristol-Myers Squibb. Subjects were co-administered 2 Glucophage® tablets and 1 Micronase® tablet during the appropriate study period.

CRITERIA FOR EVALUATION:
Serial plasma samples were collected for 48 hours after each dose for the pharmacokinetic analysis of metformin and glyburide. CMAX, TMAX, AUC(INF), and T-HALF of metformin from treatments TCA, TCB, TCC, were compared to that from treatment TCD. For glyburide, CMAX, TMAX, and AUC(0-T) from treatments TCA, TCB,TCC were compared to that from treatment TCD. Safety was assessed by monitoring vital signs, ECGs, and clinical laboratory tests.

STATISTICAL METHODS:

Sample Size:
The objective of this study was to assess the pharmacokinetics and bioavailability of metformin/glyburide combination tablets 3, 4, and 5 relative to the two agents co-administered as Glucophage® and Micronase®. Based on the sample size of 24 subjects and the results from a previous study (CV138-009) it was calculated that there would be at least 95% probability with respect to metformin AUC(INF) and CMAX for the 90% confidence interval for test-to-reference ratios to be contained in (0.80, 1.25). Similar calculations on the glyburide analyte indicated a 37% and 13% probability for AUC(0-T) and CMAX respectively.

Statistical Methods:
Subject demographics, physical examinations, laboratory data, and vital signs were summarized. Incidence of adverse events was tabulated by body system and primary term. The distributions of the pharmacokinetic variables were summarized by treatment. An analysis of variance appropriate for a 4-period 4-treatment crossover design was performed. Prior to analysis, CMAX and AUC(INF) (or AUC(0-T) for glyburide) were log transformed and TMAX was rank transformed.

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CLINICAL REPORT SYNOPSIS

Statistical Results for Metformin

For all the combination tablet treatments (TCA, TCB, TCC), bioequivalence of metformin was concluded for both CMAX and AUC(INF) with reference to the Glucophage® tablet co-administered with Micronase® (TCD). In the case of TMAX and T-HALF, there were no significant differences between any of the combination tablet treatments (TCA, TCB, TCC) in comparison to the reference treatment (TCD). Statistical results for metformin CMAX and AUC(INF) are summarized below:

Comparison	Variable	Ratio of Means	90 % C.I. for ratio of means
TCA versus TCD	CMAX	1.080	(0.991, 1.176)
	AUC(INF)	1.059	(0.990, 1.132)
TCB versus TCD	CMAX	1.050	(0.966, 1.143)
	AUC(INF)	1.013	(0.949, 1.082)
TCC versus TCD	CMAX	1.099	(1.010, 1.195)
	AUC(INF)	1.059	(0.992, 1.130)

Statistical Results for Glyburide

For all the combination tablet treatments (TCA, TCB, TCC), bioequivalence was not concluded for either CMAX or AUC(0-T) with reference to Micronase® co-administered with Glucophage® (TCD). In the case of TMAX, it was found that only treatment TCB was significantly different ($p = 0.024$) than the reference treatment, TCD. Statistical results for glyburide CMAX and AUC(0-T) are summarized below:

Comparison	Variable	Ratio of Means	90 % C.I. for ratio of means
TCA versus TCD	CMAX	0.690	(0.571, 0.835)
	AUC(0-T)	0.696	(0.598, 0.810)
TCB versus TCD	CMAX	0.952	(0.790, 1.147)
	AUC(0-T)	0.871	(0.750, 1.011)
TCC versus TCD	CMAX	0.548	(0.455, 0.660)
	AUC(0-T)	0.577	(0.498, 0.670)

SAFETY AND TOLERABILITY RESULTS:

There were no Serious Adverse Events (SAE's). A total of 118 Adverse Events (AE's) were reported in this study. None of these AE's were considered certain to be related to administration of the various drug treatments. There were 24, 36, 18, and 40 AE's reported for treatments TCA, TCB, TCC, and TCD respectively. The most frequently reported AE's were gastrointestinal disorders such as nausea and diarrhea. Other AEs reported with a lower frequency included nervous system disorders (such as headache, dizziness, and tremor), dermatologic disorders (such as ecchymosis and acne), cardiovascular disorders (such as flushing and vasovagal attack), respiratory disorders (such as rhinitis), and musculoskeletal disorders (such as musculoskeletal pain and weakness in extremity). No clinically relevant abnormalities were found in the vital signs and ECGs during or post treatment. There were no marked abnormalities (MAs) in the laboratory values during or post treatment.

CONCLUSIONS:

1. Combination tablets 3, 4, and 5 were bioequivalent in CMAX and AUC(INF) in the metformin component to the reference treatment, Glucophage® co-administered with Micronase®.

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CLINICAL REPORT SYNOPSIS

CONCLUSIONS (contd.):

2. CMAX and AUC(0-T) of the glyburide component from combination tablets 3 and 5 were found to be significantly lower than that of the reference, Micronase® tablet co-administered with Glucophage®.

3. Based on ratios of point estimates for CMAX and AUC(0-T), it was concluded that combination tablet 4 had sufficiently comparable bioavailability for both metformin and glyburide with respect to reference treatment, Glucophage® co-administered with Micronase®. Therefore, this formulation is suitable for further development.

DATE OF REPORT: June 18, 1998.

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

CLINICAL REPORT SYNOPSIS

TITLE OF STUDY: Assessment of Pharmacokinetics and Bioavailability of Metformin/Glyburide Combination Tablets Relative to Coadministered Glucophage® and Micronase®

INVESTIGATOR: [redacted]

STUDY CENTER: [redacted]

PUBLICATIONS: None

STUDY PERIOD: January 8, 1999 to February 3, 1999

CLINICAL PHASE: I

OBJECTIVES:
The objective of this study was to assess the pharmacokinetics and bioavailability of metformin/glyburide combination tablets relative to coadministered Glucophage® and Micronase®.

METHODOLOGY:
This was an open-label, randomized, single-dose, two-treatment, two-period, crossover study conducted in two parts in two separate groups of subjects (N=28 each). The treatments in each part were:

Part 1

Treatment 1	2x Metformin/Glyburide (500 mg/2.5 mg) tablet
Treatment 2	2x Glucophage® (500 mg) and 1x Micronase® (5 mg) tablet

Part 2

Treatment 1	1x Metformin/Glyburide (500 mg/5 mg) tablet
Treatment 2	1x Glucophage® (500 mg) and 1x Micronase® (5 mg) tablet

Serial plasma samples were obtained for 48 hours following dosing and were analyzed for metformin and glyburide using validated [redacted] methods, respectively.

NUMBER OF SUBJECTS:
A total of 28 subjects were enrolled in part 1 and 27 completed the study. One subject was lost to follow up. A total of 29 subjects were enrolled in part 2 and 28 completed the study. One subject was discontinued after period 1 at his request.

MAIN CRITERIA FOR INCLUSION:
Healthy young men and women between 18 and 40 years of age, within ±15% of their ideal body weight. If the female subjects were not post-menopausal, they were required to not be nursing, pregnant, capable of becoming pregnant or, if of childbearing potential, were practicing an effective method of contraception. Good health was determined by medical history, physical examination and clinical laboratory tests. The subjects agreed to prohibitions and restrictions of the study protocol and gave written informed consent.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
Metformin/Glyburide combination tablets containing 500 mg metformin HCl and 2.5 mg glyburide (Lot # 9117) and Metformin/Glyburide combination tablets containing 500 mg metformin HCl and 5 mg glyburide (Lot # 9114) were supplied by Bristol-Myers Squibb. The total dose administered orally was 1000 mg metformin and 5 mg glyburide in part 1 and 500 mg metformin and 5 mg glyburide in part 2 of the study.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
Glucophage® (500 mg) tablets (Lot # 507BGO) and Micronase® (5 mg) tablets (Lot # 118XF) were also supplied by Bristol-Myers Squibb. The total dose administered orally was 1000 mg metformin and 5 mg glyburide in part 1 and 500 mg metformin and 5 mg glyburide in part 2 of the study.

DURATION OF TREATMENT: Two single doses of metformin and glyburide either as combination tablets or reference marketed products were administered, with at least one week washout between doses.

CRITERIA FOR EVALUATION:
Serial plasma samples for pharmacokinetic analysis were collected for 48 hours after each dose. CMAX, TMAX and AUC of metformin and glyburide were compared between the two treatments. Safety was assessed by monitoring vital signs, ECGs and clinical laboratory tests.

STATISTICAL METHODS:

Sample Size:
Although the purpose of this study was not to demonstrate the bioequivalence of these formulations, the proposed sample size of 28 subjects (14 per sequence) was to provide at least 99% probability with respect to metformin CMAX and AUC(INF) for the 90% confidence interval for 2xmetformin/glyburide (500 mg/2.5 mg) tablets to 2xGlucophage® (500 mg) tablets ratios to be contained in (0.80, 1.25) for metformin, when the test and reference means are equal in part 1. Similarly, the proposed sample size was to provide at least 82% probability with respect to glyburide CMAX and 81% probability with respect to glyburide AUC(0-T) for the 90% confidence interval for 2xmetformin/glyburide (500 mg/2.5 mg) tablets to 1xMicronase® (5 mg) ratios to be contained in (0.80, 1.25) for glyburide, when the test and reference means are equal in part 1. These calculations were based on the assumptions that CMAX and AUC are log normally distributed, the within-subject estimates of variance (mean square error) are similar to 0.028 for metformin CMAX, 0.017 for metformin AUC(INF), 0.135 for glyburide CMAX, and 0.086 for glyburide AUC(0-T), and the between-subject estimates of variance (mean square subjects) are similar to 0.294 for metformin CMAX, 0.185 for metformin AUC(INF), 0.158 for glyburide CMAX, and 0.245 for glyburide AUC(0-T), and the intra-class correlations are stable among the formulations in study CV138-017. These estimates were from that study. Because the metformin variability is much less than glyburide and the amount of glyburide administered in Part 2 is the same as in part 1, the sample size and probability estimates for Part 2 were similar to Part 1.

Statistical Methods:
For each part, data listings are presented and summary statistics are tabulated for the pharmacokinetic variables by treatment. An analysis of variance model appropriate for a two-by-two crossover design was used for CMAX, AUC(INF) for metformin, and AUC(0-T) for glyburide. The factors in the analysis were sequence, subject within sequence, period, and treatment. A priori, CMAX, AUC(INF), and AUC(0-T) were log transformed and the resulting point and 90% confidence interval estimates of means and mean differences were exponentiated to express the results as geometric means and ratios of geometric means on the original scale of measurement. No analysis other than descriptive statistics was done on TMAX and T-HALF.

Subject demographics, physical examinations, laboratory data, and vital signs were summarized. Incidence of adverse events was tabulated by body system and primary term.

Analysis:

All available data from all subjects who received study medication were included in the analysis of safety data. Subject 24 who was lost to follow up after period 1 of the study and subject 51 who discontinued the study after period 1 were not included in the pharmacokinetic analysis. Subject 30 had very low concentrations of metformin and glyburide from the Glucophage® plus Micronase® treatment and he was also excluded from the pharmacokinetic analysis.

PHARMACOKINETIC RESULTS:

The pharmacokinetic results were determined using a validated ———————— protocol. Mean (SD) metformin and glyburide pharmacokinetic parameters along with the results of statistical analysis on CMAX and AUC are summarized in the following tables:

Metformin Pharmacokinetic Parameters

Part 1

Treatment	Parameter	Mean (SD)	Adjusted Geometric Mean	Ratio of Means	
				Point Estimate	90% CI
Combination tablet (500 mg/2.5 mg)	CMAX	1507(392)	1454	1.02	(0.98,1.06)
	AUC(INF)	10425(2032)	10246	0.99	(0.95,1.03)
Glucophage®	CMAX	1458(315)	1424	–	–
	AUC(INF)	10529(1801)	10397	–	–

Units for CMAX: ng/mL, AUC(INF): ng.h/mL

Part 2

Treatment	Parameter	Mean (SD)	Adjusted Geometric Mean	Ratio of Means	
				Point Estimate	90% CI
Combination tablet (500 mg/5 mg)	CMAX	923(278)	886	1.01	(0.95,1.07)
	AUC(INF)	6076(1528)	5886	0.96	(0.92,1.01)
Glucophage®	CMAX	906(234)	879	–	–
	AUC(INF)	6315(1622)	6116	–	–

Units for CMAX: ng/mL, AUC(INF): ng.h/mL

Part 1

Treatment	Parameter	Mean (SD)	Adjusted Geometric Mean	Ratio of Means	
				Point Estimate	90% CI
Combination tablet (500 mg/2.5 mg)	CMAX	119(36.6)	114	1.10	(0.98,1.25)
	AUC(0-T)	971(368)	917	1.18	(1.08,1.29)
Micronase®	CMAX	115(54.4)	104	–	–
	AUC(0-T)	854(385)	776	–	–

Units for CMAX: ng/mL, AUC(0-T): ng.h/mL

Part 2

Treatment	Parameter	Mean (SD)	Adjusted Geometric Mean	Ratio of Means	
				Point Estimate	90% CI
Combination tablet (500 mg/5 mg)	CMAX	122(43.4)	116	1.14	(0.95,1.38)
	AUC(0-T)	859(234)	831	1.07	(0.97,1.17)
Micronase®	CMAX	113(54.9)	101	–	–
	AUC(0-T)	842(327)	780	–	–

Units for CMAX: ng/mL, AUC(0-T): ng.h/mL

As indicated in the tables above, for the CMAX and AUC of metformin component from both the combination tablet strengths, the 90% confidence intervals were contained within (0.80, 1.25). Bioavailability of the glyburide component from the two tablet strengths was comparable to Micronase® coadministered with Glucophage®.

SAFETY AND TOLERABILITY RESULTS:

There were no serious or severe adverse events (AEs). All AEs were mild or moderate. A total of 65 treatment emergent AEs were reported in part 1 and a total of 34 treatment emergent AEs in part 2 of this study. The most frequently reported AEs were headache, dizziness, diarrhea, nausea/vomiting, dyspepsia/heartburn, tremor and abdominal pain. The number of total AEs reported was similar between the combination tablet and coadministered reference treatments in part 1 of the study. However, in part 2 of the study, twice as many AEs were reported on the combination tablet treatment relative to Glucophage® and Micronase®. No clinically relevant abnormalities were found in the vital signs and ECG recordings during or post treatment. There were 9 marked abnormalities in the laboratory tests observed at discharge in part 1 of the study. These included one subject with high AST, one subject with low hematocrit and low erythrocyte count, two subjects with high serum potassium, two subjects with low inorganic phosphate, one subject with high blood urea nitrogen and one subject with high lactate dehydrogenase. Four marked abnormalities in the laboratory tests were observed at discharge in part 2 of the study. They included one subject with high serum potassium and three subjects with high blood urea nitrogen. None of these marked abnormalities were considered clinically significant and were not reported as AEs by the investigator.

CONCLUSIONS:

The metformin component of metformin/glyburide combination tablets (500 mg/2.5 mg and 500 mg/5 mg) met criteria for bioequivalence relative to Glucophage® while the glyburide component showed comparable bioavailability to Micronase®.

DATE OF REPORT: July 20, 1999.

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE
CLINICAL REPORT SYNOPSIS

TITLE OF STUDY: A pilot bioavailability study of different lots of Micronase®

INVESTIGATOR: _____

STUDY CENTER: _____ _____

PUBLICATIONS: None

STUDY PERIOD: September 12, 1998 to October 5, 1998

CLINICAL PHASE: I

OBJECTIVES:
The objective of this study was to assess the bioavailability of glyburide from three different lots of Micronase® relative to lot 376JU used in a previous bioavailability study.

METHODOLOGY:
This was an open-label, randomized, single-dose, four-treatment, crossover study in 12 healthy men/women. Twelve subjects who fulfilled the inclusion and exclusion criteria were admitted to the clinic and randomized to one of 4 sequences. The four treatments were:

Treatment 1	1x5 mg Micronase® tablet lot 1 (lot 496XC)
Treatment 2	1x5 mg Micronase® tablet lot 2 (lot 118XF)
Treatment 3	1x5 mg Micronase® tablet lot 3 (lot 535XU)
Treatment 4	1x5 mg Micronase® tablet lot 4 (lot 376JU)

Treatment 4 was used as the reference treatment. This lot was used in a previous comparative bioavailability study with the metformin/glyburide combination tablet. Serial plasma samples were obtained for 48 hours following dosing and were analyzed for glyburide using a validated ——— method.

NUMBER OF SUBJECTS:
A total of 12 subjects were enrolled and all completed the study.

MAIN CRITERIA FOR INCLUSION:
Healthy young men and women between 18 and 40 years of age, within ±15% of their ideal body weight. If the female subjects were not post-menopausal, they were required to not be nursing, pregnant, capable of becoming pregnant or, if of childbearing potential, were practicing an effective method of contraception. Good health was determined by medical history, physical examination and clinical laboratory tests. The subjects agreed to prohibitions and restrictions of the study protocol and gave written informed consent.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
Three different lots of Micronase® (lot 496XC, 118XF and 535XU) available commercially were supplied by Bristol-Myers Squibb. The total dose was 5 mg (1 tablet) glyburide administered orally in each of the treatments.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
The reference lot of Micronase® (376JU) was available commercially and was provided by Bristol-Myers Squibb. All subjects received 5 mg (1 tablet) glyburide administered orally.

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

CLINICAL REPORT SYNOPSIS

TITLE OF STUDY: A Bioequivalence Study of Three Different Lots of Metformin/Glyburide Combination Tablets

INVESTIGATOR: _____

STUDY CENTER: _____

PUBLICATIONS: None

STUDY PERIOD: January 21, 1999 to February 13, 1999

CLINICAL PHASE: I

OBJECTIVES:
The primary objective of this study was to determine if the glyburide component from two test lots of metformin/glyburide combination tablet having different particle size distribution of bulk glyburide is bioequivalent to the reference lot. The secondary objective was to determine the bioequivalence of the metformin component.

METHODOLOGY:
This was an open-label, randomized, single-dose, three-treatment, three-period, crossover study in 36 healthy men/women. Subjects who fulfilled the inclusion and exclusion criteria were admitted to the clinic and randomized to one of 6 sequences. The three treatments were:

Treatment A	2x Metformin/Glyburide (500/2.5) combination tablets Lot 9101
Treatment B	2x Metformin/Glyburide (500/2.5) combination tablets Lot 9118
Treatment C	2x Metformin/Glyburide (500/2.5) combination tablets Lot 9117

The three drug product lots differed in the particle size of glyburide drug substance. Lot 9117 with specifically selected particle size distribution of glyburide was used as the reference. Serial plasma samples were obtained for 48 hours following dosing and were analyzed for metformin and glyburide using a validated _____ method, respectively.

NUMBER OF SUBJECTS:
A total of 38 subjects were enrolled and 35 completed the study. Two subjects discontinued for personal reasons and one subject discontinued due to inability to tolerate glucose solutions.

MAIN CRITERIA FOR INCLUSION:
Healthy young men and women between 18 and 40 years of age, within ±15% of their ideal body weight. If the female subjects were not post-menopausal, they were required to not be nursing, pregnant, capable of becoming pregnant or, if of childbearing potential, were practicing an effective method of contraception. Good health was determined by medical history, physical examination and clinical laboratory tests. The subjects agreed to prohibitions and restrictions of the study protocol and gave written informed consent.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
Metformin/Glyburide combination tablets containing 500 mg metformin HCl and 2.5 mg glyburide (Lot # 9101, 9118 and 9117) were supplied by Bristol-Myers Squibb. The total dose was 1000 mg metformin HCl and 5 mg glyburide (2 tablets) administered orally in each of the three treatments.

The following table describes the glyburide particle size in the three treatment lots.

Treatment	50% undersize	75% undersize
9101	[redacted]	[redacted]
9118		
9117	[redacted]	[redacted]

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
Not applicable.

DURATION OF TREATMENT: Three single doses were administered, with at least one week washout between doses.

CRITERIA FOR EVALUATION:
Serial plasma samples for pharmacokinetic analysis were collected for 48 hours after each dose. CMAX, TMAX and AUC of metformin and glyburide were compared between the two treatments. Safety was assessed by monitoring vital signs, ECGs and clinical laboratory tests.

STATISTICAL METHODS:

Sample Size:
The sample size of 36 subjects was to provide 92% power with respect to CMAX and 99% power with respect to AUC(0-T) (AUC from 0 to the last quantifiable time point) to demonstrate bioequivalence of glyburide from metformin/glyburide (500/2.5) combination tablets lots 9101 and 9118 with lot 9117 when the test and reference means are equal. These calculations were based on the assumptions that CMAX and AUC are log normally distributed and the within-subject standard deviations are similar to 0.272 for glyburide CMAX and 0.202 for glyburide AUC(0-T). Since glyburide is substantially more variable than metformin, the power for comparisons of metformin would be greater than the power for glyburide.

Statistical Methods:
An analysis of variance model appropriate for a three-by-three Latin square design was used for CMAX, AUC(INF) for metformin, and AUC(0-T) for glyburide. The factors in the analysis were sequence, subject(sequence), period, lot and carryover. A second analysis of variance model was done with carryover deleted from the analysis and estimates were based on the reduced model if carryover was not statistically significant. A priori, CMAX, AUC(INF), and AUC(0-T) were log transformed and the resulting point and interval estimates of means and mean differences were exponentiated to express the results as geometric means and ratios of geometric means on the original scale of measurement. Bioequivalence of lots 9101 and 9118 with lot 9117 was concluded if the 90% confidence intervals of the ratios of both CMAX and AUC lot geometric means are contained entirely between 0.80 and 1.25. No adjustment was made for the two comparisons. No analysis other than descriptive statistics was done on TMAX and T-HALF.

Subject demographics, physical examinations, laboratory data, and vital signs were summarized. Incidence of adverse events was tabulated by body system and primary term.

Analysis:
All available data from all subjects who received study medication were included in the analysis of safety data. Subject 36 discontinued the study after period 2 and does not have pharmacokinetic data for lot 9101. Subject 6 had very low concentrations of both metformin and glyburide for lot 9101 and data for lot 9101 from this subject was not included in the pharmacokinetic analysis.

PHARMACOKINETIC RESULTS:
The pharmacokinetic results were determined using a validated noncompartmental analysis protocol. Mean (SD) metformin and glyburide pharmacokinetic parameters along with the results of statistical analysis on CMAX and AUC are summarized in the following tables:

Metformin Pharmacokinetic Parameters

	Mean (SD)	Adjusted Geometric Mean	Ratio of Geometric Means relative to Lot 9117	
			Point Estimate	90% Confidence Interval
CMAX (ng/mL)				
Lot 9101	1461(444)	1406	0.96	(0.90,1.03)
Lot 9118	1403(336)	1364	0.93	(0.87,1.00)
Lot 9117*	1503(377)	1459	–	–
AUC(INF) (ng.h/mL)				
Lot 9101	9515(2349)	9281	0.97	(0.92,1.02)
Lot 9118	9462(2024)	9233	0.97	(0.92,1.02)
Lot 9117*	9764(2020)	9561	–	–

Glyburide Pharmacokinetic Parameters

	Mean (SD)	Adjusted Geometric Mean	Ratio of Geometric Means relative to Lot 9117	
			Point Estimate	90% Confidence Interval
CMAX (ng/mL)				
Lot 9101	90.2(34.7)	83	0.74	(0.65,0.84)
Lot 9118	125(69.9)	112	0.99	(0.87,1.12)
Lot 9117*	121(47.4)	113	–	–
AUC(0-T) (ng.h/mL)				
Lot 9101	633(277)	594	0.84	(0.78,0.90)
Lot 9118	689(247)	647	0.91	(0.86,0.97)
Lot 9117*	757(308)	709	–	–

* Reference

As indicated in the tables above, lot 9118 is bioequivalent to lot 9117 for both metformin and glyburide. Lot 9101 is bioequivalent to lot 9117 for metformin but failed to show bioequivalence with respect to glyburide. Lot 9101 was made from glyburide drug substance that had the largest particle size.

SAFETY AND TOLERABILITY RESULTS:
There were no serious or severe adverse events (AEs). All AEs were mild or moderate. A total of 75 treatment emergent AEs were reported in this study. The most frequently reported AEs were headache, diarrhea, nausea/vomiting, dizziness, rhinitis, fever and cough. The number of total AEs reported was similar between the——combination tablet lots. No clinically relevant abnormalities were found in the vital signs and ECG recordings during or post treatment. There were 5 marked abnormalities in the laboratory tests observed at discharge. These included one subject with low hemoglobin and low hematocrit, one subject with high eosinophils and one subject with high AST and ALT. None of these marked abnormalities were considered clinically significant and were not reported as AEs by the investigator.

CONCLUSIONS:
Combination tablet lot 9118 was bioequivalent to the reference lot 9117 for both metformin and glyburide components. Combination tablet lot 9101 was bioequivalent to lot 9117 for the metformin component but failed to show bioequivalence with respect to the glyburide component. Particle size of glyburide drug substance is responsible for determining the bioavailability of glyburide from the combination tablet.

DATE OF REPORT: June 29, 1999.

Glyburide Solubility for BCS-2 Classification:

Buffer System	pH	Solubility in Buffer (mg/mL)
0.1 M HCl	1.5	< 0.01
0.05 M ——— Buffer	3.0	< 0.01
0.05 M ——— Buffer	5.0	< 0.01
0.05 M ——— Buffer	6.4	< 0.01
0.05 M ——— Buffer	8.0	0.06
0.05 M ——— Buffer	8.4	0.12
0.05 M ——— Buffer	9.5	0.28
0.1 M Sodium Hydroxide	13.0	0.29

Glyburide Permeability for BCS-2 Classification:

Following administration of radiolabelled drug, glyburide dosed orally in humans shows complete absorption.

Fuccella LM, Tamassia V, Valzelli G. Metabolism and kinetics of the hypoglycemic agent glipizide in man--comparison with glibenclamide. J Clin Pharmacol New Drugs. 1973;13(2):68-75.

BRISTOL-MYERS SQUIBB

REGULATORY SCIENCE AND OUTCOMES RESEARCH
Chemistry/Manufacturing and Controls
Hopewell

Facsimile Transmission

Phone No.: 609-818-5221 Rapifax No.: 609-818-5831

DATE: July 28, 2000

TO: W. Koch (301-443-9282)

FROM: Mary Peters

MESSAGE: Glucovance™ NDA 21-178

Dear Bill,

Attached please see the letter from the FDA that makes reference to the July 1998 reinspection of ——for Glucophage® tablets.

Regards,

Mary Peters

Mary Peters
Manager, Regulatory Science and Outcomes Research - CMC
Phone: (609) 818-5221
Fax: (609) 818-5831

(2 total pages)

APPEARS THIS WAY
ON ORIGINAL

BRISTOL-MYERS SQUIBB
WORLDWIDE REGULATORY SCIENCE

Telefax Transmission Cover Sheet

Date: July 21, 2000

To: David Orloff, M.D.

From: Warren Randolph

Subject NDA 21-178

No. of Pages (including cover): 9

Message:

Dr. Orloff,

The attached pages are provided to follow up on several points we discussed this morning concerning the 5mg/500mg Glucovance tablet; their content is briefly described below:

Bioavailability
The attached synopsis of bioavailability trial CV138-024 provides tables on the last page showing the bioavailability of the glyburide component of Glucovance relative to Micronase. Please note that the confidence interval for the AUC for the 5mg/500mg tablet meets the criteria for bioequivalence to Micronase, and the corresponding confidence interval for the 2.5mg/500mg tablet barely misses bioequivalence.

Hypoglycemia
The section on hypoglycemia from the report for study CV138-011 (second line study) is attached. Table 12.5.2 lists subjects reporting symptoms of hypoglycemia or hypoglycemia decoding to serum glucose decrease. The ratio of metformin and glyburide at event onset was used to determine that 14 of these subjects were receiving the 2.5mg/500mg tablet and eight were receiving the 5mg/500mg tablet (three were receiving glyburide alone and one was on metformin alone).

As reflected in our proposed labeling language, the 5mg/500mg tablet is recommended only for switching of patients already titrated on metformin and glyburide in this ratio.

Please contact me at (609) 252-5228 with any questions.

Warren

Warren

Final Study Report: CV138-024
Report No. 910074598 July 20, 1999

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE
CLINICAL REPORT SYNOPSIS

TITLE OF STUDY: Assessment of Pharmacokinetics and Bioavailability of Metformin/Glyburide Combination Tablets Relative to Coadministered Glucophage® and Micronase®

INVESTIGATOR: [redacted]

STUDY CENTER: [redacted]

PUBLICATIONS: None

STUDY PERIOD: January 8, 1999 to February 3, 1999

CLINICAL PHASE: I

OBJECTIVES:
The objective of this study was to assess the pharmacokinetics and bioavailability of metformin/glyburide combination tablets relative to coadministered Glucophage® and Micronase®.

METHODOLOGY:
This was an open-label, randomized, single-dose, two-treatment, two-period, crossover study conducted in two parts in two separate groups of subjects (N=28 each). The treatments in each part were:

Part 1

Treatment 1	2x Metformin/Glyburide (500 mg/2.5 mg) tablet
Treatment 2	2x Glucophage® (500 mg) and 1x Micronase® (5 mg) tablet

Part 2

Treatment 1	1x Metformin/Glyburide (500 mg/5 mg) tablet
Treatment 2	1x Glucophage® (500 mg) and 1x Micronase® (5 mg) tablet

Serial plasma samples were obtained for 48 hours following dosing and were analyzed for metformin and glyburide using validated ———————— methods, respectively.

NUMBER OF SUBJECTS:
A total of 28 subjects were enrolled in part 1 and 27 completed the study. One subject was lost to follow up. A total of 29 subjects were enrolled in part 2 and 28 completed the study. One subject was discontinued after period 1 at his request.

MAIN CRITERIA FOR INCLUSION:
Healthy young men and women between 18 and 40 years of age, within ±15% of their ideal body weight. If the female subjects were not post-menopausal, they were required to not be nursing, pregnant, capable of becoming pregnant or, if of childbearing potential, were practicing an effective method of contraception. Good health was determined by medical history, physical examination and clinical laboratory tests. The subjects agreed to prohibitions and restrictions of the study protocol and gave written informed consent.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
Metformin/Glyburide combination tablets containing 500 mg metformin HCl and 2.5 mg glyburide (Lot # 9117) and Metformin/Glyburide combination tablets containing 500 mg metformin HCl and 5 mg glyburide (Lot # 9114) were supplied by Bristol-Myers Squibb. The total dose administered orally was 1000 mg metformin and 5 mg glyburide in part 1 and 500 mg metformin and 5 mg glyburide in part 2 of the study.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
Glucophage® (500 mg) tablets (Lot # 507BGO) and Micronase® (5 mg) tablets (Lot # 118XF) were also supplied by Bristol-Myers Squibb. The total dose administered orally was 1000 mg metformin and 5 mg glyburide in part 1 and 500 mg metformin and 5 mg glyburide in part 2 of the study.

DURATION OF TREATMENT: Two single doses of metformin and glyburide either as combination tablets or reference marketed products were administered, with at least one week washout between doses.

CRITERIA FOR EVALUATION:
Serial plasma samples for pharmacokinetic analysis were collected for 48 hours after each dose. CMAX, TMAX and AUC of metformin and glyburide were compared between the two treatments. Safety was assessed by monitoring vital signs, ECGs and clinical laboratory tests.

STATISTICAL METHODS:

Sample Size:
Although the purpose of this study was not to demonstrate the bioequivalence of these formulations, the proposed sample size of 28 subjects (14 per sequence) was to provide at least 99% probability with respect to metformin CMAX and AUC(INF) for the 90% confidence interval for 2xmetformin/glyburide (500 mg/2.5 mg) tablets to 2xGlucophage® (500 mg) tablets ratios to be contained in (0.80, 1.25) for metformin, when the test and reference means are equal in part 1. Similarly, the proposed sample size was to provide at least 81% probability with respect to glyburide CMAX and 81% probability with respect to glyburide AUC(0-T) for the 90% confidence interval for 2xmetformin/glyburide (500 mg/2.5 mg) tablets to 1xMicronase® (5 mg) ratios to be contained in (0.80, 1.25) for glyburide, when the test and reference means are equal in part 1. These calculations were based on the assumptions that CMAX and AUC are log normally distributed, the within-subject estimates of variance (mean square error) are similar to 0.028 for metformin CMAX, 0.017 for metformin AUC(INF), 0.135 for glyburide CMAX, and 0.086 for glyburide AUC(0-T), and the between-subject estimates of variance (mean square subjects) are similar to 0.294 for metformin CMAX, 0.185 for metformin AUC(INF), 0.158 for glyburide CMAX, and 0.245 for glyburide AUC(0-T), and the intra-class correlations are stable among the formulations in study CV138-017. These estimates were from that study. Because the metformin variability is much less than glyburide and the amount of glyburide administered in Part 2 is the same as in part 1, the sample size and probability estimates for Part 2 were similar to Part 1.

Statistical Methods:
For each part, data listings are presented and summary statistics are tabulated for the pharmacokinetic variables by treatment. An analysis of variance model appropriate for a two-by-two crossover design was used for CMAX, AUC(INF) for metformin, and AUC(0-T) for glyburide. The factors in the analysis were sequence, subject within sequence, period, and treatment. A priori, CMAX, AUC(INF), and AUC(0-T) were log transformed and the resulting point and 90% confidence interval estimates of means and mean differences were exponentiated to express the results as geometric means and ratios of geometric means on the original scale of measurement. No analysis other than descriptive statistics was done on TMAX and T-HALF.

Subject demographics, physical examinations, laboratory data, and vital signs were summarized. Incidence of adverse events was tabulated by body system and primary term.

Analysis:
All available data from all subjects who received study medication were included in the analysis of safety data. Subject 24 who was lost to follow up after period 1 of the study and subject 51 who discontinued the study after period 1 were not included in the pharmacokinetic analysis. Subject 30 had very low concentrations of metformin and glyburide from the Glucophage® plus Micronase® treatment and he was also excluded from the pharmacokinetic analysis.

PHARMACOKINETIC RESULTS:
The pharmacokinetic results were determined using a validated noncompartmental analysis protocol. Mean (SD) metformin and glyburide pharmacokinetic parameters along with the results of statistical analysis on CMAX and AUC are summarized in the following tables:

Metformin Pharmacokinetic Parameters

Part 1

Treatment	Parameter	Mean (SD)	Adjusted Geometric Mean	Ratio of Means	
				Point Estimate	90% CI
Combination tablet (500 mg/2.5 mg)	CMAX	1507(392)	1454	1.02	(0.98,1.06)
	AUC(INF)	10425(2032)	10246	0.99	(0.95,1.03)
Glucophage®	CMAX	1458(315)	1424	--	--
	AUC(INF)	10529(1801)	10397	--	--

Units for CMAX: ng/mL, AUC(INF): ng h/mL

Part 2

Treatment	Parameter	Mean (SD)	Adjusted Geometric Mean	Ratio of Means	
				Point Estimate	90% CI
Combination tablet (500 mg/5 mg)	CMAX	923(278)	886	1.01	(0.95,1.07)
	AUC(INF)	6076(1528)	5886	0.96	(0.92,1.01)
Glucophage®	CMAX	906(234)	879	--	--
	AUC(INF)	6315(1622)	6116	--	--

Units for CMAX: ng/mL, AUC(INF): ng h/mL

Part 1

Treatment	Parameter	Mean (SD)	Adjusted Geometric Mean	Ratio of Means	
				Point Estimate	90% CI
Combination tablet (500 mg/2.5 mg)	CMAX	119(36.6)	114	1.10	(0.98,1.25)
	AUC(0-T)	971(368)	917	1.18	(1.08,1.29)
Micronase®	CMAX	115(54.4)	104	--	--
	AUC(0-T)	854(385)	776	--	--

Units for CMAX: ng/mL, AUC(0-T): ng.h/mL

Part 2

Treatment	Parameter	Mean (SD)	Adjusted Geometric Mean	Ratio of Means	
				Point Estimate	90% CI
Combination tablet (500 mg/5 mg)	CMAX	122(43.4)	116	1.14	(0.95,1.38)
	AUC(0-T)	859(234)	831	1.07	(0.97,1.17)
Micronase®	CMAX	113(54.9)	101	--	--
	AUC(0-T)	842(327)	780	--	--

Units for CMAX: ng/mL, AUC(0-T): ng h/mL

As indicated in the tables above, for the CMAX and AUC of metformin component from both the combination tablet strengths, the 90% confidence intervals were contained within (0.80, 1.25). Bioavailability of the glyburide component from the two tablet strengths was comparable to Micronase® coadministered with Glucophage®.

SAFETY AND TOLERABILITY RESULTS:

There were no serious or severe adverse events (AEs). All AEs were mild or moderate. A total of 65 treatment emergent AEs were reported in part 1 and a total of 34 treatment emergent AEs in part 2 of this study. The most frequently reported AEs were headache, dizziness, diarrhea, nausea/vomiting, dyspepsia/heartburn, tremor and abdominal pain. The number of total AEs reported was similar between the combination tablet and coadministered reference treatments in part 1 of the study. However, in part 2 of the study, twice as many AEs were reported on the combination tablet treatment relative to Glucophage® and Micronase®. No clinically relevant abnormalities were found in the vital signs and ECG recordings during or post treatment. There were 9 marked abnormalities in the laboratory tests observed at discharge in part 1 of the study. These included one subject with high AST, one subject with low hematocrit and low erythrocyte count, two subjects with high serum potassium, two subjects with low inorganic phosphate, one subject with high blood urea nitrogen and one subject with high lactate dehydrogenase. Four marked abnormalities in the laboratory tests were observed at discharge in part 2 of the study. They included one subject with high serum potassium and three subjects with high blood urea nitrogen. None of these marked abnormalities were considered clinically significant and were not reported as AEs by the investigator.

CONCLUSIONS:

The metformin component of metformin/glyburide combination tablets (500 mg/2.5 mg and 500 mg/5 mg) met criteria for bioequivalence relative to Glucophage® while the glyburide component showed comparable bioavailability to Micronase®.

DATE OF REPORT: July 20, 1999.

Table 12.5.1 Discontinuation for Lack of Glycemic Control by Treatment Group

Reason for Discontinuation		Number (%) of Subjects			
		Glyburide	Metformin	Met/Gly 500/2.5	Met/Gly 500/5
	Total	N = 164	N = 153	N = 160	N = 162
Inadequate Glycemic control	42	15	24	2	1
Withdrew consent: Hyperglycemia	8	2	3	2	1
Totals	50	17 (10.4)	27 (17.6)	4 (2.5)	2 (1.2)

CV138-011
Source Appendices 8.1B, 8.1C
Note N = Number of randomized subjects included in the analysis

12.5.2 *Hypoglycemic Symptoms*

All reported incidences of "hypoglycemia", those reported events that resulted from clinical symptoms of hypoglycemia and those that were true laboratory abnormalities, are included in summary tables under the primary term "serum glucose decrease". Consequently, these events appear only in the laboratory listing of treatment emergent AEs, Appendix 12.6 and the corresponding frequency table, Supplemental Table S.12.6 and do not appear in the listings and frequency tables for clinical AEs. On further perusal of the data there were no laboratory abnormalities of hypoglycemia.

Hypoglycemic events were reported as AEs for a total of 26 subjects (4.1%) during the 16 week double-blind treatment period of this study. Investigators were given no instructions in reporting hypoglycemia as an adverse event. The availability of associated fingersticks performed at the time of the event were queried retrospectively after datalock and the site responses are included in Appendix 12.5.2. The 26 subjects are listed in Table 12.5.2. There were no cases of severe hypoglycemia reported during this study, all events were categorized as mild or moderate; 14 subjects listed have an associated fingerstick at the time of the event included in the table. Of all subjects reporting hypoglycemia, three subjects were on glyburide, one subject was on metformin monotherapy, and 22 subjects were on fixed combination metformin/glyburide therapy.

Of the 22 subjects on fixed combination therapy the lowest associated fingerstick was 51 mg/dL; this subject did not require a dose reduction and achieved a final HbA_{1c} of 6.4% on fixed combination metformin/glyburide 2000/10 mg. Of the 22 subjects on fixed combination therapy, three subjects required an incremental dose decrease, ten remained on a stable dose, seven had either a temporary interruption or a temporary dose reduction, and nine increased their total daily dose by the end of the double-blind phase.

Table 12.5.2 **Subjects Reporting Symptoms of Hypoglycemia or Hypoglycemia Decoding to a Primary Term of Serum Glucose Decrease**

Subject ID/ Age/Gender	Associated fingerstick	Total dose - event onset	Intensity/ Action	Total Dose – end of study	HbA_{1c}	
					baseline	study end
003/006 63F	'lo', < 40	glyburide 20 mg	mild/ none	glyburide 20 mg	8.4	8.0
018/001 43M	64	glyburide 20 mg	mild/ none	glyburide 20 mg	9.1	8.5
048/015 60M	none	glyburide 20 mg	mild/ none	glyburide 20 mg	7.7	8.0
112/001 M66	none	metformin 2000	moderate/ none	metformin 2000 mg	7.7	9.7
005/002 59F	58	met/gly 2000/10	moderate/ none	met/gly 2000/10	8.5	7.5
006/004 52M	none	met/gly 1000/5	mild/ interruption	met/gly 500/2.5	8.5	7.9
021/005 46F	none	met/gly 2000/10	moderate dose reduction	met/gly 2000/10	8.1	7.4
021/013 70F	none	met/gly 1000/5	moderate/ dose reduction	met/gly 2000/10	9.2	8.1
052/001 73M	none	met/gly 1500/7.5	mild/ none	met/gly 1500/7.5	9.3	6.1
052/018 62F	none, 59	met/gly 1500/7.5	mild/ none	met/gly 1500/7.5	9.5	7.2
053/004 62M	none	met/gly 1500/7.5	mild/ none	met/gly 2000/10	7.0	5.8
072/005 60M	none	met/gly 2000/10	moderate/ dose reduction	met/gly 1000/5	9.5	7.9
076/002 49M	68	met/gly 1000/5	mild/ none	met/gly 1500/7.5	10.3	6.6
076/014 59M	58, 60	met/gly 1000/5	mild/ dose reduction	met/gly 1000/5	7.6	7.3
082/004 58F	none	met/gly 1500/7.5	mild/ dose reduction	met/gly 2000/10	9.1	5.9
082/016 57F	none	met/gly 1500/7.5	mild/ none	met/gly 2000/20	8.1	6.0
084/005 73M	51	met/gly 2000/10	moderate/ none	met/gly 2000/10	8.0	6.4
104/004 47F	101	met/gly 1500/7.5	mild/ none	met/gly 1500/7.5	9.4	9.3
015/007 44M	74	met/gly 1500/15	mild/ none	met/gly 2000/20	9.3	7.3
026/004 60M	84, 64	met/gly 2000/20	mild/ none	met/gly 2000/20	6.9	7.1
052/003 72F	70	met/gly , 500/5	mild/ none	met/gly 1000/10	10.5	7.4

Table 12.5.2 Subjects Reporting Symptoms of Hypoglycemia or Hypoglycemia Decoding to a Primary Term of Serum Glucose Decrease

Subject ID/ Age/Gender	Associated fingerstick	Total dose - event onset	Intensity/ Action	Total Dose – end of study	HbA_{1c}	
					baseline	study end
052/019 49M	90	met/gly 1500/15	mild/ none	met/gly 1500/15	7.2	6.5
052/027 45M	88, 68	met/gly 1500/15	mild/ none	met/gly 1500/15	9.3	6.8
053/009 56F	none	met/gly 1500/15	mild/ none	met/gly 2000/20	10.7	6.1
071/009 46F	none	met/gly 1000/10	mild/ none	met/gly 2000/20	11.4	7.9
076/006 65M	60, 59, 57	met/gly 2000/20	mild/ dose reduction	met/gly 1500/15	9.9	7.3

CV138-011
References: Appendix 12.5.2

12.5.3 *Metformin Associated Lactic Acidosis*

There were no reported cases of lactic acidosis or suspected lactic acidosis in this 16-week double-blind study. All lactate measurements were performed on scheduled outpatient visits at the time of all other labs indicated for that specific visit. The study allowed for the measurement of lactate levels under various conditions, which include both fasting and post-prandial levels at baseline on sulfonylurea monotherapy, and then again after 16 weeks of treatment with either glyburide monotherapy, metformin monotherapy or one of two fixed combination metformin/glyburide therapies. Lactate levels were measured for data collection purposes only. No subject was discontinued from double-blind therapy due to an elevated lactate level above the specified normal range and there were no AEs associated with any elevated lactate levels.

The central laboratory normal range is 3-12 mg/dL. Baseline fasting values for all treatment groups were in the high normal range. There were no clinically significant mean changes from baseline at week 16 in any treatment group, and all fasting means except for the metformin monotherapy group remained within the high normal range. A post-prandial rise was expected in all treatment groups; however, there is not a separate

NDA 21-178
Glucovance (metformin and glyburide) Tablets

We refer to your submission dated September 30,1999. The following comment was submitted by Dr. Steven Johnson on July 10, 2000:

Particle Size

The particle size distribution specifications is generally sound. However, the 75% particle size distribution of NMT — is not acceptable. The 75% value should be designated a value NMT which is supported by the PK data presented in this application.

CLEARED FOR FAXING: [/S/] 7/10/00

Hae-Young Ahn, Ph.D. Date
Biopharmaceutics Team Leader

APPEARS THIS WAY
ON ORIGINAL

A relationship between the bioavailability of dissolution rate limited drug substances, such as glyburide, and the drug particle size when expressed as a mass fraction or distribution is well established. The Noyes-Whitney equation, which describes the critical factors involved with the process of dissolution, defines that dissolution is related to the effective surface area exhibited by a given mass of drug. Since surface area is related to particle size, drug substance particle size control can be used to assure glyburide bioavailability.

Glyburide particle size for use in the metformin hydrochloride-glyburide tablet products is measured by a ——— method ——— ———. The particle size measured by this technique is and therefore appropriately reflects the relative at the dissolution and bioavailability. Hence, this measurement technique is suitable for use as a quality control tool.

The particle size distribution measured is expressed as cumulative % particles (by volume) less than a given size, and is reported at the 25%, 50% and 75% points of the cumulative distribution. This yields the so called 25% undersize, 50% undersize and 75% undersize values.

The proposed particle size specification includes three criteria to ensure control across the whole particle size distribution and can be described in the following manner.

- 25 % undersize value not more than , i.e. 25% of the particles by volume should be less than or equal to
- 50% undersize value i.e. 50% of the particles by volume should be greater than or equal to but less than or equal to
- 75% undersize value not more than — µm, i.e. 75% of the particles by volume should be less than or equal to — µm.