CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-460

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA Number:	21-460	**Brand Name:**	Not Specified
OCPB Division (I, II, III):	DPE-II (HFD-870)	**Generic Name:**	Metformin/Glipizide
Clinical Division:	DMEDP (HFD-510)	**Drug Class:**	Biguanide/Sulfonylurea Combo
CPB Reviewer:	Steven B. Johnson, Pharm.D.	**Indication(s):**	Type 2 Diabetes Mellitus
CPB Team Leader:	Hae-Young Ahn, Ph.D.	**Dosage Form:**	Tablets
Submission Date:	21-DEC-2001	**Dosing Regimen:**	2.5/250 mg, 2.5/500 mg & 5/500 mg
CPB Review Due Date:	14-AUG-2002	**Route of Administration:**	PO (oral)
Division Due Date:	11-SEP-2002	**Sponsor:**	Bristol-Myers Squibb
PDUFA Date:	21-OCT-2002	**Priority Classification:**	Standard

Clinical Pharmacology and Biopharmaceutics Information

Information Type	"X" if included at filing	# of Studies Submitted	# of Studies Reviewed	Critical Comments (if any)
Table of Contents	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			
Labeling	X			
Reference Bio- & Analytical Methods	X			
I. Clinical Pharmacology				
Mass Balance:				
Isozyme Characterization:				
Blood/Plasma Ratio:				
Plasma Protein Binding:				
Pharmacokinetics (PK) –				
– Healthy Volunteers –				
Single-Dose:				
Multiple-Dose:				
– Patients –				
Single-Dose:				
Multiple-Dose:				
Dose Proportionality –				
Single-Dose:				
Multiple-Dose:				
Drug-Drug Interaction Studies –				
In-vivo Effects ON Primary Drug:				
In-vivo Effects OF Primary Drug:				
In-vitro Studies:				
Subpopulation Studies –				
Ethnicity:				
Sex:				
Pediatrics:				
Geriatrics:				
Renal Impairment:				
Hepatic Impairment:				
Pharmacodynamics (PD) –				
Phase 2:				
Phase 3:				
PK / PD –				
Phase 1:				
Phase 2:				
Phase 3:				
Population Analyses –				
Rich Data Set:				
Sparse Data Set:				
II. Biopharmaceutics				
Absolute Bioavailability:				
Relative Bioavailability –				
Solution as Reference				
Other Formulation as Reference:				
Bioequivalence Studies –				
– Traditional Design –				
Single-Dose:	X	2		
Multiple-Dose:				

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– Replicate Design –				
Single-Dose:				
Multiple-Dose:				
Food-Drug Interaction Studies:	X	1		
Dissolution:	X	1		
In-vitro/In-vivo Correlation:				
BCS Based Biowaiver Request:	X	1		Not BCS – proportional strength
BCS Classification Information:				
III. Other CPB Studies				
Genotype / Phenotype Studies:				
Chronopharmacokinetics:				
Pediatric Development Plan:				
Literature References:				
TOTAL # OF STUDIES		5		

Primary Reviewer Signature:	Steven B. Johnson, Pharm.D.	Date:	
Secondary Reviewer Signature:	Hae-Young Ahn, Ph.D.	Date:	

– Line Listing of Studies Included in this Application –

Study #	Study Title
CV138-044	A Pilot Bioavailability Study of Different Formulations of Metformin and Glipizide in Combination
CV138-073	Bioequivalence Study of a Metformin/Glipizide Combination Tablet Relative to Coadministered Glucophage and Glucotrol in Healthy Subjects
CV138-074	Effect of a High Fat Meal on the Pharmacokinetics of Metformin and Glipizide from a Metformin/Glipizide Combination Tablet in Healthy Subjects

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NDA #:	21-460	**RELEVANT IND:**	———
BRAND NAME:	NOT SPECIFIED	**GENERIC NAME:**	Glipizide/Metformin HCl
STRENGTH(S):	2.5/250, 2.5/500, & 5/500 mg	**DOSAGE FORM:**	Combination Tablets
APPLICANT:	Bristol-Myers Squibb Pharmaceutical Research Institute PO Box 4000, Princeton, NJ 08543-4000		
LETTER DATE:	21-DEC-2002	**PDUFA DATE:**	21-OCT-2002
OCPB DIVISION:	DPE-2	**OND DIVISION:**	DMEDP
CPB REVIEWER:	Steven B. Johnson, Pharm.D.	**CPB TEAM LEADER:**	Hae-Young Ahn, Ph.D.

EXECUTIVE SUMMARY

Bristol-Myers Squibb (BMS) has submitted NDA 21-460 to support the approval of a fixed-dose combination tablet containing two active ingredients, glipizide, a sulfonylurea marketed under the tradename GLUCOTROL by Pfizer Pharmaceuticals, and metformin hydrochloride (HCl), a biguanide marketed under the tradename GLUCOPHAGE by BMS. This new combination tablet would be commercially available in three different strengths: 2.5 mg/250 mg, 2.5 mg/500 mg, and 5 mg/500 mg (glipizide/metformin HCl) for the treatment of Type 2 diabetes mellitus.

To aid in the approval of this application the sponsor has submitted three human pharmacokinetic studies: two bioavailability/bioequivalence studies (CV138-044 and -073); and a food-effect study (CV138-074). There was also inclusion of an *in vitro* dissolution method, with appropriate data, and a biowaiver request for the 2.5 mg/250 mg glipizide/metformin HCl combination tablet that was not studied *in vivo*. Information on an alternative strength, ———, was also submitted in Section 6 of this application, but the sponsor is not currently seeking approval for this strength.

Two bioequivalence studies were conducted for glipizide/metformin HCl combination tablets: a pilot study that examined the relative rate and extent of exposure of a single dose of 2 x 2.5 mg/500 mg with 1 x 5 mg GLUCOTROL plus 2 x 500 mg GLUCOPHAGE; and a bioequivalence study that compared the 5 mg/500 mg tablet with its respective equivalent components. The results of the studies were favorable and bioequivalence was conferred on both tablet strengths.

In the third study, 1 x 5 mg/500 mg combination tablets were compared under fed and fasted conditions. Study results indicate that under fed conditions there is only a small observed food effect (i.e., C_{max} was reduced by approximately 14% [90% CI = 0.78 – 0.95] for the metformin component and increased by 9% [90% CI = 0.94 – 1.255] for the glipizide component). There was also a 1-hour delay in the fed combination tablet T_{max} for both components. However, there was no difference in the extent of absorption of either active substance, as measured by AUC. These findings are similar to current GLUCOTROL labeling, but are significantly less pronounced than that for GLUCOPHAGE (i.e., AUC and C_{max} are reduced by 40% and 25%, respectively, for metformin HCl).

Multipoint dissolution data from a single lot of each of the to-be-marketed strengths was included for evaluation. Typically, and as the relevant Guidance for Industry states, dissolution medium should fall within the pH range of 1.2 to 6.8 – unless there is compelling evidence to warrant otherwise. The sponsor used a pH — media for their proposed dissolution method, and based on the data that was provided as evidence in support of the biowaiver request, a media system utilizing a pH 6.8 medium was determined by the Agency to be more appropriate. Therefore, the sponsor will be required to pursue the use of the pH 6.8 media system as their regulatory dissolution method in a Phase 4 study – to be submitted within 6 months of application approval.

Since the individual strength formulations were shown to be proportional, dissolution was comparable between strengths, there was linear PK, and no drug interaction between the two agents, then a biowaiver for the 2.5 mg/250 mg strength not studied *in vivo* should be granted.

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Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-460 for glipizide/metformin HCl combination tablets and finds the human pharmacokinetics section of the application acceptable providing that the sponsor accepts the Phase 4 commitment described below, and relevant labeling changes. Please convey the **Phase 4** and **Labeling Comments** to the sponsor as appropriate.

Phase 4 Commitment

The use of a pH — medium for the dissolution of glipizide/metformin HCl combination tablets was found to be unacceptable by the Agency. Data submitted in this application suggests that a pH 6.8 medium should be further investigated and instituted as the regulatory dissolution method. Please provide multipoint dissolution data on each of the tablet strengths using a pH 6.8 dissolution medium. The current method will be excepted on an interim basis only. Results from the requested study should be presented to the Agency within 6 months of the — date for this application.

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SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

- Each of the 3 tablet strengths of glipizide/metformin HCl combination tablets was found to be proportionally similar in formulation;
- Two glipizide/metformin 2.5 mg/500 mg tablets are bioequivalent to one 5 mg GLUCOTROL tablet plus two 500 mg GLUCOPHAGE tablets administered concomitantly under fasting conditions; and one glipizide/metformin 5 mg/500 mg tablet is bioequivalent to one 5 mg GLUCOTROL tablet plus one 500 mg GLUCOPHAGE tablets administered concomitantly under fasting conditions
- Linear PK has been previously established between 1.25 to 5 mg glipizide, and 250 and 500 mg metformin;
- The food effects seen in the glipizide/metformin HCl study are similar to those observed in the GLUCOTROL and GLUCOPHAGE labels;
- Dissolution was similar between all three of the tablet strengths at pH — However, the proposed dissolution method was found to be unacceptable to the Agency and the sponsor is being asked to investigate a pH 6.8 — medium in a Phase 4 Commitment; and
- Sufficient data was provided to support a biowaiver for the strength that was not studied *in vivo*.

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QUESTION BASED REVIEW

General Attributes

Formulation

Do the four glipizide/metformin combination tablets have proportional formulations?

The fixed dose combination glipizide/metformin tablets are proportional to each other based on the following matrix: the 2.5 mg/250 mg strengths contain [redacted] of the components, by weight, as that of the 5 mg/500 mg strength tablets; and the [redacted] mg strengths contain [redacted] of the components, by weight, as that of the 2.5 mg/500 mg strength tablets. Tablets containing equivalent amounts of metformin HCl differ only in the amount of glipizide and primary [redacted], but are of the same total weight. (See **TABLE 1**).

TABLE 1: Fixed-dose glipizide/metformin formulation comparison

Ingredient	[redacted]	2.5 mg/250 mg	2.5 mg/500 mg	5 mg/500 mg
Metformin HCl /				
Glipizide[2]				
[redacted]				
Total Weight Uncoated				
[redacted]				
Total Weight Coated				

1 Contains [redacted] of metformin HCl and [redacted] Assumes 100.0% purity of metformin HCl.
2 Amount assumes 100.0% purity of glipizide.

Are there formulation differences between the products that were used in the clinical studies and the final commercial product?

There is a slight difference between the products that were used in the clinical studies and those that will be commercially available: color and embossment. All of the tablets used in the clinical studies were [redacted] embossment. The commercial products will appear as follows: [redacted] 2.5 mg/250 mg = [redacted] pink, "BMS" and "6081;" 2.5 mg/500 mg = white, "BMS" and "6077;" and 5 mg/500 mg = [redacted] pink, "BMS" and "6078." There were no size or shape differences between the clinical and final tablet formulations.

BCS Classification

What are the BCS classifications for glipizide and metformin?

In order to confer a BCS classification for a drug substance, two issues must be addressed – solubility and permeability. Since the compound under review is a fixed dose combination formulation, the solubility and permeability issues need to be addressed separately for each active compound.

– Metformin – (BCS Class 3)

Solubility – Metformin HCl is freely soluble across the physiological pH range of [redacted] (See ***Dissolution***).
Permeability – the absolute oral bioavailability of metformin HCl after 0.5 to 1.5 g doses is [redacted] with a lack of established dose-proportionality between 500 mg to 1500 mg, and 850 mg to 2550 mg, and there is no first pass effect.

– Glipizide – (BCS Class 2)

Solubility – Glipizide is nearly insoluble across the physiological pH range of [redacted] (See **TABLE 2**).
Permeability – The absolute oral bioavailability of glipizide is [redacted] with dose-proportionality between 2.5 and 5 mg.

TABLE 2: Glipizide Solubility in Buffer Solutions of Different pHs at 37° C			
Buffer System	**pH**	**Solubility in buffer (mg/mL)**	**Solubility in Buffer with Other Formulation Components (mg/mL)**

Dissolution

Is the dissolution method and tolerance specification appropriate for glipizide/metformin tablets?

To answer this question, the sponsor conducted a multipoint dissolution study that compared clinical (reference) and commercial (test) products by strength and active component, respectively. The dissolution method used to perform this study is described in **TABLE 3**.

TABLE 3: Proposed Glipizide/Metformin Dissolution Method and Tolerance Specifications	
Media	
pH	
USP Apparatus	
Apparatus Speed	
Temperature	
Volume	
Tolerance (Metformin HCl component)	NLT Q) @ 30 minutes
Tolerance (Glipizide component)	NLT Q) @ 30 minutes

Results of the study are presented in **TABLE 4**.

TABLE 4: Summary of Dissolution Profiles for Glipizide and Metformin HCl Tablets																
n = 12/test					**2.5 mg/250 mg**				**2.5 mg/500 mg**				**5 mg/500 mg**			
Time (min)	**Metformin**		**Glipizide**		**Metformin**		**Glipizide**		**Metformin**		**Glipizide**		**Metformin**		**Glipizide**	
	R	**T**	**R**	**T**	**R**	**T**	**R**	**T**	**R**	**T**	**R**	**T**	**R**	**T**	**R**	**T**
10																
20																
30																
45*																
60*																
f2	—	65	—	63	—	61	—	58	—	92	—	66	—	94	—	64

(R) Reference Product (Clinical Formulation)		(T) Test Product (Commercial Formulation)	
Lot Number	**Strength (glipizide/metformin)**	**Lot Number**	**Strength (glipizide/metformin)**
8MFC144		8MFC145	
8MJS280	2.5 mg/250 mg	8MLS332	2.5 mg/250 mg
8MJS281	2.5 mg/500 mg	8MLS328	2.5 mg/500 mg
8MJS283	5 mg/500 mg	8MFC184	5 mg/500 mg

* Sponsor did not use in calculating f2 values.

The results of the dissolution study are unremarkable – except for the fact that the sponsor used a dissolution medium with a pH of According to the Guidance for Industry *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, "An aqueous medium with pH range 1.2 to 6.8 should be used. A higher pH should be justified on a case-by-case basis and, in general, should not exceed pH 8.0."

In order to justify the use of the pH dissolution medium, the sponsor conducted multipoint dissolution testing on a non-commercial test tablet, , in various media (see **TABLE 5**), and their 2.5 mg/500 mg product formulated with and without disintegrant in pH (see **TABLE 6**). The latter study was done to show the discriminatory power of the proposed dissolution method.

TABLE 5: Dissolution of Glipizide and Metformin in Various Media –

Medium	% Glipizide Label Claim Dissolved – Average (Range)
pH	
pH	
pH	
	% Metformin HCl Label Claim Dissolved – Average (Range)
pH	
pH	
pH	

TABLE 6: Dissolution of Glipizide and Metformin in pH Medium – 2.5 mg/500 mg

Medium	10 min	20 min	30 min	45 min	60 min	90 min
	% Glipizide Label Claim Dissolved – Average (Range)					
With disintegrant						
Without disintegrant						
	% Metformin HCl Label Claim Dissolved – Average (Range)					
With disintegrant						
Without disintegrant						

Results of the media comparison study (**TABLE 5**) show three features quite clearly: 1) the metformin HCl component appears to be a freely soluble substance over a wide pH range; 2) the glipizide component exhibits pH dependent dissolution and is practically insoluble at pHs [redacted] the pH [redacted] system may be an appropriate alternative to the proposed pH [redacted] dissolution media.

The study to demonstrate the discriminatory power of the proposed method (**TABLE 6**) does indeed show that neither component dissolves well without the addition of a disintegrant in the formulation. However, in lieu of the results from the media study, this additional information is not sufficient to warrant the use of a pH [redacted] media, especially since the compendial dissolution method for glipizide uses a pH 6.8 medium.

As a result of the above findings, the sponsor should further investigate the use of the pH [redacted] media. Based on the data submitted for the [redacted] mg tablet, which would likely produce the worst-case-scenario for the glipizide component, the sponsor could still use a [redacted] tolerance specification for both drug components (e.g., glipizide = [redacted](Q) @ 30 minutes; metformin HCl = [redacted] (Q) @ 30 minutes).

General Biopharmaceutics

Bioequivalence

Is there a correlation between the individual components of a 2.5 mg/500 mg combination tablet and its respective equivalent components?

Study CV138-044 was a pilot bioavailability study that serves to answer the above question. Thirteen subjects (12 completers) were enrolled in an open-label, randomized, fasting, two-period, two-treatment, single-dose crossover study. Each subject was administered one of the following treatments per study period: Tx A – 2 x 2.5 mg/500 mg combination glipizide/metformin tablets; or Tx B – 1 x 5 mg GLUCOTROL plus 2 x 500 mg GLUCOPHAGE. Each treatment was administered in the morning with 240 mL of a 20% glucose solution in water. Treatments were separated by at least a one-week washout period.

Results of this study show that bioequivalence was achieved between the two 2.5 mg/500 mg combination tablets and their respective equivalent components, for both AUC and C_{max} parameters. Data summaries for the respective components are presented in **TABLES 7 and 8**.

TABLE 7: Bioequivalence Summary and Analysis – Glipizide Component

Parameter	Unit	Tx A	Tx B	Point Estimate (%)	90% Confidence Intervals	
					Low	High
AUC_{0-inf}	ng*hr/mL	2150 ± 605	2100 ± 567	1.02	0.97	1.08
C_{max}	ng/mL	211 ± 63.9	217 ± 55.0	0.95	0.81	1.12

Tx A = 2 x 2.5 mg/500 mg combination tablets; Tx B = 1 x 5 mg GLUCOTROL plus 2 x 500 mg GLUCOPHAGE
Mean ± SD

TABLE 8: Bioequivalence Summary and Analysis – Metformin Component						
Parameter	Unit	Tx A	Tx B	Point Estimate (%)	90% Confidence Intervals	
					Low	High
AUC_{0-inf}	ng*hr/mL	11027 ± 2700	10560 ± 2497	1.04	0.98	1.11
C_{max}	ng/mL	1652 ± 372	1556 ± 347	1.06	0.91	1.23
Tx A = 2 x 2.5 mg/500 mg combination tablets; Tx B = 1 x 5 mg GLUCOTROL plus 2 x 500 mg GLUCOPHAGE Mean ± SD						

Is there a correlation between the individual components of a 5 mg/500 mg combination tablet and its respective equivalent components?

Study CV138-073 was a bioequivalence study that serves to answer the above question. Twenty-four subjects (21 completers) were enrolled in an open-label, randomized, fasting, two-period, two-treatment, single-dose crossover study. Each subject was administered one of the following treatments per study period: Tx A – 1 x 5 mg/500 mg combination glipizide/metformin tablets; or Tx B – 1 x 5 mg GLUCOTROL plus 1 x 500 mg GLUCOPHAGE. Each treatment was administered in the morning with 240 mL of a ~ glucose solution in water. Treatments were separated by at least a one-week washout period.

Results of this study show that bioequivalence was achieved between one 5 mg/500 mg combination tablet and the respective equivalent components, for both AUC and C_{max} parameters. Data summaries for the respective components are presented in **TABLES 8 and 9.**

TABLE 9: Bioequivalence Summary and Analysis – Glipizide Component						
Parameter	Unit	Tx A	Tx B	Point Estimate (%)	90% Confidence Intervals	
					Low	High
AUC_{0-inf}	ng*hr/mL	1970 ± 591	2053 ± 616	1.04	1.01	1.08
AUC_{0-t}	ng*hr/mL	1938 ± 581	2017 ± 585	—	—	—
C_{max}	ng/mL	210 ± 63	205 ± 49	0.98	0.89	1.07
T_{max}	h	7 (2.5, 14)	6.5 (4, 12)	—	—	—
$t_{1/2}$	h	4.3 ± 0.9	4.3 ± 1.0	—	—	—
Tx A = 1 x 5 mg GLUCOTROL plus 1 x 500 mg GLUCOPHAGE; Tx B = 1 x 5 mg/500 mg combination tablets Mean ± SD; Median (Range)						

TABLE 10: Bioequivalence Summary and Analysis – Metformin Component						
Parameter	Unit	Tx A	Tx B	Point Estimate (%)	90% Confidence Intervals	
					Low	High
AUC_{0-inf}	ng*hr/mL	5016 ± 1003	4965 ± 943	0.99	0.94	1.04
AUC_{0-t}	ng*hr/mL	4923 ± 985	4900 ± 931	—	—	—
C_{max}	ng/mL	664 ± 133	701 ± 210	1.05	0.96	1.16
T_{max}	h	2.5 (1, 4)	2.5 (1, 5)	—	—	—
$t_{1/2}$	h	6.3 ± 1.5	5.6 ± 1.1	—	—	—
Tx A = 1 x 5 mg GLUCOTROL plus 1 x 500 mg GLUCOPHAGE; Tx B = 1 x 5 mg/500 mg combination tablets Mean ± SD; Median (Range)						

Has dose proportionality been established between any of the proposed strength tablets?
There was no single study that addressed the issue of dose proportionality between the proposed strengths of glipizide/metformin combination tablets in this submission. However, two 2.5 mg/500 mg combination tablets were found to be bioequivalent to one 5 mg GLUCOTROL tablet co-administered with two 500 mg GLUCOPHAGE tablets, and previously reviewed data indicates that glipizide and metformin exhibit linear pharmacokinetics from 1.25 mg to 5 mg and 250 mg to 500 mg, respectively.

Food Effect
Does food alter the bioavailability of the glipizide/metformin combination tablet?

To determine the effect of food on glipizide/metformin tablets, an open-label, two-period, two-treatment, randomized crossover study was conducted in 24 healthy male and female subjects (18 completers) [study

CV138-074]. Treatments were as follows: Tx A – 1 x 5 mg/500 mg combination tablet administered fasting (test); or Tx B - 1 x 5 mg/500 mg combination tablet administered after a standard FDA high fat meal (reference). Each treatment was administered in the morning with 240 mL of a — glucose solution in water. Treatments were separated by at least a 7-day washout period.

The summaries of findings from the food-effect study are presented in **TABLES 9 and 10.** These results show that when the combination tablet is compared under fed and fasted conditions, a small food-effect is present for both the glipizide and metformin components. The C_{max} point estimate for the fed:fasted comparison was 1.09 and 0.86, with corresponding 90% confidence intervals of 0.94, 1.255 and 0.78, 0.95, respectively, for the glipizide and metformin components. The T_{max} for both compounds was also delayed by approximately 1 hour when the combination tablet was administered under fed conditions. There was no effect on extent of absorption, as measured by AUC. These findings are similar to current GLUCOTROL labeling, but are significantly less pronounced than that for GLUCOPHAGE (i.e., AUC and C_{max} are reduced by 40% and 25%, respectively, for metformin HCl) – NOTE: GLUCOPHAGE was administered with water under fasting conditions, not with a —, oral glucose solution.

TABLE 9: Bioequivalence Summary and Analysis – Glipizide Component

Parameter	Unit	Tx A	Tx B	Point Estimate (%)	90% Confidence Intervals	
					Low	High
AUC_{0-inf}	ng*hr/mL	2164 ± 736	2256 ± 767	1.03	0.98	0.94
AUC_{0-t}	ng*hr/mL	2103 ± 673	2209 ± 707	—	—	—
C_{max}	ng/mL	212 ± 47	235 ± 78	1.09	1.08	1.255
T_{max}	h	6 (2, 10)	7 (1, 14)	—	—	—
$t_{1/2}$	h	5.2 ± 1.8	4.7 ± 1.2	—	—	—

Tx A = 1 x 5 mg/500 mg combination tablets – fasted; Tx B = 1 x 5 mg/500 mg combination tablets – high fat meal
Mean ± SD; Median (Range)

TABLE 10: Bioequivalence Summary and Analysis – Metformin Component

Parameter	Unit	Tx A	Tx B	Point Estimate (%)	90% Confidence Intervals	
					Low	High
AUC_{0-inf}	ng*hr/mL	5087 ± 1068	5076 ± 1015	0.99	0.91	1.07
AUC_{0-t}	ng*hr/mL	4998 ± 1100	5000 ± 1000	—	—	—
C_{max}	ng/mL	663 ± 152	563 ± 146	0.86	0.78	0.95
T_{max}	h	3 (1, 4)	4 (1, 8)	—	—	—
$t_{1/2}$	h	6.1 ± 1.6	5.1 ± 0.8	—	—	—

Tx A = 1 x 5 mg/500 mg combination tablets – fasted; Tx B = 1 x 5 mg/500 mg combination tablets – high fat meal
Mean ± SD; Median (Range)

Biowaiver

Can the biowaiver request be granted for the —— mg and 2.5 mg/250 mg combination tablets?

In order to grant a biowaiver for a product that is not studied *in vivo*, several criteria must be considered. These criteria include proportional formulations, linear pharmacokinetics, and similar dissolution profiles between the proposed strengths – as determined by f_2 comparisons. The results of the studies that address these criteria are presented below:

Formulation Proportionality – The —— mg and 2.5 mg/250 mg tablets are exactly — the total weight and composition of the 2.5 mg/500 mg and 5 mg/500 mg tablets, respectively;

Linear Pharmacokinetics – Data submitted in the original NDAs for glipizide and metformin have shown that these two compounds exhibit linear pharmacokinetics between 1.25 mg to 5 mg and 250 mg to 500 mg, respectively

Dissolution Profile Comparison –

Reference Product		Test Product		Metformin HCl	Glipizide
Lot Number	Strength	Lot Number	Strength	f2	f2
8MFC184	5 mg/500 mg	8MLS328	2.5 mg/500 mg	92	63
		8MLS332	2.5 mg/250 mg	88	70
		8MFC145	1.25 mg/250 mg	83	65

Since this product meets all three of the criteria listed above, a biowaiver should be considered for the — mg and 2.5 mg/250 mg glipizide/metformin tablets that were not studied *in vivo*.

Analytical

Have the analytical methods been sufficiently validated?

Metformin and glipizide concentrations in plasma were determined using validated analytical methods. An assay with and a lower limit of quantification (LLQ) was used to measure metformin plasma concentrations in Study CV138-044. Glipizide plasma concentrations were determined using a method with an LLQ methods with an LLQ of were used to quantify metformin and glipizide plasma concentrations in Studies CV138-073 and CV138-074. The validation study results for the respective assays are presented in **TABLE 11**.

TABLE 11: Assay Validation Study Summary

	Glipizide					Metformin				
LLOQ (ng/mL)										
Calibration (ng/mL)										
Quality Control										
Mean	3.96	201	393	10.7	21.8	26.1	166	161	1600	1550
SD	0.16	10	21	1.46	1.76	2.92	16.5	5.32	52.0	52.7
% CV (precision)										
Accuracy (%)										
N	18	18	18	6	6	6	6	6	6	6

Labeling Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Package Insert labeling for glipizide/metformin HCl tablets and it acceptable as written.

WITHHOLD 31 PAGE (S)

FINAL REPORT SYNOPSIS

TITLE OF STUDY: A Pilot Bioavailability Study of Different Formulations of Metformin and Glipizide in Combination

INVESTIGATORS: Evren Atillasoy, M.D.

STUDY CENTERS: Bristol-Myers Squibb Clinical Research Center

PUBLICATIONS: None

STUDY PERIOD: Date first subject enrolled: 08-Jun-1999

Date last subject completed: 30-Jun-1999

CLINICAL PHASE: I

OBJECTIVES:

Part 1. To assess the bioavailability of metformin and glipizide from a metformin•HCl/glipizide combination tablet relative to coadministered Glucophage® and Glucotrol®.

Part 2. To assess metformin bioavailability from a metformin•fumarate single entity tablet relative to a metformin•fumarate/glipizide combination tablet.

METHODOLOGY:

This study consisted of two parts. Each part was an open-label, single-dose, randomized, two-period, two-treatment crossover study. Subjects in the two parts of the study were randomized separately, and subjects were not allowed to participate in both parts. The treatments were as follows:

Part 1 (N = 12 subjects):

Treatment A: 2 x metformin•HCl/glipizide (500 mg/2.5 mg) combination tablets

Treatment B: 2 x Glucophage® (500 mg) and 1 x Glucotrol® (5 mg) tablets

Part 2 (N = 12 subjects):

Treatment C: 2 x metformin•fumarate (565 mg) single entity tablets

Treatment D: 2 x metformin•fumarate/glipizide (565 mg/2.5 mg) combination tablets

After an overnight fast, each treatment was administered in the morning with 240 mL of a — glucose solution in water. Each treatment was separated by at least a one-week washout period. Serial blood samples for metformin and glipizide pharmacokinetics were collected for 24 h after each dose. Metformin and glipizide plasma concentrations were determined by validated analytical methods. Only metformin was analyzed in Part 2 of the study. Cmax, Tmax, AUC, and T-HALF were calculated for each treatment by noncompartmental analysis.

NUMBER OF SUBJECTS: A total of 13 subjects enrolled in Part 1 and 12 completed the study. One subject was lost to follow-up (i.e., the subject did not return for crossover treatment and assessment). A total of 12 subjects enrolled in Part 2 and 12 subjects completed the study.

MAIN CRITERIA FOR INCLUSION: Healthy male and female volunteers between the ages of 18 and 40 years and within ± 15% of ideal body weight. Female subjects were required to not be nursing or

pregnant, and if of childbearing potential, they must have been practicing an effective method of contraception. Good health was determined by medical history, physical examination, and clinical laboratory tests. All subjects gave written informed consent.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

Metformin•HCl/glipizide (500 mg/2.5 mg) combination tablets (batch number N99053) and metformin•fumarate single entity (565 mg) tablets (batch number N99052) were administered orally.

DURATION OF TREATMENT:

In Part 1, single doses of metformin and glipizide, as combination tablets and as reference marketed products, were administered with a one week washout period between treatments. In Part 2, single doses of metformin•fumarate single entity and metformin•fumarate/glipizide combination tablets were administered with a one week washout period between treatments.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS

Glucophage® (metformin•hydrochloride; 500 mg) tablets (batch number 507BGO), Glucotrol® (glipizide; 5 mg) tablets (batch number 78P006A), and metformin•fumarate/glipizide (565 mg/2.5 mg) combination tablets (batch number N98175) were administered orally.

CRITERIA FOR EVALUATION:

Safety: Safety was assessed by monitoring for the occurrence of adverse events (AEs), and by physical examinations, vital signs, clinical laboratory tests, and ECGs.

Pharmacokinetics: Serial blood samples were collected for 24 h post-dose. Metformin plasma concentrations were determined using a validated method with [redacted]. Glipizide plasma concentrations were determined by a validated method. The pharmacokinetic parameters Cmax, Tmax, AUC(0-T), AUC(INF), and T-HALF were determined from metformin and glipizide plasma concentration *vs.* time data by a validated noncompartmental analysis protocol, and summarized by treatment.

Pharmacodynamics: Not applicable.

STATISTICAL METHODS:

Parts 1 and 2 of the study were analyzed separately.

Sample Size: Although not based on statistical power considerations, the sample size of 12 subjects (6 subjects per sequence) for Part 1 provided 90% confidence that the point estimates for the ratio of the metformin•HCl/glipizide combination tablet relative to coadministered Glucophage® and Glucotrol® differed from the true population ratio by at most 6.4% for metformin AUC(INF), 12.4% for metformin Cmax, 5.2% for glipizide AUC(0-T), and 14.0% for glipizide Cmax. These calculations were based on the assumptions that AUC(INF), AUC(0-T), and Cmax were log-normally distributed and on estimated among-subject mean squares for log[AUC(INF)] and log(Cmax) of 0.007 and 0.025, respectively, for metformin, and for log[AUC(0-T)] and log(Cmax) of 0.005 and 0.031, respectively, for glipizide obtained from study CV138-041.

The sample size of 12 subjects (6 subjects per sequence) for Part 2 provided 90% confidence that the point estimates for the ratios of metformin from the single entity metformin•fumarate tablets to metformin•fumarate/glipizide combination tablets differed from the true population ratio by at most 6.4% for AUC(INF) and 12.4% for Cmax. These calculations were based on the same assumptions as above.

Statistical Methods: For Part 1, to assess the effect of formulation, an analysis of variance model appropriate for a two-period, two-treatment crossover design was used for Cmax (metformin and glipizide), AUC(INF) for metformin, and AUC(0-T) for glipizide. The factors in the analysis were sequence, subject within sequence, period, and formulation. *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 measurements. No analysis other than descriptive statistics was done for Tmax and T-HALF.

Identical analyses were performed in Part 2, but only for metformin. No statistical comparisons of data from Parts 1 and 2 of the study were conducted.

Analysis: Statistical analyses were performed by the Department of Biostatistics and Data Management of the Bristol-Myers Squibb Pharmaceutical Institute. All available data from all subjects who received study medication were included in the summaries of physical examination findings, clinical laboratory data, vital signs, and adverse events.

PHARMACOKINETIC RESULTS: Metformin and glipizide pharmacokinetic parameters and the results of statistical analysis are presented in the following tables:

Metformin Pharmacokinetic Parameters – Part 1

Treatment	Parameter	Arithmetic Mean (SD)	Geometric Mean	Ratio of Geometric Means	
				Point Estimate	90% C.I.
A	Cmax (ng/mL)	1652 (372)	1610	1.06	(0.91, 1.23)
	AUC(INF) (ng•h/mL)	11027 (2700)	10704	1.04	(0.98, 1.11)
B	Cmax (ng/mL)	1556 (347)	1520	—	—
	AUC(INF) (ng•h/mL)	10560 (2497)	10293	—	—

A = 2 x metformin•HCl/glipizide (500 mg/2.5 mg) combination tablets

B = 2 x Glucophage® (500 mg) and 1 x Glucotrol® (5 mg) tablets

Glipizide Pharmacokinetic Parameters – Part 1

Treatment	Parameter	Arithmetic Mean (SD)	Geometric Mean	Ratio of Geometric Means	
				Point Estimate	90% C.I.
A	Cmax (ng/mL)	211 (63.9)	202	0.95	(0.81, 1.12)
	AUC(0-T) (ng•h/mL)	2150 (605)	2067	1.02	(0.97, 1.08)
B	Cmax (ng/mL)	217 (55.0)	212	—	—
	AUC(0-T) (ng•h/mL)	2100 (567)	2026	—	—

A = 2 x metformin•HCl/glipizide (500 mg/2.5 mg) combination tablets

B = 2 x Glucophage® (500 mg) and 1 x Glucotrol® (5 mg) tablets

In Part 1, metformin was bioequivalent in the combination tablet and coadministered tablet treatments with respect to Cmax and AUC(INF) since the 90% confidence intervals for these parameters were entirely

contained between 0.80 and 1.25. Median (min, max) Tmax values for metformin were similar for the combination tablet [2 (1, 3) h] and coadministered tablet [2 (1, 4) h] treatments. Mean ± SD metformin T-HALF values were 5.6 ± 1.2 h and 6.4 ± 2.1 h for the combination tablet and coadministered tablet treatments, respectively.

Glipizide was bioequivalent in the combination tablet and coadministered tablet treatments with respect to Cmax and AUC(0-T) since the 90% confidence intervals for these parameters were entirely contained between 0.80 and 1.25. Median (min, max) Tmax values were similar for the combination tablet [7.5 (1.5, 12) h] and coadministered tablet [8 (1, 10) h] treatments.

Metformin Pharmacokinetic Parameters - Part 2

Treatment	Parameter	Arithmetic Mean (SD)	Geometric Mean	Ratio of Geometric Means	
				Point Estimate	90% C.I.
C	Cmax (ng/mL)	1373 (430)	1316	1.00	(0.88, 1.13)
	AUC(INF) (ng•h/mL)	9891 (2359)	9643	0.96	(0.91, 1.00)
D	Cmax (ng/mL)	1370 (406)	1318	—	—
	AUC(INF) (ng•h/mL)	10375 (2648)	10072	—	—

C = 2 x metformin•fumarate (565 mg) single entity tablets

D = 2 x metformin•fumarate/glipizide (565 mg/2.5 mg) combination tablets

In Part 2, metformin was bioequivalent in the metformin•fumarate single entity and metformin•fumarate/glipizide combination tablet treatments with respect to Cmax and AUC(INF) since the 90% confidence intervals for these parameters were entirely contained between 0.80 and 1.25. Median (min, max) Tmax values were similar for the single entity tablet [2.8 (2, 4) h] and combination tablet [2.5 (1.5, 4) h] treatments. Mean ± SD metformin T-HALF values were 6.8 ± 2.1 h and 6.5 ± 1.9 h for the single entity tablet and combination tablet treatments, respectively.

PHARMACODYNAMIC RESULTS: Not applicable.

SAFETY AND TOLERABILITY RESULTS: There were no serious adverse events. Few adverse events were reported, all of which were mild to moderate in intensity, resolved prior to discharge of the subject from the study, and were judged unrelated to study drug by the Investigator. No clinically significant vital sign, laboratory test, or ECG abnormalities were reported.

CONCLUSIONS:

- Metformin and glipizide were bioequivalent in the metformin•HCl/glipizide combination tablet and coadministered Glucophage® + Glucotrol® treatments with respect to Cmax and AUC.
- Metformin was bioequivalent with respect to Cmax and AUC in the metformin•fumarate single entity and metformin•fumarate/glipizide combination tablet treatments. Thus, glipizide does not affect metformin bioavailability when formulated with metformin•fumarate in a combination tablet.

DATE OF REPORT: 14-Nov-2001

FINAL REPORT SYNOPSIS

TITLE OF STUDY: Bioequivalence Study of a Metformin/Glipizide Combination Tablet Relative to Coadministered Glucophage and Glucotrol in Healthy Subjects

INVESTIGATORS:

STUDY CENTERS:

PUBLICATIONS: None

STUDY PERIOD: Date first subject enrolled: 01-Jun-2001

Date last subject completed: 09-Jun-2001

CLINICAL PHASE: I

OBJECTIVES:

The primary objective was to demonstrate bioequivalence of metformin and glipizide from a metformin/glipizide combination tablet relative to coadministered Glucophage® and Glucotrol®. The secondary objective was to assess the safety of metformin and glipizide, when administered as a metformin/glipizide combination tablet and as coadministered Glucophage® and Glucotrol®.

METHODOLOGY:

This was an open-label, randomized, two-period, two-treatment, crossover study in fasted healthy subjects. Twenty-four (24) subjects received metformin/glipizide combination tablets or coadministered Glucophage® and Glucotrol® in one of two randomly assigned treatment sequences. For each treatment period, subjects were admitted to the clinical facility the evening prior to dosing (Day -1) and were confined until 32 hours post-dose. Blood samples were collected for pharmacokinetic analysis up to 32 hours post-dose. Subjects were monitored closely for adverse events throughout the study.

NUMBER OF SUBJECTS:

A total of 24 subjects enrolled and completed the study.

MAIN CRITERIA FOR INCLUSION:

Healthy subjects as determined by medical history, physical examination, 12-lead electrocardiogram, and clinical laboratory evaluations. Women of child bearing potential were not nursing, not pregnant, and were using an acceptable method of contraception for at least one month prior to dosing. Women of childbearing potential must have had a negative serum pregnancy test within 24 hours prior to each dose of study medication.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

Metformin/glipizide (500 mg/5 mg) combination tablets (batch number 8MFC184) were orally administered.

DURATION OF TREATMENT:

Each subject was administered two single doses of metformin and glipizide, once as a metformin/glipizide combination tablet and again as coadministered Glucophage® and Glucotrol®, according to a randomization schedule, with at least a 7-day washout period between each dose.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

Glucophage® (metformin•hydrochloride: 500 mg) tablets (lot # 1C53090) and Glucotrol® (glipizide, 5 mg) tablets (lot # 08T001E) were orally administered.

CRITERIA FOR EVALUATION:

Safety: Safety assessments were based on medical review of adverse event reports, vital sign measurements, and clinical laboratory tests. The incidences of observed adverse events were tabulated and reviewed for potential significance and clinical importance.

Pharmacokinetics: Serial blood samples were collected for 32 h post-dose. Plasma samples were assayed for metformin and glipizide concentrations by ——— methods. The pharmacokinetic parameters Cmax, Tmax, AUC(0-T), AUC(INF), and T-HALF were determined from metformin and glipizide plasma concentration vs. time data using a validated noncompartmental analysis protocol and summarized.

Pharmacodynamics: Not applicable.

STATISTICAL METHODS:

Sample Size: If there was no difference between the bioavailabilities of metformin and glipizide from the combination tablet relative to coadministered Glucophage® and Glucotrol®, then 20 subjects were to provide 92.6% power to conclude bioequivalence with respect to metformin Cmax, 99% power with respect to metformin AUC(INF), 85.3% power with respect to glipizide Cmax, and 99% power with respect to glipizide AUC(INF). These calculations used the approach described by Diletti et al. and assumed that Cmax and AUC(INF) were log-normally distributed with intrasubject standard deviations of 0.1975 for metformin log(Cmax), 0.2191 for glipizide log(Cmax), 0.0894 for metformin log[AUC(INF)], and 0.0707 for glipizide log[AUC(INF)], as reported in Study CV138-044. To allow for dropouts, 24 subjects were enrolled.

Statistical Methods: Bioequivalence was concluded if the 90% confidence intervals for the ratios of population geometric means of both metformin and glipizide from a metformin/glipizide combination tablet relative to coadministered Glucophage® and Glucotrol® were contained within 80% to 125% for Cmax and AUC(INF). The confidence intervals were constructed from the results of analyses of variance on log(Cmax) and log[AUC(INF)].

Analysis: To determine the bioequivalence of the combination tablet relative to coadministered Glucophage® and Glucotrol®, analyses of variance were performed on log(Cmax) and log[AUC(INF)]. The factors in the analysis were sequence group, subject within sequence, period, and treatment. Since subjects were random effects nested within sequences, F-statistics for sequence effects were the ratios of the type I mean squares for sequence and subjects within sequence. The F-statistic for period was the ratio of the type I mean square for period and the mean square for error. Point estimates and 90% confidence intervals for treatment differences on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale. No adjustment was made for multiplicity.

Geometric means and coefficients of variation were reported for Cmax, AUC(INF), and AUC(0-T), by treatment. Medians, minima, and maxima were reported for Tmax, by treatment. Means and standard deviations were provided for T-HALF, by treatment.

PHARMACOKINETIC RESULTS:

Metformin:

Summary of Metformin Pharmacokinetic Parameters

	Glucophage® (500 mg) + Glucotrol® (5 mg) Tablets (N = 21)	Metformin/Glipizide (500 mg/5 mg) Combination Tablet (N = 21)
Cmax (ng/mL) Geometric Mean (%C.V.)	664 (22)	701 (30)
Tmax (h) Median (Min, Max)	2.5 (1, 4)	2.5 (1, 5)
AUC(INF) (ng•h/mL) Geometric Mean (%C.V.)	5016 (20)	4965 (19)
AUC(0-T) (ng•h/mL) Geometric Mean (%C.V.)	4923 (20)	4900 (19)
T-HALF (h) Mean (S.D.)	6.3 (1.5)	5.6 (1.1)

The geometric mean metformin Cmax value for the combination tablet was 5% higher than that for the coadministered tablets. The geometric mean metformin AUC(INF) value for the combination tablet was 99% of that for the coadministered tablets.

Statistical Analyses of Metformin Pharmacokinetic Parameters

	Adjusted Geometric Means		Ratio of Geometric Means	
	Coadministered Tablets	Combination Tablet	Point Estimate	90% Confidence Interval
Cmax (ng/mL)	664	700	1.05	(0.96, 1.16)
AUC(INF) (ng•h/ml.)	5021	4960	0.99	(0.94, 1.04)

The metformin/glipizide (500 mg/5 mg) combination tablet was bioequivalent to the coadministered Glucophage® (500 mg) + Glucotrol® (5 mg) tablets with respect to metformin Cmax and AUC(INF).

PHARMACOKINETIC RESULTS:

Metformin:

Summary of Metformin Pharmacokinetic Parameters

	Glucophage® (500 mg) + Glucotrol® (5 mg) Tablets (N = 21)	Metformin/Glipizide (500 mg/5 mg) Combination Tablet (N = 21)
Cmax (ng/mL) Geometric Mean (%C.V.)	 664 (22)	 701 (30)
Tmax (h) Median (Min, Max)	 2.5 (1, 4)	 2.5 (1, 5)
AUC(INF) (ng•h/mL) Geometric Mean (%C.V.)	 5016 (20)	 4965 (19)
AUC(0-T) (ng•h/mL) Geometric Mean (%C.V.)	 4923 (20)	 4900 (19)
T-HALF (h) Mean (S.D.)	 6.3 (1.5)	 5.6 (1.1)

The geometric mean metformin Cmax value for the combination tablet was 5% higher than that for the coadministered tablets. The geometric mean metformin AUC(INF) value for the combination tablet was 99% of that for the coadministered tablets.

Statistical Analyses of Metformin Pharmacokinetic Parameters

	Adjusted Geometric Means		Ratio of Geometric Means	
	Coadministered Tablets	Combination Tablet	Point Estimate	90% Confidence Interval
Cmax (ng/mL)	664	700	1.05	(0.96, 1.16)
AUC(INF) (ng•h/mL)	5021	4960	0.99	(0.94, 1.04)

The metformin/glipizide (500 mg/5 mg) combination tablet was bioequivalent to the coadministered Glucophage® (500 mg) + Glucotrol® (5 mg) tablets with respect to metformin Cmax and AUC(INF).

All AEs were rated mild or moderate in intensity by the Investigator and resolved prior to discharge. One subject required treatment for a moderate headache. There were no serious AEs or discontinuations due to AEs.

CONCLUSIONS:

- Metformin and glipizide were bioequivalent in the metformin/glipizide (500 mg/5 mg) combination tablet and coadministered Glucophage® (500 mg) + Glucotrol® (5 mg) treatments with respect to Cmax and AUC.
- Single doses of metformin and glipizide, administered as a metformin/glipizide (500 mg/5 mg) combination tablet and as Glucophage® (500 mg) + Glucotrol® (5 mg) tablets, were well-tolerated in healthy subjects.

DATE OF REPORT: 15-Nov-2001

FINAL REPORT SYNOPSIS

TITLE OF STUDY: Effect of a High Fat Meal on the Pharmacokinetics of Metformin and Glipizide from a Metformin/Glipizide Combination Tablet in Healthy Subjects

INVESTIGATORS: [redacted]

STUDY CENTERS: [redacted]

PUBLICATIONS: None

STUDY PERIOD: Date first subject enrolled: 03-Jun-2001

Date last subject completed: 12-Jun-2001

CLINICAL PHASE: I

OBJECTIVES:

The primary objective was to assess the effect of a high fat meal on the pharmacokinetics of metformin and glipizide from a metformin/glipizide combination tablet in healthy subjects. The secondary objective was to assess the safety of a metformin/glipizide combination tablet.

METHODOLOGY:

This was an open-label, randomized, two-period, two-treatment, crossover study in healthy subjects. Twenty-four (24) subjects were randomized to receive a single oral dose of a 500 mg/5 mg metformin/glipizide combination tablet in a fasted condition (Treatment A) or within 5 minutes of consuming a standard high fat breakfast (Treatment B). The alternate treatment was administered during Period 2. For each treatment period, subjects were admitted to the clinical facility on the evening prior to the morning of dosing (Day -1) and were confined until 32 hours post-dose. Blood samples were collected for pharmacokinetic analysis up to 32 hours post-dose. Subjects were monitored closely for adverse events throughout the study.

NUMBER OF SUBJECTS:

A total of 24 subjects enrolled and 20 subjects completed the study. Four (4) subjects discontinued, 3 per their request and 1 due to non-compliance.

MAIN CRITERIA FOR INCLUSION:

Healthy subjects as determined by medical history, physical examination, 12-lead electrocardiogram, and clinical laboratory evaluations were eligible to participate. Women of childbearing potential were not nursing, not pregnant, and were using an acceptable method of contraception for at least 1 month before dosing. Women of childbearing potential had a negative serum pregnancy test within 24 hours prior to each dose of study medication.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

Metformin/glipizide (500 mg/5 mg) combination tablets (batch number 8MFC184) were administered orally.

DURATION OF TREATMENT:

Each subject was administered two single doses of a 500 mg/5 mg metformin/glipizide combination tablet, with at least a 7-day washout period between each dose.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

Not applicable.

CRITERIA FOR EVALUATION:

Safety:

Safety assessments were based on medical review of adverse event reports, the results of vital sign measurements, and clinical laboratory tests. The incidences of observed adverse events were tabulated and reviewed for potential significance and clinical importance.

Pharmacokinetics:

Serial blood samples were collected for 32 h post-dose. Plasma samples were assayed for metformin and glipizide concentrations by validated methods. The pharmacokinetic parameters Cmax, Tmax, AUC(0-T), AUC(INF), and T-HALF were determined from metformin and glipizide plasma concentration *vs.* time data using a validated noncompartmental analysis protocol and summarized.

Pharmacodynamics: Not applicable.

STATISTICAL METHODS:

Sample Size: If there was no effect of food, then data from 20 subjects would provide 92.6% power to conclude absence of a food effect with respect to metformin Cmax, 85.3% power to conclude absence of a food effect with respect to glipizide Cmax, and 99% power with respect to both metformin and glipizide AUC(INF). These calculations used the approach described by Diletti et al. and assumed that metformin and glipizide Cmax and AUC(INF) were log-normally distributed with intrasubject standard deviations of 0.1975 for metformin log(Cmax), 0.2191 for glipizide log(Cmax), 0.0894 for metformin log[AUC(INF)], and 0.0707 for glipizide log[AUC(INF)] as reported in Study CV138-044. To allow for dropouts, 24 subjects were enrolled.

Statistical Methods: The primary pharmacokinetic outcome measures were the maximum observed plasma concentration (Cmax) and the area under the concentration-time curve from time zero extrapolated to infinite time [AUC(INF)] of both metformin and glipizide. "Absence of a food effect" was concluded if the corresponding 90% confidence interval for the ratio of population geometric means of fed to fasted treatments were contained within an equivalence interval of 80% to 125% for metformin and glipizide AUC(INF) and Cmax. The presence of a food effect on Cmax or AUC(INF) for either analyte was concluded if the 90% confidence interval was entirely outside the corresponding equivalence interval. Otherwise, the conclusion was "indeterminate."

Analysis: To assess the effects of food on oral bioavailability, analyses of variance was performed on log(Cmax) and log[AUC(INF)] for both metformin and glipizide. The factors in the analysis were sequence group, subject within sequence, period, and dietary treatment. Since subjects were random effects nested within sequences, F-statistics for sequence effects were the ratios of the type I mean squares for sequence and subjects within sequence. The F-statistic for period was the ratio of the type I mean square for period and the mean square for error. Point estimates and 90% confidence intervals for means and differences between means on the log scale were exponentiated to obtain estimates for geometric means and ratios of geometric means on the original scale. No adjustment was made for multiplicity.

Geometric means and coefficients of variation were provided for metformin and glipizide AUC(INF), AUC(0-T), and Cmax by dietary treatment. Medians, minima, and maxima were provided for metformin and glipizide Tmax by dietary treatment. Means and standard deviations were provided for metformin and glipizide T-HALF by dietary treatment.

PHARMACOKINETIC RESULTS:

Metformin:

Summary of Metformin Pharmacokinetic Parameters

	Fasted (N = 18)	High Fat Meal (N = 18)
Cmax (ng/mL)		
Geometric Mean	663	563
(%C.V.)	(23)	(26)
Tmax (h)		
Median	3	4
(Min, Max)	(1, 4)	(1, 8)
AUC(INF) (ng•h/mL)		
Geometric Mean	5087	5076
(%C.V.)	(21)	(20)
AUC(0-T) (ng•h/mL)		
Geometric Mean	4998	5000
(%C.V.)	(22)	(20)
T-HALF (h)		
Mean	6.1	5.1
(S.D.)	(1.6)	(0.8)

As shown in the table below, the geometric mean metformin Cmax value after a high fat meal was 86% of the geometric mean Cmax value in the fasted state. The geometric mean metformin AUC(INF) value after a high fat meal was 99% of the geometric mean metformin AUC(INF) value in the fasted state.

Statistical Analysis of Metformin Pharmacokinetic Parameters

	Adjusted Geometric Means		Ratio of Geometric Means	
	Fasted	High Fat Meal	Point Estimate	90% Confidence Interval
Cmax (ng/mL)	664	571	0.86	(0.78, 0.95)
AUC(INF) (ng•h/mL)	5066	5005	0.99	(0.91, 1.07)

Metformin AUC(INF) satisfied the criterion for absence of an effect of food. Although the effect of food on metformin Cmax was, strictly speaking, indeterminate, the 90% confidence interval nearly satisfied the criterion for the absence of an effect of food.

Glipizide:

Summary of Glipizide Pharmacokinetic Parameters

	Fasted (N = 18)	High Fat Meal (N = 18)
Cmax (ng/mL)		
Geometric Mean	212	235
(%C.V.)	(22)	(33)
Tmax (h)		
Median	6	7
(Min, Max)	(2, 10)	(1, 14)
AUC(INF) (ng•h/mL)		
Geometric Mean	2164	2256
(%C.V.)	(34)	(34)
AUC(0-T) (ng•h/mL)		
Geometric Mean	2103	2209
(%C.V.)	(32)	(32)
T-HALF (h)		
Mean	5.2	4.7
(S.D.)	(1.8)	(1.2)

As shown in the table below, the geometric mean glipizide Cmax value after a high fat meal was 109% of the geometric mean glipizide Cmax value in the fasted state. The geometric mean glipizide AUC(INF) value after a high fat meal was 103% of the geometric mean glipizide AUC(INF) value in the fasted state.

Statistical Analysis of Glipizide Pharmacokinetic Parameters

	Adjusted Geometric Means		Ratio of Geometric Means	
	Fasted	High Fat Meal	Point Estimate	90% Confidence Interval
Cmax (ng/mL)	218	237	1.09	(0.94, 1.255)
AUC(INF) (ng•h/mL)	2244	2306	1.03	(0.98, 1.08)

Glipizide AUC(INF) satisfied the criterion for absence of an effect of food. Although the effect of food on glipizide Cmax was, strictly speaking, indeterminate, the 90% confidence interval nearly satisfied the criterion for the absence of an effect of food.

PHARMACODYNAMIC RESULTS: Not applicable.

SAFETY AND TOLERABILITY RESULTS:

Single doses of a metformin/glipizide 500 mg/5 mg combination tablet administered in the fasted state and with a high fat meal were considered safe and well-tolerated in this study. The most frequently reported adverse events (AEs) that counted included: headache (9 events), nausea/vomiting (9 events), dizziness

(5 events), and diarrhea (3 events). All AEs were rated mild or moderate in intensity by the Investigator, and resolved prior to discharge or upon follow-up. There were no serious AEs and no discontinuations due to AEs.

CONCLUSIONS:

- Metformin and glipizide AUC were not affected by a high fat meal. The effect of a high fat meal on metformin and glipizide Cmax was indeterminate. The modest differences observed in metformin and glipizide pharmacokinetics and bioavailability in the fed *vs.* fasted state are not expected to be clinically meaningful.
- Single doses of a 500 mg/5 mg metformin/glipizide combination tablet were well-tolerated in healthy subjects in the fasted and fed states.

DATE OF REPORT: 14-Nov-2001

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

/s/

Steve Johnson
10/10/02 10:29:14 AM
BIOPHARMACEUTICS

Hae-Young Ahn
10/10/02 11:28:27 AM
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