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RESEARCH**

APPLICATION NUMBER:

21-748

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-748	Submission Dates: 04-06-2005
Brand Name	Glumetza™
Generic Name	Metformin extended-release tablets
Reviewer	Xiaoxiong (Jim) Wei, M.D., Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM division	Division of Endocrine and Metabolic Drug Products (HFD-510)
Sponsor	Biovail Technologies, Ltd.
Relevant IND(s)	57,548; ✓
Submission Type; Code	Resubmission (a complete response to the Agency's approvable letter)
Formulation; Strength(s)	Extended release tablets; 500 mg, 1000 mg
Dosing regimen	Start with 1000 mg once a day up to 2000 mg dependent on individual patients' glucose levels
Indication	Type 2 or non-insulin-dependent diabetes mellitus (INDDM)

Table of Contents

1.	Executive Summary.....	1
1.1	Recommendation.....	2
2.	QBR.....	2

1 Executive Summary

Biovail did not accept the Agency's recommendation for dissolution specifications for NDA 21-748 for Glumetza. As a result, the sponsor received an approvable letter for Glumetza. On April 6, 2005, the sponsor submitted a complete response to the Agency's approvable letter with modified dissolution specifications based on IVIVC model. This submission contains results of the computations using \pm — range. The estimated AUC and Cmax ratios (Upper Limit: Lower limit) were approximately 102% and 120%, respectively. The resulting proposed specifications are: 2hr: — 4hr: — 12hr: NLT —

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed the information provided in the complete response to the Agency's approvable letter dated February 25 for NDA 21-748 for Glumetza™. OCPB has found the dissolution specifications modified by the sponsor acceptable. Therefore, the Agency revises the recommendation for dissolution specifications for Glumetza™ tablets as follows:

Apparatus type	USP Apparatus-1 (—)
Medium	/
Temperature of medium	37°C
Speed of rotation	—
Specification	2 hr: — , 4 hr: — , 12 hr: NLT —

This recommendation should be conveyed to the sponsor as appropriate.

2. QBR

Does the Agency accept the modified dissolution specifications proposed by the sponsor?

In the approvable letter for NDA #21-748 dated February 25, 2005, the dissolution specifications recommended by the Agency were as follows:

2hr: — , 4hr: — , 12hr: NLT —

The sponsor performed the computations using \pm — range of dissolution.

—

Differences in plasma metformin concentrations predicted from in-vitro dissolution ranges are shown in Figure I. The pharmacokinetic parameters, Cmax and AUC(0-24h), were determined from the simulated plasma concentrations for the upper and lower specification limits and compared to each other as well as to those observed for the Standard or Target Metformin formulation. Metformin Cmax was taken directly from the simulated data while the AUC was calculated using the trapezoidal rule. The relative bioavailability in % was calculated as ratios of the predicted parameters to those computed from mean observed concentrations for the target or standard formulation; upper limit : lower limit ratio was also calculated (Table 1).

Figure 1: Plasma metformin concentrations predicted from + dissolution ranges relative to the target.

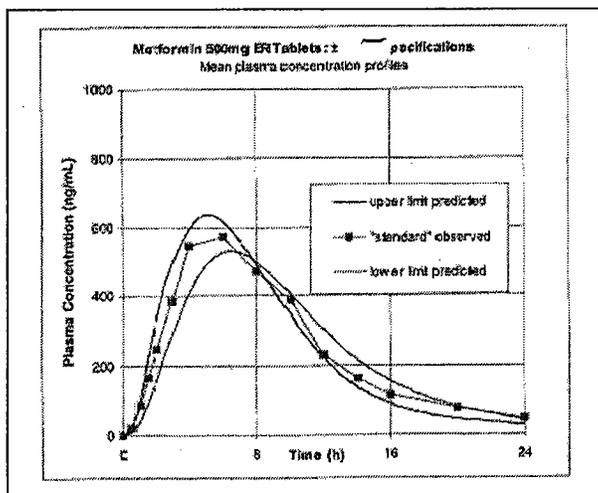


Table 1. Relative bioavailability of predicted upper and lower dissolution limits relative to the Target or Standard formulation.

Parameter	Relative bioavailability (%)					
	Predicted UL	Predicted LL	Observed Standard	UL/LL	UL/Standard	LL/Standard
Cmax	636.14	529.14	570.80	120.2	111.4	92.7
AUC 90-24h)	5985.70	5876.58	5906.58	101.9	101.3	99.5

Based on the Level A correlation between in vitro and in vivo release rates, the sponsor has proposed the dissolution specifications for Glumetza™ tablets supported by the IVIVC model (\pm), as follows:

Table 2. Proposed dissolution specifications for Glumetza™ Tablets.

Time (h)	Lower Limit (% released)	Upper Limit (% released)
2		
4		
12	NLT	

Therefore, we accept the re-proposed dissolution specifications.

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

/s/

Xiao-xiong Wei
5/27/05 11:51:46 AM
BIOPHARMACEUTICS

Hae-Young Ahn
5/27/05 12:04:50 PM
BIOPHARMACEUTICS

Addendum

4.3 Individual Study Review

NDA: 21-748 (N-000)

Drug name: Glumetza (Metformin HCl extended release tablets, 500 mg and 1000 mg)

Indication: Treatment of type 2 diabetes

Submission date: 04-27-2004

Reviewer: Xiaoxiong (Jim) Wei

Team Leader: Hae-Young Ahn

OCPB: DPE2

OND: DMEDP (Division of Metabolic and Endocrine Drug Products, HFD-510)

Table of Contents

	Study #	Title
1	81-0011 (2607)	Open-label, randomized, crossover study to compare the pharmacokinetics, safety, and tolerability of Metformin HCl 500mg extended release (M-ER) tablets and metformin immediate release (M-IR) tablets in healthy male and female subjects.
2	81-0018 (2624)	A randomized, steady state, three-way crossover, open-label, fed comparative pharmacokinetic study of metformin HCl 500 mg extended release (M-ER) tablets (2x500 mg qd or 500 mg bid) versus Glucophage tablets 500 mg bid in healthy male and female subjects.
3	BO3- 618PK- PO0112	An open label, randomized, crossover study to compare the pharmacokinetics, safety, and tolerability of metformin HCl 500 mg extended release (M-ER) tablets and Glucophage 500mg tablets in normal healthy non-smoking male and female subjects.
4	B03- 646PK- P0112 (R03-608)	Dosage Strength Proportionality Study: A Two-Way, Crossover, Open-Label, Single Dose, Fed, Comparative Bioavailability Study of Two Formulations (1x1000 mg vs 2x500 mg) of Metformin HCl ER Tablets in Normal Healthy Non-Smoking Male and Female Subjects
5	81-0019 (2625)	Dose Proportionality Study: A Four-Way, Single-Dose, Open-Label, Dose- Escalation, Comparative Pharmacokinetic, Dose Characterization Study of Metformin HCl Extended Release (M-ER) Tablets (1x500 mg, 2x500 mg, 3x500 mg, 5x500 mg QD) in Healthy Male and Female Subjects.
6	00-09	Food Effect Study: Comparison of Metformin Pharmacokinetics Under Fed and Fasted Conditions in Healthy Volunteers
7	81-0016 (2621)	Drug Interaction Study A Two-Way, Single-Dose, Randomized, Crossover, Open-Label, Comparative Pharmacokinetic Study of Metformin HCl 500 mg Extended-Release (M-ER) Tablets Alone and in Combination With Diaβeta® 5 mg Tablets in Healthy Male and Female Subjects
8	81-0020 (2626)	Special Population Study A Study of Single-Dose Pharmacokinetics of Metformin HCl Extended-Release (M-ER) Tablets (500 mg) in Subjects With Normal Renal Function and in Subjects With Mild and Moderate Renal Impairment
9	81-0017 (2622)	1. A Four-Way, Single-Dose, Randomized, Cross-over Open-label, Comparative Pharmacokinetic Study of Metformin HCl 500 mg ED Tablets for IVIVC

		2. Characterization by a Level A in vitro-in vivo Correlation and Setting Biorelevant In vitro Release Specifications (Metformin HCl 500mg ER tablets)
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**APPEARS THIS WAY
ON ORIGINAL**

Study #: 81-0011 (2607)

Title: Open-label, randomized, crossover study to compare the pharmacokinetics, safety, and tolerability of Metformin HCl 500mg extended release (M-ER) tablets and metformin immediate release (M-IR) tablets in healthy male and female subjects.

Objectives:

The primary objectives are: to compare the pharmacokinetic profiles of Metformin ER 500 mg Tablets once or twice a day (bid) versus Glucophage 500 mg Tablet twice a day and to compare the peak and systemic exposure of Metformin from Metformin ER 500 mg Tablets versus Glucophage 500 mg Tablets. The secondary objective is to assess the tolerability and safety of Me Metformin ER 500mg Tablets versus Glucophage 500mg Tablets.

Number of subjects (planned and analyzed):

Thirty (30) subjects were planned to be entered into the study. There were thirty (30) subjects dosed in period I, twenty-six (26) of whom completed the study. Pharmacokinetic and statistical analyses were performed on twenty-six (26) subjects that completed the study.

Test product, lot number and mode of administration:

Treatment A: Two (2) Metformin ER 500 mg Tablets given after complete ingestion of dinner (20:00 hr) Lot #: YT5402, administered orally With 100 mL of ambient temperature water (total dose 1000 mg). Treatment B: One (1) Metformin ER 500 mg Tablet given after complete ingestion of dinner (20:00 hr) and one (1) Metformin ER 500mg Tablet given approximately 12 hours later (08:00 hr) after complete ingestion of breakfast, Lot #: VT5402, each administered orally with 100 mL of ambient temperature water (total dose 1000 mg).

Reference therapy, lot number and mode of administration:

Treatment C: One (1) Glucophage 500 mg Tablet given after complete ingestion of dinner (20:00 hr) and one (1) Glucophage 500 mg Tablet given approximately 12 hours later (08:00 hr) after complete ingestion of breakfast, Lot #: 1F475 10, each administered orally with 100 mL of ambient temperature water. (total dose 1000 mg).

Criteria for evaluation:

Pharmacokinetics:

The following pharmacokinetic parameters for metformin HCl were calculated by standard non-compartmental methods: AUC_{0-t}, AUC_{0-inf}, C_{max}, K_{el} and t_{1/2}.

Statistical methods:

Using GLM procedures in SAS, analysis of variance (ANOVA) was performed on natural log (Ln)-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} and on untransformed T_{max}, K_{el}, and t_{1/2} at the significant level of 0.05. The in-subject coefficient of variation (CV) ratios of means (Treatment A/Treatment C and Treatment B/Treatment C) based on the geometric means from the ANOVA, and the 90% geometric confidence

interval (CI) were calculated for the Ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} for comparisons of bioavailability of Metformin ER Tablets (dosed qd or bid) with Glucophage® Tablets (dosed bid).

Summary and Conclusions:

Fig. PK profiles

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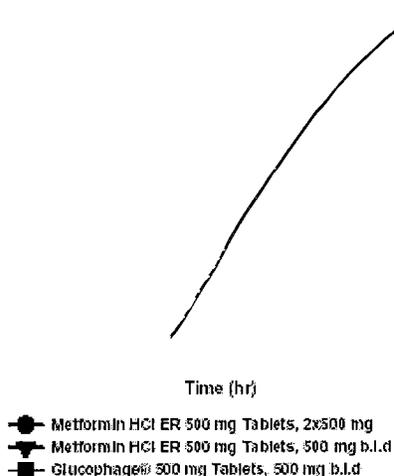


Table 3. Summary of PK parameters on Day 5

PK Parameter	Glumetza 2X500mg	Glumetza 1X500mg BID	Glucophage 1X500mg BID
AUC ₀₋₃₆ (ng.hr/mL)	14182±2415	15260±3496	15342±3398
C _{max} (ng/mL)	1301.4±285.7	811.9±173.7	959.1±204.0
T _{max} (hr)	7.5±1.2	7.1±1.2	4.2±1.6

Table 4. Summary of statistics comparing Glumetza and Glucophage

PK parameter	Glumetza 2X500mg Versus Glucophage 500mg BID	
	Ratio of geometric means	90% CI
AUC ₀₋₃₆	93.50%	89.45 – 97.72
C _{max}	135.31%	128.89 – 142.05
PK parameter	Glumetza 500mg BID Versus Glucophage 500mg BID	
	Ratio of geometric means	90% CI
AUC ₀₋₃₆	99.00%	94.72 – 103.48
C _{max}	84.18%	80.19 – 88.38

Based on plasma metformin concentration data from 26 completing subjects (14 males and 12 females, mean age = 36), both 2x500 mg and 500 mg BID dosing of the ER tablets showed equivalent systemic exposure of metformin to the reference given 500 mg

BID. The ratios of geometric means for AUC and the corresponding 90% geometric confidence intervals (C.I.) were within 80 -125%. 2x500 mg of the ER tablets resulted in a 35% higher mean C_{max} than that of the reference. When the ER tablets were given 500 mg BID, C_{max} was found to be equivalent to that of the reference with the 90% C.I. falling within 80 - 125%. The mean T_{max} for the ER tablet was longer than that of the reference with both once-daily and BID dosing. This difference in T_{max} reflected the characteristics of an extended release formulation.

Reviewer's comments:

This study revealed that the plasma profile was consistent with a modified release providing similar systemic exposure and some extension of plasma levels with a broader peak plasma concentration and a longer T_{max} . When both products were given as 500 mg twice daily, the ER tablets demonstrated equivalent peak and systemic exposure of metformin to the reference.

**APPEARS THIS WAY
ON ORIGINAL**

Study #: 81-0018 (2624)

Title: A randomized, steady state, three-way crossover, open-label, fed comparative pharmacokinetic study of metformin HCl 500 mg extended release (M-ER) tablets (2x500 mg qd or 500 mg bid) versus Glucophage tablets 500 mg bid in healthy male and female subjects.

Objectives: Primary objective is to compare the pharmacokinetic profiles of two M-ER 500 mg tablets given once daily (qd) or one M-ER tablet given twice daily (bid) versus Glucophage 500 mg tablets given twice daily (bid), under steady-state conditions. Secondary objective is to assess the tolerability and safety of M-ER tablets under steady-state conditions.

Number of subjects (planned and analyzed):

Thirty (30) subjects were planned to be entered into the study. There were thirty (30) subjects dosed in period I twenty-four (24) of whom completed the study. Pharmacokinetic and statistical analyses were performed on twenty-four (24) subjects that completed the study.

Test product, lot number and mode of administration:

Treatment A: Two Metformin ER 500 mg Tablets Lot #: YT5402 (potency value = — of label claim), administered orally after dinner (starting at 20:00 hours), with 180 mL of ambient temperature water. The drug was administered to subjects one tablet at a time, but both tablets were ingested within two minutes.

Treatment B: One Metformin ER, 500 mg Tablet. Lot #: YT5402 (potency value = — % of label claim), administered orally after dinner starting at 20:00 hours and one Metformin ER, 500 mg Tablet administered 12 hours later (08:00 hours) after breakfast. Each tablet was administered orally with 180 mL of ambient temperature water.

Reference therapy, lot number and mode of administration:

Treatment C: One Glucophage® 500 mg Tablet, Lot #: 1F47510, given after dinner starting at 20:00 hours and one Glucophage 500 mg Tablet given 12 hours later (08:00 hours) after breakfast, each administered orally with 180 mL of ambient temperature water.

Criteria for evaluation:**Pharmacokinetics:**

The following pharmacokinetic parameters for metformin were calculated by standard Non-compartmental methods: AUC_τ, C_{max}, C_{min}, C_{avg}, T_{max}, % Swing, % fluctuation and C_{trough}.

Statistical methods:

Using GLM procedures in SAS, analysis of variance (ANOVA) was performed on natural log (Ln) transformed AUC_τ, C_{max}, C_{min}, C_{avg} and C_{trough} and untransformed T_{max}, % Swing, % fluctuation at the significance level of 0.05. The intra-subject coefficient of variation (CV), ratio of means (Treatment/Treatment B, Treatment

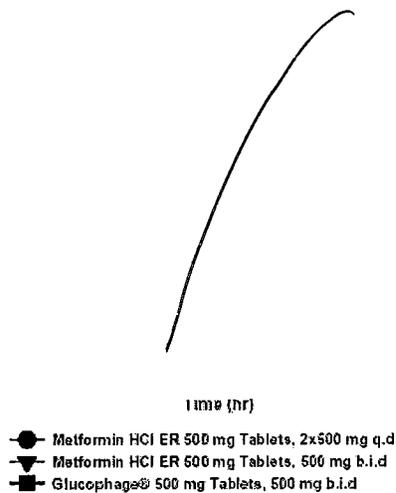
A/Treatment C, Treatment B / Treatment C) based on the geometric means from the ANOVA, and the 90% geometric confidence interval (CI) were calculated for the difference in the Least Squares Means of the Ln-transformed AUC_τ and C_{max} for comparisons of bioavailability of Metformin ER, 500 mg Tablets with Glucophage 500 mg tablets.

Summary and Conclusions:

SUMMARY OF PHARMACOKINETIC RESULTS: Metformin (Day 5)

Pharmacokinetic Parameters	<u>Metformin ER</u> <u>2 x 500 mg Tablets - (qd)</u> (A) n = 24 Mean ± SD	<u>Metformin ER, 1 x 500 mg</u> <u>Tablets (bid) (B)</u> n = 24 Mean ± SD	<u>Glucophage® 1 x 500 mg</u> <u>Tablets (bid) (C)</u> n = 24 Mean ± SD
AUC _τ (ng.hr/mL)	12907 ± 2011	13329 ± 2581	13930 ± 2565
C _{max} (ng/mL)	1249 ± 246	817 ± 175	986 ± 193
C _{min} (ng/mL)	97 ± 30	386 ± 151	240 ± 59
C _{ave} (ng/mL)	538 ± 84	555 ± 108	580 ± 107
T _{max} (hr)	7.30 ± 1.40	6.88 ± 1.68	4.60 ± 1.38
Fluctuation (%)	213.72 ± 25.33	78.89 ± 34.12	128.61 ± 14.02
Swing (%)	1280.37 ± 439.94	149.43 ± 122.55	324.07 ± 85.54
C _{trough} (ng/mL)	64 ± 19* 70 ± 16† 83 ± 20** 88 ± 25‡ 97 ± 30***	398 ± 131* 410 ± 162† 388 ± 129** 441 ± 156‡ 386 ± 151***	123 ± 49* 206 ± 53† 181 ± 42** 192 ± 56‡ 240 ± 59***

* Day 2 † Day 3 **Day 4 ‡ Day 5 ***Day 6



Based on plasma metformin concentration data from 24 completing subjects (13 males and 11 females, mean age = 39), both 2x500 mg QD and 500 mg BID administration of the Glumetza tablets showed equivalent systemic exposure (AUC_{0-24}) of metformin to the reference given as 500 mg BID. With 2x500 mg QD administration, the (ER vs Reference) ratio of geometric means for C_{max} was approximately 126%. When given as 500 mg BID, the C_{max} was about 17% lower than that of the reference. Under both QD and BID dosing, the mean T_{max} for the ER tablets was significantly longer than the reference ($p < 0.05$).

Reviewer's comments:

Once-daily 2x500 mg administration of Glumetza resulted in equivalent systemic exposure but higher peak exposure than the immediate release reference administered twice daily at steady state. The Glumetza 500 mg BID demonstrated lower peak and but similar systemic exposure to the immediate release reference (500 mg BID) under steady-state.

**APPEARS THIS WAY
ON ORIGINAL**

Study #: Bo3-618PK-PO112 (2668)

Title: An open label, randomized, crossover study to compare the pharmacokinetics, safety, and tolerability of metformin HCl 500 mg extended release (M-ER) tablets and Glucophage 500mg (Canadian reference) tablets in normal healthy non-smoking male and female subjects.

Objectives:

The objective of this study was to compare the pharmacokinetic profiles, safety and tolerability of Metformin HCl 500 mg Extended Release Tablets taken once daily (qd) (Treatment A) or twice daily (bid) (Treatment B) versus Glucophage 500 mg Tablets taken twice daily (QD) (Treatment C) under fed conditions.

Number of subjects (planned and analyzed):

Thirty (30) subjects were planned to be entered into the study. There were thirty (30) subjects dosed in period I, twenty-seven (27) of whom completed the study. Pharmacokinetic and statistical analyses were performed on twenty-seven (27) subjects that completed the study.

Test product, lot number and mode of administration:

Treatment A & B: Metformin ER 500 mg Tablets Lot #: YT5402 (potency value of label claim), administered orally with 180 mL of ambient temperature water within five minutes following complete ingestion of a high fat content meal.

Reference therapy, lot number and mode of administration:

Treatment C: Glucophage® 500 mg Tablet, Lot #: 8014503, administered orally with 180 mL of ambient temperature water within five minutes following complete ingestion of a high fat content meal.

Criteria for evaluation:**Pharmacokinetics:**

The following pharmacokinetic parameters for metformin were calculated by standard Non-compartmental methods: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, Kel, and t_{1/2}.

Statistical methods:

Using GLM procedures in SAS, analysis of variance (ANOVA) was performed on natural log (Ln) transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} and on untransformed T_{max}, Kel and t_{1/2} at the significance level of 0.05. The intra-subject coefficient of variation (CV), ratio of means (Treatment/Treatment B, Treatment A/Treatment C, Treatment B / Treatment C) based on the geometric means from the ANOVA, and the 90% geometric confidence interval (CI) were calculated for the difference in the Least Squares Means of the Ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}.

Summary and Conclusions:

SUMMARY OF PHARMACOKINETIC RESULTS:

Pharmacokinetic Parameters	Geometric Mean Arithmetic Mean (%CV)		
	<i>Metformin ER, 2x500mg Tablets (qd) (Treatment A)</i> n = 27	<i>Metformin ER, 1x500mg Tablets (bid) (Treatment B)</i> n = 27	<i>Glucophage® 1x500mg Tablets (bid) (Treatment C)</i> n = 27
	AUC _{0-t} (ng.hr/mL)	11806.435 12012.91 (18.87)	12951.929 13193.45 (19.94)
AUC _{0-inf} (ng.hr/mL)	12299.329 12499.30 (18.20)*	13274.498 13537.98 (20.60)	12852.582 13043.21 (16.82)**
C _{max} (ng/mL)	1110.6492 1132.51 (20.23)	690.3509 700.32 (17.34)	817.2132 830.97 (18.45)
T _{max} (hr) ☉	7.04 (21.40)	6.74 (16.75)	3.34 (35.88)
t _{1/2} (hr) ☉	7.56 (67.69)*	4.14 (23.54)	4.10 (12.15)**
K _{e1} (hr ⁻¹) ☉	1.06E-01 (2.65E+01)*	1.75E-01 (1.82E+01)	1.71E-01 (1.13E+01)**

☉ Expressed as arithmetic mean (%CV)

*N=25

**N=26

Parameter	<i>Metformin ER, 500 mg Tablets (A) vs. Glucophage® 500 mg Tablets (C)</i>		
	Potency Uncorrected		
	90% Confidence Interval	Ratio of Means	Intra-Subject CV
AUC _{0-t}	91.65% - 97.64%	94.60%	6.94%
AUC _{0-inf}	91.21% - 97.50%	94.30%	6.98%
C _{max}	130.41% - 141.37%	135.78%	8.84%
	Potency Corrected		
	90% Confidence Interval	Ratio of Means	
	AUC _{0-t}	88.91% - 94.73%	91.77%
C _{max}	126.51% - 137.14%	131.72%	

Parameter	<i>Metformin ER, 500 mg Tablets (B) vs. Glucophage® 500 mg Tablets (C)</i>		
	Potency Uncorrected		
	90% Confidence Interval	Ratio of Means	Intra-Subject CV
AUC _{0-t}	100.86% - 107.46%	104.11%	6.94%
AUC _{0-inf}	101.31% - 108.09%	104.64%	6.98%
C _{max}	81.21% - 88.04%	84.56%	8.84%
	Potency Corrected		
	90% Confidence Interval	Ratio of Means	
	AUC _{0-t}	97.85% - 104.25%	101.00%
C _{max}	78.79% - 85.41%	82.03%	

**APPEARS THIS WAY
ON ORIGINAL**

DepoMed's novel Metformin ER, 500 mg Tablet formulation demonstrated comparable peak and systemic exposures of metformin when compared to Glucophage 500 mg Tablets when, both formulations were administered twice daily. Metformin ER, 500 mg Tablet formulation demonstrated similar systemic exposure but higher peak exposure than Glucophage 500mg Tablets administered twice daily when novel metformin formulation was administered as 1000 mg once daily. The potency corrected ADO and Cmax, indicated similar results. The pharmacokinetic plasma profile for Metformin ER, 500mg Tablets is consistent with a modified release providing comparable bioavailability and some extension of plasma levels with a somewhat diminished (for a comparable dosing regimen) and broader peak plasma concentration and a prolonged Tmax. With once daily administration the plasma concentration at 24 hours is reduced compared to twice daily administration.

Reviewer's comments: The study results are consistent with the results derived from the Study 81-0011 with US Glucophage reference.

**APPEARS THIS WAY
ON ORIGINAL**

Study #: B03-646PK-P0112 (R03-608)

Title: A Two-Way, Crossover, Open-Label, Single Dose, Fed, Comparative Bioavailability Study of Two Formulations (1x1000 mg vs 2x500 mg) of Metformin HCl ER Tablets in Normal Healthy Non-Smoking Male and Female Subjects.

Objective:

This study evaluated the relative bioavailability (rate and extent of absorption) of the Metformin HCl ER 1000mg Tablets by Biovail Technologies Ltd. (Test Product A) compared to Metformin ER Tablets 500mg by DepoMed, Inc. Oral Drug Delivery Systems (Test Product B) in forty-eight (48) healthy adult subjects (19 males and 29 females) when administered in the evening under fed conditions using a randomized, two-way crossover design.

Dose Administration:

Volunteers received the two treatments separated by a seven day washout according to a randomized crossover design. Treatment A (Test Product) was Metformin HCl ER 1000mg Tablets (Biovail Technologies Ltd.) and Treatment B (Test Product) was Metformin ER Tablets, 500 mg (DepoMed, Inc. Oral Drug Delivery Systems). At 45 minutes before dosing, subjects were served a standardized dinner. The dinner was completed within 5 minutes of drug administration at 2000 hour (8PM). A single, oral dose (1 x 1000 mg tablet or 2 x 500 mg tablets) was administered with 240 mL of room temperature water. Subjects then maintained a fast until 4 hours after drug administration.

Blood Sample Collections:

Seventeen (17) blood samples (per subject each period) were collected by direct venipuncture within 1 hour prior to dosing (0 hour) and after dose administration at 1,2,3,4,5,6,7,8,9, 10, 12, 16,20,24, 36, and 48 hours. The blood samples were collected in potassium (K3) EDTA vacutainers, centrifuged, and the plasma pipetted into polypropylene tubes, frozen and stored at approximately -20°C until shipment for analysis.

Pharmacokinetic and statistical analysis:

Plasma concentration data from 43 of 48 subjects were used in the statistical analysis. Subject 21 elected to withdraw prior to Period II dosing. Subject 23 was dropped by the investigator prior to Period II dosing secondary to positive check-in drug screen. Subject 43 was excluded from the statistical analysis due to emesis during study Period I within the dosing interval of Test Product A (1x 1000 mg). Subjects 30 and 33 were excluded from the analysis due to emesis during study Period II within the dosing intervals of test Product A (1x1000 mg). The following pharmacokinetics parameters were reported: C_{max}, AUC_{0-t}, AUC_{inf}, T_{max}, elimination rate constant, and elimination half-life. Loge transformation (Ln) was performed and evaluated for C_{max}, AUC_{0-t}, and AUC_{inf}.

Summary and conclusions:

Statistical Analysis Summary

Parameter	Metformin HCl ER (1 x 1000 mg) Tablets	Metformin ER (2 x 500 mg) Tablets	% Ratio	90% Confidence Interval
C_{max} (ng/mL)	1293.17 ± 368.39	1109.10 ± 216.89	112.37	(102.14, 123.63)
AUC_{0-t} (ng-hr/mL)	12680.0 ± 3431.46	13156.53 ± 2433.87	92.71	(85.34, 100.72)
AUC_{inf} (ng-hr/mL)	12949.79 ± 3431.14	13350.93 ± 2459.91	93.50	(86.22, 101.4)
T_{max} (hr)	9.23 ± 2.27	7.72 ± 1.80	-	-
t_{1/2} (hr)	11.94 ± 5.94	9.85 ± 3.60	-	-
k_{elim} (1/hr)	0.0702 ± 0.03	0.0801 ± 0.03	-	-

Reviewer's comments: The bioavailability (C_{max}, AUC_{0-48 hr} and AUC_{0-inf}) of metformin after receiving one 1000 mg tablet relative to receiving two 500 mg tablets was approximately 92.7 - 112%. 90% confidence intervals remained to be within 80 - 125%. Therefore, bioequivalence between the two dosage strengths is established. Since 1000 mg metformin ER tablets were not used in phase 3 clinical trials, this BE study is pivotal to market 1000 mg dosage strength.

**APPEARS THIS WAY
ON ORIGINAL**

Study #: 81-0019 (2625)

Title: A Four-Way, Single-Dose, Open-Label, Dose- Escalation, Comparative Pharmacokinetic, Dose Characterization Study of Metformin HCl Extended Release (M-ER) Tablets (1x500 mg, 2x500 mg, 3x500 mg, 5x500 mg QD) in Healthy Male and Female Subjects

Objectives:

The primary objective was to investigate the pharmacokinetics of Metformin ER, 500 mg Tablets once daily (qd) over the 500mg to 2500mg dose range and the deviation from linearity of AUCs and C_{max} with dose. The secondary objective was to assess the tolerability and safety of Metformin ER 500mg Tablets.

Number of subjects (planned and analyzed):

36 subjects were planned to enter the study. There were 36 subjects dosed in Period I, 35 of whom completed the study. Pharmacokinetic and statistical analyses were performed on 35 subjects that completed the study.

Test product, lot number and mode of administration:

Each treatment was administered orally with 240 mL water, in the following order: Treatment A; One Metformin ER, 500mg Tablet, Lot #:YT5402 (potency value = — of the label claim), given once (qd) within five minutes following the complete ingestion of breakfast starting at 06:30 (total daily dose = 500 mg). Treatment B: Two Metformin ER, 500mg Tablets, Lot #:Y15402, given once (qd) within five minutes following the complete ingestion of breakfast starting at 06:30 (total daily dose = 1000 mg). The drugs were given to subjects one tablet at a time, but both tablets were ingested within five minutes. Treatment C: Three Metformin ER 500 mg Tablets, Lot # Y15402, given once (qd) within five minutes following the complete ingestion of breakfast starting at 06:30 (total daily dose = 1500 mg). The drugs were given to subjects one tablet at a time, but all tablets were ingested within five minutes. Treatment D: Five Metformin ER, 500 mg Tablets, Lot #YT5402, given once (qd) within five minutes following the complete ingestion of breakfast starting at 06:30 (total daily dose = 2500 mg), The drugs were given to subjects one tablet at a time, but all tablets were ingested within five minutes.

Criteria for evaluation:

Pharmacokinetics:

The following pharmacokinetic parameters for metformin were calculated by standard non-compartmental methods: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and t_{1/2}.

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Statistical methods:

Using dose-corrected data, the GLM procedures in SAS were employed, analysis of variance (ANOVA) was performed on natural log (Ln) transformed AUC_{0-t} , AUC_{0-inf} and C_{max} and on untransformed T_{max} , K_{el} and $t_{1/2}$ at the significance level of 0.05. The intra-subject coefficient of variation (CV), ratio of means based on the geometric means from the ANOVA, and the 90% geometric confidence interval (C.I.) were calculated for the difference in the Least Squares Means of the Ln-transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} .

Linear regression analysis was performed to define the functional relationship between the Ln-transformed AUC_{0-t} , AUC_{0-inf} and C_{max} with metformin doses using SAS regression procedures.

Results:

Based on the data from 35 completing subjects, AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} of metformin increased as the administered dose increased in the range of 500 to 2500 mg. Linear regression analysis indicated that there was a linear relationship of the AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} of metformin with the investigated metformin doses. It appeared that the ratio of the metformin PK parameters (AUC_{0-t} , AUC_{0-int} and C_{max}) at investigated doses deviated from the linearity of the parameters with metformin dose at high dosage.

A dose proportionality study of Glumetza™ at the dosage levels of 1x500 mg, 2x500 mg, 3x500 mg, and 5x500 mg in healthy male volunteers was conducted under fed conditions (after dinner) (Study 81-0019). The study followed a dose-escalated, four-period, single-dose design involving 36 subjects (18 males and 18 females, mean age = 33). The four treatments were given to all subjects after breakfast in the following order separated by a one-week washout. Blood samples for pharmacokinetic analysis were collected from 0-24 hours. A summary of the mean pharmacokinetic parameters is presented in Table 7.

Table 7. Pharmacokinetic parameters of Glumetza™ ranging from 500 mg to 2500 mg with dose-correction (N=35)

Parameter	Glumetza™			
	1x500 mg	2x500 mg	3x500 mg	5x500 mg
C_{max} (ng/nL)	473 ± 145	434 ± 112	390 ± 99	326 ± 80
AUC_{0-24 hr} (ng.hr/mL)	3348 ± 830	3194 ± 921	2964 ± 945	2691 ± 944
AUC_{0-inf} (ng.hr/mL)	3501 ± 796	3351 ± 959	3097 ± 946	2831 ± 887
T_{max}	3.9 ± 0.5	4.1 ± 0.5	3.9 ± 0.3	3.8 ± 0.4
T_{1/2}	6.9 ± 3.1	7.2 ± 2.5	7.5 ± 3.2	9.9 ± 8.6

Linear regression analysis revealed that the ratio of 4.02: 2.66: 1.91:1 was observed for AUC_{0-24} of metformin at doses of 2500, 1500, 1000, and 500 mg, respectively. The similar ratios were observed for AUC_{0-inf} and C_{max} . It seemed that at

the higher doses, there was approximately a 20% - 30% deviation from the linearity of the AUCs and Cmax with metformin doses.

ANOVAs were also performed on dose-corrected log-transformed AUC₀₋₂₄, AUC_{0-inf}, and Cmax. The resulting p values of the t-test from the pair-wise comparisons among treatments A, B, C, and D are presented in the following table (Table 8). The AUCs obtained within the metformin dose range of 500 mg to 1500mg were similar (p values were greater than 0.05 for Treatments A and B and Treatments A and C). However, the AUCs of 2500 mg were significant different from the AUCs generated with 500mg of metformin (p values were less than 0.05 for Treatments A and D). The Cmax was similar in the dose range of 500 and 1000 mg but was different at the higher doses. This is consistent with the results from the linearity analysis, of the observed deviation from the linearity of the AUCs and Cmax with metformin doses.

Table 8. p Values for paired comparison among treatments A, B, C, and D

Treatment	A vs. B	A vs. C	A vs. D
AUC 0-t	0.4604	0.0610	0.0009
AUC 0-∞	0.4358	0.0490	0.0013
Cmax	0.2543	0.0068	<0.0001

Reviewer's comments: From literature and in-house data, we are aware that metformin has a linear PK at lower dose range, but its high dose range of 1500 or 2000 to 2500 mg is off linear relationship to some extent. Therefore, the study results are consistent with existing information.

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Study #:00-09

Title: Comparison of Metformin Pharmacokinetics Under Fed and Fasted Conditions in Healthy Volunteers

Objective: To assess the effect of food on the Glumetza™ 500 mg tablets

Study design: This was a three-way, single-center, single-dose, open-label, randomized, two-period crossover study with a 7 day washout period between treatments. Subjects (seven males and 17 females, mean age = 29) were randomly assigned to one of the three 2x500 mg once treatments in three study periods separated by a one-week washout. The treatments involved drug administration after a 10-hour overnight fast, after an American Heart Association 30% fat breakfast or after a high fat breakfast. Blood samples for pharmacokinetic analysis were collected from 0 - 24 hours. All 24 subjects completed the study but three subjects vomited post drug administration during the study. Pharmacokinetic and statistical analyses were carried out from 21 subjects. Tables 9 and 10 are the summaries of the mean pharmacokinetic parameters and statistics.

Table 9. Pharmacokinetic parameters after Glumetza given after overnight fasting, AHA 30% and high fat breakfast (N=21)

Parameter	2X 500 mg Fasting	2X500mg AHA 30% Breakfast	2X500mg High Fat Breakfast
Cmax (ng/nL)	1021.5 ± 270.7	992.1 ± 213.3	1018.0 ± 190.4
AUC _{0-24 hr} (ng.hr/mL)	6994 ± 2145	9636 ± 3008	12104 ± 2627
AUC _{0-inf} (ng.hr/mL)	7506 ± 2220	10200 ± 3167	13306 ± 2944
Tmax	3.2 ± 0.8	6.2 ± 1.5	6.3 ± 1.5
T _{1/2}	8.2 ± 3.5	5.4 ± 1.5	5.7 ± 2.0

Table 10. Summary of statistics comparing two fed conditions

Parameter	High fat breakfast versus AHA 30% fat breakfast	
	Ratio of geometric mean	90% Geometric confidence interval
AUC _{0-t}	128%	115.9 – 141.5
AUC _{0-∞}	133%	121.0 – 145.2
Cmax	103%	93.8 – 113.3

Therefore, a significant food effect was observed on the novel Glumetza 500 mg tablets. Administration of the ER tablets after either a high fat or an AHA 30% fat meal resulted in a significant increase in the systemic exposure of metformin but no effect on the peak exposure. The time to reach peak exposure was delayed in the presence of food. Glumetza 1000 mg tablets were not tested in food studies.

Study #:81-0016 (2621)

Title: A Two-Way, Single-Dose, Randomized, Crossover, Open-Label, Comparative Pharmacokinetic Study of Metformin HCl 500 mg Extended-Release (M-ER) Tablets Alone and in Combination With Diabeta® 5 mg Tablets in Healthy Male and Female Subjects

Objective: To study the effect of glyburide on pharmacokinetics of Glumetza.

Study design: The sponsor conducted a two-way, single-dose, crossover drug interaction study comparing the pharmacokinetic profile of Metformin HCl ER 500 mg tablets given once versus administration in combination with glyburide 5 mg tablets in 28 subjects (14 males and 14 females, mean age = 32). Since metformin and glyburide may often be used in combination therapy for Type II diabetes, it is therefore important to demonstrate the absence of a significant pharmacokinetic interaction between the two drugs. In this study, subjects were randomly assigned to one of the two treatments in two study periods separated by a one-week washout. The first treatment involved administering one ER 500 mg tablet after breakfast, and the second treatment involved administering one ER 500 mg tablet and one glyburide 5 mg tablet after breakfast. Blood samples for pharmacokinetic analysis were collected from 0 - 24 hours.

Results:

There is no pharmacokinetic drug interaction between two drugs. Summaries of the mean pharmacokinetic parameters and statistics are shown in Tables 14.

Table 14. Summary of PK parameters and statistical analysis for metformin ER 500mg with and without glyburide

Pharmacokinetic Parameters (N=28)	Treatment A	Treatment B	Metformin/Metformin+Glyburite	
	Metformin HCl ER 500 mg	Metformin HCl ER 500 mg with glyburite 5 mg	Ratio of Geometric mean	90% CI
AUC _{0-t} (ng.hr/mL)	5115 ± 1978	5082 ± 1878	100.35	89.75 – 112.21
AUC _{0-∞} (ng.hr/mL)	5713 ± 2017	5609 ± 1995	100.55	88.81 – 113.85
C _{max} (ng/mL)	517.5 ± 146.2	515.2 ± 140.0	100.47	91.75 – 110.02

The caveat of the study is that metformin ER 500 mg is sub-clinical dose for treatment of diabetes. The usual dose is to start with 1000 mg and it can be increased up to 2500 mg per day. Since this study is to investigate the effect of glyburide on pharmacokinetics of metformin ER, 5 mg is a therapeutic dose for glyburide, this reviewer agrees with the sponsor's study design.

Study #: 81-0020 (2626)

Title: A Study of Single-Dose Pharmacokinetics of Metformin HCl Extended-Release (M-ER) Tablets (500 mg) in Subjects With Normal Renal Function and in Subjects With Mild and Moderate Renal Impairment

Objective: To study the impact of renal impairment on pharmacokinetics of Glumetza.

Study design: The sponsor conducted a multi-center, single dose, parallel design study to evaluate the pharmacokinetics of Glumetza 500 mg tablets in renal impairment patients and healthy subjects. The study involved three groups of subjects (10 per group): Patients with mild renal impairment (creatinine clearance of 51-80 mL/min), patients with moderate renal impairment (creatinine clearance of 30-50 mL/min) and healthy subjects with normal renal function (creatinine clearance of >80 mL/min). Subjects in each group were given one Glumetza 500 mg tablet after breakfast. Blood samples for pharmacokinetic analysis were collected from 0 - 36 hours. Urine samples were also collected at specified times over 36 hours following dosing to determine the renal clearance of Glumetza.

Results:

The mean plasma metformin concentration versus time plot is presented in Figure 6. Summaries of the mean pharmacokinetic parameters and statistics are shown in Tables 11 - 13.

Figure 6: Mean Plasma Metformin Concentration Versus Time Plot (n=30, 10 per group)

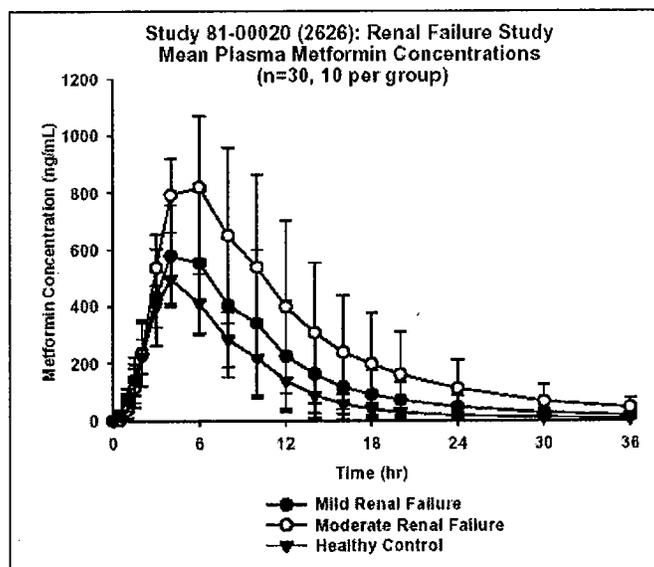


Table 11. Summary of Mean Pharmacokinetic Parameters after a single dose of 500 mg Glumetza

Pharmacokinetic Parameters	A	B	C
	Mild Renal Failure	Moderate Renal Failure	Healthy Normal
AUC _{0-t} (ng*hr/mL)	6030 ± 3140 (CV = 52%)	9861 ± 4804 (CV=49%)	4169 ± 1033 (CV=25%)
AUC _{0-∞} (ng*hr/mL)	7173 ± 3008 (CV=42%)	10539 ± 5094 (CV=48%)	4469 ± 989 (CV=22%)
C _{max} (ng/mL)	653.4 ± 229.7 (CV=35%)	898.3 ± 220.8 (CV=25%)	515.9 ± 77.7 (CV=15%)
T _{max} (hr)	4.5 ± 1.1	5.0 ± 1.5	5.0 ± 1.9
CL/F (mL/min)	1307 ± 433	959 ± 417	1939 ± 383

Table 12. Summary of Mean Urinary Pharmacokinetic Parameters after a single dose of 500 mg Glumetza

Pharmacokinetic Parameters	A	B	C
	Mild Renal Failure	Moderate Renal Failure	Healthy Normal
Total amount of metformin excreted, A _e (mg)	90.33 ± 35.22	84.62 ± 34.28	80.77 ± 26.69
Renal clearance, CL _R (mL/min)	278.28 ± 93.30	156.85 ± 55.06	332.46 ± 125.58

Table 13. Summary of statistics comparing mild and moderate renal failure patients against normal control group

Pharmacokinetic Parameters	Mild Renal Failure vs. normal control		Moderate Renal Failure vs. normal control	
	Ratio	p-value	Ratio	p-value
AUC _{0-t}	1.45	0.3390	2.37	0.0010
AUC _{0-∞}	1.61	0.002	2.36	0.0448
C _{max}	1.27	0.4439	1.74	0.0021
CL/F	0.67	0.0448	0.50	0.0002
A _e	1.12	0.7349	1.05	0.9495
CL _R	0.84	0.4011	0.47	<0.0001

Patients with moderate renal impairment showed a 50% decrease ($p = 0.0002$) in the oral clearance (CL/F) when compared to healthy subjects. In patients with mild renal impairment, CL/F was 33% ($p = 0.0448$) lower than the values observed in healthy subjects. Renal clearance (CL_R) of metformin was 16% lower in patients with mild renal impairment when compared to subjects with normal renal function ($p = 0.4011$). Patients

with moderate renal impairment demonstrated a 53% decrease in metformin CL_R ($p < 0.0001$) in comparison to subjects with normal renal function. There were no statistically significant differences in the amount of metformin excreted in 36 hours (A_e) between all groups.

Therefore, caution is required when treating patients with renal insufficiency where metformin accumulation can occur and result in potential lactic acidosis. Dose adjustment should be made for renal impairment patients.

27 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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Xiao-xiong Wei
2/25/05 03:57:06 PM
BIOPHARMACEUTICS

Hae-Young Ahn
2/25/05 04:48:59 PM
BIOPHARMACEUTICS

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-748	Submission Dates: 04-27-2004, 01-27-2005, 01-31-2005, 02-21-2005
Brand Name	Glumetza™
Generic Name	Metformin extended-release tablets
Reviewer	Xiaoxiong (Jim) Wei, M.D., Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM division	Division of Endocrine and Metabolic Drug Products (HFD-510)
Sponsor	Biovail Technologies, Ltd.
Relevant IND(s)	57,548; —
Submission Type; Code	505 (b) (1), 1S
Formulation; Strength(s)	Extended release tablets; 500 mg, 1000 mg
Dosing regimen	Start with 1000 mg once a day up to 2000 mg dependent on individual patients' glucose levels
Indication	Type 2 or non-insulin-dependent diabetes mellitus (INDDM)

Table of Contents

1.	Executive Summary.....	2
1.1	Recommendation.....	2
1.2	Phase IV Commitments.....	3
1.3	Summary of CLinical pharmacology and biopharmaceutics.....	3
2.	QBR.....	4
2.1	General Attributes of the Drug	4
2.2	General Clinical Pharmacology	7
2.3	Intrinsic Factors	12
2.4	Extrinsic Factors	17
2.5	General Biopharmaceutics.....	18
2.6	Analytical Section.....	26
3.	Detailed Labeling Recommendation.....	26
4.	Appendices	
4.1	Proposed Package Insert: (see a separate file).....	27
4.2	OCPB Filing/Review Form	28

4.3 Individual Study Review (see Addendum as a separate file) 33

1 Executive Summary

Biovail submitted a 505 (b) (1) NDA for marketing of Glumetza™, an extended release tablets of metformin hydrochloride. A total 12 studies were submitted, 3 of which were preliminary studies for formulation development. Nine phase 1 pharmacokinetic studies were to support the section of Clinical Pharmacology and Biopharmaceutics.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed the information provided in the original NDA 21-748 for Glumetza™ in the section of human pharmacokinetics and biopharmaceutics. OCPB has found the application acceptable provided that the sponsor agrees with the Agency's recommendations for dissolution specifications as follows:

Apparatus type	USP Apparatus-1 —
Medium	/
Temperature of medium	37°C
Speed of rotation	—
Specification	2 hr: — , 4 hr: — , 12 hr: NLT —

1.2 Phase IV Commitments

N/A

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

• **Relative bioavailability after single dose:**

The relative bioavailability of Glumetza™ to Glucophage® in healthy subjects was compared for the following scheme: Treatment A received Glumetza (2 x 500 mg tablets) after meal in the evening; Treatment B received Glumetza (1 x 500 mg tablet) given after meal in the evening and one 12 hours later after breakfast; and Treatment C received one reference tablet Glucophage® (500 mg tablet) after meal in the evening and one after breakfast. Both 2x500 mg and 500 mg BID dosing of the ER tablets showed equivalent systemic exposure of metformin to the reference given 500 mg BID. The ratios of geometric means for AUC and the corresponding 90% geometric confidence intervals (C.I.) were within 80 -125%. The 2x500 mg of the ER tablets resulted in a 35% higher mean C_{max} than that of the reference. When the ER tablets were given 500 mg BID, C_{max} was found to be equivalent to that of the reference with the 90% C.I. falling within 80 - 125%. The mean T_{max} for the ER tablet was longer than that of the reference with both once-daily and BID dosing. This difference of 3 hours in T_{max} reflected the characteristics of an extended release formulation.

- **Relative bioavailability after multiple doses:**

The steady state pharmacokinetics of Glumetza was compared with Glucophage® after 5 days of treatment in healthy subjects. The treatments involved administering two Glumetza tablets once daily (2x500 mg QD), one Glumetza tablet twice daily (500 mg BID), or one reference tablet twice daily (Glucophage 500 mg BID) after meal for five days. Both treatments of 2x500 mg QD and 500 mg BID administrations of the Glumetza tablets showed equivalent systemic exposure (AUC_{0-24}) of metformin to the reference given as 500 mg BID. With 2x500 mg QD administration, the (ER vs Reference) ratio of geometric means for C_{max} was approximately 126%. When given as 500 mg BID, the C_{max} was about 17% lower than that of the reference. Under both QD and BID dosing, the mean T_{max} for the ER tablets was significantly longer (2 – 2.7 hours) than the reference.

- **Dose proportionality:**

A dose proportionality study of Glumetza™ at the dosage levels of 1x500 mg, 2x500 mg, 3x500 mg, and 5x500 mg in healthy male volunteers was conducted under fed conditions. The four treatments were given to all subjects after breakfast separated by a one-week washout. The AUCs obtained within the metformin dose range of 500 mg to 1500mg were proportional. However, its high dose range from 1500 to 2500 mg is off linear relationship to some extent.

- **Renal impairment:**

Patients with mild and moderate renal impairment showed 33% and 50% decrease, respectively, in the oral clearance (CL/F) when compared to healthy subjects. Patients with mild and moderate renal impairment demonstrated 16% and 53% decrease, respectively, in metformin CL_R in comparison to subjects with normal renal function.

- **Drug interaction:**

The effect of glyburide on Glumetza™ pharmacokinetics was assessed in a single-dose drug interaction study in healthy subjects. Co-administration of 500 mg Glumetza™ and 5 mg glyburide did not result in any changes in metformin pharmacokinetics measured as AUC, C_{max} as well as T_{max} .

- **Food effect:**

The effect of food on the absorption of Glumetza™ after a single oral dose of 1000 mg (2x500 mg) in healthy male volunteers was assessed. The treatments involved drug administration after a 10-hour overnight fast, after an American Heart Association 30% fat breakfast or after a high fat breakfast. Low-fat and high-fat meals increased the systemic exposure as measured by AUC from Glumetza™ tablets by about 38% and

73%, respectively, relative to fasting. Both meals prolonged metformin T_{max} by approximately 3 hours but C_{max} was not affected.

- **Dosage form equivalence:**

One dosage form equivalence study for 500 mg and 1000 mg tablets was conducted. The bioavailability (C_{max} , $AUC_{0-48\text{ hr}}$ and $AUC_{0-\infty}$) of metformin after receiving one 1000 mg tablet relative to receiving two 500 mg tablets was approximately 92.7 - 112%. 90% confidence intervals remained to be within 80 -125%. Therefore, the dosage form bioequivalence between the two dosage strengths is established. Since 1000 mg metformin ER tablets were not used in phase 3 clinical trials, this BE study is pivotal to market 1000 mg dosage strength.

- **IVIVC:**

The in vitro dissolution rates and the in vivo bioavailability of (ER) 500 mg tablets were investigated in order to generate the data sets necessary for developing an in vitro-in vivo correlation (IVIVC). In addition, the immediate release product Glucophage® was administered in the comparative pharmacokinetic study to obtain the unit impulse response of the body system for metformin hydrochloride. The model independent numerical deconvolution and convolution technique based on the trapezoidal formula was applied for the calculation of the in vivo release kinetics and for the simulation of plasma concentration profiles. Evaluation of internal predictability was performed. The issue is that the release rates were so close to each other that it is not sensitive to differentiate the real difference. The sponsor did not try IVIVC for 1000 mg strength.

- **Analytical assay:**

Three assay methods were used for quantitation of metformin: LC/MS, LC/MS/MS, and HPLC-UV. Most PK studies were completed with LC/MS method with measurement ranging from 10 ng/mL to 2001 ng/mL. Pre-study validation runs were conducted to verify system performance, calibration standard, and quality control pool preparation.

2 QUESTION BASED REVIEW (QBR)

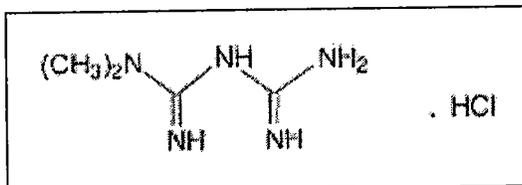
2.1 GENERAL ATTRIBUTES OF THE DRUG

- **What are the highlights of the chemistry and physical-chemical properties of the drug substance?**

Glumetza™ is an extended release formulation of metformin HCL. Metformin

hydrochloride (N, N-dimethylimidodicarbonimidic diamide hydrochloride) is a member of the biguanide class of oral antihyperglycemics.

The empirical formula of metformin hydrochloride is $C_4H_{11}N_5 \cdot HCl$ and its molecular weight is 165.63. Metformin hydrochloride is a white to off-white crystalline powder that is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.



- **What are the highlights of the formulation of drug product?**

GLUMETZA 500 mg tablets are an extended-release dosage form. The formulation and clinical trials were mainly developed by DepoMed. Biovail has gained authority to develop Glumetza 500 mg tablets from DepoMed. For Glumetza 500 mg tablets, though it has been modified in a few stages, the proposed commercial formulation is identical to the Phase 3 formulations, with the exception that the nonfunctional tablet coating is white instead of (Table 1). Dissolution release profiles for Glumetza 500 mg white-coated versus tablets show that the change in nonfunctional coat color does not impact tablet dissolution.

Table 1. Composition of Glumetza 500 mg tablets in Phase 3 clinical formulation and proposed commercial formulation

Raw Material	Phase 3		Commercial	
	Wt/Tab	%w/w	Wt/Tab	%w/w
A. UNCOATED TABLET				
Metformin Hydrochloride, EP [Active ingredient]	500 mg	—	500 mg	—
Polyethylene Oxide, NF				
Hypromellose, USP				
Microcrystalline Cellulose, NF				
Hypromellose, USP				
Magnesium Stearate, NF				
TOTAL COATED TABLET:				
B. COATED TABLET	Wt/Tab	%w/w	Wt/Tab	%w/w

TOTAL COATED TABLET:	1025 mg	100%	1025 mg	100%
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Biovail developed Glumetza 1000 mg tablets using a different formulation, which have never been used in clinical trials except for one relative bioavailability study to establish dosage form equivalence between 500 mg and 1000 mg tablets for Glumetza. The composition of Glumetza 1000 mg tablet formulation is listed in Table 2.

Table 2. Composition of Glumetza 1000 mg tablet formulation

Raw Material	Composition		Function
	Wt/Tab	%w/w	
Metformin Hydrochloride, EP	1000 mg		Active ingredient
Silicon Dioxide, NF ()			
Polyvinyl Alcohol, USP			
Crospovidone, NF ()			
Glyceryl Behenate, NF ()			
Ethylcellulose, NF			
Povidone, USP			
Dibutyl Sebacate, NF			
TOTAL COATED TABLET:	1160 mg	100%	-

• **What is the proposed mechanism of drug action and the therapeutic indications?**

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see PRECAUTIONS) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting plasma insulin levels and day-long plasma insulin response may actually decrease.

- **What is the proposed dosage and route of administration?**

Dosage of Glumetza must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose of 2000 mg. Glumetza therapy should generally be initiated with 1000 mg daily which must be taken with food preferably in the evening in order to maximize therapeutic efficacy. In general, clinically significant responses are not seen at doses below 1500 mg per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms. The starting dose of GLUMETZA is 1000 mg once daily. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2000 mg once daily with the evening meal. If glycemic control is not achieved on GLUMETZA 2000 mg once daily, a trial of GLUMETZA 1000 mg twice daily should be considered.

2.2 GENERAL CLINICAL PHARMACOLOGY

- **What is bioavailability of Glumetza™ relative to Glucophage® after a single dose?**

The firm has conducted a three-way single dose crossover study (Study 81-0011) evaluating the relative peak and systemic exposure of Glumetza 500 mg tablets against the US immediate release reference Glucophage® 500 mg tablets in 30 subjects (15 males and 15 females, mean age = 35). Subjects were randomly assigned to one of the three treatments in three study periods separated by a one-week washout. The treatments involved administering two ER tablets once (2x500 mg) after meal in the evening, one ER tablet given after meal in the evening and one 12 hours later after breakfast (500 mg BID), or one reference tablet given after meal in the evening and one after breakfast (500 mg BID). Blood samples for pharmacokinetic analysis were collected in 0 - 36 hours post doses. The mean plasma metformin concentrations versus time plots are presented in Figure 1. Summaries of the mean pharmacokinetic parameters and statistics are shown in Tables 3 and 4.

Figure 1. Mean Plasma metformin concentration versus time plot

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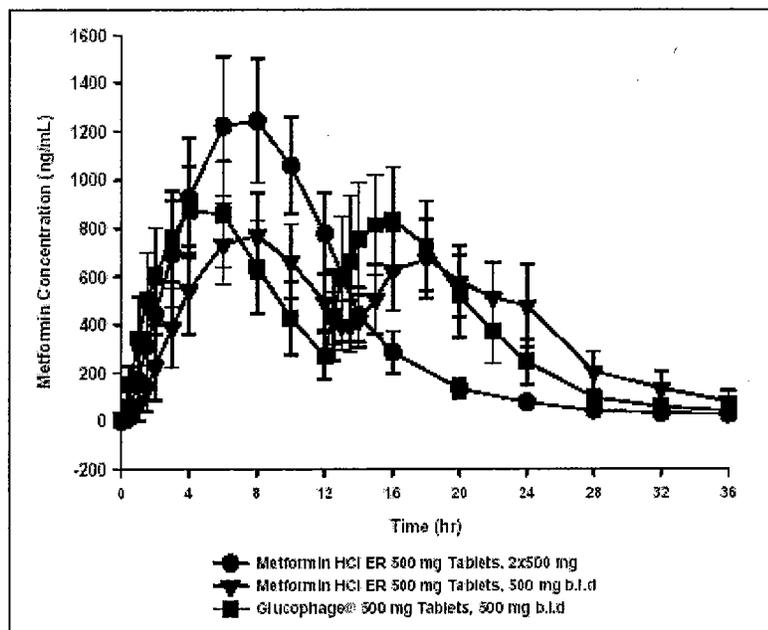


Table 3. Summary of PK parameters after one day dosing

PK Parameter	Glumetza 2X500mg	Glumetza 1X500mg BID	Glucophage 1X500mg BID
AUC ₀₋₃₆ (ng.hr/mL)	14182±2415	15260±3496	15342±3398
C _{max} (ng/mL)	1301.4±285.7	811.9±173.7	959.1±204.0
T _{max} (hr)	7.5±1.2	7.1±1.2	4.2±1.6

Table 4. Summary of statistics comparing Glumetza and Glucophage

PK parameter	Glumetza 2X500mg Versus Glucophage 500mg BID	
	Ratio of geometric means	90% CI
AUC ₀₋₃₆	93.50%	89.45 – 97.72
C _{max}	135.31%	128.89 – 142.05
PK parameter	Glumetza 500mg BID Versus Glucophage 500mg BID	
	Ratio of geometric means	90% CI
AUC ₀₋₃₆	99.00%	94.72 – 103.48
C _{max}	84.18%	80.19 – 88.38

Based on plasma metformin concentration data from 26 completing subjects (14 males and 12 females, mean age = 36), both 2x500 mg and 500 mg BID dosing of the ER tablets showed equivalent systemic exposure of metformin to the reference given 500 mg BID. The ratios of geometric means for AUC and the corresponding 90% geometric confidence intervals (C.I.) were within 80 -125%. The 2x500 mg ER tablets resulted in a 35% higher mean C_{max} than that of the reference. When the ER tablets were given 500 mg BID, C_{max} was found to be equivalent to that of the reference with the 90% C.I. falling within 80 - 125%. The mean T_{max} for the ER tablet was longer than that of the reference with both once-daily and BID dosing. This difference in T_{max} reflected the characteristics of an extended release formulation.

This study revealed that the Glumetza plasma profile was consistent with the characteristics of a modified release providing similar systemic exposure and some extension of plasma levels with a broader peak plasma concentration and a longer T_{max} . When both products were given as 500 mg twice daily, the ER tablets demonstrated equivalent peak and systemic exposure of metformin to the reference.

Similar results were obtained when the ER tablets were compared to the Canadian reference in Study B03-618PK-P0112 (2668).

- **What is bioavailability of Glumetza™ relative to Glucophage after multiple doses?**

The firm has conducted a three-way, multiple-dose, crossover bioavailability study (Study 81-0018) of Glumetza™ 500 mg tablets relative to Glucophage® 500 mg tablets in 30 subjects (15 males and 15 females, mean age = 32). Subjects were randomly assigned to one of the three treatments in three study periods separated by a one-week washout. The treatments involved administering two Glumetza tablets once daily (2x500 mg QD), one Glumetza tablet twice daily (500 mg BID), or one reference tablet twice daily (Glucophage 500 mg BID) after meal for five days. The mean plasma metformin concentrations versus time plots are presented in Figure 2. Summaries of the mean pharmacokinetic parameters and statistics are shown in Tables 5, and 6.

Figure 2. Mean steady state plasma metformin concentrations

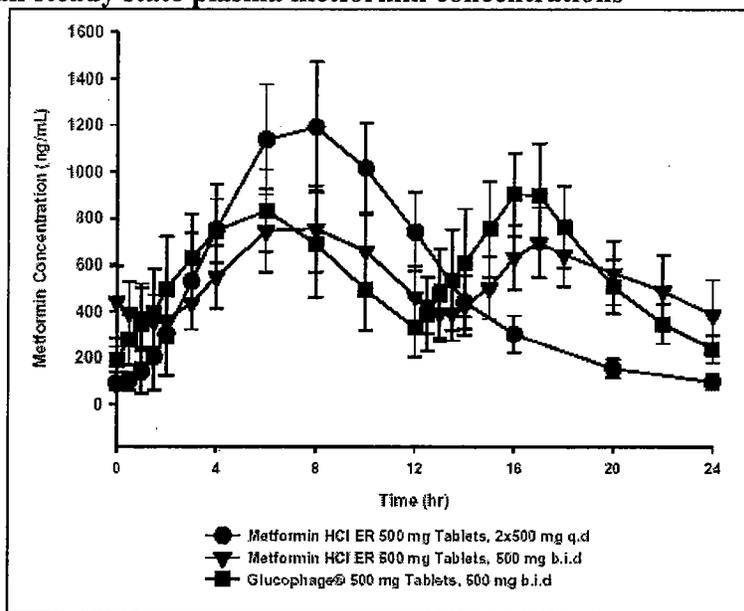


Table 5. Summary of PK parameters on Day 5

PK Parameter	Glumetza 2X500mg	Glumetza 1X500mg	Glucophage
--------------	------------------	------------------	------------

	QD	BID	1X500mg BID
AUC ₀₋₂₄ (ng.hr/mL)	12907±2011	13329±2581	13930±2565
C _{max} (ng/mL)	1249±246	817±175	986±193
T _{max} (hr)	7.3±1.40	6.88±1.68	4.60±1.38

Table 6. Summary of statistics comparing Glumetza and Glucophage

PK parameter	Glumetza 2X500mg QD Versus Glucophage 500mg BID	
	Ratio of geometric means	90% CI
AUC ₀₋₂₄	92.62%	89.13 – 96.25
C _{max}	126.23%	121.16 – 131.52
Glumetza 500mg BID Versus Glucophage 500mg BID		
AUC ₀₋₂₄	95.59%	91.99 – 99.34
C _{max}	82.85%	79.52 – 86.32

Based on plasma metformin concentration data from 24 completing subjects (13 males and 11 females, mean age = 39), both 2x500 mg QD and 500 mg BID administration of the Glumetza tablets showed equivalent systemic exposure (AUC₀₋₂₄) of metformin to the reference given as 500 mg BID. With 2x500 mg QD administration, the (ER vs Reference) ratio of geometric means for C_{max} was approximately 126%. When given as 500 mg BID, the C_{max} was about 17% lower than that of the reference. Under both QD and BID dosing, the mean T_{max} for the ER tablets was significantly longer than the reference ($p < 0.05$).

In conclusion, once-daily 2x500 mg administration of Glumetza resulted in equivalent systemic exposure but higher peak exposure than the immediate release reference administered twice daily at steady state. The Glumetza 500 mg BID demonstrated lower peak and but similar systemic exposure to the immediate release reference (500 mg BID) under steady-state.

- **What is the dose-concentration relationship for Glumetza™?**

A dose proportionality study of Glumetza™ at the dosage levels of 1x500 mg, 2x500 mg, 3x500 mg, and 5x500 mg in healthy male volunteers was conducted under fed conditions (after dinner) (Study 81-0019). The study followed a dose-escalated, four-period, single-dose design involving 36 subjects (18 males and 18 females, mean age = 33). The four treatments were given to all subjects after breakfast separated by a one-week washout. Blood samples for pharmacokinetic analysis were collected from 0-24 hours. A summary of the mean pharmacokinetic parameters is presented in Table 7.

Table 7. Pharmacokinetic parameters of Glumetza™ ranging from 500 mg to 2500 mg with dose-correction (N=35)

Parameter	Glumetza™			
	1x500 mg	2x500 mg	3x500 mg	5x500 mg
C _{max} (ng/nL)	473 ± 145	434 ± 112	390 ± 99	326 ± 80
AUC _{0-24 hr}	3348 ± 830	3194 ± 921	2964 ± 945	2691 ± 944

(ng.hr/mL)				
AUC _{0-inf} (ng.hr/mL)	3501 ± 796	3351 ± 959	3097 ± 946	2831 ± 887
T _{max}	3.9 ± 0.5	4.1 ± 0.5	3.9 ± 0.3	3.8 ± 0.4
T _{1/2}	6.9 ± 3.1	7.2 ± 2.5	7.5 ± 3.2	9.9 ± 8.6

Linear regression analysis revealed that the ratio of 4.02: 2.66: 1.91:1 was observed for AUC₀₋₂₄ of metformin at doses of 2500, 1500, 1000, and 500 mg, respectively. The similar ratios were observed for AUC_{0-inf} and C_{max}. It seemed that at the higher doses, there was approximately a 20% - 30% deviation from the linearity of the AUCs and C_{max} with metformin doses.

ANOVAs were also performed on dose-corrected log-transformed AUC₀₋₂₄, AUC_{0-inf}, and C_{max}. The resulting p values of the t-test from the pair-wise comparisons among treatments A, B, C, and D are presented in the following table (Table 8). The AUCs obtained within the metformin dose range of 500 mg to 1500mg were similar (p values were greater than 0.05 for Treatments A and B and Treatments A and C). However, the AUCs of 2500 mg were significant different from the AUCs generated with 500mg of metformin (p values were less than 0.05 for Treatments A and D). The C_{max} was similar in the dose range of 500 and 1000 mg but was different at the higher doses. This is consistent with the results from the linearity analysis, of the observed deviation from the linearity of the AUCs and C_{max} with metformin doses.

Table 8. p Values for paired comparison among treatments A, B, C, and D

Treatment	A vs. B	A vs. C	A vs. D
AUC 0-t	0.4604	0.0610	0.0009
AUC 0-∞	0.4358	0.0490	0.0013
C _{max}	0.2543	0.0068	<0.0001

Reviewer's comments: From literature and in-house data, we are aware that metformin has a linear PK at lower dose range, but its high dose range of 2000 to 2500 mg is off linear relationship to some extent. Therefore, the study results are consistent with existing information.

- **What is the effect of food on the bioavailability of Glumetza™?**

Study 00-09 was conducted to assess the effect of food on the Glumetza™ 500 mg tablets in 24 healthy subjects (seven males and 17 females, mean age = 29). This was a three-way, single-center, single-dose, open-label, randomized, two-period crossover study with a 7 day washout period between treatments. Subjects were randomly assigned to one of the three 2x500 mg once treatments in three study periods separated by a one-week washout. The treatments involved drug administration after a 10-hour overnight fast, after an American Heart Association 30% fat breakfast or after a high fat breakfast. Blood samples for pharmacokinetic analysis were collected 0 - 24 hours post doses. All

24 subjects completed the study but three subjects vomited post drug administration during the study. Pharmacokinetic and statistical analyses were carried out from 21 subjects. Tables 9 and 10 are the summaries of the mean pharmacokinetic parameters and statistics.

Table 9. Pharmacokinetic parameters after Glumetza given after overnight fasting, AHA 30% and high fat breakfast (N=21)

Parameter	2X 500 mg Fasting	2X500mg AHA 30% Breakfast	2X500mg High Fat Breakfast
C_{max} (ng/nL)	1021.5 ± 270.7	992.1 ± 213.3	1018.0 ± 190.4
AUC_{0-24 hr} (ng.hr/mL)	6994 ± 2145	9636 ± 3008	12104 ± 2627
AUC_{0-inf} (ng.hr/mL)	7506 ± 2220	10200 ± 3167	13306 ± 2944
T_{max}	3.2 ± 0.8	6.2 ± 1.5	6.3 ± 1.5
T_{1/2}	8.2 ± 3.5	5.4 ± 1.5	5.7 ± 2.0

Table 10. Summary of statistics comparing two fed conditions

Parameter	High fat breakfast versus AHA 30% fat breakfast	
	Ratio of geometric mean	90% Geometric confidence interval
AUC_{0-t}	128%	115.9 – 141.5
AUC_{0-∞}	133%	121.0 – 145.2
C_{max}	103%	93.8 – 113.3

Therefore, a significant food effect was observed on Glumetza 500 mg tablets. Administration of the ER tablets after either a high fat or an AHA 30% fat meal resulted in a significant increase in the systemic exposure of metformin but no effect on the peak exposure. The time to reach peak exposure was delayed in the presence of food. Glumetza 1000 mg tablets were not tested in food studies.

2.3 INTRINSIC FACTORS

2.3.1 Age, Gender, Race:

- **Do age, gender, and race impact the pharmacokinetics of Glumetza?**

The influence of age, gender, and race factors on the pharmacokinetic behaviour of metformin were evaluated by analyzing data across all nine pharmacokinetic studies that were performed with Glumetza™ and Glucophage® (in three studies). A total of 255 subjects (128 females and 127 males; average age = 36) completed the studies of which 72.5% were Caucasians, 18.0 % were Blacks, 4.7% were Hispanics and 4.7% were Asians.

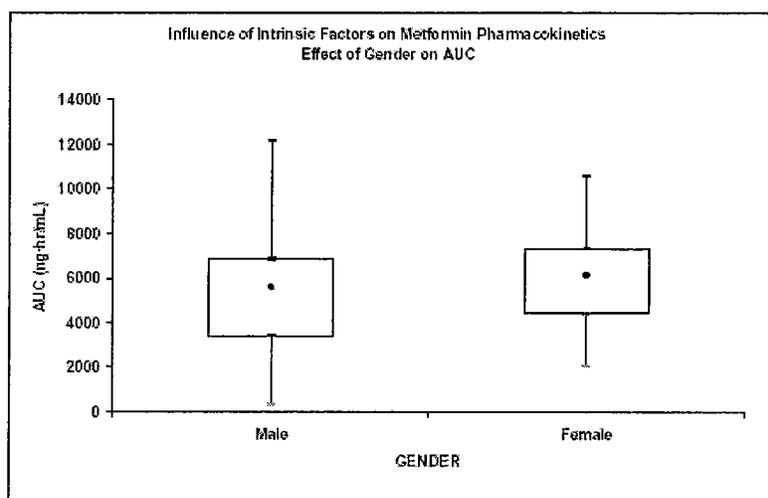
The pharmacokinetic parameters that were considered in the analysis were C_{max}, AUC_{0-∞} and t_{1/2} for metformin. Where appropriate, data for Glumetza were compared

with the corresponding data for the commercial Glucophage. The pharmacokinetic data from all studies were pooled, and scatter plots and box and whisker plots were generated to evaluate the effects of age, gender, race (intrinsic factors), and body weight (extrinsic factor). The findings from these evaluations are discussed below.

Gender

Gender effects were evaluated for $AUC_{0-\infty}$, C_{max} and $t_{1/2}$ values for metformin. The representative plot for AUC comparison is presented in Figure 3.

Figure 3. Box Plot for Metformin AUC Values in Male and Female Subjects



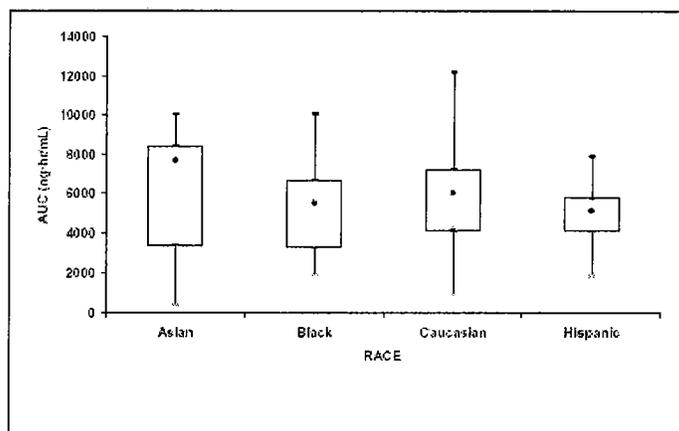
The gender differences for AUC is not statistically significant ($p=0.5229$).

Race

The same analysis of the pharmacokinetic parameter values was performed for the different racial groups (Caucasian, Black, Hispanic and Asian). The majority of subjects who participated in the studies were Caucasian. The next largest group was Black subjects followed by an equal number of Asian and Hispanic subjects.

No definitive conclusions can be reached on the differences between the races with respect to the pharmacokinetics of metformin because of the imbalance in the respective sizes of the racial groups. However, the data suggest that higher C_{max} and $AUC_{0-\infty}$ values for metformin are obtained in Asian subjects compared with Caucasian subjects. The findings for $AUC_{0-\infty}$ for the different racial groups are illustrated in the box and whisker plot provided in Figures 4.

Figure 4. Box Plot for AUC Values by Race for Metformin

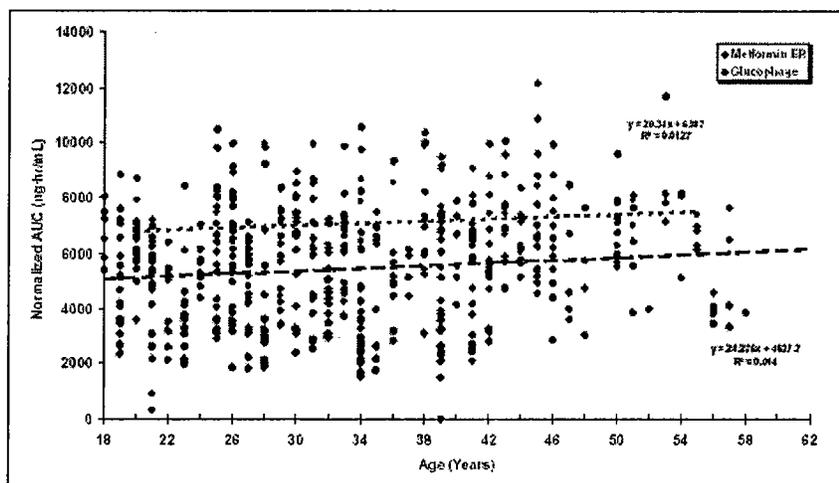


Age

Scatter plots for $AUC_{0-\infty}$ versus age and C_{max} versus age for metformin were constructed to evaluate the effects of age on the performance of the pharmacokinetics of metformin HCl ER. The regression analysis in all cases showed that there were no age-related changes in the pharmacokinetic parameter values for metformin. In addition, the analysis showed that the same relationship was observed between the pharmacokinetic values and age for metformin ER and Glucophage.

The regression coefficients for the least square fits of the AUC data were 0.014 and 0.0127 for metformin ER and Glucophage, respectively. This finding is illustrated in the case of the relationship between the AUC for metformin and age in Figure 5. A similar relationship was revealed between C_{max} and age as well.

Figure 5. Scatter Plot for AUC by Age for Metformin and Glucophage™ in all Studies



Although data are consistent with the information provided in the approved labeling for Glucophage, all subjects across study protocols are young adult and adults

for age of less than 60 years old. There were no senior adults (age of > 65 years). The analysis did not provide the information how different the pharmacokinetics would be in senior adults.

2.3.2 Renal impairment:

- **Dose renal impairment decrease Glumetza clearance?**

The sponsor conducted a multi-center, single dose, parallel design study to evaluate the pharmacokinetics of Glumetza 500 mg tablets in renal impairment patients and healthy subjects. The study involved three groups of subjects (10 per group): Patients with mild renal impairment (creatinine clearance of 51-80 mL/min), patients with moderate renal impairment (creatinine clearance of 30-50 mL/min) and healthy subjects with normal renal function (creatinine clearance of >80 mL/min). Subjects in each group were given one Glumetza 500 mg tablet after breakfast. Blood samples for pharmacokinetic analysis were collected from 0 - 36 hours. Urine samples were also collected at specified times over 36 hours following dosing to determine the renal clearance of Glumetza. The mean plasma metformin concentrations versus time plots are presented in Figure 6. Summaries of the mean pharmacokinetic parameters and statistics are shown in Tables 11 - 13.

Figure 6: Mean Plasma Metformin Concentration Versus Time Plot (n=30, 10 per group)

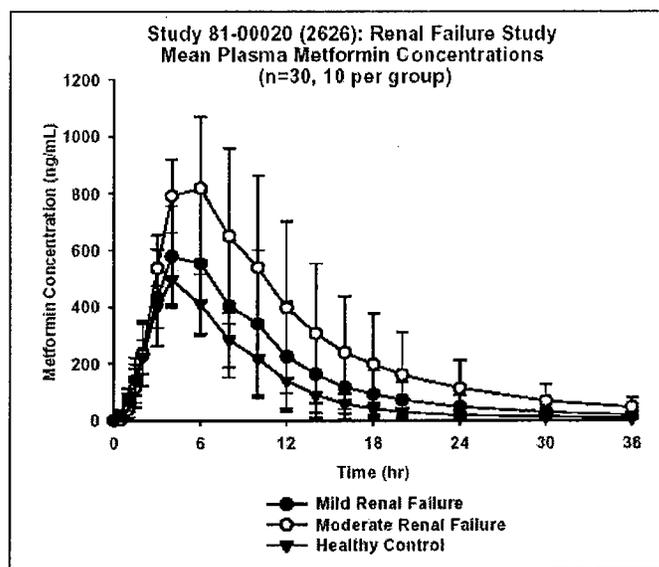


Table 11. Summary of Mean Pharmacokinetic Parameters after a single dose of 500 mg Glumetza

Pharmacokinetic Parameters	A	B	C
	Mild Renal Failure	Moderate Renal Failure	Healthy Normal
AUC_{0-t} (ng*hr/mL)	6030 ± 3140 (CV = 52%)	9861 ± 4804 (CV=49%)	4169 ± 1033 (CV=25%)
AUC_{0-∞} (ng*hr/mL)	7173 ± 3008 (CV=42%)	10539 ± 5094 (CV=48%)	4469 ± 989 (CV=22%)
C_{max} (ng/mL)	653.4 ± 229.7 (CV=35%)	898.3 ± 220.8 (CV=25%)	515.9 ± 77.7 (CV=15%)
T_{max} (hr)	4.5 ± 1.1	5.0 ± 1.5	5.0 ± 1.9
CL/F (mL/min)	1307 ± 433	959 ± 417	1939 ± 383

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Table 12. Summary of Mean Urinary Pharmacokinetic Parameters after a single dose of 500 mg Glumetza

Pharmacokinetic Parameters	A	B	C
	Mild Renal Failure	Moderate Renal Failure	Healthy Normal
Total amount of metformin excreted, Ae (mg)	90.33 ± 35.22	84.62 ± 34.28	80.77 ± 26.69
Renal clearance, CLR (mL/min)	278.28 ± 93.30	156.85 ± 55.06	332.46 ± 125.58

Table 13. Summary of statistics comparing mild and moderate renal failure patients against normal control group

Pharmacokinetic Parameters	Mild Renal Failure vs. normal control		Moderate Renal Failure vs. normal control	
	Ratio	p-value	Ratio	p-value
AUC _{0-t}	1.45	0.3390	2.37	0.0010
AUC _{0-∞}	1.61	0.002	2.36	0.0448
Cmax	1.27	0.4439	1.74	0.0021
CL/F	0.67	0.0448	0.50	0.0002
Ae	1.12	0.7349	1.05	0.9495
CLR	0.84	0.4011	0.47	<0.0001

Patients with moderate renal impairment showed a 50% decrease ($p = 0.0002$) in the oral clearance (CL/F) when compared to healthy subjects. In patients with mild renal impairment, CL/F was 33% ($p = 0.0448$) lower than the values observed in healthy subjects. Renal clearance (CLR) of metformin was 16% lower in patients with mild renal impairment when compared to subjects with normal renal function ($p = 0.4011$). Patients with moderate renal impairment demonstrated a 53% decrease in metformin CLR ($p < 0.0001$) in comparison to subjects with normal renal function. There were no statistically significant differences in the amount of metformin excreted in 36 hours (Ae) between all groups.

Therefore, caution is required when treating diabetic patients with renal insufficiency where metformin accumulation can occur and result in potential lactic acidosis. Dose adjustment should be made for renal impairment patients.

2.3.3 Hepatic impairment, Pediatric:

No studies were conducted with Glumetza™.

2.4 Extrinsic Factors:

Does glyburide impact the pharmacokinetics of metformin?

The sponsor conducted a two-way, single-dose, crossover drug interaction study comparing the pharmacokinetic profile of Metformin HCl ER 500 mg tablets given once versus administration in combination with glyburide 5 mg tablets in 28 subjects (14 males and 14 females, mean age = 32). Since metformin and glyburide may often be used in combination therapy for Type II diabetes, it is therefore important to demonstrate the absence of a significant pharmacokinetic interaction between the two drugs. In this study, subjects were randomly assigned to one of the two treatments in two study periods separated by a one-week washout. The first treatment involved administering one ER 500 mg tablet after breakfast, and the second treatment involved administering one ER 500 mg tablet and one glyburide 5 mg tablet after breakfast. Blood samples for pharmacokinetic analysis were collected from 0 - 24 hours. Results show there is no pharmacokinetic drug interaction between two drugs. Summaries of the mean pharmacokinetic parameters and statistics are shown in Tables 12.

Table 14. Summary of PK parameters and statistical analysis for metformin ER 500mg with and without glyburide

Pharmacokinetic Parameters (N=28)	Treatment A	Treatment B	Metformin/Metformin+Glyburide	
	Metformin HCl ER 500 mg	Metformin HCl ER 500 mg with glyburide 5 mg	Ratio of Geometric mean	90% CI
AUC _{0-t} (ng.hr/mL)	5115 ± 1978	5082 ± 1878	100.35	89.75 – 112.21
AUC _{0-∞} (ng.hr/mL)	5713 ± 2017	5609 ± 1995	100.55	88.81 – 113.85
C _{max} (ng/mL)	517.5 ± 146.2	515.2 ± 140.0	100.47	91.75 – 110.02

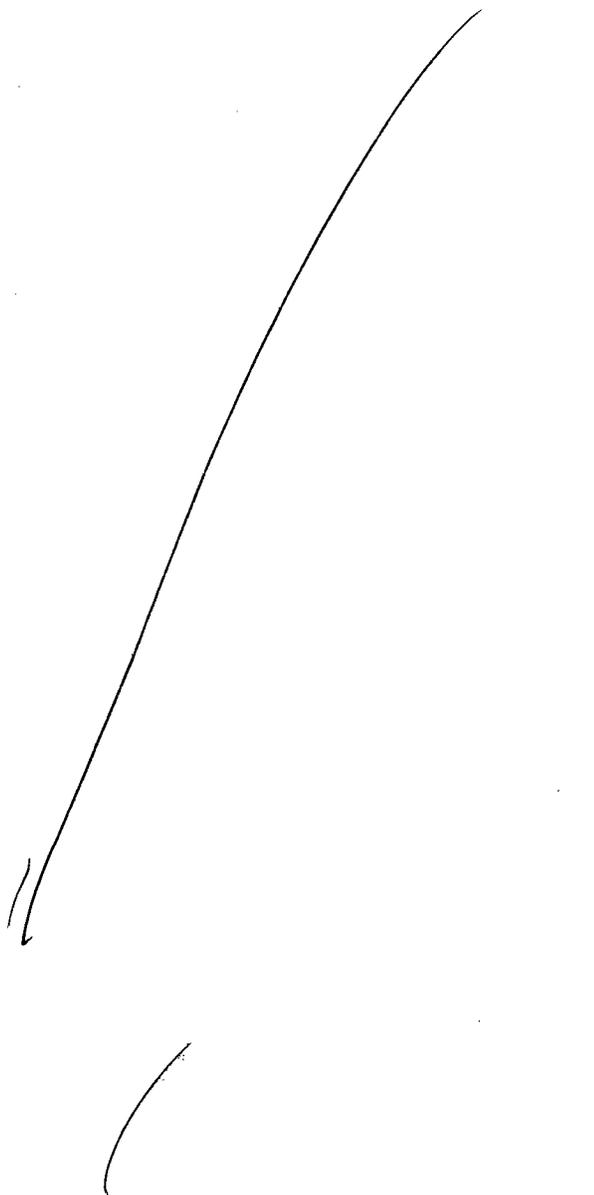
The caveat of the study is that metformin ER 500 mg is sub-clinical dose for treatment of diabetes. The usual dose is to start with 1000 mg and it can be increased up to 2000-2500 mg per day. Since this study is to investigate the effect of glyburide on pharmacokinetics of metformin ER, 5 mg is a therapeutic dose for glyburide, this reviewer agrees with the sponsor's study design.

2.5 General Biopharmaceutics

- **Has a Level A in vitro-in vivo Correlation (IVIVC) been established?**

The in vitro dissolution rate and the in vivo performance of Metformin Hydrochloride Extended Release (ER) 500 mg Tablets, were investigated in order to generate the data sets necessary for developing an in vitro-in vivo correlation (IVIVC). In addition, the immediate release

product Glucophage® was administered in the comparative pharmacokinetic study to obtain the unit impulse response of the body system for metformin hydrochloride in the same study group. The model independent numerical deconvolution and convolution technique based on the trapezoidal formula were applied for the calculation of the in vivo release kinetics and for the simulation of plasma concentration profiles.

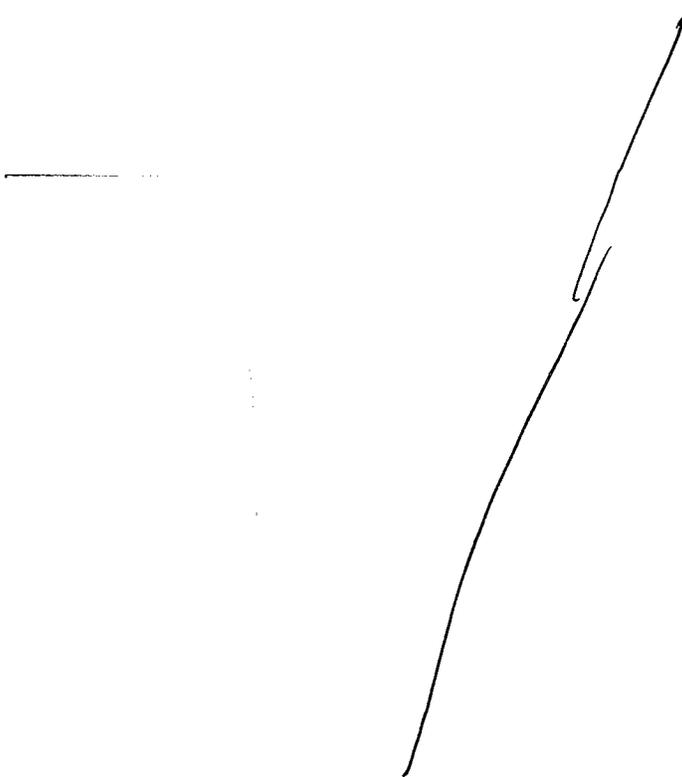


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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



The sponsor has concluded that a Level A In Vitro/In Vivo Correlation is established based on three release rates of formulations, a single dose, four-way crossover pharmacokinetics study, correlation of in vivo release and in vitro release and evaluation of internal predictability. This reviewer noticed that both in vivo and in vitro release profiles are very close to each other, especially in vivo release profiles, which means these release kinetics may not be sensitive enough to discriminate the difference. The consequence is that prediction derived from such IVIVC simulation may overstate actual situation. The sponsor did not try IVIVC for 1000 mg strength.

• **What is the association between formulation development and clinical studies?**

DepoMed developed metformin ED 500 mg tablets. Using pilot formulation and lots, the sponsor conducted three Phase 1 bioavailability studies relative to metformin immediate release form Glucophage and one Phase 2 four-week clinical efficacy and safety study. Using scale-up formulation and lots, the sponsor conducted nine Phase 1 pharmacokinetic studies and three Phase 3 clinical trials. Lots YT540R, YT623R and YT624R used in Phase 3 Clinical and PK studies, as well as primary stability studies, were manufactured using the same process and equipment as those intended for future commercial production. The only difference between the Phase 3 scale-up process and formulation, and batches representing future commercial production (Lot Nos. 03T264DM and 03T265DM), is the change in color of the non-functional film coat, from — white. All process parameters and equipment remain unchanged. Biovail

developed metformin ED 1000 mg tablets with different formulation. The commercial formulation and production process remain the same as the scale-up. and Though 1000 mg tablets have never been used in any pivotal clinical trials, a dosage form equivalence between 500 mg and 1000 mg metformin ER tablets is demonstrated (Study B03-646PK-P0112). The relationship of formulations, batch size, and clinical studies is summarized in Table 14.

Table 14. Glumetza™ lots and study protocol

Dosage (mg)	Lot Type	Lot No./ (Batch size)	Phase 1	Phase 2	Phase 3
500	Pilot	000012	CLREPKA003	00-04	N/A
	Scaled up production	YT520R (YT5201; YT5202)	B03-618PK-P0112 (2668) B03-646PK-P0112 (R03-608) 81-0011 (2607) 81-0016 (2621) 81-0017 (2622) 81-0018 (2624) 81-0019 (2625) 81-0020 (2626) 00-09	N/A	81-0003
		YT623R			81-0013 81-0014
		YT624R	N/A	N/A	81-0013 81-0014
1000	Scaled up production	26390503	B03-646PK-P0112 (R03-608)	N/A	N/A

- **Has the dosage form equivalence been established between 500 mg and 1000 mg?**

The firm conducted one dosage equivalence study for two different formulations for metformin ER tablets developed by Biovail for 1000 mg and by DepoMed for 500 mg. Study PRACS R03-608 was a two-way crossover, open-label, single-dose bioequivalence study of two dosage strengths of 500 mg and 1000 mg Glumetza™ from two strength lots (Lot 5402R for 500 mg and Lot No. 26390503D for 1000 mg) in 48 healthy subjects (19 males and 29 females, mean age = 29) with a one-week washout period between treatments. The objective of this study was to demonstrate dosage form equivalence between the two formulations under fed conditions. Blood samples for pharmacokinetic analysis were collected from 0 - 48 hours. A total of 46 subjects completed the study. Three subjects were excluded from statistical analysis due to emesis during the study periods. The pharmacokinetic data from 43 subjects were used for bioequivalence analysis.

Table 15. Summary of Pharmacokinetics parameters

Parameter	Mean \pm SD (N=43)		Relative Bioavailability (%)	90% Confidence Interval
	One 1000 mg Tablet	2 X 500 mg Tablets		
Cmax (ng/nL)	1293.17 \pm 368.39	1109.10 \pm 216.89	112.37	102.14 – 123.63
AUC_{0-48 hr} (ng.hr/mL)	12680.0 \pm 3431.46	13156.53 \pm 2433.87	92.71	85.34 – 100.72
AUC_{0-inf} (ng.hr/mL)	12949.79 \pm 3431.14	13350 \pm 2459.91	93.50	86.22 – 101.4
Tmax	9.23 \pm 2.27	7.72 \pm 1.80	-	-
T_{1/2}	11.94 \pm 5.94	9.85 \pm 3.60	-	-

The bioavailability (Cmax, AUC_{0-48 hr} and AUC_{0-inf}) of metformin after receiving one 1000 mg tablet relative to receiving two 500 mg tablets was approximately 92.7 - 112%. 90% confidence intervals remained to be within 80 -125%. Therefore, bioequivalence between the two dosage strengths is established. Since 1000 mg metformin ER tablets were not used in phase 3 clinical trials, this BE study is pivotal to market 1000 mg dosage strength.

- **What are the proposed dissolution method and specification?**

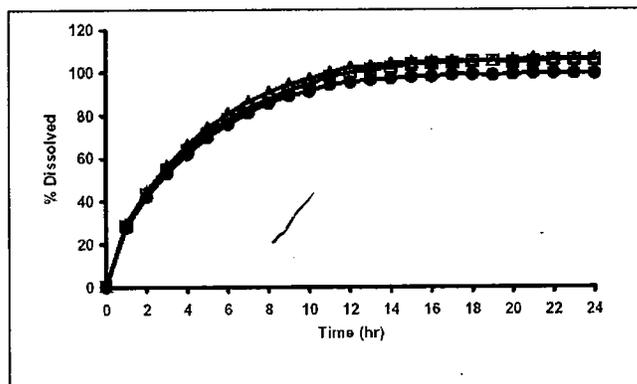
In-vitro drug release is determined in accordance with USP <711> using apparatus 1  at a speed of  rpm with ultraviolet (UV) detection. The drug release limits are evaluated in accordance with the acceptance criteria specified in the Extended-Release Articles - General Drug Release Standard.

Representative mean dissolution profiles in various media for the 500 mg and 1000 mg strengths are presented below. These batches were used in the pivotal pharmacokinetic program.

Metformin HCl ER 500 mg Tablets

Figure 12 shows representative mean dissolution profiles in  for Lot YT5402 of the ER 500 mg Tablets used in study 81-0017 (2622) (In-vitro/In-vivo Correlation Study). This batch has the same qualitative and quantitative composition as the proposed commercial formulation apart from the tablet coat color.

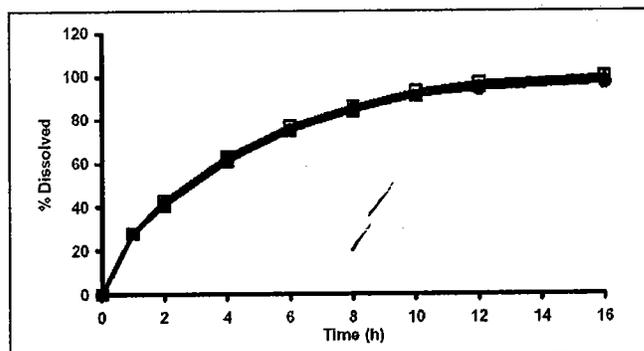
Figure 12. Comparative Dissolution Profiles of Metformin HCl ER 500 mg Tablets in Three Different Dissolution Media (Lot YT5402, N=12)



In-vitro dissolution profiles (Figure 13) were later generated for the ER 500 mg tablets (Lot YT5401) over 16 hours in the following three media:

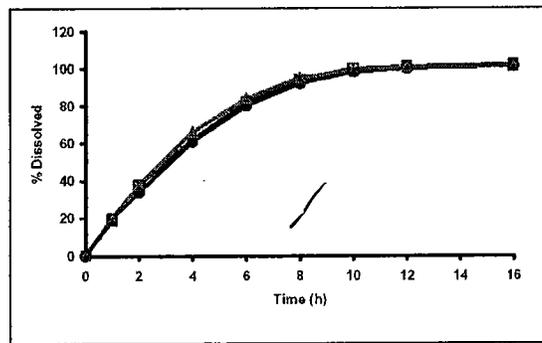
The reason for repeating the analysis was to generate comparative dissolution profiles of the 500 mg and 1000 mg strengths in the same media and provide relevant data to calculate the Similarity Factor (f_2) between the two strengths. Lots YT5402 and YT5401 belong to a common bulk — Lot YT540R that has the same qualitative composition as the proposed commercial formulation. The lot numbers YT5402 and YT5401 were used to differentiate the two types of packaging. This batch has the same qualitative composition as the proposed commercial formulation apart from the tablet coat color (Note: proposed formulation is white tablets. Please refer to comparative dissolution profile of white versus — tablets in the CMC section).

Figure 13. Comparative Dissolution Profiles of Metformin ER 500 mg Tablets in Three Different Dissolution Media (Lot YT5401, n=12)



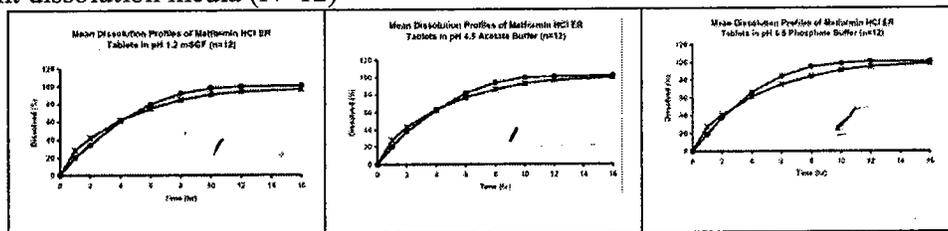
Metformin HCl ER 1000 mg Tablets Figure 14 shows representative mean dissolution profiles over 16 hours in _____) for Lot 26390503C of the ER 1000 mg Tablets. Lots 26390503C and 26390503D belong to a common bulk _____ Lot 26390503 that has the same qualitative and quantitative composition as the proposed commercial formulation. The lot numbers 26390503C and 26390503D were used to differentiate the two types of packaging.

Figure 14. Comparative Dissolution Profiles of Metformin HCl ER 1000 mg strength in Three Different Dissolution Media (Lot 26390503C, N=12)



Comparative dissolution profiles demonstrating the similarity of the in-vitro release of the 500 mg and 1000 mg strengths in three media _____ are depicted in Figures 22a

Figure 15. Comparative dissolution profiles of metformin HCl ER tablets in three different dissolution media (N=12)



Drug Release Specifications

The in-vitro drug release for 500 mg and 1000 mg strengths were studied in various dissolution media. Drug release specifications were established with _____ Based on the Level A IVIVC model generated from an in-vitro/in-vivo correlation (IVIVC) study, the in-vitro drug release specification

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for the 500 mg and 1000 mg strengths were finalized based on results generated with α at 37°C (USP α , (Apparatus I)). A summary of the drug release method and proposed specification is presented in Table 16.

Table 16. Proposed dissolution method and specifications for metformin ED 500 mg and 1000 mg tablets

Apparatus type	USP Apparatus-1 (α)
Medium	/
Temperature of medium	37°C
Speed of rotation	RPM
Specification	2 hr: α , 4 hr: α , 12 hr: NLT α

Using these proposed in vitro dissolution specifications, the in vivo release profiles were then convoluted to calculate the corresponding plasma concentrations. The relative bioavailability of predicted upper and lower dissolution limits for C_{max} is 27.4% (Table 17), which is beyond the maximum 20% allowed range for point estimate to maintain bioequivalence between the upper and lower limit of the specifications.

Table 17. Relative bioavailability of predicted upper and lower dissolution limits ($\pm 20\%$)

PK-parameters	Predicted UL	Predicted LL	Ratio (upper/lower) (%)
C_{max} (ng/mL)	671.05	501.19	27.4
AUC(0-24h) (ng.h/mL)	5999.67	5791.87	3.5

The reviewer conveyed the sponsor the concerns of wide in vitro specifications, which apparently reached outside of BE criteria. The sponsor submitted additional calculation based on \pm deviation from the mean in vitro release profile. However, the relative bioavailability of predicted upper and lower dissolution limits for C_{max} is 22.5% (Table 18), which is still beyond the maximum 20% allowed range for point estimate to maintain bioequivalence between the upper and lower limit of the specifications.

Table 18. Relative bioavailability of predicted upper and lower dissolution limits ($\pm 15\%$)

PK-parameters	Predicted UL	Predicted LL	Ratio (upper/lower) (%)
C_{max} (ng/mL)	652.68	505.83	22.5
AUC(0-24h) (ng.h/mL)	5990.57	5845.98	2.4

Therefore, the proposed in vitro dissolution specifications by the sponsor are not acceptable. The following specifications are suggested: 2 hour: α , 4 hour: α , 12 hour: NLT α

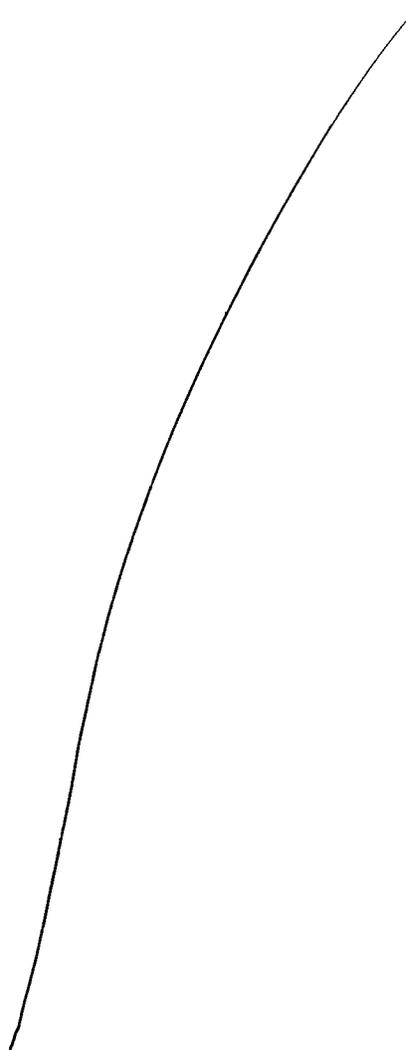
2.6 Analytical Section

- **What is the property of analytical method?**

For the quantitation of plasma metformin concentration, the bioanalytical portion of the pivotal human pharmacokinetic program was carried out with three different assays since the studies were conducted in different Clinical Research Organizations (CROs). 7 out of 9 pivotal PK studies used LC/MS for the quantitation of plasma/urine metformin concentrations. The other two employed validated HPLC-UV and LC/MS/MS assays. The sensitivity of methods with LC/MS, LC/MS/MS, and HPLC-UV is 10-2001 ng/mL, 5-1500 ng/mL, and 10-2500ng/mL, respectively.

Pre-study validation runs were conducted to verify system performance, calibration standard, and quality control pool preparation, prior to the analysis of study samples. For LC/MS method, the intra-batch accuracy and precision expressed in relative error (%RE) and coefficient of variation (%CV) ranged from 5.6% to 8.3% and 1.1% to 10.0%, respectively. The inter-batch accuracy (%RE) and precision (%CV) ranged from 1.1% to 10.2% and 2.7% to 14.3%, respectively. The percentage recovery for metformin was 87.4%. For LC/MS/MS method, the intra-batch accuracy and precision expressed in relative error (%RE) and coefficient of variation (%CV) ranged from -13.1% to -1.4% and 1.3% to 3.5%, respectively. The inter-batch accuracy (%RE) and precision (%CV) ranged from -8.2% to -4.3% and 0.9% to 3.8%, respectively. The percentage recovery for metformin was 99.7%. For HPLC-UV method, the intra-batch accuracy and precision expressed in relative error (%RE) and coefficient of variation (%CV) ranged from 1.8 % to 17.7 % and 6.2% to 9.6%, respectively. The inter-batch accuracy (%RE) and precision (%CV) ranged from 0.0% to 2.7% and 7.7% to 8.2%, respectively. The overall percentage recovery for metformin was 76.4%.

3. DETAILED LABELING RECOMMENDATIONS *ad*



4. Appendices:

4.1 OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics <i>New Drug Application Filing and Review Form</i>			
<i>General Information About the Submission</i>			
NDA Number	21-748	Brand Name	Glumetza™
OCPB Division (I, II, III)	DPE II	Generic Name	Metformin HCL extended release tablets
Medical Division	HFD-510	Drug Class	Anti-diabetic

OCPB Reviewer	Xiaoxiong (Jim) Wei	Indication(s)	Diabetes, NIDDM
OCPB Team Leader	Hae-Young Ahn	Dosage Form	500 mg and 1000 mg tablets
		Dosing Regimen	1000 mg – 2000 mg /Day
Date of Submission	04-27-04	Route of Administration	P.O.
Estimated Due Date of OCPB Review	12-13-04	Sponsor	Biovail Labs
PDUFA Due Date	02-27-05	Priority Classification	S1
Division Due Date	02-21-05		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	3		
multiple dose:	X	1		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1		
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				

Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		
replicate design; single / multi dose:				
Food-drug interaction studies:	X	3		
Dissolution:				
(IVIVC):	X	1		
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		12		
Fileability and QBR comments				
	"X" if yes	Comments		
Application fileable ?	YES			
Comments sent to firm ?	NO			

Briefing In Content:

Biovail Laboratories, Inc. has submitted their NDA for GLUMETZA™ for the treatment of type 2 diabetes as a 505(b)1 application. GLUMETZA™ is extended release forms of metformin HCL. The sponsor conducted twelve human pharmacokinetic studies and four efficacy and safety studies. The proposed marketing dosage strengths are 500 mg and 1000 mg tablets. The proposed dosing regimen is to start with 1000 mg once daily with the evening meal. Dose may be increased up to 2000 mg a day. The dosage form equivalence between the 1000 mg and 500 mg tablets is established. The proposed commercial formulation for 500 mg tablets has been modified from the Phase 3 formulation, by using white coating instead of [redacted]. Dissolution release profiles for GLUMETZA 500 mg white-coated versus [redacted] tablets show that the change in non-functional coat color does not impact tablet dissolution. The commercial formulation for 1000 mg tablets is the same as the phase 3 formulation. Attached are summaries of these individual studies.

Table 1
Overview of Pivotal Pharmacokinetic Studies

Study Number	Study Title	Treatments or Groups	Sample Size	Previous Agency Responses on Study Design
Bioavailability Studies				
81-0011 (2607) * Study with US reference (Treatment C)	Open-Label, Randomized, Crossover Study to Compare The Pharmacokinetics, Safety, and Tolerability of Metformin HCl Extended Release (M-ER) Tablets And Metformin HCl Immediate Release (M-IR) Tablets in Healthy Male and Female Subjects	A. Metformin HCl ER 500 mg Tablets, 2x500 mg at 20:00 hour after dinner. B. Metformin HCl ER 500 mg Tablets, 500 mg at 20:00 hour after dinner, and 500 mg at 08:00 hour after breakfast. C. Glucophage® Tablets, 500 mg at 20:00 hour after dinner, and 500 mg at 08:00 hour after breakfast.	26 Completed (14 M & 12 F) Non-smokers	Agency agreed to the study design
81-0018 (2624)	A Randomized, Steady-State, Three-Way Crossover, Open-Label, Fed, Comparative Pharmacokinetic Study Of Metformin HCl 500 mg Extended-Release (M-ER) Tablets (2x500 mg QD or 500 mg BID) Versus Glucophage® Tablets (500 mg BID) in Healthy Male and Female Subjects	A. Metformin HCl ER 500 mg Tablets, 2x500 mg at 20:00 hour after dinner for 5 days. B. Metformin HCl ER 500 mg Tablets, 500 mg at 20:00 hour after dinner, and 500 mg at 08:00 hour after breakfast for 5 days. C. Glucophage® Tablets, 500 mg at 20:00 hour after dinner, and 500 mg at 08:00 hour after breakfast for 5 days.	24 Completed (13 M & 11 F) Non-smokers	Agency agreed to the study design
B03-618PK-P0112 (2668) * Study with Canadian reference (Treatment C)	An Open-Label, Randomized, Crossover Study To Compare The Pharmacokinetics, Safety and Tolerability Of Metformin HCl 500 mg Extended Release (M-ER) Tablets and Glucophage® 500 mg Tablets in Normal Healthy Non-Smoking Male and Female Subjects	A. Metformin HCl ER 500 mg Tablets, 2x500 mg at 20:00 hour after dinner. B. Metformin HCl ER 500 mg Tablets, 500 mg at 20:00 hour after dinner, and 500 mg at 08:00 hour after breakfast. C. Glucophage® Tablets, 500 mg at 20:00 hour after dinner, and 500 mg at 08:00 hour after breakfast.	27 Completed (14 M & 13 F) Non-smokers	Agency agreed to the study design

Table 1
Overview of Pivotal Pharmacokinetic Studies (continued)

Study Number	Study Title	Treatments or Groups	Sample Size	Previous Agency Responses on Study Design
Dosage Strength Proportionality Study				
B03-646PK-P0112 (R03-608)	A Two-Way, Crossover, Open-Label, Single Dose, Fed, Comparative Bioavailability Study of Two Formulations (1x1000 mg vs 2x500 mg) of Metformin HCl ER Tablets in Normal Healthy Non-Smoking Male and Female Subjects	A. Metformin HCl ER 1000 mg Tablet at 20:00 hour after dinner. B. Metformin HCl ER 500 mg Tablets, 2x500 mg at 20:00 hour after dinner.	46 Completed (18 M & 28 F) Non-smokers	Agency agreed to the study design
Dose Proportionality Study				
81-0019 (2625)	A Four-Way, Single-Dose, Open-Label, Dose-Escalation, Comparative Pharmacokinetic, Dose Characterization Study of Metformin HCl Extended Release (M-ER) Tablets (1x500 mg, 2x500 mg, 3x500 mg, 5x500 mg QD) in Healthy Male and Female Subjects	A. Metformin HCl ER 500 mg Tablets, 1x500 mg after breakfast. B. Metformin HCl ER 500 mg Tablets, 2x500 mg after breakfast. C. Metformin HCl ER 500 mg Tablets, 3x500 mg after breakfast. D. Metformin HCl ER 500 mg Tablets, 5x500 mg after breakfast.	35 Completed (17 M & 18 F) Non-smokers	Agency agreed to the study design
<i>In-vitro/In-vivo</i> Correlation Study				
81-0017 (2622)	A Four-Way, Single-Dose, Randomized, Crossover, Open-Label, Comparative Pharmacokinetic Study of Metformin HCl 500 mg Extended-Release (M-ER) Tablets in Healthy Male and Female Subjects for Investigation of <i>In-vitro/In-vivo</i> Correlation	A. Metformin HCl ER 500 mg Tablet after breakfast. B. Metformin HCl ER 500 mg Tablet after breakfast. C. Metformin HCl ER 500 mg Tablets after breakfast. D. Glucophage [®] 500 mg Tablet after breakfast.	15 Completed (7 M & 8 F) Non-smokers	Agency agreed to the study design

Table 1
Overview of Pivotal Pharmacokinetic Studies (continued)

Study Number	Study Title	Treatments or Groups	Sample Size	Previous Agency Responses on Study Design
Food Effect Study				
00-09	Comparison of Metformin Pharmacokinetics Under Fed and Fasted Conditions in Healthy Volunteers	A. Metformin HCl ER 500 mg Tablets, 2x500 mg fasting. B. Metformin HCl ER 500 mg Tablets, 2x500 mg after an AHA 30% fat breakfast. C. Metformin HCl ER 500 mg Tablets, 2x500 mg after a high fat breakfast.	24 Completed (7 M & 17 F) Non-smokers	Agency agreed to the study design
Drug Interaction Study				
81-0016 (2621)	A Two-Way, Single-Dose, Randomized, Crossover, Open-Label, Comparative Pharmacokinetic Study of Metformin HCl 500 mg Extended-Release (M-ER) Tablets Alone and in Combination With DiaBeta [®] 5 mg Tablets in Healthy Male and Female Subjects	A. Metformin HCl ER 500 mg Tablet after breakfast. B. Metformin HCl ER 500 mg Tablet and DiaBeta [®] 5 mg Tablet after breakfast.	28 Completed (14 M & 14 F) Non-smokers	Agency agreed to the study design
Special Population Study				
81-0020 (2626)	A Study of Single-Dose Pharmacokinetics of Metformin HCl Extended-Release (M-ER) Tablets (500 mg) in Subjects With Normal Renal Function and in Subjects With Mild and Moderate Renal Impairment	A. Group 1 (Patients with mild renal impairment): Oral dose of one Metformin ER 500 mg Tablet after breakfast. B. Group 2 (Patients with moderate renal impairment): Oral dose of one Metformin ER 500 mg Tablet after breakfast. C. Group 3 (Normal Healthy Controls): Oral dose of one Metformin ER 500 mg Tablet after breakfast.	10 Patients with mild renal impairment (9 M & 1 F) 10 Patients with moderate renal impairment (6 M & 4 F) 10 Normal healthy controls (8 M & 2 F)	Agency agreed to the study design

Table 2
Overview of Pilot Pharmacokinetic Studies

Study Number	Study Title	Treatments or Groups	Sample Size
99-003	Comparison of Metformin Pharmacokinetics For ER Tablets Versus Immediate Release (IR) Tablets in Healthy Volunteers	A. Metformin HCl ER 500 mg Tablet after breakfast. B. Metformin HCl ER 500 mg Tablet after breakfast. C. Glucophage® 500 mg Tablet after breakfast.	14 Completed (6 M & 8 F) Non-smokers
00-01	Steady State Comparison of Pharmacokinetics For Extended Release (ER) Metformin Tablets Versus Immediate Release (IR) Metformin Tablets in Healthy Volunteers	A. Metformin HCl ER 500 mg Tablets, 2x500 mg QD, at 08:00 hour after a low fat breakfast for 5 days. B. Glucophage® Tablets, 500 mg BID at 08:00 hour after a 30% low fat breakfast and at 20:00 hour after a low fat meal for 5 days.	14 Completed (3 M & 11 F) Non-smokers
81-0007	Pharmacoscintigraphic and Pharmacokinetic Evaluation of Metformin ER in Healthy Volunteers	A. One Glucophage® 500 mg Tablet after a high-fat breakfast. B. Radiolabeled Metformin HCl ER 500 mg Tablet co-administered with a radiolabeled after a high fat breakfast. C. Radiolabeled Metformin HCl ER 500 mg Tablet co-administered with a radiolabeled after an AHA 30% fat breakfast. D. Radiolabeled placebo formulation co-administered with a radiolabeled after an AHA 30% fat breakfast. E. Radiolabeled placebo formulation co-administered with a radiolabeled after an AHA 30% fat breakfast.	13 Completed (10 M & 3 F) Non-smokers

4.2 Proposed Package Insert (separate file)

4.3 Individual Study Review (see Addendum as a separate file)

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/s/

Xiao-xiong Wei
2/24/05 02:43:34 PM
BIOPHARMACEUTICS

Hae-Young Ahn
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