

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-591

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

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-591

Submission Date: 11/14/02

Proposed Trade Name: Riomet

ORM Division: Metabolic and Endocrine
Drug Products

Generic Name: Metformin HCL Solution,
100 mg/ml

OCPB Division: DPE II

Sponsor: Ranbaxy Pharmaceuticals, Inc

Team Leader: Hae-young Ahn, Ph.D.

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Addendum to Clinical
Pharmacology Review

Background

Metformin solution, 100 mg/ml is proposed in NDA 21-591 as a new formulation for use in adult & pediatric patients. Three studies including two relative bioavailability studies and one food-effect study have been submitted in support of the safety and efficacy of the metformin solution formulation. No clinical data has been submitted in support of the application.

At the request of the Division of Metabolic and Endocrine Drug Products (HD-510), the Division of Scientific Investigations (DSI) carried out an inspection of the analytical portion of study 05/METFO-500/01, entitled "A RANDOMIZED, TWO-TREATMENT, TWO-PERIOD, TWO-SEQUENCE, SINGLE DOSE, CROSSOVER BIOAVAILABILITY STUDY ON METFORMIN FORMULATIONS COMPARING METFORMIN HYDROCHLORIDE LIQUID 500 mg/5 ml OF RANBAXY LABORATORIES WITH GLUCOPHAGE 1000 mg TABLETS OF BRISTOL-MYERS SQUIBB IN HEALTHY, ADULT MALE AND FEMALE VOLUNTEERS UNDER FED CONDITIONS, FOLLOWING A 1000 mg DOSE" (See Appendix 1 for individual study summary). Following the inspection, DSI issued a Form-483 to _____ outlining the objectionable findings (See Appendix 2). In brief, the DSI report concluded that 2 out of 13 analytical runs were not acceptable. Subsequently, PK data from subjects 1, 2, 3, 37 & 38 were deemed not acceptable for review.

Pursuant to the DSI report, PK data in study 05/METFO-500/01, excluding data from subjects 1, 2, 3, 37 & 38, were re-analyzed for bioequivalence of metformin solution and Glucophage tablet using WinNonlin v 4.0 (Pharsight Corp., CA).

Re-analysis Results

Bioequivalence of two drug formulations is inferred if the 90% confidence interval for the mean ratios of AUC and Cmax lie within the acceptable range of 80-125%.

Results of re-analysis of the PK data in study 05/METFO-500/01, excluding data from subjects 1, 2, 3, 37 & 38, indicate that the PK data still conform to the bioequivalence criteria.

Summary of the least squares mean ratio estimates and 90% confidence intervals for bioequivalence assessment following administration of single 1000 mg doses of the metformin solution and Glucophage tablet to healthy subjects under fed conditions

| PK Parameter | Least Squares Mean Ratio (%) | 90% Confidence Interval |
|---|------------------------------|-------------------------|
| Original Analysis | | |
| $-C_{max}$ | 91.8 | (87.4-96.5) |
| $AUC_{0-\infty}$ | 97.0 | (92.9-101.2) |
| Re-analysis without subjects 1, 2, 3, 38 & 38 | | |
| C_{max} | 93.6 | (88.3-111.7) |
| $AUC_{0-\infty}$ | 99.1 | (92.4-107.6) |

Agency Recommendations

Re-analysis of the PK data from study 05/METFO-500/01, excluding data from subjects 1, 2, 3, 37 & 38, was performed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/DPE II), and from the view point of OCPB, the study is acceptable for review and hence, the study findings as cited in the original review still stand.

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Appendix 1

Individual Study Review

NDA: 21-591/ Study 05/METFO-500/01

Type of Submission: Comparative Bioavailability Study Under Fed Conditions

Study 05/METFO-500/01 is entitled,

“A RANDOMIZED, TWO-TREATMENT, TWO-PERIOD, TWO-SEQUENCE, SINGLE DOSE, CROSSOVER BIOAVAILABILITY STUDY ON METFORMIN FORMULATIONS COMPARING METFORMIN HYDROCHLORIDE LIQUID 500 mg/5 ml OF RANBAXY LABORATORIES WITH GLUCOPHAGE 1000 mg TABLETS OF BRISTOL-MYERS SQUIBB IN HEALTHY, ADULT MALE AND FEMALE VOLUNTEERS UNDER FED CONDITIONS, FOLLOWING A 1000 mg DOSE”.

Objectives

- To compare the bioavailability of metformin hydrochloride solution 100 mg/ml of Ranbaxy with Glucophage® 1000 mg tablets of Bristol-Myers following administration of a single 1000 mg dose to healthy adult subjects under fed conditions.

Study Design

Healthy adult male and female subjects (n = 38, Age 31.3 ± 6.3 yrs, Wt 69.5 ± 8.5 kg) received single 1000 mg doses of either metformin HCl solution 100mg/ml (lot # AA192) or a Glucophage® tablet (1000 mg; lot # MHM19) under fed conditions during each period. The study was conducted in a randomized, single dose, two-treatment, two-period, crossover fashion. Treatment periods were separated by a 7-day washout period. In each treatment period, blood samples were drawn for determination of metformin at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5.5, 5, 6, 7, 8, 10, 12, 16 and 24 hrs post-dose.

Analytical Assay

Plasma samples were analyzed for metformin using an LC/MS method validated over a linear range of

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each treatment using non-compartmental analysis: t_{max} , C_{max} , $t_{1/2}$, Ke , AUC_{0-t} and $AUC_{0-\infty}$. Bioequivalence of the two treatments was assessed by calculating the ratio of least square means as well as 90% confidence intervals for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} .

Results

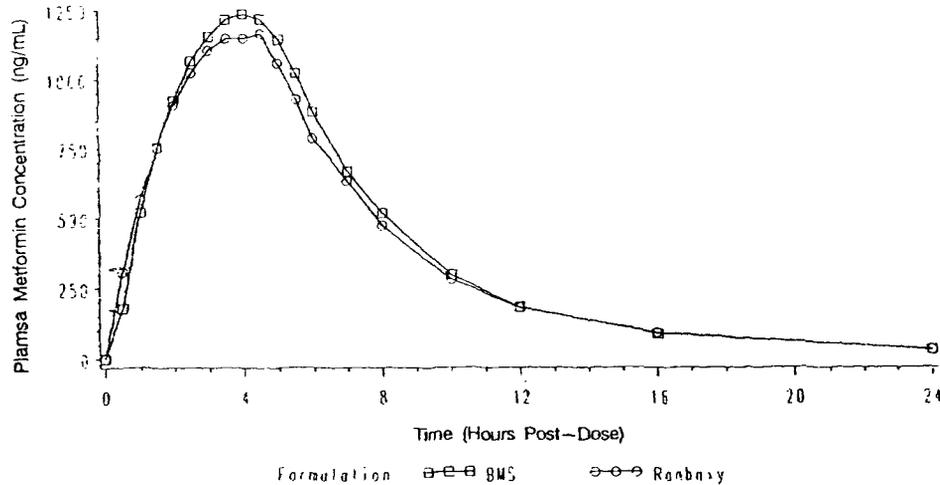


Fig. 2. Mean plasma metformin conc.-time profile following administration of single 1000 mg doses of metformin solution and Glucophage® tablets under fed conditions.

Table 2. Summary of the least squares mean ratio estimates and 90% confidence

| PK Parameter | Least Squares Mean Ratio (%) | 90% Confidence Interval |
|-----------------------|------------------------------|-------------------------|
| \bar{C}_{\max} | 91.8 | (87.4-96.5) |
| AUC _{0-last} | 96.8 | (92.9-100.9) |
| AUC _{0-∞} | 97.0 | (92.9-101.2) |

Reviewer's Comments

The study findings demonstrate that Metformin hydrochloride solution 100 mg/ml of Ranbaxy and Glucophage® 1000 mg tablets of Bristol-Myers are bioequivalent under fed conditions.

Appendix 2

DSI Inspection Report

4 Page(s) Withheld

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

| | Information | | Information |
|-----------------------------------|-----------------------|-------------------------|------------------------------|
| NDA Number | 21-591 | Proposed Brand Name | Riomet |
| OCPB Division (I, II, III) | II | Generic Name | Metformin Hydrochloride |
| Medical Division | Metabolic & Endocrine | Drug Class | Hypoglycemic Agent |
| OCPB Reviewer | Suliman AlFayoumi | Indication(s) | |
| OCPB Team Leader | Hae-young Ahn | Dosage Form | 100 mg/ml Solution |
| | | Dosing Regimen | 500 mg BID with Meals |
| Date of Submission | 1/13/03 | Route of Administration | Oral |
| Estimated Due Date of OCPB Review | 8/10/03 | Sponsor | Ranbaxy Pharmaceuticals, Inc |
| PDUFA Due Date | 9/14/03 | Priority Classification | Standard |
| Estimated Division Due Date | 8/14/03 | | |

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) - | | | | |
| <i>Healthy Volunteers-</i> | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Patients ← | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Dose proportionality - | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| Drug-drug interaction studies - | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| Subpopulation studies - | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| 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: | X | 1 | 1 |
| Bioequivalence studies - | | | | |
| | traditional design; single / multi dose: | | | |
| | replicate design; single / multi dose: | | | |
| | Food-drug interaction studies: | X | 2 | 2 |
| Dissolution: | | | | |
| (IVVC): | | | | |
| 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 | | 3 | 3 |
| Filability and QBR comments | | | | |
| | | "X" if yes | Comments | |
| | Application filable ? | X | | |
| | Comments sent to firm ? | Not needed at this time | | |
| | QBR questions (key issues to be considered) | What is the oral bioavailability of the solution formulation relative to the approved RLD (Glucophage® tablet) under fasting as well as fed conditions? | | |
| | Other comments or information not included above | | | |
| | Primary reviewer Signature and Date | | | |
| | Secondary reviewer Signature and Date | | | |

CC: NDA 21-591, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-510(weber), HFD-870(Al-Fayoumi, ahnh, Malinowski, Hunt), CDR

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-591

Submission Date: 11/14/02

Proposed Trade Name: Riomet

ORM Division: Metabolic and Endocrine
Drug Products

Generic Name: Metformin HCL Solution,
100 mg/ml

OCPB Division: DPE II

Sponsor: Ranbaxy Pharmaceuticals, Inc

Team Leader: Hae-young Ahn, P.D.

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Original NDA-
505(b)(2) application

I. Executive Summary

Glucophage® (metformin HCL) immediate release (IR) tablet is currently approved as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. The recommended starting oral dosage is 500 mg twice daily administered with meals. Dosage of Glucophage® must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose of 2550 mg in adults and 2000 mg in pediatric patients (10-16 years of age). Glucophage® IR is available as 500, 850 & 1000 mg tablet strengths.

The absolute bioavailability of metformin following oral administration of a 500 mg Glucophage® tablet under fasting conditions is 50-60%. Over 90% of an oral dose of metformin is excreted unchanged in the urine within 24 hrs following administration with an elimination half-life of 6.2 hrs. At usual clinical doses and dosing schedules, steady-state plasma concentrations of metformin are reached within 24-48 hrs and are generally less than 1 µg/ml. Food decreases the extent of (by 25%) and delays the absorption of metformin relative to administration under fasting conditions.

In the current NDA, metformin solution, 100 mg/ml is proposed as a new formulation for use in adult & pediatric patients. Three studies including two relative bioavailability studies and one food-effect study have been submitted in support of the safety and efficacy of the metformin solution formulation. No clinical data has been submitted in support of the application.

In the submitted studies, bioequivalence was demonstrated for the metformin solution and the Glucophage® tablet under fed conditions, but not under fasting conditions. Nevertheless, the PK profiles of the metformin solution and Glucophage® tablet were comparable under fasting conditions. Additionally, both low and high fat meals had a similar effect on the PK of the metformin solution.

Overall, the rate and extent of absorption of the metformin oral solution is comparable to that of Glucophage® tablets under fasting and fed conditions.

Recommendation

NDA 21-591 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/DPE II), and from the view point of OCPB, the submission is acceptable provided that a satisfactory agreement is reached on the package insert between the Agency and the sponsor. See Appendix 1 for the Agency's proposed revisions to the Clinical Pharmacology-related sections of the package insert of the metformin solution.

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II. Summary of CPB Findings

The currently approved IR Reference Listed Drug (RLD) for metformin is Glucophage® IR tablet 1000 mg (NDA 20-357). On 11/14/02, NDA 21-591 was submitted under a 505(b)(2) application seeking the same adult and pediatric indications as those of Glucophage® tablets. In this application, the sponsor submitted data from two relative bioavailability studies comparing the solution formulation with the approved tablet formulation (Glucophage®) under fasting and fed conditions as well as data from one food-effect study. No clinical safety and efficacy studies were conducted using the solution formulation.

In study 04/METFO-500/01, the relative bioavailability of the solution formulation was determined relative to Glucophage® tablet under fasting conditions in a two-way crossover study in 36 healthy adult subjects. The study demonstrated that the solution formulation was comparable but not bioequivalent to the Glucophage® tablet.

In study 05/METFO-500/01, the relative bioavailability of the solution formulation was determined under fed conditions relative to Glucophage® tablet in a two-way crossover study in 38 healthy adult subjects. The study demonstrated that the solution formulation was bioequivalent to the Glucophage® tablet under fed conditions.

In study METFO-500/02, the effect of a high fat meal as well as a low fat meal on the PK of the solution formulation were evaluated relative to that of the solution administered under fasting conditions in a three-way crossover study in 33 healthy adult subjects. The study demonstrated that albeit the solution formulation administered under fasting conditions was not bioequivalent to the metformin solution administered with either the low fat meal or the high fat meal, the deviations from the bioequivalence criteria appeared to be marginal. In addition, bioequivalence was demonstrated for the solution formulation when administered with either the low fat or the high fat meal.

Based on the three submitted studies and given that metformin is to be administered in clinical practice along with meals, the metformin solution formulation is deemed an appropriate new dosage form for use in adult & pediatric patients.

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II. Table of Contents

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III. Question-Based Review

A. General Attributes

Glucophage® (metformin HCL) IR tablet, an oral anti-hyperglycemic agent, was first approved for use in patients with type 2 diabetes in 1995. Metformin has been shown to exert its effect through decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. Glucophage® IR tablet currently is being marketed at 500, 850 and 1000 mg tablets to be administered in divided doses with meals.

The absolute bioavailability of metformin following oral administration of a 500 mg Glucophage® tablet under fasting conditions is 50-60%. Over 90% of an oral dose of metformin is excreted unchanged in the urine within 24 hrs following administration with an elimination half-life of 6.2 hrs.

B. General Biopharmaceutics

1. What is the nature of the formulation?

Table 1. Qualitative composition of the metformin solution formulation

| Ingredient | Function | Amount |
|---------------------------|----------|----------|
| Metformin Hydrochloride | API | 100.0 mg |
| Saccharin Calcium USP | | |
| Potassium Bicarbonate USP | | |
| Xylitol NF | | |
| Artificial Cherry Flavor | | |
| Hydrochloride Acid NF | | |
| Purified Water USP | | |

2. Is the metformin solution bioequivalent to the RLD (Glucophage® tablet 1000 mg) under fasting and fed conditions?

In study 04/METFO-500/01, the relative bioavailability of the solution formulation was determined relative to that of the Glucophage® tablet under fasting conditions in a two-way crossover study in 36 healthy adult subjects. The study demonstrated that the solution formulation was comparable but not bioequivalent to the Glucophage® tablet (Table 2).

Table 2. Summary of the least squares mean ratio estimates and 90% confidence intervals for bioequivalence assessment following administration of single 1000 mg doses of the metformin solution and Glucophage tablet to healthy subjects under fasting conditions.

| PK Parameter | Least Squares Mean Ratio (%) | 90% Confidence Interval |
|------------------|------------------------------|-------------------------|
| C_{max} | 81.2 | (76.3-86.4) |
| AUC_{0-last} | 80.2 | (76.0-84.8)* |
| $AUC_{0-\infty}$ | 81.2 | (76.9-85.6)* |

* Calculated by CPB reviewer.

In study 05/METFO-500/01, the relative bioavailability of the solution formulation was determined under fed conditions relative to Glucophage[®] tablet in a two-way crossover study in 38 healthy adult subjects. The study demonstrated that the solution formulation was bioequivalent to the Glucophage[®] tablet under fed conditions (Table 3).

Table 3. Summary of the least squares mean ratio estimates and 90% confidence intervals for bioequivalence assessment following administration of single 1000 mg doses of the metformin solution and Glucophage tablet to healthy subjects under fed conditions.

| PK Parameter | Least Squares Mean Ratio (%) | 90% Confidence Interval |
|------------------|------------------------------|-------------------------|
| C_{max} | 91.8 | (87.3-114.5) |
| AUC_{0-last} | 96.8 | (92.9-100.9) |
| $AUC_{0-\infty}$ | 97.0 | (92.9-101.2) |

3. Is there a food-effect on the PK of the metformin solution?

In study METFO-500/02, the effect of a high fat meal as well as a low fat meal on the PK of the solution formulation were determined relative to the solution administered under fasting conditions in a three-way crossover study in 33 healthy adult subjects. The study demonstrated that although the solution formulation administered under fasting conditions was not bioequivalent to the metformin solution administered with either the low fat meal or the high fat meal, deviations from the bioequivalence criteria appeared to be marginal (Table 4). Overall, food decreased the extent of absorption of the metformin solution by 12-16% regardless of the fat content of the meal.

Table 4. Summary of the least squares mean ratio estimates and 90% confidence intervals for bioequivalence assessment following administration of single 1000 mg doses of the metformin solution to healthy subjects under fasting conditions (A), with a low fat meal (B) or with a high fat meal (C).

| PK Parameter | Least Squares Mean Ratio (%) | 90% Confidence Interval |
|------------------|------------------------------|-------------------------|
| A vs B | | |
| C_{max} | 94.6 | (84.0-106.5)* |
| AUC_{0-last} | 116.0 | (103.1-130.0)* |
| $AUC_{0-\infty}$ | 115.6 | (103.6-128.9)* |
| A vs C | | |
| C_{max} | 89.4 | (79.4-100.6)* |
| AUC_{0-last} | 112.6 | (100.1-126.6)* |
| $AUC_{0-\infty}$ | 112.6 | (100.9-125.6)* |
| B vs C | | |
| C_{max} | 105.8 | (94.0-119.2)* |
| AUC_{0-last} | 103.0 | (91.6-115.8)* |
| $AUC_{0-\infty}$ | 102.7 | (92.0-114.6)* |

* Calculated by CPB reviewer.

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Appendix 1

Proposed Package Insert

18 Draft Labeling Page(s) Withheld

Appendix 2

Individual Study Reviews

NDA: 21-591/ Study 04/METFO-500/01

Type of Submission: Comparative Bioavailability Study Under Fasting Conditions

Study 04/METFO-500/01 is entitled,

“A RANDOMIZED, TWO-TREATMENT, TWO-PERIOD, TWO-SEQUENCE, CROSSOVER BIOAVAILABILITY STUDY ON METFORMIN FORMULATIONS COMPARING METFORMIN HYDROCHLORIDE LIQUID 500 mg/5 ml OF RANBAXY LABORATORIES WITH GLUCOPHAGE 1000 mg TABLETS OF BRISTOL-MYERS SQUIBB IN HEALTHY, ADULT MALE AND FEMALE VOLUNTEERS UNDER FASTING CONDITIONS, FOLLOWING A 1000 mg DOSE”.

Objectives

- To compare the bioavailability of metformin hydrochloride solution 100 mg/ml of Ranbaxy with Glucophage® 1000 mg tablets of Bristol-Myers following administration of a single 1000 mg dose to healthy adult subjects under fasting conditions.

Study Design

Healthy adult male and female subjects (n = 36, Age 30.9 ± 7.4 yrs, Wt 67.3 ± 9.3 kg) received single 1000 mg doses of either metformin HCl solution 100mg/ml (lot # AA192) or a Glucophage® tablet (1000 mg; lot # MHM19) under fasting conditions during each period. The study was conducted in a randomized, single dose, two-treatment, two-period, crossover fashion. Treatment periods were separated by a 7-day washout period. In each treatment period, blood samples were drawn for determination of metformin at 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16 and 24 hrs post-dose.

Analytical Assay

Plasma samples were analyzed for metformin using an LC/MS method validated over a linear range of

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each treatment using non-compartmental analysis: t_{max} , C_{max} , $t_{1/2}$, K_e , AUC_{0-t} and $AUC_{0-\infty}$. Bioequivalence of the two treatments was assessed by calculating the ratio of least square means as well as 90% confidence intervals for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} .

Results

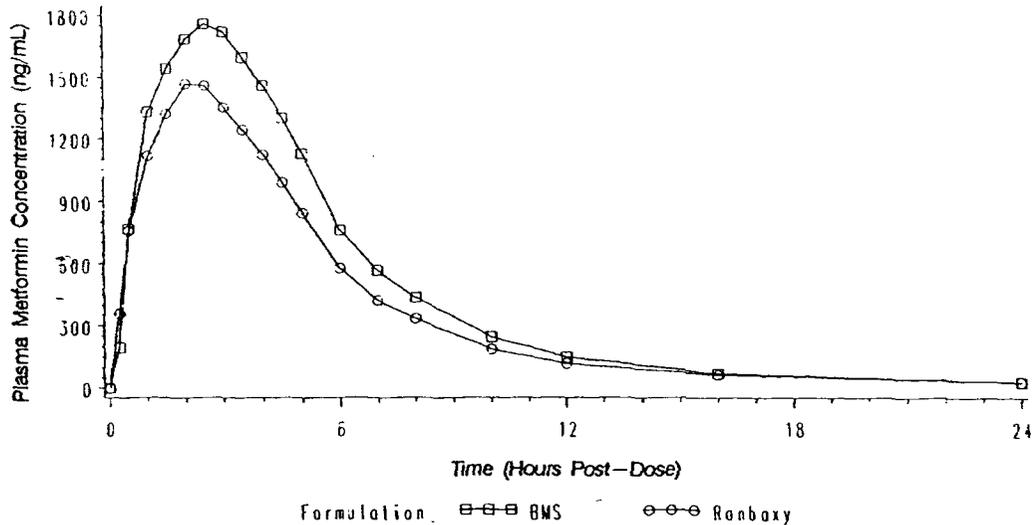


Fig. 1. Mean plasma metformin conc.-time profile following administration of single 1000 mg doses of metformin solution and Glucophage tablets under fasting conditions.

Table 1. Summary of the least squares mean ratio estimates and 90% confidence

| PK Parameter | Least Squares Mean Ratio (%) | 90% Confidence Interval |
|------------------|------------------------------|-------------------------|
| C_{max} | 81.2 | (76.3-86.4) |
| AUC_{0-last} | 80.2 | (84.8-76.0)* |
| $AUC_{0-\infty}$ | 81.2 | (76.9-85.6)* |

* Calculated by CPB reviewer

Reviewer's Comments

- The study findings indicate that Metformin hydrochloride solution 100 mg/ml of Ranbaxy and Glucophage® 1000 mg tablets of Bristol-Myers are not bioequivalent under fasting conditions.
- Contrary to conventional wisdom, the Glucophage® tablet formulation exhibited a rate and extent of absorption that were on average 20% greater than those of the metformin solution. The sponsor did not attempt to provide a plausible explanation

for this observation. However, this might be related to the limited absorption window within the small intestines, which has been reported for metformin.

NDA: 21-591/ Study 05/METFO-500/01

Type of Submission: Comparative Bioavailability Study Under Fed Conditions

Study 05/METFO-500/01 is entitled,

“A RANDOMIZED, TWO-TREATMENT, TWO-PERIOD, TWO-SEQUENCE, SINGLE DOSE, CROSSOVER BIOAVAILABILITY STUDY ON METFORMIN FORMULATIONS COMPARING METFORMIN HYDROCHLORIDE LIQUID 500 mg/5 ml OF RANBAXY LABORATORIES WITH GLUCOPHAGE 1000 mg TABLETS OF BRISTOL-MYERS SQUIBB IN HEALTHY, ADULT MALE AND FEMALE VOLUNTEERS UNDER FED CONDITIONS, FOLLOWING A 1000 mg DOSE”.

Objectives

- To compare the bioavailability of metformin hydrochloride solution 100 mg/ml of Ranbaxy with Glucophage® 1000 mg tablets of Bristol-Myers following administration of a single 1000 mg dose to healthy adult subjects under fed conditions.

Study Design

Healthy adult male and female subjects (n = 38, Age 31.3 ± 6.3 yrs, Wt 69.5 ± 8.5 kg) received single 1000 mg doses of either metformin HCl solution 100mg/ml (lot # AA192) or a Glucophage® tablet (1000 mg; lot # MHM19) under fed conditions during each period. The study was conducted in a randomized, single dose, two-treatment, two-period, crossover fashion. Treatment periods were separated by a 7-day washout period. In each treatment period, blood samples were drawn for determination of metformin at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5.5, 5, 6, 7, 8, 10, 12, 16 and 24 hrs post-dose.

Analytical Assay

Plasma samples were analyzed for metformin using an LC/MS method validated over a linear range of —

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each treatment using non-compartmental analysis: t_{max} , C_{max} , $t_{1/2}$, Ke , AUC_{0-t} and $AUC_{0-\infty}$. Bioequivalence of the two treatments was assessed by calculating the ratio of least square means as well as 90% confidence intervals for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} .

Results

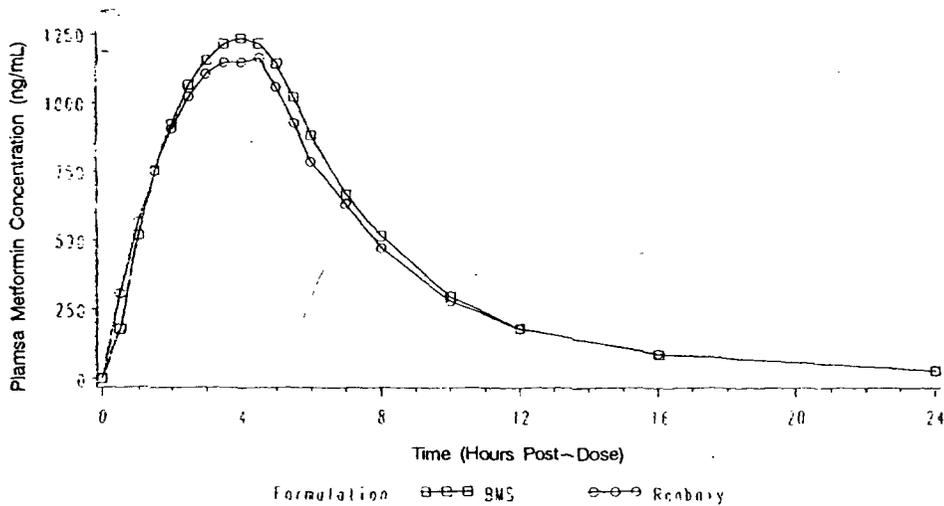


Fig. 2. Mean plasma metformin conc.-time profile following administration of single 1000 mg doses of metformin solution and Glucophage® tablets under fed conditions.

Table 2. Summary of the least squares mean ratio estimates and 90% confidence

| PK Parameter | Least Squares Mean Ratio (%) | 90% Confidence Interval |
|------------------|------------------------------|-------------------------|
| C_{max} | 91.8 | (87.4-96.5) |
| AUC_{0-last} | 96.8 | (92.9-100.9) |
| $AUC_{0-\infty}$ | 97.0 | (92.9-101.2) |

Reviewer's Comments

The study findings demonstrate that Metformin hydrochloride solution 100 mg/ml of Ranbaxy and Glucophage® 1000 mg tablets of Bristol-Myers are bioequivalent under fed con

NDA: 21-591/ Study METFO-500/02

Type of Submission: Food-Effect Study

Study METFO-500/02 is entitled,

"A RANDOMIZED, THREE-TREATMENT, THREE-PERIOD, SIX-SEQUENCE, SINGLE DOSE, CROSSOVER PHARMACOKINETIC STUDY ON METFORMIN HYDROCHLORIDE SOLUTION 100 mg/ml OF RANBAXY LABORATORIES COMPARING THE PHARMACOKINETIC PROFILE METFORMIN UNDER FASTING CONDITION, AFTER A LOW FAT MEAL AND AFTER A HIGH FAT MEAL IN HEALTHY ADULT, HUMAN SUBJECTS".

Objectives

- To compare the single dose oral bioavailability of metformin hydrochloride solution 100 mg/ml of Ranbaxy in healthy adult subjects under various fed conditions.

Study Design

Healthy adult male and female subjects (n = 33, Age 19-39 yrs, Wt 42-75 kg) received single 1000 mg doses of metformin HCL solution 100 mg/ml were administered either under fasting conditions (treatment A) or with a low fat breakfast (500-700 Kcal; treatment B) or with a high fast breakfast (consistent with Agency recommended high fat meal; treatment C). The study was conducted in a randomized, single dose, three-treatment, three-period, crossover fashion. Successive treatment periods were separated by a 7-day washout period. In each treatment period, blood samples were drawn for determination of metformin at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16 and 24 hrs post-dose.

Analytical Assay

Plasma samples were analyzed for metformin using an HPLC method validated over a linear range of

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each treatment using non-compartmental analysis: t_{max} , C_{max} , $t_{1/2}$, Ke , AUC_{0-t} and $AUC_{0-\infty}$. Bioequivalence of the metformin solution under fed and fasted conditions was assessed by calculating the ratio of least square means as well as 90% confidence intervals for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} .

Results

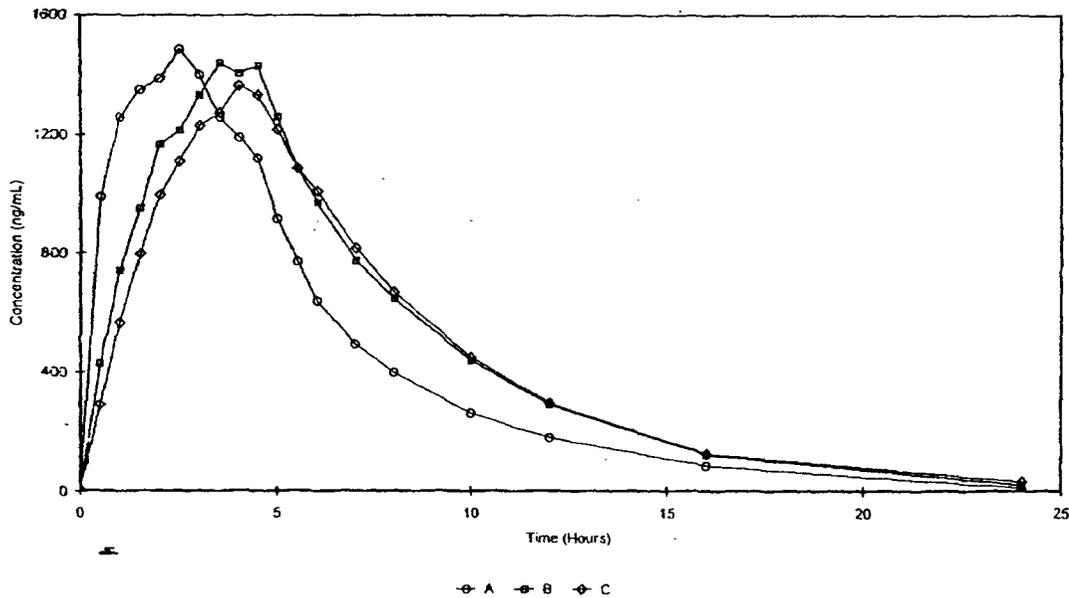


Fig. 1. Mean plasma metformin conc.-time profile following administration of single 1000 mg doses of metformin solution under a) fasting conditions, b) a low fat meal or c) a high fat meal.

Table 3. Summary of the least squares mean ratio estimates and 90% confidence intervals

| PK Parameter | Least Squares Mean Ratio (%) | 90% Confidence Interval |
|------------------|------------------------------|-------------------------|
| A vs B | | |
| C_{max} | 94.6 | (84.0-106.5)* |
| AUC_{0-last} | 116.0 | (103.1-130.3)* |
| $AUC_{0-\infty}$ | 115.6 | (103.6-128.9)* |
| A vs C | | |
| C_{max} | 89.4 | (79.4-100.6)* |
| AUC_{0-last} | 112.6 | (100.1-126.6)* |
| $AUC_{0-\infty}$ | 112.6 | (100.9-125.6)* |
| B vs C | | |
| C_{max} | 105.8 | (94.0-119.2)* |
| AUC_{0-last} | 103.0 | (91.6-115.8)* |
| $AUC_{0-\infty}$ | 102.7 | (92.0-114.6)* |

* Calculated by CPB Reviewer

Reviewer's Comments

- Food decreased the extent of absorption of the metformin solution by 12-16% regardless of the fat content of the meal.
- Administration of the metformin solution with either a low fat meal or a high fat meal resulted in a similar food-effect on the rate and extent of absorption of the metformin solution.
- Administration of the metformin solution under fasting conditions and along with a high fat meal did not meet the strict bioequivalence criteria. However, deviations from the set (80-125)% bioequivalence goalposts for the 90% confidence interval appeared to be marginal.

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/s/

Suliman Alfayoumi
8/19/03 10:10:50 AM
BIOPHARMACEUTICS

Hae-Young Ahn
8/19/03 03:46:11 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

| NEW DRUG APPLICATION FILING AND REVIEW FORM | | | | |
|---|-----------------------------|--------------------------|----------------------------|----------------------------|
| General Information About the Submission | | | | |
| Information | | | Information | |
| NDA Number: | 21-591 | Brand Name: | | |
| OCBP Division (I, II, III): | DPE 2 | Generic Name: | Metformin HCl | |
| Clinical Division: | DMEDP | Drug Class: | Biguanide | |
| CPB Reviewer: | Steven B. Johnson, Pharm.D. | Indication(s): | Type 2 Diabetes | |
| CPB Team Leader: | Hae-Young Ahn, Ph.D. | Dosage Form: | Solution, 100 mg/mL | |
| Submission Date: | 14-NOV-2002 | Dosing Regimen: | BID or TID | |
| CPB Review Due Date: | 14-JUL-2003 | Route of Administration: | Oral | |
| Division Due Date: | 14-AUG-2003 | Sponsor: | Ranbaxy Laboratories, LTD. | |
| PDUFA Date: | 12-SEP-2003 | Priority Classification: | Standard | |
| Clinical Pharmacology and Biopharmaceutics Information | | | | |
| Information Type | "X" if included at filing | # of Studies Submitted | # of Studies Reviewed | Critical Comments (if any) |
| Table of Contents | X | | | |
| Tabular Listing of All Human Studies | X | | | |
| Human PK Summary | X | | | |
| Labeling | X | | | |
| Reference Bio- & Analytical Methods | X | | | |
| I. Clinical Pharmacology | | | | |
| Mass Balance: | | | | |
| Isozyme Characterization: | | | | |
| Blood/Plasma Ratio: | | | | |
| Plasma Protein Binding: | | | | |
| Pharmacokinetics (PK) – | | | | |
| – Healthy Volunteers – | | | | |
| Single-Dose: | | | | |
| Multiple-Dose: | | | | |
| – Patients – | | | | |
| Single-Dose: | | | | |
| Multiple-Dose: | | | | |
| Dose Proportionality – | | | | |
| Single-Dose: | | | | |
| Multiple-Dose: | | | | |
| Drug-Drug Interaction Studies – | | | | |
| In-vivo Effects ON Primary Drug: | | | | |
| In-vivo Effects OF Primary Drug: | | | | |
| In-vitro Studies: | | | | |
| Subpopulation Studies – | | | | |
| Ethnicity: | | | | |
| Sex: | | | | |
| Pediatrics: | | | | |
| Geriatrics: | | | | |
| Renal Impairment: | | | | |
| Hepatic Impairment: | | | | |
| Pharmacodynamics (PD) – | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| PK / PD – | | | | |
| Phase 1: | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| Population Analyses – | | | | |
| Rich Data Set: | | | | |
| Sparse Data Set: | | | | |
| II. Biopharmaceutics | | | | |
| Absolute Bioavailability: | | | | |
| Relative Bioavailability – | | | | |
| Solution as Reference | | | | |
| Other Formulation as Reference: | | | | |
| Bioequivalence Studies – | | | | |
| – Traditional Design – | | | | |
| Single-Dose: | X | 2 | | |
| Multiple-Dose: | | | | |

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| | | | |
|--|---|---|--|
| - Replicate Design - | | | |
| Single-Dose: | | | |
| Multiple-Dose: | | | |
| Food-Drug Interaction Studies: | X | 1 | |
| Dissolution: | | | |
| In-vitro/In-vivo Correlation: | | | |
| BCS Based Biowaiver Request: | | | |
| BCS Classification Information: | | | |
| III. Other CPB Studies | | | |
| Genotype / Phenotype Studies: | | | |
| Chronopharmacokinetics: | | | |
| Pediatric Development Plan: | | | |
| Literature References: | X | | |
| TOTAL OF STUDIES | | 3 | |

| Filability and QBR Comments | |
|---|--|
| | "X" if Yes |
| Is the Application Filable? | X |
| Comments to the Firm: | NONE |
| QBR Questions (key issues to be considered) | Is the metformin HCl solution bioequivalent to metformin HCl tablets under fed and fasting conditions? |
| Other Comments or Information not Included Above | <ul style="list-style-type: none"> • Labeling for this product should state that _____ • Also, _____ |
| Additional | <p>Since this metformin HCl oral solution will serve as the reference listed product and no clinical studies will be conducted for this product's approval, a DSI audit should be requested as-soon-as possible.</p> <p>NOTE: A formal letter, signed by Dr. Orloff, will need to be sent to DSI requesting that an audit be conducted - this is required for all foreign audits.</p> <p>Clinical Study #013396, Protocol # 05/METFO-500/01</p> |
| Primary Reviewer Signature: | Steven B. Johnson, Pharm.D. Date: 2-JAN-03 |
| Secondary Reviewer Signature: | Hae-Young Ahn, Ph.D. Date: |

| - Line Listing of Studies Included in this Application - | |
|---|--|
| Study # | Study Title |
| METFO-500/02 | A randomized, three-treatment, three-period, six-sequence, single-dose, crossover pharmacokinetic study on metformin hydrochloride solution 100 mg/mL of Ranbaxy Laboratories comparing the pharmacokinetic profile of metformin under fasting conditions, after a low fat meal, and after a high fat meal in healthy, adult, human subjects. |
| 013395 | A randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioavailability study on metformin formulations comparing metformin hydrochloride liquid 500 mg/5 mL of Ranbaxy Laboratories with GLUCOPHAGE of Bristol-Myers Squibb in healthy, adult, male and female volunteers under fasting conditions following a 1000 mg dose. |
| 013396 | A randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioavailability study on metformin formulations comparing metformin hydrochloride liquid 500 mg/5 mL of Ranbaxy Laboratories with GLUCOPHAGE 1000 mg tablets of Bristol-Myers Squibb in healthy, adult, male and female volunteers under fed conditions, following a 1000 mg dose. |

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this page is the manifestation of the electronic signature.**

/s/

Steve Johnson
1/6/03 01:37:05 PM
BIOPHARMACEUTICS

Hae-Young Ahn
1/14/03 04:07:10 PM
BIOPHARMACEUTICS