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*APPLICATION NUMBER:*

**21-591**

**PHARMACOLOGY REVIEW(S)**

**PHARMACOLOGY/TOXICOLOGY COVER SHEET**

NDA number: 21-591

Review number: 001

Sequence number/date/type of submission: 000/Nov. 15, 2002/Commercial

Information to sponsor: Yes ( ) No (x)

Sponsor: Ranbaxy Laboratories Ltd., Gurgaon, India

Agent: Ranbaxy Pharmaceuticals Inc., Princeton, NJ. Mr. Abha Pant (609)720-5666

Manufacturer for drug substance: Metformin HCl (Glucophage Tablet 1000 mg) will be manufactured by \_\_\_\_\_ based on DMF No. \_\_\_\_\_ of \_\_\_\_\_

\_\_\_\_\_ and protocols that were described under NDA20-357 (Bristol-Myers Squibb Company, USA). The US agent is responsible for packaging at 34 West Fulton Street, Gloversville, NY.

Reviewer name: Herman Rhee, Ph.D.

Division name: DMEDP

HFD #: 510

Review completion date: Jan. 30, 2003

Drug:

Trade name: Riomet™ (Metformin HCl) Oral solution, 100 mg/ml, or  
\_\_\_\_\_ (Metformin HCl) Oral solution, 100 mg/ml, or  
\_\_\_\_\_ (Metformin HCl) Oral solution, 100 mg/ml

Generic name (list alphabetically): Metformin HCl

Cas registry number: 657-24-9 (metformin); 1115-70-4 (metformin hydrochloride)

Chemical name: N, N-dimethylimidodicarbonimidic diamide hydrochloride

Molecular formula/molecular weight: C<sub>4</sub>H<sub>11</sub>N<sub>5</sub>.HCl / Metformin(165.6)

Chemical Structure: (CH<sub>3</sub>)<sub>2</sub>N-C(NH)-NH-C(NH)-NH<sub>2</sub> . HCl

Relevant INDs/NDAs/DMFs: IND63,783/NDA20-357/DMF \_\_\_\_\_

Drug class: Biguanides

Indication: Antidiabetic

Clinical formulation and components: Metformin HCl Oral Solution

Metformin HCl	100.0 mg
Saccharin Calcium USP	_____
Potassium Bicarbonate USP	_____
Xylitol NF	_____
Artificial Cherry Flavor #349	_____
Hydrochloric Acid NF	_____
Purified Water USP	_____

Route of administration: Oral

Proposed use: As an adjunct to diet and exercise to improve glycemic control in patients with type II diabetes

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

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## *Executive Summary*

### I. Recommendations

✓ A. Recommendation on Approvability:  
Approval.

B. Recommendation for Nonclinical Studies:

There are no new components in the new formulation of Riomet™ Solution. Thus, the new NDA#21-591 application of Riomet™ Solution is approvable based on previous NDA#20-357, although there are no new preclinical data.

✓ C. -Recommendations on Labeling:

It appears that the sponsor's labeling instruction including the warning of lactic acidosis is appropriate.

### II. Summary of Nonclinical Findings

✓ A. Brief Overview of Nonclinical Findings:

There are no new nonclinical findings except limited bioequivalence data that were obtained from comparative pharmacokinetic studies on Metformin HCl Oral Solution (Riomet™) and metformin tablets. In 36 healthy nondiabetic adult subjects, several pharmacokinetic parameters were determined after single oral doses of 1000 mg Riomet™ solution and metformin tablets. The results show that C<sub>max</sub>, AUC and t<sub>max</sub> were comparable between the two drugs. Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which were confirmed by the comparative pharmacokinetic studies of metformin tablets and of Riomet™ solution. It appears that there were no significant differences in pharmacokinetic parameters between Metformin HCl Oral Solution (Riomet™) and metformin tablets.

B. Pharmacologic Activity:

It appears that Metformin HCl Oral Solution (Riomet™) and metformin tablets had comparable effects in reduction of fasting plasma glucose, HbA<sub>1c</sub>, and blood insulin levels.

C. Nonclinical Safety Issues Relevant to Clinical Use:

One of the metabolic complications of metformin is lactic acidosis, which is not an exception with the use of Metformin HCl Oral Solution (Riomet™). The risk of lactic acidosis may increase with renal dysfunction, excessive alcohol intake, and in elderly patients.

III. ~~Administrative~~

A. Reviewer signature: Herman Rhee, Ph.D.

B. Supervisor signature: Concurrence - \_\_\_\_\_

Non-Concurrence - \_\_\_\_\_

(See memo attached)

C. cc: list: HFD-510/ElhageJ/RheeH

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## I. PHARMACOLOGY SUMMARY:

There are no new preclinical pharmacology and toxicology data in this NDA because the sponsor will rely on the nonclinical pharmacology/toxicology data and clinical safety/efficacy data approved under NDA20-357. However, the sponsor performed a few clinical bioavailability and bioequivalence studies as summarized below.

The sponsor evaluated human bioavailability of Metformin HCl Oral Solution (Riomet™) in comparison to the commercially available metformin tablets under fasting and fed condition. In 36 healthy nondiabetic adult subjects, several pharmacokinetic parameters were determined after a single oral dose of 1000 mg Riomet™ solution or a comparable dose of metformin tablets. The results show that PK data such as C<sub>max</sub>, AUC, and t<sub>max</sub> were comparable between the two drug products as summarized below. It appears that they behaved comparably in fed state as shown by the percentage of ratios of the pharmacokinetic parameters.

Study	Fasting State			Fed State		
	C <sub>max</sub> (ng/ml)	AUC <sub>0-∞</sub> (ng.h/ml)	T <sub>max</sub> (hr)	C <sub>max</sub> (ng/ml)	AUC <sub>0-∞</sub> (ng.h/ml)	T <sub>max</sub> (hr)
Riomet™	1540	9070	2.2	1235	8950	4.1
Metformin	1885	11100	2.5	1361	9308	3.7
R/M ratio(%)	83	83	-	93	98	-

\*R and M indicate Riomet™ Solution and Metformin Tablets, respectively.

The sponsor also compared the effect of a high fat and high calorie meal on the bioavailability of the two drugs in healthy volunteers. Single oral doses of 1000 mg of Riomet™ solution or metformin tablets were given to 33 healthy fasting subjects for the determination of pharmacokinetic parameters, which are summarized below. It appears that a low fat/low calorie meal or a high fat/high calorie meal did not significantly affect C<sub>max</sub>, AUC or t<sub>max</sub> in fasting healthy subjects, which was demonstrated in the ratios of the two products as shown below.

Effects of Low Fat/Low Calorie and High Fat/High Calorie Meals on Pharmacokinetic Data of Metformin Tablets and Riomet™ Solution in 33 Healthy Fasting Subjects*			
Parameter	Cmax (ng/ml)	AUC <sub>0-∞</sub> (ng.h/ml)	Tmax (hr)
Fasting State(F)	1642	9983	2.5
Low fat/low calorie(L)	1526	11542	3.9
High fat/high calorie mean (H)	1433	11185	3.9
L/F (%)	99.3	120.9	-
H/F (%)	92.7	116.7	-
L/H (%)	110.0	105.8	-

\*F, L, and H indicate fasting, low fat/low calorie, and high fat/high calorie meals, respectively.

Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance. These findings were confirmed by comparative pharmacokinetic studies of metformin tablets (Glucophage) and Riomet™ solution. In patients with decreased renal function, the plasma and blood T<sub>1/2</sub> of metformin was prolonged and the renal clearance was reduced in proportion to the decrease in creatinine clearance. No pharmacokinetic studies of Riomet™ solution were conducted in patients with hepatic insufficiency and in pediatric populations. It appears that there were no significant differences in tested pharmacokinetic parameters between sexes, and whites and Hispanic populations. The sponsor also performed some clinical studies that deal with the determination of FPG, HbA<sub>1c</sub>, body weight, and serum lipids to compare Riomet™ Solution and commercial antidiabetic drugs such as insulin and glyburide.

## II. Proposed Labeling:

### Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4X the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. However, there was an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

2 Draft Labeling Page(s) Withheld

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/s/

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Herman Rhee  
5/23/03 01:59:56 PM  
PHARMACOLOGIST

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5/23/03 02:09:54 PM  
PHARMACOLOGIST