

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-591**

**ADMINISTRATIVE DOCUMENTS AND  
CORRESPONDENCE**

**RANBAXY**  
LABORATORIES LIMITED

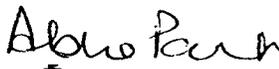
SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001  
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

**ITEM 14: PATENT CERTIFICATION**

This New Drug Application refers to the listed drug, Glucophage<sup>®</sup> (Metformin Hydrochloride) Tablets 1000 mg, which is manufactured by Bristol-Myers Squibb, the holder of the approved application, NDA 20-357, and which is listed in the 2002 Approved Drug Products with Therapeutic equivalence Evaluation, 22<sup>nd</sup> Edition.

**Paragraph II Patent Certification**

The applicant certifies that in the opinion and to the best of its knowledge, there are no un-expired patent claims for the above identified drug product that have been submitted to the FDA.



Abha Pant  
U.S. Agent for Ranbaxy Laboratories Limited

EXCLUSIVITY SUMMARY for NDA # 21-591 SUPPL

Trade Name: Riomet™ Oral Soln. Generic Name: Metformin HCl

Applicant Name: Ranbaxy Labs

HFD-510

Approval Date: September 11, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

- a) Is it an original NDA? YES/\_/ NO /\_/\_/
- b) Is it an effectiveness supplement? YES /\_/\_/ NO /\_/

If yes, what type(SE1, SE2, etc.)?

- c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /\_/\_/ NO //

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

- d) Did the applicant request exclusivity?

YES /\_/\_/ NO //

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /  / NO /  /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /  / NO /  /

If yes, NDA # \_\_\_\_\_ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /  / NO /  /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**  
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration?

Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /\_✓/ NO /\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA 20-357 Glucophage (metformin HCL) Tablets

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_/ NO /\_✓\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_/ NO /✓/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

1. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_/ NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/ NO / /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO / /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

2. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and;

2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- (a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO / /
Investigation #2	YES /___/	NO /_/
Investigation #3	YES /___/	NO /_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____	Study # _____
NDA # _____	Study # _____
NDA # _____	Study # _____

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_/
Investigation #2	YES /___/	NO /_/
Investigation #3	YES /___/	NO /_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____	Study # _____
NDA # _____	Study # _____
NDA # _____	Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #\_\_, Study #

Investigation #\_\_, Study #

Investigation #\_\_, Study #

3. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
!  
YES / / ! NO / \_\_/ Explain:  
!

Investigation #2 ! !  
!  
YES /\_/ ! NO / \_/ Explain:  
!  
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!	
YES /___/ Explain _____	!	NO /_/ Explain _____
_____	!	_____
_____	!	_____
	!	
Investigation #2	!	
YES /___/ Explain _____	!	NO /_/ Explain _____
_____	!	_____
_____	!	_____
	!	

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/                      NO / /

If yes, explain: \_\_\_\_\_

Jena Weber  
 Signature of Preparer  
 Title: PM

Date: 9/10/03

Signature of Office or Division Director

Date

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/s/

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Jena Weber  
9/12/03 08:49:26 AM

**RANBAXY**  
PHARMACEUTICALS INC.

July 8, 2003

Center for Drug Evaluation and Research  
Food and Drug Administration  
Central Document Room  
12229 Wilkins Avenue  
Rockville, Maryland 20852

**DEBARMENT CERTIFICATION**

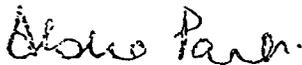
Reference: NDA 21-591  
Metformin Hydrochloride Oral Solution 100 mg/mL

Dear Sir/Madam:

In accordance with the requirement of section 306(k) of the Federal Food, Drug, and Cosmetic Act, I, the undersigned, hereby certify that Ranbaxy Laboratories Ltd. did not use any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this NDA and the studies listed in Item 6, nor will Ranbaxy Laboratories use any such person in connection with this NDA.

Furthermore, I, the undersigned, certifies that, no employee of an affiliated company used by Ranbaxy who would have been among the employees overseeing work on data for the development or submission of this NDA, has been convicted within the last five years for acts described in subsection (a) and/or (b) of section 306.

Sincerely,



Abha Pant  
U.S. Agent for Ranbaxy Laboratories Limited

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

**PROJECT MANAGER LABELING REVIEW**

**Application Number:** 21-591

**Name of Drug:** Riomet® (metformin HCl Oral Solution) 500 mg/5 mL

**Sponsor:** Ranbaxy Labs, Inc.

**Material Reviewed:** Draft package insert, carton and container labels.

**Submission Date:** November 13, 2002      **Receipt Date:** November 14, 2002

**Background and Summary:** Metformin HCl Oral Solution as monotherapy, is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. It is also indicated in patients 10 years of age and older. Metformin HCl Oral Solution may be used concomitantly with a sulfonylurea or insulin to improve glycemic control in adults (17 years of age and older).

**Review:** Metformin tablets were first approved for the treatment of type 2 diabetes mellitus on March 3, 1995 (NDA 20-357), under the tradename, "Glucophage." This NDA submission from Ranbaxy specifies that the oral solution was developed for patients who find it difficult to swallow tablets.

**Container Labels:**

500 mg/5 mL; NDC 63304-206-01 (4 oz./118 mL)

500 mg/5 mL; NDC 63304-206-02 (16 oz./473 mL)

**These are acceptable.**

**Carton:**

500 mg/5 mL; NDC 63304-206-01 (4 oz./118 mL)

500 mg/5 mL; NDC 63304-206-02 (16oz./473 mL)

**These are acceptable.**

**Package Insert:** Acceptable; all recommended changes from the Agency have been implemented. —

**Conclusion:** Issue approval (AP) letter and request FPL for carton and container packages.

**Addendum to NDA approval:** This application was approved on September 11, 2003. Ranbaxy has

APPEARS THIS WAY  
ON ORIGINAL



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/s/

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Jena Weber  
9/12/03 09:18:54 AM  
CSO

Division of Metabolic and Endocrine Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: 21-591

Name of Drug: Riomet (metformin HCl oral solution) 100 mg/mL

Sponsor: Ranbaxy

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Paper

Submission Date: November 13, 2002.

Receipt Date: November 14, 2002.

Filing Date: January 13, 2003.

User-fee Goal Date: September 14, 2002.

Proposed Indication:

Review

PART I: OVERALL FORMATTING<sup>a,d,e</sup>

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	✓		1.1
2. Form FDA 356h (original signature)	✓		1.1
a. Establishment information  (facilities ready for inspection?)	✓		1.1
b. Reference to DMF(s) & Other Applications	✓		1.1

3. User Fee FDA Form 3397	✓	1.1
4. Patent information & certification		
5. Debarment certification (Note: Must have a definitive statement)	✓	1.1
6. Field Copy Certification	✓	1.1
7. Financial Disclosure	✓	1.1
8. Comprehensive Index	✓	1.1
9. Pagination	✓	1.1
10. Summary Volume	✓	1.1
11. Review Volumes	✓	1.1
12. Labeling (PI, container, & carton labels)	✓	1.1
a. unannotated PI	✓	1.1
b. annotated PI	✓	1.1
c. immediate container	✓	1.1
d. carton	✓	1.1
e. patient package insert (PPI)		N/A
f. foreign labeling (English translation)	✓	1.1
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)		✓
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)		✓

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY<sup>b,d,e</sup>

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	✓		1.1
2. Foreign Marketing History	✓		1.1
3. Summary of Each Technical Section	✓		1.1 -
a. Chemistry, Manufacturing, & Controls (CMC)	✓		1.2 - 1.4
b. Nonclinical Pharmacology/Toxicology	✓		1.5
c. Human Pharmacokinetic & Bioavailability	✓		1.6 - 1.21
d. Microbiology			N/A
e. Clinical Data & Results of Statistical Analysis			N/A
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	✓		1.1
5. Summary of Safety			N/A
6. Summary of Efficacy			N/A

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS<sup>c,d,e</sup>

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	✓		1.1 (p.009)

2. Controlled Clinical Studies		✓	3 Biopharm studies performed.
a. Table of all studies	✓		
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	✓		1.1 (no CLN & STT submitted to NDA)
c. Optional overall summary & evaluation of data from controlled clinical studies		✓	
3. Integrated Summary of Efficacy (ISE)		✓	
4. Integrated Summary of Safety (ISS)		✓	
5. Drug Abuse & Overdosage Information		✓	
6. Discussion of Benefits & Risks of the Drug	✓		1.1
7. Gender/Race/Age Safety & Efficacy Analysis of Studies	✓		1.1 Gender & Age

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS<sup>d,e</sup>

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		✓	
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)		✓	
a. Proposed unannotated labeling in	✓		

MS WORD			1.1
b. Stability data in SAS data set format (only if paper submission)		✓	
c. Efficacy data in SAS data set format (only if paper submission)		✓	
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)	✓		
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		✓	
3. Exclusivity Statement (optional)			N/A

Y=Yes (Present), N=No (Absent)

**Conclusions**

**/S/**  
Name  
Regulatory Project Manager

**ADMINISTRATIVE REVIEW**

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/s/

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Jena Weber  
9/12/03 08:53:10 AM  
CSO

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-591	Efficacy Supplement: N/A	Supplement Number: N/A
Drug: Riomet (metformin HCl oral soln) 100 mg/mL		Applicant: Ranbaxy Labs
RPM: J. Weber	HFD-510	Phone # 76422
Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)		Reference Listed Drug: NDA 20-357 Glucophage (metformin HCl)
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		NN
❖ User Fee Goal Dates		September 14, 2003.
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input checked="" type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		NN
• OC clearance for approval		NN
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input type="checkbox"/> Verified 355(b)(2)
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input checked="" type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified
❖ Exclusivity Summary (approvals only)		<input checked="" type="checkbox"/>
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		<input checked="" type="checkbox"/>

General Information	
❖ Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	NO
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	✓
• Original applicant-proposed labeling	✓
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	✓
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	
• Reviews	✓
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NO
• Documentation of discussions and/or agreements relating to post-marketing commitments	NO
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Division Director 9/10/03
❖ Clinical review(s) (indicate date for each review)	9/8/03 – for Debarment & financial disclosure only.
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NN
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	NN
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	NO
❖ Statistical review(s) (indicate date for each review)	NN
❖ Biopharmaceutical review(s) (indicate date for each review)	8/19/03
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NN
• Bioequivalence studies	8/19/03
CMC Information	
❖ CMC review(s) (indicate date for each review)	9/8/03
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	9/8/03
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	9/8/03
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	NN
❖ Facilities inspection (provide EER report)	Date completed: 6/3/03 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested
Nonclinical Pharmacology Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	5/23/03
❖ Nonclinical inspection review summary	NN
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NN
❖ CAC/ECAC report	NN

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/s/  
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TIME USE 05'59  
PAGES SENT 22  
RESULT OK

### TELEFAX

TO: Ranbaxy Labs

ATTENTION: MIKE YEFIMENKO

REFERENCE: NDA 21-591  
AP!

FAX#: 609-514-9797

PHONE#: " 720-5617

FROM: Jena M. Weber, Project Manager, 151  
Food & Drug Administration  
Division of Metabolic & Endocrine Drug Products, HFD-510  
5600 Fishers Lane, Rockville, MD 20857-1706

Fax: 301-443-9282 Phone: 301-827-6422

DATE: 9/11/03

PAGES: 21

LETTER + CBL

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

DATE: September 8, 2003

FROM: David G. Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-591  
Riomet (metformin HCl) oral solution 100 mg/dL  
Ranbaxy

SUBJECT: NDA review issues and recommended action

**Background**

This is a 505(b)(2) application for a metformin oral solution which includes CMC and Biopharmaceutics information. The intent is to provide a product for patients who find it difficult to swallow tablets. No clinical data are required.

**Biopharmaceutics**

Bioavailability studies were done in both fasted and fed states to compare the pharmacokinetics of Riomet solution with Glucophage tablets. In the fed state, the two are bioequivalent. The recommended mode of administration of metformin tablets and solution is "with meals" and thus it is assumed that the two products are therapeutically equivalent.

**Chemistry/ Microbiology**

The chemistry, manufacturing, and controls information is satisfactory and the application can be approved from the standpoint of ONDC. There are no phase 4 commitments. A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency. The facilities inspections were all acceptable.

**DSI/Data Integrity**

The PK data from two analytical runs were not deemed acceptable for review. The bioequivalence determination was based on the data from the remaining 11 analytical runs at the recommendation of DSI.

**Financial disclosure**

The financial disclosure information is in order and is summarized in Dr. Misbin's review.

**Labeling**

NDA #21-591  
Drug: Riomet (metformin oral solution)  
Proposal: — (equivalent to Glucophage)  
09/10/03

The labeling for Riomet contains the bioavailability data comparing the solution to Glucophage tablets. Based on these results, the Glucophage label has been adapted to Riomet by deleting references to "tablets" in the discussion of the clinical safety and efficacy data supporting the use of metformin in the recommended doses. This is to avoid confusion by consumers. In addition, dosing information includes both volume of solution and mass of drug, again to avoid confusion in dispensing. Finally, the

**Pediatric labeling**

The labeling for Riomet includes the pediatric studies information from the Glucophage label, as it is no longer protected by exclusivity. No further pediatric studies of Riomet are required.

**ODS/nomenclature**

Acceptable

**Recommendation**

Approve

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ON ORIGINAL**

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/s/

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David Orloff  
9/10/03 12:29:14 PM  
MEDICAL OFFICER

# Memo

**To:** David Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products, HFD-510

**From:** Denise Toyer, Pharm.D.  
Team Leader, Division of Medication Errors and Technical Support, HFD-420

**Through:** Carol Holquist, R.Ph.  
Deputy Director, Division of Medication Errors and Technical Support, HFD-420

**CC:** Jena Weber, R.Ph.  
Project Manager, Division of Metabolic and Endocrine Drug Products, HFD-510

**Date:** August 25, 2003

**Re:** ODS Consult 02-0209-1; Riomet [Metformin Hydrochloride Oral Solution] NDA 21-591

---

This memorandum is in response to the July 7, 2003 request from your Division for a re-review of the proprietary name, Riomet. In our consult, dated January 15, 2003 (ODS consult # 02-0209), DMETS did not have any objections to the use of the proprietary name Riomet. DMETS also reviewed the draft container labels and package insert labeling in that review. The sponsor did not submit revised container labels with this consult, therefore DMETS refers to the label and labeling recommendations listed in the January 15, 2003 review. However, the sponsor submitted draft carton labels and a \_\_\_\_\_ of the proposed proprietary name, with this review, which DMETS will review for safety issues relating to possible medication errors.

Since the initial Riomet proprietary review, DMETS has not identified any additional proprietary or established names that have the potential for confusion with Riomet. Therefore, we have no objections to the use of the proprietary name, Riomet.



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/s/  
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Denise Toyer  
8/25/03 03:08:05 PM  
PHARMACIST

Jerry Phillips  
8/25/03 03:16:32 PM  
DIRECTOR

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**REQUEST FOR CONSULTATION**

TO (Division/Office): DDMAC – Attention: Laura Pincock, HFD-42

DATE 03	IND NO. N/A	NDA NO. 21-591	TYPE OF DOCUMENT: PI	DATE OF DOCUMENT: 11/13/03
NAME OF DRUG: Metformin HCl Oral Solution 100 mg/mL		PRIORITY CONSIDERATION: NO	CLASSIFICATION OF DRUG: Oral Hypoglycemic	DESIRED COMPLETION DATE: 8/15/03

NAME OF FIRM: Ranbaxy Labs

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

**III. BIOPHARMACEUTICS**

<input type="checkbox"/> SOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES	<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST
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**IV. DRUG EXPERIENCE**

<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS
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**V. SCIENTIFIC INVESTIGATIONS**

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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**COMMENTS/SPECIAL INSTRUCTIONS:** This NDA is a 505(b)(2); please review & comment pm on package insert labeling (attached).  
The UFGD is September 14, 2003; internal labeling meeting with DMEDP (HFD-510) is 8/27/03.

SIGNATURE OF REQUESTER: Jena Weber via DFS (x76422)	METHOD OF DELIVERY (Check one) DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

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Laura Pincock  
8/5/03 03:27:29 PM

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**REQUEST FOR CONSULTATION**

TO (Division/Office):  
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420  
Attention: Sammie Beam, R.Ph.; Rm. 15B-03, Pkln. Bld.

FROM: Division of Metabolic & Endocrine Drug Products, HFD-510  
Jena Weber, Project Manager

DATE 5/27/03	IND NO. 63,783	NDA NO. 21-591	TYPE OF DOCUMENT: Final review of tradename - Riomet	DATE OF DOCUMENT: 2/12/03
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NAME OF DRUG: Metformin HCl Oral Soln 100 mg/mL	PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG: Oral hypoglycemic agent.	DESIRED COMPLETION DATE: 8/1/03
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NAME OF FIRM: Ranbaxy Labs, Inc.

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                       |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                              |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                                   |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                         |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                                  |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

**III. BIOPHARMACEUTICS**

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

**IV. DRUG EXPERIENCE**

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

**V. SCIENTIFIC INVESTIGATIONS**

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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See attached document; Original tradename request sent on 11/19/02. ODS review & comments received 1/31/03; these sent as a Discipline Review letter to the company on 2/3/03. Ranbaxy has agreed to all recommendations from DMETS. Request **final** review of proposed tradename "Riomet." User Fee Goal Date is September 14, 2003.

ATTACHMENTS: PI LBL; will place in DES for signoff.

SIGNATURE OF REQUESTER: Jena Weber, x76422	METHOD OF DELIVERY: DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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**CONSULTATION RESPONSE**  
**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**  
**OFFICE OF DRUG SAFETY**  
**(DMETS; HFD-420)**

**DATE RECEIVED:** 11/19/02

**DUE DATE:** 1/19/03

**ODS CONSULT #:** 02-0209

**TO:**

David Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products  
HFD-510

**THROUGH:**

Jena Weber  
Project Manager  
HFD-510

**PRODUCT NAME:**

**Riomet**  
(Metformin Hydrochloride Oral Solution)  
100 mg/mL

**NDA SPONSOR:** Ranbaxy Labs, Ltd.

**NDA: 21-591**

**SAFETY EVALUATOR:** Hye-Joo Kim, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) has performed a review of the proposed proprietary name "Riomet" to determine the potential for confusion with approved proprietary and established names as well as pending names.

**DMETS RECOMMENDATION:** DMETS has no objection to the use of the proprietary name, "Riomet." In addition, DMETS recommends revising the labels and labeling as outlined in section III of this review. DDMAC finds the proprietary name Riomet acceptable from a promotional perspective.

DMETS decision is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

/s/

/s/

Carol Holquist, RPh  
Deputy Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, RPh  
Associate Director  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Food and Drug Administration

**Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** January 15, 2003

**NDA:** 21-591

**NAME OF DRUG (S):** **Riomet**  
Metformin Hydrochloride Oral Solution  
100 mg/mL

**NDA HOLDER:** Ranbaxy Labs, Ltd.

**I. INTRODUCTION:**

This consult is written in response to a November 19, 2002 request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for an assessment of the proposed proprietary name, Riomet, regarding potential name confusion with other proprietary and/or established names. The draft container label and package insert labeling were reviewed for possible interventions in minimizing medication errors.

**PRODUCT INFORMATION**

Riomet, which contains the active ingredient, metformin hydrochloride, is an oral antihyperglycemic drug. Riomet, as monotherapy, is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Riomet may be used concomitantly with a sulfonylurea or insulin to improve glycemic control in adults. For adults, the usual starting dose of Riomet is 500 mg twice daily or 850 mg once daily, given with meals. Dosage increases should be made in increments of 500 mg weekly or 850 mg every 2 weeks, up to a total of 2000 mg daily, given in divided doses. For pediatric patients, the usual starting dose is 500 mg twice daily, given with meals. Dosage increases should be made in increments of 500 mg twice daily up to a maximum of 2000 mg daily, given in divided daily doses. Riomet will be available as oral solution in one strength: 100 mg/mL in bottles of 4 oz or 16 oz.

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1, 2</sup> as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to Riomet to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database<sup>4</sup> and the Saegis<sup>5</sup> Pharma-In-Use database were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies, outpatient and inpatient, and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

### A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Riomet. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The expert panel consists of members of DMETS Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified several names that were thought to have the potential for confusion with Riomet. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual FDA-approved dosage.
2. DDMAC has no objection to the proposed name Riomet with regards to promotional claims.

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<sup>1</sup> MICROMEDEX Healthcare Intranet Series, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2003).

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

<sup>4</sup> WWW location <http://www.uspto.gov/tmdb/index.html>

<sup>5</sup> Data provided by Thomson and Thomson' SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com).

Table 1

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
Riomet	Metformin Hydrochloride Oral Solution; 100 mg/mL	500 mg (5 mL) BID or 850 mg (8.5 mL) QD	
Ri-Mag (OTC)	Magaldrate (aluminum magnesium hydroxide sulfate) Suspension; 540 mg/5 mL	5 mL to 10 mL between meals and at bedtime	SA*
Sinemet	Carbidopa-Levodopa Tablets; 10 mg/100 mg, 25 mg/100mg and 25 mg/250 mg	25 mg/100 mg TID 10 mg/100 mg TID to QID Dosage may be increased by 1 tablet every day or every other day, as necessary, until a dosage of 8 tablets a day is reached.	SA/LA*
Sinemet CR	Carbidopa-Levodopa Sustained Release Tablets; 25 mg/100 mg and 50 mg/200 mg	50 mg/200 mg BID to TID	SA/LA*
Rymed	Pseudoephedrine/Guaifenesin	No longer marketed.	SA*

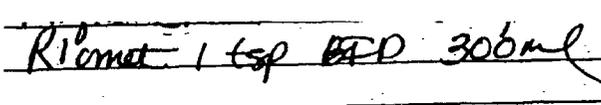
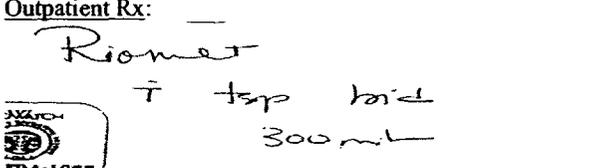
\*SA= Sound-alike \*LA= Look-alike

**B. PRESCRIPTION ANALYSIS STUDIES**

**I. Methodology**

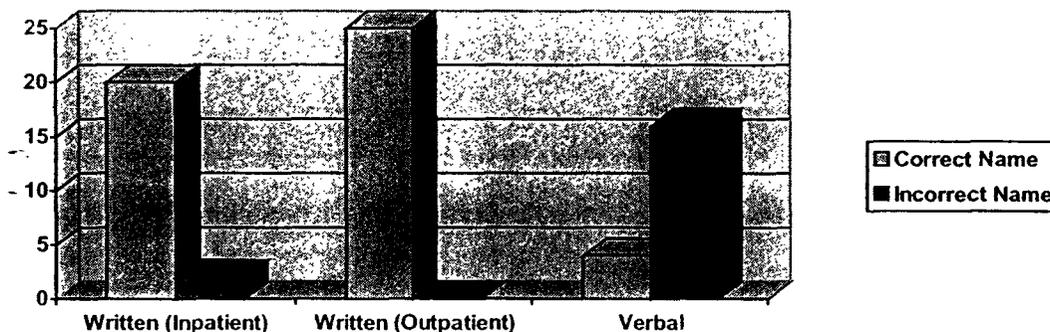
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Riomet with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Riomet (see below). These prescriptions were optically scanned and were delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

**Riomet**

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Inpatient Rx:</u></p> 	<p><u>Verbal Rx:</u> Riomet 1 teaspoonful twice daily. 300 mL.</p>
<p><u>Outpatient Rx:</u></p> 	

## 2. Results for Riomet

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	39	22 (56%)	20 (91%)	2 (9%)
Written Outpatient	35	25 (71%)	25 (100%)	0 (0%)
Verbal	32	20 (63%)	4 (20%)	16 (80%)
Total	106	67 (63%)	49 (73%)	18 (27%)



Among the verbal prescription study participants for **Riomet**, 16 of 32 (80 %) participants interpreted the name incorrectly. The majority of the responses were phonetic variations of “Riomet.” The incorrect responses were *Riamet* (5), *Ryamet* (4), *Rimet* (1), *Riamac* (1), *Rynec* (1), *Riamec* (1), *Rylet* (1), *Ryamec* (1) and *Ryland* (1). The misinterpretations did not overlap with any of the currently approved drug names.

Among the written prescription study participants for **Riomet**, 2 of 47 (4%) participants interpreted the name incorrectly. The incorrect responses were *Ricmet* (1) and *Rlomet* (1). The misinterpretations did not overlap with any of the currently approved drug names.

### C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name “Riomet”, the primary concerns raised were related to sound-alike and look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with Riomet were Sinemet and Ri-Mag.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Riomet and Sinemet or Ri-Mag. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Riomet. The misinterpretations also did not overlap with any of the currently approved drug names. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size.

The proposed proprietary name, Riomet, and the currently available name, Sinemet, look and sound similar. Sinemet is also available as Sinemet CR, a sustained-release formulation. Sinemet/Sinemet CR is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication. The names, Sinemet and Riomet, sound similar, because they share the suffix, “met,” however, the prefixes

“Sine” and “Rio” are different enough to distinguish one name from the other. Additionally the names, Sinemet and Riomet, are visually similar; the first letters “S” and the “R” and the third letters “n” and “o” can look similar when scripted (see below).

*Sinemet*      *Riomet*

Sinemet is available in 10 mg/100 mg, 25 mg/100 mg, and 25 mg/250 mg combination strength tablets. Sinemet CR is also available as 50 mg/200 mg and 25 mg/100 mg combination strength tablets. Riomet, on the other hand, will be available in a single strength: 100 mg/mL oral solution. We acknowledge that Sinemet and Riomet share the strength “100 mg”, however, Sinemet is expressed with both strengths (e.g., 10 mg/100 mg, 25 mg/100 mg, and 25 mg/250 mg), further decreasing the risk of medication errors between Riomet and Sinemet. Furthermore, a prescription for Sinemet will likely be written with a strength, because Sinemet is available in multiple strengths. However, a prescription for Riomet may be written without a strength, because it is available in one strength. Lastly, Sinemet and Riomet do not share overlapping dosing intervals. Sinemet is dosed three to four times daily while Riomet will be dosed once or twice daily. We acknowledge that both Sinemet CR and Riomet can be dosed twice daily, however, the modifier “CR” should further distinguish one name from the other.

The proposed name, Riomet and the currently marketed product, Ri-Mag are phonetically similar, because they share the prefix, Ri. Ri-Mag contains the active ingredient, magaldrate, which is aluminum magnesium hydroxide sulfate. Ri-Mag is an antacid that neutralizes and reduces stomach acid relieving heartburn and indigestion. Riomet may have sound-alike qualities with Ri-Mag. Riomet and Ri-Mag also share similar dosage forms: oral solution versus oral suspension. However, the dosing intervals are different. Riomet is dosed once to twice daily whereas Ri-Mag is dosed between meals and at bedtime. In addition, the Rx/OTC differences between these products may further distinguish them. Lastly, the suffixes “omet” and “Mag” are different enough to distinguish one name from the other.

The sponsor has proposed a new dosage formulation (oral solution) of metformin that has never been marketed by another competitor. Since the strengths of oral solutions/suspensions are commonly expressed as “per 5 mL” (e.g., Amoxil 250 mg/5 mL),

**III. LABELING, PACKAGING AND SAFETY RELATED ISSUES**

In the review of the container labels and insert labeling of Riomet, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

**A. CONTAINER LABEL**

We recommend that the established name be printed in letters that are at least half as large as the letters comprising the proprietary name to be in accordance with 21 CFR 201.10 (g) (2).

**B. PACKAGE INSERT LABELING**

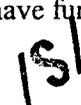
Dosage and Administration

We recommend revising the statement, "  
" to read "patients started on metformin 500 mg and glyburide 20 mg were titrated to 1000 mg/20 mg, 1500 mg/20 mg, 2000 mg/20 mg or 2500 mg/20 mg of metformin and glyburide..." so that the strengths are clearly expressed as "mg" for each active ingredient.

**IV. RECOMMENDATIONS**

- A. DMETS has no objection to the use of the proprietary name, "Riomet." DMETS decision is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review.
- C. DDMAC finds the proprietary name Riomet acceptable from a promotional perspective.

We would appreciate feedback of the final outcome of this consult. We would also be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarification, please contact Sammie Beam at 301-827-3242.

  
 \_\_\_\_\_  
 Hye-Joo Kim Pharm.D.  
 Safety Evaluator  
 Division of Medication Errors and Technical Support  
 Office of Drug Safety

Concur:

  
 \_\_\_\_\_  
 Alina R. Mahmud, R.Ph.  
 Team Leader  
 Division of Medication Errors and Technical Support  
 Office of Drug Safety

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Hye-Joo Kim  
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PHARMACIST

Alina Mahmud  
1/31/03 02:48:56 PM  
PHARMACIST

Carol Holquist  
1/31/03 03:43:38 PM  
PHARMACIST

**NDA REGULATORY FILING REVIEW**

NDA 21-591 Riomet (metformin HCl oral solution) 100 mg/mL  
Applicant: Ranbaxy Laboratories, Inc.

Date of Application: November 13, 2002  
Date of Receipt: November 14, 2002  
Date of Filing Meeting: January 6, 2003  
Filing Date: January 13, 2003

Indication(s) requested: For the treatment of patients with type 2 diabetes mellitus.

Type of Application: Full NDA  Supplement \_\_\_\_\_  
(b)(1) \_\_\_\_\_ (b)(2)   
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classifications: S  P \_\_\_\_\_  
Resubmission after a withdrawal or refuse to file N/A  
Chemical Classification: (1,2,3 etc.) 3  
Other (orphan, OTC, etc.) N/A

User Fee Status: Paid NO Waived (e.g., small business, public health) \_\_\_\_\_  
Exempt (orphan, government) \_\_\_\_\_  
Form 3397 (User Fee Cover Sheet) submitted: YES  NO \_\_\_\_\_  
User Fee ID# N/A 505(b)(2)  
Clinical data? YES \_\_\_\_\_ NO  Referenced to \_\_\_\_\_  
Date clock started after UN \_\_\_\_\_

User Fee Goal date: **September 14, 2003**

Note: If an electronic NDA: all certifications require a signature and must be in paper.

- Does the submission contain an accurate comprehensive index? YES
- Form 356h included with authorized signature? YES  
**If foreign applicant, the U.S. Agent must countersign or submit a separate certification.**
- Submission complete as required under 21 CFR 314.50? YES  
If no, explain:
- If electronic NDA, does it follow the Guidance? N/A
- Patent information included with authorized signature? YES

- Exclusivity requested? NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES  
**If foreign applicant, the U.S. Agent must countersign or submit a separate certification.**

Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that \_\_\_\_\_ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix \_\_\_\_." Applicant may not use wording such as, "To the best of my knowledge, ...."

- Financial Disclosure included with authorized signature? YES  
 (Forms 3454 and/or 3455)  
**If foreign applicant, the U.S. Agent must countersign or submit a separate certification.**

- Pediatric Rule appears to be addressed for all indications? NO

- Pediatric assessment of all ages? NO  
 (If multiple indications, answer for each indication.)  
 If NO, for what ages was a waiver requested? \_\_\_\_\_  
 For what ages was a deferral requested? \_\_\_\_\_

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

**Refer to 21 CFR 314.101(d) for Filing Requirements**

PDUFA and Action Goal dates correct in COMIS/DSS? YES  
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. YES

List referenced IND numbers: IND 63,783

End-of-Phase 2 Meeting? NO  
 If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? NO  
 If yes, distribute minutes before filing meeting.

**Project Management**

Copy of the labeling (PI) sent to DDMAC? YES (7/14/03)  
Trade name and labeling (PI) sent to ODS? YES (11/19/02)  
Advisory Committee Meeting needed? NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NN

**Chemistry**

- Did sponsor request categorical exclusion for environmental assessment? YES  
If no, did sponsor submit a complete environmental assessment? N/A
- EA consulted to Nancy Sager (HFD-357)? NO
- Establishment Evaluation Request (EER) package submitted? YES
- Parenteral Applications Consulted to Sterile Products (HFD-805)? NN
- 

**505(b)(2)**

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug: Glucophage (metformin HCL) Tablets; NDA 20-357.

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? NO  
(Normally, FDA will refuse-to-file such applications.)

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? NO

If yes, the application must be refused for filing under 314.54(b)(1)

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? NO

If yes, the application must be refused for filing under 314.54(b)(2)

For a 505(b)(2) application, which of the following does the application contain? Note that a patent certification must contain an authorized signature.

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Patent II Certification).

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

*If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference? YES
- Submit a statement as to whether the listed drug(s) identified have received a period of marketing exclusivity? NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? YES

If the application is a 505(b)(2), has the Director, Div. of Regulatory Policy II, HFD-007 been notified? YES

3 Page(s) Withheld

ATTACHMENT

FILING MEETING MINUTES

DATE: January 6, 2003

ATTENDEES: Robert Misbin, M.D., Sharon Kelly, Ph.D., Hae-Young Ahn, Ph.D., Steven Johnson, Pharm.D., Herman Rhee, Ph.D., Kati Johnson, R.Ph., Jena Weber, BS.

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Orloff
Secondary Medical:	Misbin
Statistical:	NN
Pharmacology:	Rhee
Statistical Pharmacology:	NN
Chemist:	Kelly
Environmental Assessment (if needed):	
Biopharmaceutical:	Johnson
Microbiology, sterility:	NN
Microbiology, clinical (for antimicrobial products only):	NN
DSI:	Vishwanathan
Project Manager:	Weber
Other Consults:	ODS - Beam

Is the application affected by the application integrity policy (AIP) NO

Per reviewers, all parts in English, or English translation? YES

CLINICAL – File

Clinical site inspection needed: NN

MICROBIOLOGY CLINICAL – N/A

STATISTICAL – NN

BIOPHARMACEUTICS – File

Biopharm. inspection Needed: YES (DSI)

PHARMACOLOGY – File

CHEMISTRY – File

- Establishment ready for inspection? YES

REGULATORY CONCLUSIONS/DEFICIENCIES:

✓ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

Jena Weber 1/6/03  
Project Manager, HFD-510

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

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

-----  
Jena Weber  
9/12/03 08:58:17 AM  
CSO

# REQUEST FOR CONSULTATION

O (Division/Office):  
Director, Division of Medication Errors and Technical  
Support (DMETS), HFD-420, Attention: Sammie Beam  
KLN Rm. 6-34

FROM: Division of Metabolic and Endocrine Drug Products,  
HFD-510  
Attention: Jena Weber

11/19/02	IND NO. 63,783	NDA NO. 21-591	TYPE OF DOCUMENT: Original NDA application	DATE OF DOCUMENT: 11/13/02
NAME OF DRUG: Metformin HCl Oral Soln. 100 mg/mL		PRIORITY CONSIDERATION: Standard (10-month clock)	CLASSIFICATION OF DRUG: Oral Hypoglycemic agent	DESIRED COMPLETION DATE: 05/01/03

NAME OF FIRM: Ranbaxy Labs, Ltd.

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                       |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                              |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                                   |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                         |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                                  |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

#### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

#### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

#### V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
-----------------------------------	--------------------------------------

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: Proprietary names for Metformin HCl Oral Solution 100 mg/mL; in order of preference:  
1. Riomet (metformin hydrochloride) Oral Solution, 100 mg/mL  
2.  
3.

PDUFA DATE: September 14, 2003.

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

SIGNATURE OF REQUESTER: Jena Weber, Project Manager	METHOD OF DELIVERY (Check one) DFS <i>pending S. Beam signature in DFS 11/19/02</i>
	SIGNATURE OF DELIVERER <i>JSI</i>

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297  
Expiration Date: February 29, 2004.

# USER FEE COVER SHEET

**See Instructions on Reverse Side Before Completing This Form**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Ranbaxy Laboratories Limited  
Sector 18, Udyog Vihar Industrial Area  
Gurgaon - 122 011, INDIA

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER  
NDA 021591

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES  NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

\_\_\_\_\_  
(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

( ) 91-1246-343125

3. PRODUCT NAME

Metformin Hydrochloride Oral Solution, 10 mg/mL

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92  
(Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE  
(See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act  
(See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act  
(See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY  
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES  NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
BER, HFM-99  
401 Rockville Pike  
Rockville, MD 20852-1448

Food and Drug Administration  
CDER, HFD-94  
and 12420 Parklawn Drive, Room 3046  
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Abha Pant

TITLE

Abha Pant

DATE

11/12/02

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Please see the attached list of investigators	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Abha Pant	TITLE Director, Regulatory Affairs Official US Agent for Ranbaxy Laboratories Limited
FIRM / ORGANIZATION Ranbaxy Pharmaceuticals, Inc.	
SIGNATURE <i>Abha Pant</i>	DATE 11/13/02

### Paperwork Reduction Act Statement

This agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

0008

Metformin Hydrochloride Oral Solution, 100 mg/mL  
ITEM 19: FINANCIAL INFORMATION

**SECTION 19: FINANCIAL INFORMATION**

A list of the covered clinical studies and the names of the investigators who participated in these studies are provided below:

<b>Study Number</b>	<b>Clinical Investigator</b>	<b>Certification (Form 3454)</b>	<b>Disclosure (Form 3455)</b>
012/METFO- 500/02		X	
		X	
		X	
		X	
<hr/>			
Protocol 013395		X	
		X	
and		X	
		X	
Protocol 013396		X	
		X	
		X	
		X	
		X	
		X	

22 Draft Labeling Page(s) Withheld