CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-591

CHEMISTRY REVIEW(S)

NDA 21-591

RIOMET (Metformin HCl) 500 mg/ 5 ml Oral Suspension

Ranbaxy Laboratories LTD

Sharon L. Kelly
Division of Metabolic and Endocrine Drug Products,
HFD-510

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-591

2. REVIEW #: 1

3. REVIEW DATE: 26-AUG-03

4. REVIEWER: Sharon L. Kelly

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	13-NOV-2002
Amendment	26-JUN-2003
Amendment	06-AUG-2003
Amendment	21-AUG-2003
Amendment	27-AUG-2003
Amendment	28-AUG-2003
Amendment	29-AUG-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Ranbaxy Laboratories Limited
Address:	Sector 18, Udyog Vihar Industrial Area Gurgaon - 122 001 India
Representative:	Abha Pant, US Agent Ranbaxy Pharmaceuticals Inc. 600 College Road East Princeton, NJ 08540
Telephone:	(609) 720-5666

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Riomet (metformin hydrochloride) Oral Solution, 100 mg/ml
b) Non-Proprietary Name (USAN): metformin hydrocholride

CHEMISTRY REVIEW

c) Code Name/# (ONDC only): Not Applicable
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Antihyperglycemic agent

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 100 mg/ml

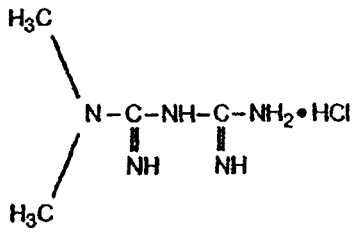
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed
___X___ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

N,N-dimethylimidodicarbonimidic diamide hydrochloride
CAS registry number: 657-24-9 (metformin); 1115-70-4 (metformin hydrochloride).
MW 165.63
$C_4H_{11}N_5 \cdot HCl$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Letters of Authorization supplied for all

DMF #	TYPE	HOLDER	ITEM REFERENCED[1,2]	CODE	STATUS	DATE REVIEW COMPLETED	COMMENTS
/	II	/	Metformin Hydrochloride,	3	Adequate	27-MAR-2002	API

	Drug Substance			
	III	1	N/A	
	III	4	N/A	See also DMF review 07-MAY-1999
	III	4	N/A	
	III	4	N/A	
	III	4	N/A	See also DMF review 24-JUL-1999
	III	4	N/A	See also DMF review 12-FEB-2003
	III	4	N/A	
	III	4	N/A	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Document	Application No.	Description
NDA	20-357	Glucophage® (metformin hydrochloride tablets) (Approved)
IND	63,783	Metformin Hydrochloride Oral Solution, 100 mg/ml

18. STATUS:

ONDC:

Consults/CMC related reviews	Recommendation	Date	Reviewer
EES	Acceptable	03 - JUN - 2003	
Methods Validation	Pending		
EA	N/A		

The Chemistry Review for NDA 21-591

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information is Satisfactory for NDA 21-591 to market Metformin Hydrochloride Oral Solution, 500 mg/ 5 ml. From a CMC perspective, this Application can be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable : Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

This NDA refers to the listed drug, Glucophage (metformin hydrochloride) Tablet 1000 mg manufactured by Bristol-Myers Squibb Company, USA, the holder of the approved application, NDA 20-357. The Drug Product that is the subject of NDA 21-591, Metformin Hydrochloride Oral Solution, 500 mg/ 5 ml has been developed as an alternate dosage form for patients who would find it difficult to swallow the tablets.

Metformin, a biguanide (dimethylbiguanide), is an oral antihyperglycaemic agent used in the management of non-insulin dependent diabetes mellitus. It reduces blood glucose levels, predominantly by improving hepatic and peripheral tissue sensitivity to insulin without affecting the secretion of this hormone.

Signature Pharmaceuticals was the initial developer of the oral solution formulation of metformin hydrochloride, and was acquired by Ranbaxy Pharmaceuticals, Inc.

Metformin Hydrochloride Oral Solution contains 500 mg of Metformin Hydrochloride per 5 ml and the following inactive ingredients: Saccharin Calcium, Potassium Bicarbonate, Xylitol, Hydrochloric Acid, Purified Water and Cherry Flavor.

Three pharmacokinetic studies in healthy volunteers are presented in this NDA in order to support that Metformin Hydrochloride Oral Solution 500 mg/ 5 ml (10 ml dose) is bioequivalent to the reference product Glucophage Tablets, 1000 mg, when the product

is administered under fed conditions, which is the labeled condition of administration of the reference product.

Drug Substance:
The drug substance is manufactured by — , under DMF — The DMF was previously reviewed for CMC and found to be Adequate. Ranbaxy holds the regulatory specifications and performs the regulatory testing of the drug substance.

Metformin Hydrochloride drug substance is a white to off-white crystalline compound. It is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

B. Description of How the Drug Product is Intended to be Used

The usual starting dose for Adults of Metformin Hydrochloride Oral Solution is 500 mg twice a day or 850 mg once a day, given with meals. The maximum daily dose is 2550 mg per day. The usual starting dose for Pediatrics is 500 mg twice a day, given with meals. The maximum daily dose is 2000 mg per day. How supplied and Storage conditions are as follows:

Metformin Hydrochloride Oral Solution is available in one strength; 500 mg/ 5 ml, in two bottle presentations:
Bottles of 4oz (118ml)
Bottles of 16 oz (473ml)

Store at controlled room temperature 15° - 30°C (59° - 86°F) [See USP].

The Applicant provided six months of stability data at accelerated conditions and controlled room temperature in the Original NDA submission. They requested a shelf life of — However, they were informed that based on the available stability data, a shelf life of — would be granted. Consequently a stability update was submitted in Amendment dated August 21, 2003. Based on — , of stability data, a shelf life of 18 months can be granted at this time.

C. Basis for Approvability or Not-Approval Recommendation

There are no significant CMC deficiencies. Based on the evaluation of the information provided in the submission, this application can be approved from the Chemistry, Manufacturing and Control (CMC) standpoint.

III. Administrative

A. Reviewer's Signature (Electronic, in DFS)

B. Endorsement Block

Chemist: Sharon L. Kelly/ 26-AUG-2003
ChemistryTeamLeader: Stephen Moore/
ProjectManager Jena Weber/

C. CC Block

Org. NDA 21-591
HFD-510/Division File
HFD-510/SKelly
HFD-510/SMoore
HFD-510/JWeber
HFD-510/D-GWu
HFD-820/EDuffy

29 Page(s) Withheld

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

/s/

Sharon Kelly
9/5/03 10:13:39 PM
CHEMIST

Stephen Moore
9/8/03 10:47:35 AM
CHEMIST