

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212595Orig1s000**

**OTHER REVIEW(S)**

---

MEMORANDUM  
REVIEW OF REVISED LABELS AND LABELING  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

---

Date of This Memorandum: August 29, 2019

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: NDA 212595

Product Name and Strength: Riomet ER (metformin hydrochloride) extended release suspension, 500 mg per 5 mL (100 mg/mL)

Applicant/Sponsor Name: Sun Pharmaceutical Industries (Sun Pharma)

FDA Received Date: August 29, 2019

OSE RCM #: 2018-2402-1

DMEPA Safety Evaluator: Ariane O. Conrad, PharmD, BCACP, CDE

DMEPA Team Leader: Hina Mehta, PharmD

---

## 1 PURPOSE OF MEMORANDUM

Sun Pharma submitted revised container labels and carton labeling received on August 29, 2019 for Riomet ER. We reviewed the revised labels and labeling for Riomet ER (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>a</sup>

## 2 CONCLUSION

The revised trade container labels and carton labeling are acceptable from a medication error perspective. We have no additional recommendations at this time.

---

<sup>a</sup> Purcell J. Human Factors Study Report and Label and Labeling Review for Riomet ER (NDA 212595). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Aug 16. RCM No.: 2018-2402 and 2018-2403.

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

ARIANE O CONRAD  
08/29/2019 12:03:02 PM

HINA S MEHTA  
08/29/2019 01:44:16 PM

t

---

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

---

Date of This Review:	August 16, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 212595
Product Type:	Single-Ingredient Combination Product
Drug Name and Strength:	Riomet ER (metformin hydrochloride) extended release suspension, 500 mg per 5 mL (100 mg/mL)
Device Constituent:	(b) (4) Container Closure System (b) (4) contains solid drug pellets and (b) (4) contains drug diluent) For Reconstitution
Rx or OTC:	Rx
Applicant Name:	Sun Pharmaceutical Industries
Submission Date:	November 2, 2018; February 7, 2019; May 24, 2019; June 17, 2019
OSE RCM #:	2018-2402 and 2018-2403
DMEPA Human Factors Evaluator:	Janine Purcell, MS
DMEPA Safety Evaluator (Labeling):	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Associate Director:	Mishale Mistry, PharmD, MPH

---

## 1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted by Sun Pharmaceutical Industries (Sun Pharma) under NDA 212595 for Riomet ER (metformin hydrochloride extended release suspension). This is a single-ingredient combination product with a proposed container closure system device constituent.

### 1.1 PRODUCT INFORMATION

Riomet (metformin hydrochloride) 500 mg/5 mL oral solution was approved on September 11, 2003 under NDA 021591 as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus. Riomet is typically administered in divided doses. Under NDA 212595, Sun Pharma proposes to introduce Riomet ER oral suspension for the same indication, which once reconstituted, supplies 500 mg/5 mL of metformin hydrochloride extended release, intended for once daily administration.

Sun Pharma proposes to supply the oral suspension in two different container closure systems (identified as "round bottle" (b) (4) in the submission<sup>a</sup>). Both systems will include a bottle containing metformin hydrochloride extended release drug pellets and a bottle containing the diluent. Pharmacists and pharmacy technicians must reconstitute Riomet ER prior to dispensing. (b) (4)

The round bottle presentation requires users to remove the cap of each bottle and pour the drug pellets into the diluent bottle. Both bottle presentations require the user to shake the (b) (4) bottle, now containing the drug diluent and drug pellets, to form the oral suspension.

### 1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On September 20, 2017 and November 29, 2017, Sun Pharma submitted their human factors (HF) validation study protocol.

On December 19, 2017, we provided recommendations for the HF validation study protocol and requested that Sun Pharma address identified areas of concern prior to commencing the HF validation study<sup>b</sup>.

On January 31, 2018, Sun Pharma submitted a response to the FDA's recommendation to the protocol review. We provided further responses to Sun Pharma, including recommendations related to areas of concern and requested that Sun Pharma address the identified areas of concern prior to commencing the HF validation study.

---

<sup>a</sup> The term "(b) (4) bottle design" is used in the product PI; "Container Closure System 1" is the term Sun Pharma used in the HF validation study materials submitted to the Agency.

<sup>b</sup> Rahimi L. Human Factors Validation Study Protocol Review for metformin hydrochloride extended release oral suspension (IND 127945). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Dec 19. RCM No.: 2017-1940.

On April 3 and 18, 2018, we provided addendum memorandums with recommendations to Sun Pharma to express further concerns, including a design feature that could lead to a delay in therapy. We requested that Sun Pharma address the concerns prior to commencing their HF validation study.<sup>c</sup>

On May 3, 2018, Sun Pharma submitted a response to the recommendations to the protocol. Sun Pharma agreed to the recommendation.

On May 17, 2018, we acknowledged that Sun Pharma was in agreement with our previously communicated recommendations and no further recommendations were provided.<sup>d</sup>

On November 2, 2018, Sun Pharma submitted a human factors validation study report and labels and labeling as part of this NDA submission.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for the material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C – N/A
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The sections below provide a summary of the study design use errors, close calls, and use difficulties observed and our analysis to determine if the results support safe and effective use of the proposed product (Tables 2.1, 2.2, and 2.3). We also provide our assessment of the proposed product labels and labeling (Sections 4.1 and 4.2, and Appendix E).

---

<sup>c</sup> Rahimi L. Human Factors Validation Study Protocol and Label and Labeling Review Memorandum for metformin hydrochloride extended release oral suspension (IND 127945). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Apr 3. RCM No.: 2017-1940-1.

Rahimi L. Human Factors Validation Study Protocol Review Memorandum for metformin hydrochloride extended release oral suspension (IND 127945). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Apr 18. RCM No.: 2017-1940-2.

<sup>d</sup> Rahimi L. Human Factors Validation Study Protocol Review Memorandum for metformin hydrochloride extended release oral suspension (IND 127945). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 May 17. RCM No.: 2017-1940-3.

### 3.1 SUMMARY OF HUMAN FACTORS VALIDATION STUDY DESIGN

We previously reviewed the HF validation study protocol under IND 127945 and note that our recommendations were implemented. We find the study methodology acceptable.

The purpose of this HF validation study was to demonstrate that the (b) (4) bottle design<sup>e</sup> and its associated materials (Prescribing Information with preparation instructions, patient Instructions for Use (IFU), packaging, and labeling) supports safe and effective use by the intended user populations, in the intended use environments, for the intended use scenarios; and ensure that use-related risks associated with the (b) (4) bottle design have been effectively mitigated.

The HF validation study included four groups of representative users of the product: 15 pharmacists, 15 pharmacy technicians, 15 patients, and 15 caregivers. Participants did not receive training.

Pharmacist and pharmacy technician participants attempted two reconstitutions. Patient and caregiver participants attempted two dosing tasks. Each caregiver and patient participant interacted with different dose amounts in a counterbalanced design to minimize any learning effects. For all participants, each task was followed by post-task questions to cover any issues or concerns participants had with that task and knowledge question to assess usability and effectiveness of the accompanying documentation.

We note that the report documented a deviation from the study protocol previously reviewed by the Agency regarding the patient and caregiver study methodology. Midway through the validation study, Sun Pharma's clinical team provided data that supported the stability and uniformity of the medication post-reconstitution by pharmacists or pharmacy technicians, which justified the removal of the instruction "shake at least 10 seconds before each use." Task completion for the relevant step was executed in the validation and the test data was included in the report. The report states that the data is not relevant and does not reflect intended use. We discuss this task in Table 2.2 below.

### 3.2 RESULTS AND ANALYSES – HUMAN FACTORS VALIDATION STUDY

Tables 2.1, 2.2, and 2.3 capture the study results, Sun Pharma's analyses of the results, and DMEPA's analyses and recommendations for the Pharmacist/Pharmacy Technicians, Patients/Caregivers, and Knowledge Tasks respectively.

51 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

<sup>e</sup> The term "(b) (4) bottle design" is used in the product PI; "Container Closure System 1" is the term Sun Pharma used in the HF validation study materials submitted to the Agency.

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

JANINE A PURCELL  
08/16/2019 02:40:29 PM

ARIANE O CONRAD  
08/16/2019 02:43:51 PM

HINA S MEHTA  
08/16/2019 02:49:30 PM

MISHALE P MISTRY on behalf of QUYNHNHU T NGUYEN  
08/16/2019 03:41:48 PM

MISHALE P MISTRY  
08/16/2019 03:46:32 PM

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: August 14, 2019

To: Lisa Yanoff, M.D.  
Acting Director  
**Division of Metabolism and Endocrinology Products  
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Sharon W. Williams, MSN, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Samantha Bryant, PharmD, BCPS  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and  
Instructions for Use (IFU)

Drug Name (established name): RIOMET ER (metformin hydrochloride)

Dosage Form and Route: for extended-release oral suspension

Application Type/Number: NDA 212595

Applicant: Sun Pharmaceutical Industries Ltd.

## 1 INTRODUCTION

On November 2, 2018, Sun Pharmaceutical Industries Ltd. submitted for the Agency's review a New Drug Application (NDA 212595) for RIOMET ER (metformin-hydrochloride) extended-release, oral suspension. The purpose of the submission is to gain approval for RIOMET ER (metformin-hydrochloride) extended-release, oral suspension and is indicated as an adjunct to diet and exercise to improve glycemic control in patients 10 years of age and older with type 2 diabetes mellitus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on November 9, 2018 for DMPP and OPDP to review the Applicant's proposed PPI for RIOMET ER (metformin-hydrochloride) extended-release, oral suspension.

## 2 MATERIAL REVIEWED

- Draft RIOMET ER (metformin hydrochloride) extended-release, oral suspension PPI and IFU received on November 2, 2018, and received by DMPP on August 5, 2019.
- Draft RIOMET ER (metformin hydrochloride) extended-release, oral suspension PPI and IFU received on November 2, 2018, and received by OPDP on August 5, 2019.
- RIOMET ER (metformin hydrochloride) extended-release, oral suspension Prescribing Information (PI) received on November 2, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on August 5, 2019.
- RIOMET ER (metformin hydrochloride) extended-release, oral suspension Prescribing Information (PI) received on November 2, 2018, revised by the Review Division throughout the review cycle, and received by OPDP on August 5, 2019.
- Approved RIOMET (metformin hydrochloride) extended-release, oral suspension labeling dated, November 6, 2018.

## 3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible

- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

- The PPI and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

---

/s/

---

SHARON W WILLIAMS  
08/14/2019 08:08:02 AM

SAMANTHA E BRYANT  
08/14/2019 08:09:02 AM

LASHAWN M GRIFFITHS  
08/14/2019 08:18:41 AM

**FOOD AND DRUG ADMINISTRATION**  
**Center for Drug Evaluation and Research**  
**Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** August 7, 2019

**To:** Callie Cappel-Lynch, Regulatory Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)  
  
Monika Houstoun, Associate Director for Labeling, (DMEP)

**From:** Samantha Bryant, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Twyla Thompson, Acting Team Leader, OPDP

**Subject:** OPDP Labeling Comments for RIOMET ER™ (metformin hydrochloride)  
for extended-release oral suspension

**NDA:** 212595

---

In response to DMEP's consult request dated November 9, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI)/Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Riomet ER.

**PI and PPI/IFU:** OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMEP (Callie Cappel-Lynch) on August 5, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI/IFU will be sent under separate cover.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DMEP (Callie Cappel-Lynch) on August 7, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Samantha Bryant at (301) 348-1711 or [Samantha.Bryant@fda.hhs.gov](mailto:Samantha.Bryant@fda.hhs.gov).

35 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

SAMANTHA E BRYANT  
08/07/2019 01:14:29 PM