

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208574Orig1s000**

**208574Orig2s000**

**OTHER REVIEW(S)**

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## MEMORANDUM

### REVIEW OF REVISED LABEL 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)

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|                                |                                                                         |
|--------------------------------|-------------------------------------------------------------------------|
| Date of This Memorandum:       | February 18, 2020                                                       |
| Requesting Office or Division: | Division of Hematologic Malignancies 2 (DHM 2)                          |
| Application Type and Number:   | NDA 208574                                                              |
| Product Name and Strength:     | Romidepsin Injection, 10 mg/ 2 mL(5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL) |
| Applicant/Sponsor Name:        | Teva Pharmaceuticals USA, Inc. (Teva)                                   |
| OSE RCM #:                     | 2019-1175-2                                                             |
| DMEPA Safety Evaluator:        | Nicole Iverson, PharmD, BCPS                                            |
| DMEPA Team Leader:             | Hina Mehta, PharmD                                                      |

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#### 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on February 13, 2020 for Romidepsin. We reviewed the revised container labels and carton labeling for Romidepsin (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 Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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<sup>a</sup> Iverson N. Label and Labeling Review for Romidepsin (NDA 208574). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 30. RCM No.: 2019-1175-1.

## APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON FEBRUARY 13, 2020

### Container labels

(b) (4)



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HINA S MEHTA  
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## MEMORANDUM

### REVIEW OF REVISED LABEL 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)

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|                                |                                                                         |
|--------------------------------|-------------------------------------------------------------------------|
| Date of This Memorandum:       | January 30, 2020                                                        |
| Requesting Office or Division: | Division of Hematologic Malignancies 2 (DHM 2)                          |
| Application Type and Number:   | NDA 208574                                                              |
| Product Name and Strength:     | Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL) |
| Applicant/Sponsor Name:        | Teva Pharmaceuticals USA, Inc. (Teva)                                   |
| OSE RCM #:                     | 2019-1175-1                                                             |
| DMEPA Safety Evaluator:        | Nicole Iverson, PharmD, BCPS                                            |
| DMEPA Team Leader:             | Hina Mehta, PharmD                                                      |

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#### 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on January 23, 2020 for Romidepsin. We reviewed the revised container labels and carton labeling for Romidepsin (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 container labels and carton labeling are unacceptable from a medication error perspective. For the container labels and carton labeling, we recommend decreasing the font size of the quantity per milliliter (5 mg/mL) to bring prominence to the total quantity per total volume (10 mg/ 2mL and 27.5 mg/5.5 mL) on the principal display panel in accordance with USP General Chapter <7>. In addition, we recommend the diluent appear using official nomenclature on the principal display panel. For the carton labeling, we recommend relocating and increasing the prominence of the word, "Sterile" to the bottom of the side panel.

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<sup>a</sup> Garrison N. Label and Labeling Review for Romidepsin (NDA 208574). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 04. RCM No.: 2019-1175.

### 3 RECOMMENDATIONS FOR TEVA PHARMACEUTICALS USA, INC. (TEVA)

We recommend the following be implemented prior to approval of this NDA:

#### A. General Comments (Container labels & Carton labeling)

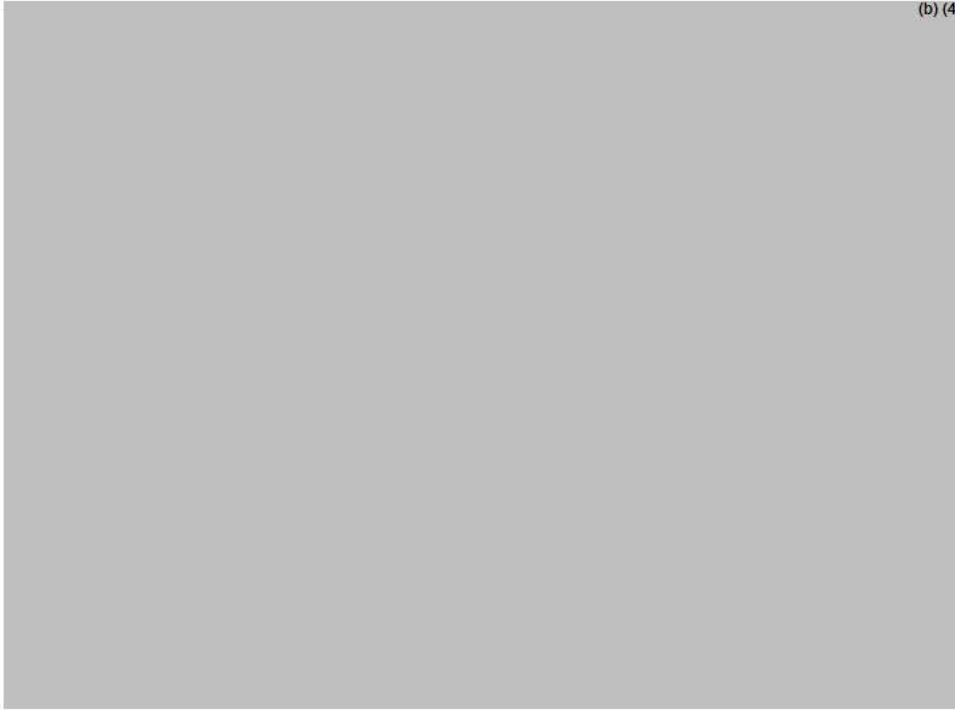
1. As currently presented, the quantity per total volume (10 mg/2 mL and 27.5 mg/5.5 mL) is not the primary and prominent expression on the principal display panel in accordance with USP General Chapter <7> as both are expressed with the same font size. We recommend decreasing the font size of the quantity per milliliter (5 mg/mL) to bring prominence to the total quantity per total volume to prevent confusion.
2. Revise the statement, “ ...0.9% sodium chloride injection, USP” to use official nomenclature and appear as “...0.9% Sodium Chloride Injection, USP” on the principal display panel of the container labels and carton labeling.

#### B. Carton Labeling

1. We recommend relocating and increasing the prominence of the word, “Sterile” to the bottom of the side panel as this is important information to the end user and as currently displayed it is difficult to read.

**APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JANUARY 23, 2020**

**Container labels**



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HINA S MEHTA  
01/30/2020 03:43:35 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: January 24, 2020

To: Kimberly Scott, RN, BSN, OCN®  
Senior Regulatory Health Project Manager  
**Division of Hematologic Malignancies 2 (DHM2)**

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

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Ruth Mayrosh, PharmD  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Rachael Conklin, MS, RN  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): Romidepsin Injection

Dosage Form and Route: injection, for intravenous use

Application Type/Number: NDA 208574

Applicant: Teva Pharmaceuticals USA Inc.

## 1 INTRODUCTION

On November 22, 2019, Teva Pharmaceuticals USA Inc. submitted for the Agency's review a New Drug Application (NDA) 208574 for Romidepsin Injection, in response to the Agency's Complete Response Letter issued on November 4, 2019 citing facility deficiencies. The Reference Listed Drug for this application is ISTODAX (romidepsin) for injection, NDA 022393. The proposed indication for Romidepsin Injection is for:

- the treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy
- peripheral T-cell lymphoma (PTCL) in adult patients who have received at least one prior therapy.

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 Hematologic Malignancies 2 (DHM2) on January 14, 2020, and January 10, 2020, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Romidepsin Injection.

## 2 MATERIAL REVIEWED

- Draft Romidepsin Injection PPI received on January 14, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 15, 2020.
- Draft Romidepsin Injection Prescribing Information (PI) received on January 14, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 15, 2020.
- Approved ISTODAX (romidepsin) for injection comparator labeling dated November 27, 2018.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, 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 document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The PPI is 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 is 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.

Please let us know if you have any questions.

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RACHAEL E CONKLIN  
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BARBARA A FULLER  
01/24/2020 02:10:35 PM

LASHAWN M GRIFFITHS  
01/24/2020 04:30:13 PM

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

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

**Memorandum**

**Date:** 1/17/20

**To:** Kimberly Scott, Regulatory Project Manager, DHMII  
Stacy Shord, Associate Director of Labeling, OHOP

**From:** Rachael Conklin, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Kevin Wright, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for ROMIDEPSIN injection, for intravenous use

**NDA:** 208574

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In response to consult request dated January 10, 2020, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the 505(b)2 submission for ROMIDEPSIN injection, for intravenous use (romidepsin).

**PI and PPI:** OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on January 16, 2020, and are provided below.

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

Thank you for your consult. If you have any questions, please contact Rachael Conklin at 240-402-8189 or [rachael.conklin@fda.hhs.gov](mailto:rachael.conklin@fda.hhs.gov).

**PI**

OPDP does not have any comments on the PI at this time.

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

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

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

**Memorandum**

**Date:** 1/17/20

**To:** Kimberly Scott, Regulatory Project Manager, DHMII  
Stacy Shord, Associate Director of Labeling, OHOP

**From:** Rachael Conklin, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Kevin Wright, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for ROMIDEPSIN injection, for intravenous use

**NDA:** 208574

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In response to consult request dated October 15, 2019, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the 505(b)2 submission for ROMIDEPSIN injection, for intravenous use (romidepsin).

This memo is in response to DHM2's labeling consult request dated October 15, 2019. Reference is made to a Complete Response letter that was issued on November 4, 2019. Therefore, OPDP defers comment on the proposed labeling at this time.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at 240-402-8189 or [rachael.conklin@fda.hhs.gov](mailto:rachael.conklin@fda.hhs.gov).

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RACHAEL E CONKLIN  
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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**REVIEW DEFERRAL MEMORANDUM**

Date: November 5, 2019

To: Ann Farrell, MD  
Director  
**Division of Hematology Products (DHP)**

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

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Ruth Mayrosh, PharmD  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: Review Deferred: Patient Package Insert (PPI)

Drug Name (established name): Romidepsin Injection

Dosage Form and Route: injection, for intravenous use only

Application Type/Number: NDA 208574

Applicant: Teva Pharmaceuticals USA Inc.

## **1 INTRODUCTION**

On May 29, 2019, Teva Pharmaceuticals USA Inc. submitted for the Agency's review a Class 2 Resubmission 505(b)(2) New Drug Application (NDA) 208574 for Romidepsin Injection, in response to the Agency's Complete Response Letter that was issued on June 2, 2017 due to facility deficiencies. The proposed indication for Romidepsin Injection is for the treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy or peripheral T-cell lymphoma (PTCL) in adult patients who have received at least one prior therapy.

On October 15, 2019, the Division of Hematology Products (DHP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for Romidepsin Injection.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI for Romidepsin Injection.

## **2 CONCLUSIONS**

Due to outstanding facility deficiencies, DHP issued a Complete Response (CR) letter dated November 4, 2019. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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11/05/2019 09:03:51 AM

LASHAWN M GRIFFITHS  
11/05/2019 09:54:04 AM

## Division of Hematology Products Associate Director for Labeling Review of the Prescribing Information

|                                                   |                                           |
|---------------------------------------------------|-------------------------------------------|
| <b>Product Title</b>                              | ROMIDEPSIN injection, for intravenous use |
| <b>Applicant</b>                                  | Teva Pharmaceuticals USA, Inc.            |
| <b>Application/Supplement Number</b>              | NDA 208574                                |
| <b>Is Proposed Labeling in Old Format? (Y/N)</b>  | N                                         |
| <b>Is Labeling Being Converted to PLR? (Y/N)</b>  | N                                         |
| <b>Is Labeling Being Converted to PLLR? (Y/N)</b> | N                                         |
| <b>Approved Indication(s)</b>                     | n/a                                       |
| <b>Date FDA Received Application</b>              | 05/29/19                                  |
| <b>Review Classification (Priority/Standard)</b>  | Standard                                  |
| <b>Action Goal Date</b>                           | 11/29/19                                  |
| <b>Review Date</b>                                |                                           |
| <b>Reviewer</b>                                   | Virginia Kwitkowski, MS, ACNP-BC          |

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the Warnings and Precautions section of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements<sup>1</sup>
- Is consistent with labeling guidance recommendations<sup>3</sup> and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

**Background:** The Applicant has submitted a new NDA pursuant to 505(b)(2) of the Federal FD&C Act for Romidepsin Injection, 10 mg/2 mL (5 mg/mL) ready to use formulation for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy (per FDA Form 356h).

This application references the Listed Drug NDA 22393, Istodax (romidepsin) for injection of Celgene.

**Reviewer Comments:** The USPI was reviewed for consistency with current regulations and guidances as well as with the currently approved Istodax labeling (last revised on 11/27/18). The draft labeling with revisions by me and other reviewers is appended below.

<sup>1</sup> See [January 2006 Physician Labeling Rule](#); 21 CFR [201.56](#) and [201.57](#); and [December 2014 Pregnancy and Lactation Labeling Rule](#) (the PLLR amended the PLR regulations). For applications with labeling in non-PLR “old” format, see 21 CFR [201.56\(e\)](#) and [201.80](#).

<sup>3</sup> See [PLR Requirements for PI](#) website for PLR labeling guidances.

**Regulatory Recommendation:** This NDA is recommended for approval upon completion of labeling negotiations.

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LABEL 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\*\*\*

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|                                |                                                                         |
|--------------------------------|-------------------------------------------------------------------------|
| Date of This Review:           | September 4, 2019                                                       |
| Requesting Office or Division: | Division of Hematology Products (DHP)                                   |
| Application Type and Number:   | NDA 208574                                                              |
| Product Name and Strength:     | Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL) |
| Product Type:                  | Single Ingredient Product                                               |
| Rx or OTC:                     | Prescription (Rx)                                                       |
| Applicant/Sponsor Name:        | Teva Pharmaceuticals USA, Inc. (Teva)                                   |
| FDA Received Date:             | May 29, 2019 and July 18, 2019                                          |
| OSE RCM #:                     | 2019-1175                                                               |
| DMEPA Safety Evaluator:        | Nicole Garrison, PharmD, BCPS                                           |
| DMEPA Team Leader:             | Hina Mehta, PharmD                                                      |

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## 1 REASON FOR REVIEW

As part of the approval process for NDA 208574 Romidepsin Injection, 10 mg/2 mL (5mg/mL) and 27.5 mg/5.5 mL (5 mg/mL), this review evaluates the proposed container labels, carton labeling, Patient Information and Prescribing Information (PI) for areas that may lead to medication errors.

### 1.1 REGULATORY HISTORY

Teva submitted Romidespin Injection (NDA 208574) on August 18, 2015, as a 505(b)(2) application which relies upon the listed drug, Istodax (romidepsin) for Injection under NDA 022393. The application received a Complete Response (CR) letter on June 1, 2016 due to product quality issues. Teva submitted a response to the CR letter for Romidespin Injection on December 29, 2016. Subsequently, the application for Romidepsin Injection received another CR letter on June 2, 2017 due to facility inspection issues. Teva submitted a response to the second CR letter for Romidespin Injection on May 29, 2019.

Istodax for Injection is currently marketed as 10 mg per vial. Unlike the listed drug (LD), Romidespin Injection will be available as 10 mg/2 mL and 27.5 mg/5.5 mL single dose vials .

## 2 MATERIALS REVIEWED

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

| Table 1. Materials Considered for this Label and Labeling Review |                                               |
|------------------------------------------------------------------|-----------------------------------------------|
| Material Reviewed                                                | Appendix Section<br>(for Methods and Results) |
| Product Information/Prescribing Information                      | A                                             |
| Previous DMEPA Reviews                                           | B                                             |
| Human Factors Study                                              | C-N/A                                         |
| ISMP Newsletters*                                                | D-N/A                                         |
| FDA Adverse Event Reporting System (FAERS)*                      | E-N/A                                         |
| Other                                                            | F-N/A                                         |
| Labels and Labeling                                              | G                                             |

N/A=not applicable for this review

\*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

### 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Teva submitted a 505(b)(2) application to obtain marketing approval of Romidepsin Injection. Romidepsin is indicated for the treatment of cutaneous T-cell lymphoma and peripheral T-cell lymphoma in adult patients who have received at least one prior therapy. We note that the proposed Romidepsin Injection will have the same indication, route of administration, recommended dosage, and storage as the LD Istodax. However, there are differences in the proposed presentations as Romidepsin Injection will be available as an aqueous solution in 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL) single dose vials; unlike the LD Istodax which is a 10 mg lyophilized powder requiring reconstitution. Both Romidepsin Injection and LD Istodax (when reconstituted) have the same final concentration and must be further diluted in 500 mL of 0.9% Sodium Chloride Injection, USP. See Appendix A for product characteristics comparison of the LD Istodax (NDA 022393) and the proposed Romidepsin Injection product (NDA 208574).

From a medication error perspective, the introduction of a solution of Romidepsin that does not require reconstitution may reduce the risk of compounding errors and reduces the number of needle entries into the vial, which is valuable with regard to aseptic technique. We also recognize that the introduction of two additional presentations (10 mg/2 mL and 27.5/5.5 mL) of Romidepsin Injection that does not require reconstitution, but results in the same concentration, 5 mg/mL, may result in preparation errors if the labeling is overlooked and mistaken for LD Istodax for Injection. Therefore, it is important to ensure that labels and labeling contain warning statements regarding further dilution and include prominent concentration information.

We performed a risk assessment of the proposed container labels, carton labeling, Patient Information and Prescribing Information to determine whether there are significant concerns in terms of safety related to preventable medication errors. We identified areas of the proposed labels and labeling that could be revised to improve clarity and readability of important information.

For the Division, we recommend removing abbreviations and revising storage statements for clarity. For the Applicant, we recommend changes to the carton and container labels to improve readability and prominence of important information. Specifically, we recommend increasing prominence of the final concentration, defining the expiration date, and including

product identifiers. In addition, we recommend revising the color scheme of the strength presentation and storage information on the labeling.

#### 4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. We provide recommendations below in Section 4.1 for the Division and Section 4.2 for Teva Pharmaceuticals USA, Inc. (Teva) to address our concerns. We advise these recommendations are implemented prior to approval of this product.

##### 4.1 RECOMMENDATIONS FOR THE DIVISION

###### A. Highlights of Prescribing Information

###### 1. Dosage and Administration Section

- a. The dosage and administration section (b) (4) (b) (4), for the route of administration. The route of administration should be described (b) (4) therefore we recommend deleting (b) (4) (b) (4) (b) (4).

###### B. Prescribing Information

###### 1. How Supplied/Storage and Handling Section

- a. Consider revising the statements (b) (4) to appear as "Store at 20°C-25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) in the carton [see USP Controlled Room Temperature]. Protect from light."

###### C. Patient Information

1. In Section, "How will I receive Romidepsin?", contains (b) (4) (b) (4), for the route of administration. The route of administration should be described (b) (4) therefore we recommend deleting (b) (4) (b) (4).

##### 4.2 RECOMMENDATIONS FOR TEVA PHARMACEUTICALS USA, INC. (TEVA)

We recommend the following be implemented prior to approval of this BLA:

###### A. General Comments (Container labels & Carton Labeling)

1. Relocate the final concentration, “5 mg/mL” into the color text box directly below the statement of strength for increased prominence.
2. The Rx Only Statement appears prominent the principal display panel of the container labels and carton labeling. Decrease the prominence by debolding the Rx Only statement.
3. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling. See draft guidance <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>
4. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
5. Consider revising the statements (b) (4)  
 to appear as “Recommended Storage: Store at 20°C-25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) in the carton [see USP Controlled Room Temperature]. Protect from light.”
6. Relocate the word, “Sterile” from the principal display panel to decrease clutter and move to the side panel.

#### B. Container Labels

1. Romidepsin has a cytotoxic component; however this information not omitted from on the container labels. Cytotoxic products require special handling

procedures. Include the statement in bold font on the side display panel, “CAUTION: Cytotoxic Agent”.

2. Revise the statement, (b) (4) to “Dosage: See Prescribing Information.”

#### C. Carton Labeling

1. Romidepsin has a cytotoxic component; however this information not omitted from on the carton labeling. Cytotoxic products require special handling procedures. Include the statement in bold font on the principal display panel, (b) (4)
2. Include the net quantity statement (i.e. one vial) on the PDP in accordance with CFR 201.51. Consider “One Single-Dose Vial”.
3. Revise the statement, “ (b) (4) to “Dosage: See Prescribing Information.”

# APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

## APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Romidepsin received on May 29, 2019 from Teva Pharmaceuticals USA, Inc. (Teva), and the listed drug (LD).

| Table 2. Relevant Product Information for Romidepsin and the Listed Drug |                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                    |
|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Product Name                                                             | Romidepsin                                                                                                                                                                                                                                                                                                     | Istodax <sup>a</sup>                                                                                                                                                                                                                                               |
| Initial Approval Date                                                    | N/A                                                                                                                                                                                                                                                                                                            | November 5, 2009                                                                                                                                                                                                                                                   |
| Active Ingredient                                                        | romidepsin                                                                                                                                                                                                                                                                                                     | romidepsin                                                                                                                                                                                                                                                         |
| Indication                                                               | <ul style="list-style-type: none"> <li>For the treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy</li> <li>For the treatment of peripheral T-cell lymphoma (PTCL) in adult patients who have received at least one prior therapy</li> </ul> |                                                                                                                                                                                                                                                                    |
| Route of Administration                                                  | Intravenous infusion                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                    |
| Dosage Form                                                              | Injection                                                                                                                                                                                                                                                                                                      | Lyophilized powder for injection                                                                                                                                                                                                                                   |
| Strength                                                                 | 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL)                                                                                                                                                                                                                                                              | 10 mg per vial                                                                                                                                                                                                                                                     |
| Dose and Frequency                                                       | The recommended dose is 14 mg/m <sup>2</sup> administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle.                                                                                                                                                                           |                                                                                                                                                                                                                                                                    |
| How Supplied                                                             | <ul style="list-style-type: none"> <li>10 mg/2 mL (5 mg/mL) single dose vial</li> <li>27.5 mg/5.5 mL (5 mg/mL) single dose vial</li> </ul>                                                                                                                                                                     | Istodax for injection kit contains one 10 mg single dose vial containing 11 mg of romidepsin and 22 mg of the bulking agent, povidone, USP. In addition, each kit includes a single-dose sterile diluent vial containing 2.4 mL (2.2 mL deliverable volume) of 80% |

<sup>a</sup> Istodax [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 AUG 23. Available from: <https://www.accessdata.fda.gov/spl/data/4de9bc05-56a5-4cf1-9233-da3794743800/4de9bc05-56a5-4cf1-9233-da3794743800.xml>.

|         |                                                                                                                                                                                |                                                                                                                            |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
|         |                                                                                                                                                                                | propylene glycol, USP, and 20% dehydrated alcohol, USP.                                                                    |
| Storage | Stored at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to °86°F). [see USP Controlled Room Temperature]. Store vial in carton. Protect from light. | The carton must be stored at 20° to 25°C, excursions permitted between 15° to 30°C. (See USP Controlled Room Temperature.) |

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 22, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Romidepsin. Our search identified 2 previous label and labeling reviews<sup>b,c</sup> for the listed drug, and we confirmed that our previous recommendations were implemented.

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<sup>b</sup> Ayres, E. Label and Labeling Review for Romidepsin (NDA 208574). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JAN 11. RCM No.: 2015-2243.

<sup>c</sup> Rahimi, L. Label and Labeling Review for Romidepsin (NDA 208574). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 APR 18. RCM No.: 2017-22.

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>d</sup> along with postmarket medication error data, we reviewed the following Romidepsin labels and labeling submitted by Teva Pharmaceuticals USA, Inc. (Teva).

- Container labels received on May 29, 2019
- Carton labeling received on May 29, 2019
- Patient Information received on July 18, 2019
- Prescribing Information (Image not shown) received on July 18, 2019

### G.2 Label and Labeling Images

#### Container labels



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<sup>d</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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NICOLE B GARRISON  
09/04/2019 01:57:56 PM

HINA S MEHTA  
09/04/2019 03:26:45 PM

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

**REVIEW DEFERRAL MEMORANDUM**

Date: May 12, 2017

To: Ann Farrell, MD  
Director  
**Division of Hematology Products (DHP)**

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

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Shawna Hutchins, MPH, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: Review Deferred: Patient Package Insert (PPI)

Drug Name (established name): romidespin

Dosage Form and Route: injection, for intravenous infusion

Application Type/Number: NDA 208574

Applicant: Teva Pharmaceuticals

## **1 INTRODUCTION**

On December 29, 2016, Teva Pharmaceuticals, resubmitted for the Agency's review an original New Drug Application (NDA) for romidespin injection, for intravenous infusion. This NDA was originally submitted on August 18, 2015, but received a Complete Response (CR) letter issued by the Agency on June 01, 2016. On February 15, 2017, the Division of Hematology Products (DHP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for romidespin injection, for intravenous infusion.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI for romidespin injection, for intravenous infusion.

## **2 CONCLUSIONS**

Due to outstanding Chemistry Manufacturing and Controls (CMC) deficiencies, DHP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/  
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SHAWNA L HUTCHINS  
05/12/2017

BARBARA A FULLER  
05/12/2017

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## **LABEL 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\*\*\***

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|                                       |                                          |
|---------------------------------------|------------------------------------------|
| <b>Date of This Review:</b>           | April 18, 2017                           |
| <b>Requesting Office or Division:</b> | Division of Hematology Products (DHP)    |
| <b>Application Type and Number:</b>   | NDA 208574                               |
| <b>Product Name and Strength:</b>     | Romidepsin Injection, 10 mg/2mL (5mg/mL) |
| <b>Product Type:</b>                  | Single-Ingredient                        |
| <b>Rx or OTC:</b>                     | Rx                                       |
| <b>Applicant/Sponsor Name:</b>        | Teva Pharmaceuticals                     |
| <b>Submission Date:</b>               | December 29, 2016                        |
| <b>OSE RCM #:</b>                     | 2017-22                                  |
| <b>DMEPA Primary Reviewer:</b>        | Leeza Rahimi, Pharm.D.                   |
| <b>DMEPA Team Leader:</b>             | Hina Mehta, Pharm.D.                     |

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## 1 REASON FOR REVIEW

Teva Pharmaceuticals submitted a class-2 resubmission in response to a Complete Response (CR) issued by the Agency for Romidepsin injection under pending NDA 208574. The proposed strength for Romidepsin injection is 10 mg/2 mL (5mg/mL) aqueous solution.

The Division of Hematology Products (DHP) consulted DMEPA to review the labels and labeling of the product for areas of vulnerability that may lead to medication errors.

### 1.1 BACKGROUND HISTORY

The Applicant previously submitted NDA 208574 under section 505 (b)(2) for approval on August 18, 2015. Romidepsin Injection differs from Reference Listed Drug (RLD) Istodax that is a lyophilized powder for injection requiring reconstitution. The route of administration and storage requirements are the same as RLD Istodax. However, unlike RLD Istodax, Romidepsin Injection will not be indicated for the treatment of peripheral T-cell lymphoma (PTCL) due to exclusivity protection.

On June 1, 2016 the application received a Complete Response by FDA due to deficiencies observed in product quality. Thus, Teva re-submitted the application on December 29, 2016 for Agency's review.

DMEPA completed a review of label and labeling on January 11, 2016 <sup>a</sup> prior to application receiving a CR.

## 2 MATERIALS REVIEWED

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

| Table 1. Materials Considered for this Label and Labeling Review |                                               |
|------------------------------------------------------------------|-----------------------------------------------|
| Material Reviewed                                                | Appendix Section<br>(for Methods and Results) |
| Product Information/Prescribing Information                      | A                                             |
| Previous DMEPA Reviews                                           | B                                             |
| Human Factors Study                                              | C-N/A                                         |
| ISMP Newsletters                                                 | D-N/A                                         |
| FDA Adverse Event Reporting System (FAERS)*                      | E-N/A                                         |
| Other                                                            | F-N/A                                         |
| Labels and Labeling                                              | G                                             |

N/A=not applicable for this review

\*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

### **3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED**

Teva Pharmaceuticals submitted a class-2 resubmission for Romidepsin Injection. We performed a risk assessment of the Prescribing Information (PI), carton and container labels to identify deficiencies that may lead to medication errors and other areas of improvement. We note that the Applicant has implemented our previous recommendations to the PI and container labels. However, we identified an area in carton label that could be improved to promote the safe use of the product.

For the Applicant, we recommend a change in the carton labeling to increase the prominence of final concentration (5mg/mL). We provide our recommendation for the Applicant in section 4.1.

### **4 CONCLUSION & RECOMMENDATIONS**

DMEPA concludes that the proposed carton label can be improved to increase the readability and prominence of important information, and promote the safe use of the product and mitigate any confusion. We provide our recommendation for the Applicant in section 4.1 of this review.

#### **4.1 RECOMMENDATIONS FOR TEVA PHARMACEUTICALS**

We recommend the following be implemented prior to approval of this NDA:

A. Carton Label:

1. Please re-align the presentation of final concentration “(5mg/mL)” in the primary display panel. As currently presented, the statement is difficult to read. We recommend you increase the spacing between the blue box containing “10 mg/2 mL” and “(5mg/mL)” to be consistent with the container labels.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Romidepsin that Teva Pharmaceuticals submitted on December 29, 2016, and the listed drug (LD).

| <b>Table 2. Relevant Product Information for Romidepsin and the Listed Drug</b> |                                                                                                                                                                      |                                                                                                                                                                                                                                                                                          |
|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Product Name</b>                                                             | <b>Romidepsin</b>                                                                                                                                                    | <b>Istodax</b>                                                                                                                                                                                                                                                                           |
| <b>Initial Approval Date</b>                                                    | N/A                                                                                                                                                                  | November 5, 2009                                                                                                                                                                                                                                                                         |
| <b>Active Ingredient</b>                                                        | Romidepsin                                                                                                                                                           | Romidepsin                                                                                                                                                                                                                                                                               |
| <b>Indication</b>                                                               | <ul style="list-style-type: none"> <li>- Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.</li> </ul> | <ul style="list-style-type: none"> <li>- Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.</li> <li>- Treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy.</li> </ul> |
| <b>Route of Administration</b>                                                  | Intravenous infusion                                                                                                                                                 | Intravenous infusion                                                                                                                                                                                                                                                                     |
| <b>Dosage Form</b>                                                              | Intravenous solution                                                                                                                                                 | Lyophilized powder for injection                                                                                                                                                                                                                                                         |
| <b>Strength</b>                                                                 | 10 mg/2 mL (5 mg/mL)                                                                                                                                                 | 10 mg per vial                                                                                                                                                                                                                                                                           |
| <b>Dose and Frequency</b>                                                       | 14 mg/m <sup>2</sup> administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle                                                          | 14 mg/m <sup>2</sup> administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle                                                                                                                                                                              |
| <b>How Supplied</b>                                                             | 10 mg/2 mL single dose vial                                                                                                                                          | Istodax kit includes: One single use vial of romidepsin for injection, 10 mg and 1 vial of diluent for romidepsin, 2 mL per carton                                                                                                                                                       |
| <b>Storage</b>                                                                  | Store at 20° to 25°C (68° to 77°F), excursions permitted between 15° to 30°C (59° to 86°F)                                                                           | Must be stored at 20° to 25°C, excursions permitted between 15° to 30°C                                                                                                                                                                                                                  |

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On March 11, 2017, we searched the L:drive and AIMS using the terms, Romidepsin to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified one relevant review <sup>a</sup>, and we confirmed that our previous recommendations were implemented.

<sup>a</sup> Whales, E. Label and Labeling Review for Romidepsin NDA 208574. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); January 11, 2016. RCM # 2015-2243.

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>a</sup> along with postmarket medication error data, we reviewed the following Romidepsin labels and labeling submitted by Teva Pharmaceuticals on December 29, 2016.

- Container label
- Carton labeling
- Prescribing Information

### **G.2 Label and Labeling Images**

#### **Container Label:**



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<sup>b</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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LEEZA RAHIMI  
04/18/2017

HINA S MEHTA  
04/19/2017

**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: April 18, 2016

To: Ann Farrell, MD  
Director  
**Division of Hematology Products (DHP)**

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

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Rowell Medina, PharmD  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Rachael Conklin, MS, RN  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): Romidepsin injection

Dosage Form and Route: injection, for intravenous use

Application Type/Number: NDA 208574

Applicant: Teva Pharmaceutical Industries LTD

## 1 INTRODUCTION

On August 18, 2015, Teva Pharmaceutical Industries LTD submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 208574 for romidepsin injection. The Reference Listed Drug for this application is ISTODAX (romidepsin) for injection, NDA 022393. The proposed indication for romidepsin injection is for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.

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 Hematology Products (DHP) on October 19, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for romidepsin injection.

## 2 MATERIAL REVIEWED

- Draft romidepsin injection PPI received on August 18, 2015, and received by DMPP and OPDP on April 6, 2016.
- Draft romidepsin injection Prescribing Information (PI) received on August 18, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 6, 2016.
- Approved ISTODAX (romidepsin) comparator labeling dated October 15, 2014.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI, the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, 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 have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

#### **4 CONCLUSIONS**

The PPI is 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 is 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.

Please let us know if you have any questions.

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/s/  
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ROWELL MEDINA  
04/18/2016

RACHAEL E CONKLIN  
04/18/2016

BARBARA A FULLER  
04/18/2016

LASHAWN M GRIFFITHS  
04/18/2016

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

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

Memorandum

**Date:** 04/13/2016

**To:** Kimberly Scott, Regulatory Project Manager  
Division of Hematology Products (DHP)

**From:** Rachael Conklin, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Through:** Kathleen Davis, Team Leader, OPDP

**Subject:** Comments on draft labeling (Package Insert) for ROMIDEPSIN injection, for intravenous use  
NDA 208574

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In response to your labeling consult request dated October 19, 2015, we have reviewed the draft Package Insert (PI) for ROMIDEPSIN injection, for intravenous use (Romidepsin injection). This review is based upon the version of the draft PI e-mailed to OPDP on April 6, 2016.

If you have any questions, please contact Rachael Conklin at (240) 402-8189 or [Rachael.Conklin@fda.hhs.gov](mailto:Rachael.Conklin@fda.hhs.gov).

Package Insert

| <u>Section</u>                                     | <u>Statement from Draft<br/>(if applicable)</u>                                                                                                                                                                                                                        | <u>OPDP Comment</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 7.2 Drugs That Inhibit Cytochrome P450 3A4 Enzymes | "Monitor for toxicity related to increased romidepsin exposure and follow the dose modifications for toxicity [see <i>Dosage and Administration</i> (2.2)] when romidepsin is <b>initially</b> co-administered with strong CYP3A4 inhibitors . . . ." (emphasis added) | <p>We are concerned with the use of the word "initially" in this sentence as it implies that monitoring and dose modification of Romidepsin are only necessary at the outset of co-administration with a CYP3A4 inhibitor.</p> <p>As dose changes of the CYP3A4 inhibitors would impact romidepsin exposure, would it be appropriate to revise this sentence to delete the word "initially" in order to better convey the importance of consistent monitoring/dose modification when</p> |

|                                   |  |                                                                                                                                                                                                                                                                                                           |
|-----------------------------------|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                   |  | <p>romidepsin is co-administered with a CYP3A4 inhibitor?</p> <p>“Monitor for toxicity related to increased romidepsin exposure and follow the dose modifications for toxicity [<i>see Dosage and Administration (2.2)</i>] when romidepsin is co-administered with strong CYP3A4 inhibitors . . . .”</p> |
| (b) (4)                           |  |                                                                                                                                                                                                                                                                                                           |
| 17 PATIENT COUNSELING INFORMATION |  | <p>Would it be possible to add a subheading for lactation? For example:</p> <p>Lactation</p> <p>Advise patients that breastfeeding is not recommended during romidepsin treatment</p> <p>(b) (4)</p>                                                                                                      |

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/s/  
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RACHAEL E CONKLIN  
04/13/2016

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### **LABEL 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\*\*\***

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|                                       |                                               |
|---------------------------------------|-----------------------------------------------|
| <b>Date of This Review:</b>           | January 11, 2016                              |
| <b>Requesting Office or Division:</b> | Division of Hematology Products (DHP)         |
| <b>Application Type and Number:</b>   | NDA 208574                                    |
| <b>Product Name and Strength:</b>     | Romidepsin Injection,<br>10 mg/2 mL (5 mg/mL) |
| <b>Product Type:</b>                  | Single-ingredient                             |
| <b>Rx or OTC:</b>                     | Rx                                            |
| <b>Applicant/Sponsor Name:</b>        | Teva                                          |
| <b>Submission Date:</b>               | August 8, 2015 and October 16, 2015           |
| <b>OSE RCM #:</b>                     | 2015-2243                                     |
| <b>DMEPA Primary Reviewer:</b>        | Ebony Ayres, PharmD, BCPPS                    |
| <b>DMEPA Team Leader:</b>             | Yelena Maslov, PharmD                         |

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## 1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Romidepsin Injection (NDA 208574) for areas of vulnerability that could lead to medication errors. DHP requested this review as part of their evaluation of the 505(b)(2) submission for Romidepsin Injection. The reference listed drug (Istodax, NDA 022393) was approved in November 2009.

## 2 MATERIALS REVIEWED

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

| <b>Table 1. Materials Considered for this Label and Labeling Review</b> |                                                   |
|-------------------------------------------------------------------------|---------------------------------------------------|
| <b>Material Reviewed</b>                                                | <b>Appendix Section (for Methods and Results)</b> |
| Product Information/Prescribing Information                             | A                                                 |
| Previous DMEPA Reviews                                                  | B                                                 |
| Human Factors Study                                                     | C (N/A)                                           |
| ISMP Newsletters                                                        | D                                                 |
| FDA Adverse Event Reporting System (FAERS)*                             | E                                                 |
| Other                                                                   | F (N/A)                                           |
| Labels and Labeling                                                     | G                                                 |

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed container labels, carton labeling, and Prescribing Information (PI) for Romidepsin Injection, NDA 208574. Romidepsin Injection is supplied as a 10 mg/2 mL (5 mg/mL) aqueous solution. This differs from RLD Istodax which is a lyophilized powder for injection requiring reconstitution. The route of administration and storage requirements are the same as RLD Istodax; however, unlike RLD Istodax, Romidepsin Injection will not be indicated for the treatment of peripheral T-cell lymphoma (PTCL) due to exclusivity protection.

Both Romidepsin Injection and RLD Istodax (when reconstituted) have the same final concentration. Additionally, Romidepsin Injection is in solution form and does not require reconstitution; however, as with RLD Istodax, further dilution is required. Eliminating the need for reconstitution may help to reduce the risk of compounding errors and reduces the number of needle entries into the vial, which is valuable with regard to aseptic technique.

We searched the FAERS database and did not identify any medication error cases relevant to this review.

With regards to the carton labeling and container labels, the Applicant uses the phrase (b) (4) to indicate the route of administration on the principal display panel (PDP). However, we recommend revision of this term to “for intravenous infusion” as Romidepsin Injection should be infused over four hours. Additionally, we note that the Prescribing Information contains error-prone symbols, which can lead to misinterpretation and dosing errors. To mitigate this risk, the PI can be revised to include the intended meaning in place the symbols.

## **4 CONCLUSION & RECOMMENDATIONS**

DMEPA concludes that the proposed labels, labeling and prescribing information can be improved to increase the readability and prominence of information on the label.

### **4.1 RECOMMENDATIONS FOR THE DIVISION**

- A. Romidepsin Prescribing Information
  - a. Section 2 Dosage and Administration
    - i. Error-prone symbols that are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout this section.<sup>1</sup> In particular, the following symbols appear frequently:  $\geq$  and  $\leq$ . Please revise these symbols to reflect their intended meanings and to prevent misinterpretation and confusion.
  - b. Section 3 Dosage Forms and Strengths
    - i. Revise the phrase (b) (4) to “...single dose vial”.<sup>2</sup> We recommend this revision to accurately reflect the package type.
  - c. Section 16 How Supplied/Storage and Handling
    - i. See recommendation A.b.i. and revise accordingly.

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<sup>1</sup> ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2015 OCT 28]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

<sup>2</sup> See Draft Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015 Oct [cited 2015 DEC 23]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>.

## 4.2 RECOMMENDATIONS FOR THE TEVA

We recommend the following changes be implemented prior to approval of NDA 208574:

### A. Romidepsin Carton Labeling

- a. Consider revising the statement (b) (4) to “For intravenous infusion after dilution”. We recommend this revision to minimize the risk of administering the drug as an intravenous bolus and to minimize the risk of the product being administered without dilution.
- b. If space permits, consider relocating the statement “Must be diluted in 500 mL of 0.9% sodium chloride injection, USP” from the side panel to the principal display panel (PDP). We recommend this revision to increase the visibility of the dilution instructions.
- c. Revise the phrase (b) (4) to “Single Dose Vial”.<sup>2</sup>

### B. Romidepsin Container Label

- a. See recommendations A.a. through A.c. and revise accordingly.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Romidepsin that Teva submitted on August 8, 2015 and October 16, 2015, and the listed drug (LD).

| <b>Table 2. Relevant Product Information for Romidepsin and the Listed Drug</b> |                                                                                                                                                                      |                                                                                                                                                                                                                                                                                          |
|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Product Name</b>                                                             | <b>Romidepsin</b>                                                                                                                                                    | <b>Istodax</b>                                                                                                                                                                                                                                                                           |
| <b>Initial Approval Date</b>                                                    | N/A                                                                                                                                                                  | November 5, 2009                                                                                                                                                                                                                                                                         |
| <b>Active Ingredient</b>                                                        | Romidepsin                                                                                                                                                           | Romidepsin                                                                                                                                                                                                                                                                               |
| <b>Indication</b>                                                               | <ul style="list-style-type: none"> <li>- Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.</li> </ul> | <ul style="list-style-type: none"> <li>- Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.</li> <li>- Treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy.</li> </ul> |
| <b>Route of Administration</b>                                                  | Intravenous infusion                                                                                                                                                 | Intravenous infusion                                                                                                                                                                                                                                                                     |
| <b>Dosage Form</b>                                                              | <b>Intravenous solution</b>                                                                                                                                          | Lyophilized powder for injection                                                                                                                                                                                                                                                         |
| <b>Strength</b>                                                                 | <b>10 mg/2 mL (5 mg/mL)</b>                                                                                                                                          | 10 mg per vial                                                                                                                                                                                                                                                                           |
| <b>Dose and Frequency</b>                                                       | 14 mg/m <sup>2</sup> administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle                                                          | 14 mg/m <sup>2</sup> administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle                                                                                                                                                                              |
| <b>How Supplied</b>                                                             | <b>10 mg/2 mL single use vial</b>                                                                                                                                    | Istodax kit includes: 1 single use vial of romidepsin for injection, 10 mg and 1 vial of diluent for romidepsin, 2 mL per carton                                                                                                                                                         |
| <b>Storage</b>                                                                  | Store at 20° to 25°C (68° to 77°F), excursions permitted between 15° to 30°C (59° to 86°F)                                                                           | Must be stored at 20° to 25°C, excursions permitted between 15° to 30°C                                                                                                                                                                                                                  |

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On October 30, 2015, we searched the L:drive and AIMS using the term romidepsin to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified two previous postmarketing medication error reviews for RLD Istodax, which reported difficulty withdrawing the full contents of Istodax (romidepsin) were described.<sup>3</sup> <sup>4</sup> Romidepsin Injection does not require reconstitution. DHP submitted an Information Request to the Sponsor regarding the withdrawal volume. The Sponsor responded with results from an internal study which demonstrated that the labeled withdrawal of 2 mL of Romidepsin Injection can be consistently met.<sup>5</sup> Therefore, we have no further concerns regarding withdrawal of the full contents of the vial.

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<sup>3</sup> Vee, Sarah. Signal Workup Istodax NDA 22393. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 OCT 18. RCM No.: 2012-2093.

<sup>4</sup> Ayres, Ebony. Postmarketing Review Memo Istodax NDA 22393. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 9. RCM No.: 2015-1990.

<sup>5</sup> Teva. Response to FDA Request for Information – Quality. NDA 208574. 2015 DEC 23.

## APPENDIX D. ISMP NEWSLETTERS

### D.1 Methods

On October 28, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

| ISMP Newsletters Search Strategy |                                                                                                                |
|----------------------------------|----------------------------------------------------------------------------------------------------------------|
| ISMP Newsletter(s)               | Acute Care<br>Community<br>Nursing<br>Joint Commission<br>PA Patient Safety<br>QAA Acute Care<br>QAA Community |
| Search Strategy and Terms        | Match Exact Word or Phrase: romidepsin                                                                         |

### D.2 Results

Our search identified one newsletter which reported medication errors in which health care practitioners were unable to withdraw the full contents of reconstituted Istodax (romidepsin).<sup>6</sup> Romidepsin Injection does not require reconstitution. Additionally, romidepsin is included on the ISMP List of Additional Drug Names with Tall Man Letters and is listed as “romiDEPsin”.<sup>7</sup>

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<sup>6</sup> Institute for Safe Medication Practices. Safety briefs: Full content cannot be withdrawn from Istodax vial. ISMP Med Saf Alert Acute Care. 2012;17(18):2.

<sup>7</sup> FDA and ISMP Lists of Look-Alike Drug names With Recommended Tall Man Letters [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2011 [cited 2015 OCT 28]. Available from: <http://www.ismp.org/tools/tallmanletters.pdf>.

## APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

### E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on October 27, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.<sup>8</sup>

| Table 3: FAERS Search Strategy |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Date Range                     | FDA Rcvd. Date To: 20151001                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Product                        | Romidepsin [active ingredient]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Event (MedDRA Terms)           | <b>DMEPA Official FBIS Search Terms Event List:</b><br>Contraindicated Drug Administered (PT)<br>Drug Administered to Patient of Inappropriate Age (PT)<br>Inadequate Aseptic Technique in Use of Product (PT)<br>Medication Errors (HLGT)<br>Overdose (PT)<br>Prescribed Overdose (PT)<br>Prescribed Underdose (PT)<br>Product Adhesion Issue (PT)<br>Product Compounding Quality Issue (PT)<br>Product Formulation Issue (PT)<br>Product Label Issues (HLT)<br>Product Packaging Issues (HLT)<br>Product Use Issue (PT)<br>Underdose (PT) |
| Country                        | USA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

### E.2 Results

Our search identified four cases, but after further evaluation, we didn't identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

We excluded the three cases because they described reconstitution errors specific to RLD Istodax. In the aforementioned cases, health care practitioners reported difficulties

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<sup>8</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

withdrawing the full contents of Istodax vials after reconstitution. Additionally, we excluded one case because it did not describe a medication error; it reported a comment regarding the use of the brand name “Coumadin” in Section 7 Drug Interactions of the Prescribing Information. A review of the PI for the RLD Istodax notes that Section 7.1 is titled “Warfarin and Coumarin Derivatives”; therefore, no further intervention is warranted.

### **E.3 Description of FAERS**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>9</sup> along with postmarket medication error data, we reviewed the following Romidepsin labels and labeling submitted by Teva on August 8, 2015 and October 16, 2015.

- Container label
- Carton labeling
- Prescribing Information (not pictured)

### **G.2 Label and Labeling Images**

- Container label



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<sup>9</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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