

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208574Orig1s000

208574Orig2s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

TO: File for NDA 208574

FROM: Brenda J Gehrke, PhD
Pharmacology-Toxicology Acting Team Leader
(Primary Reviewer for NDA 208574)
Division of Hematology Oncology Toxicology
Office of Oncologic Diseases

THROUGH: Haleh Saber, PhD
Deputy Division Director
Division of Hematology Oncology Toxicology
Office of Oncologic Diseases

DATE: January 14, 2020

SUBJECT: NDA Resubmission

NDA: 208574

DRUG: Romidepsin Injection, 10 mg/vial (5 mg/mL)

INDICATION: Treatment of cutaneous T-cell lymphoma (CTCL)

APPLICANT: Teva Pharmaceuticals USA

Romidepsin (Istodax) is a histone deacetylase (HDAC) inhibitor approved for the treatment of cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy. NDA 208574 is a 505(b)(2) application and was initially submitted as a ready-to-use liquid formulation of romidepsin (Romidepsin Injection, 10 mg/2mL) for the CTCL indication with Istodax as the listed drug in 2015. The primary pharmacology/toxicology review of NDA 208574 was completed and filed in April 2016. There were no pharmacology/toxicology concerns with the application. The FDA issued a Complete Response letter to the Applicant in June 2016 with a quality deficiency related to extractables/leachables.

The current submission, Supporting Document 21 for NDA 208574, is a resubmission. To address the issue of the extractables and potential leachables from

(b) (4)

was submitted under Module 3.2.P.2. in the May 29, 2019 submission. Below is a brief summary of the methods and assessment provided by the Applicant.

(b) (4)

(b) (4) The extractables were detected at concentrations below their MACs. The overall conclusion of the toxicological assessment was that the (b) (4) and (b) (4) (b) (4) were toxicologically qualified and there is no concern that arises from the levels of the compounds that can potentially leach into the romidepsin ready-to-use drug product solution.

The pharmacology/toxicology team has reviewed the data and concluded that based on the available information on the compounds in the toxicological assessment report, the known toxicities observed with the treatment of romidepsin, and the proposed indication of CTCL, there are no pharmacology/toxicology concerns (b) (4)

Recommendation:

Recommending approval. There are no pharmacology/toxicology issues for NDA 208574 to preclude approval of the drug for the proposed indication.

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/s/

BRENDA J GEHRKE
01/15/2020 08:51:25 AM

HALEH SABER
01/15/2020 08:53:54 AM

MEMORANDUM

TO: File for NDA 208574

FROM: Brenda J Gehrke, PhD
Pharmacology-Toxicology Reviewer
Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

THROUGH: Christopher Sheth, PhD
Pharmacology-Toxicology Supervisor
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Office of Hematology and Oncology Products

DATE: May 3, 2017

SUBJECT: NDA Resubmission

NDA: 208574

DRUG: Romidepsin Injection, 10 mg/vial (5 mg/mL)

INDICATION: Treatment of cutaneous T-cell lymphoma (CTCL)

APPLICANT: Teva Pharmaceuticals USA

Romidepsin (Istodax) is a histone deacetylase (HDAC) inhibitor approved for the treatment of cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy. NDA 208574 was initially submitted as a 505(b)(2) application for a ready-to-use liquid formulation of romidepsin (Romidepsin Injection, 10 mg/2mL) for the CTCL indication with Istodax as the listed drug in August 2015. The primary pharmacology/toxicology review of NDA 208574 was completed and filed on April 28, 2016. There were no pharmacology/toxicology concerns with the application and the recommended regulatory action from pharmacology/toxicology was approval. The FDA issued a Complete Response letter to the Applicant in June 2016 with quality deficiencies. The following text was provided in the Complete Response letter:

“...the rationale used to support potential extractables/leachables from the (b) (4)
(b) (4)
Address this concern as it relates to
the proposed manufacturing conditions, taking into consideration any worst case
scenario such as (b) (4). Please include data and/or
study results to support your conclusions (b) (4)
”

The current submission, Supporting Document 10 for NDA 208574, is a Class 2 Resubmission. To address the deficiency mentioned above, a study to identify the extractables and potential leachables from the (b) (4) of the romidepsin ready-to-use drug product was conducted. In the NDA resubmission, a report titled “ (b) (4)

(b) (4)

”

(b) (4)

(b) (4) was provided under Module 3.2.P.3.5. The report did not include a safety assessment of the compounds which were found above the Analytical Evaluation Threshold (AET) limit, therefore, an information request to provide this information was sent to the Applicant from CMC on March 30, 2017. In the response to the information request (Supporting Document 11) received on April 6, 2017, a second study report titled “

(b) (4)

”

(b) (4) was provided under Module 3.2.P.3.5. along with the corresponding report for the

(b) (4)

in Module 5.4.

In the extraction study, the (b) (4) were exposed to different solutions (b) (4) and temperatures (25 °C and 50 °C), and the extracts were analyzed for (b) (4). The toxicological assessment report provided an evaluation and conclusion on the safety of the levels of each of the extractable and leachable compounds detected above the AET. Based on the recommended dose of romidepsin of 14 mg/m² administered intravenously on Days 1, 8, and 15 of a 28-day cycle and a body surface area of (b) (4) m², a maximum dose of (b) (4) mg/day romidepsin was used to calculate the maximum daily exposure levels (µg/day) for each compound. The list of the extractable and leachable compounds detected above the AET was (b) (4) including the following presented with the maximum daily exposure levels in the table below.

Compound	Maximum daily exposure level
(b) (4)	

Computational analyses for toxicological alerts were conducted with the Nexus platform version 2.1.0, consisting of the expert rule-based Derek (version 5.1.0) for the mutagenicity and skin irritation/sensitization endpoints and the statistical-based Sarah (version 1.2.0) for the mutagenicity endpoint. All the known compounds with structures were negative for mutagenicity in the (Q)SAR analyses. The toxicological assessment report reviewed the available toxicological information from the literature for each of the compounds or the class of compounds and calculated the permitted daily exposure (PDE) values where there was sufficient

information to do so. The overall conclusion of the toxicological assessment was that all the compounds were toxicologically qualified and there is no concern that arises from the levels of the compounds that can potentially leach into the romidepsin ready-to-use drug product solution. Based on the available information on the compounds in the toxicological assessment report, the known toxicities observed with the treatment of romidepsin, and the proposed indication of CTCL, there are no pharmacology/toxicology concerns with the levels of the compounds that may potentially leach from the manufacturing components into the romidepsin ready-to-use drug product.

Recommendation:

Recommending approval. There are no pharmacology/toxicology issues for NDA 208574 to preclude approval of the drug for the proposed indication.

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/s/

BRENDA J GEHRKE
05/03/2017

CHRISTOPHER M SHETH
05/03/2017

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 208574
Supporting document/s: 1
Applicant's letter date: August 18, 2015
CDER stamp date: August 18, 2015
Product: Romidepsin Injection, 10 mg/vial (5 mg/mL)
Indication: Treatment of cutaneous T-cell lymphoma
(CTCL)
Applicant: Teva Pharmaceuticals USA
Review Division: Division of Hematology Oncology Toxicology
(for Division of Hematology Products)
Reviewer: Brenda J Gehrke, PhD
Supervisor/Team Leader: Christopher M Sheth, PhD
Division Director: John Leighton, PhD, DABT
Ann Farrell, MD (DHP)
Project Manager: Kimberly L Scott, RN, BSN, OCN

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208574 are owned by Teva Pharmaceuticals USA or are data for which Teva Pharmaceuticals USA has obtained a written right of reference. Any information or data necessary for approval of NDA 208574 that Teva Pharmaceuticals USA does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208574.

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1 Executive Summary

1.1 Introduction

Romidepsin (Istodax) is a histone deacetylase (HDAC) inhibitor approved for the treatment of cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy. Istodax is supplied as a kit containing two single-use vials, one containing romidepsin as a sterile lyophilized white powder and one containing the diluent as a sterile clear solution. Istodax is reconstituted using the supplied diluent prior to intravenous administration. NDA 208574 has been submitted as a 505(b)(2) application for a ready-to-use liquid formulation of romidepsin (Romidepsin Injection, 10 mg/2mL) for the CTCL indication with Istodax as the listed drug. Romidepsin Injection also differs from Istodax by containing an additional inactive ingredient, α -tocopherol (b) (4). The Applicant is relying on the FDA's previous finding of safety and efficacy for Istodax.

1.3 Recommendations

1.3.1 Approvability

Recommended for approval. The previous findings of safety and efficacy for the listed drug Istodax provide sufficient information to support the use of Romidepsin Injection for the proposed indication.

1.3.2 Additional Non Clinical Recommendations

None

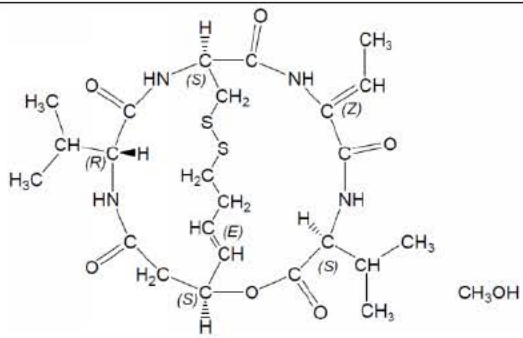
1.3.3 Labeling

The proposed labeling is consistent with the label for Istodax. No new pharmacology or toxicology information was added to the proposed label. Changes were made to the pregnancy related sections of the prescribing information in order for the label to be in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

2 Drug Information

2.1 Drug

CAS Registry Number	128517-07-7
Generic Name	Romidepsin
Chemical Name	(1S,4S,7Z,10S,16E,21R)-7-ethylidene-4,21-bis(1-methylethyl)-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone
Molecular Formula/ Molecular Weight	C ₂₄ H ₃₆ N ₄ O ₆ S ₂ ·CH ₄ O/ 572.74 g/mol

Structure or Biochemical Description	
Pharmacologic class	Histone deacetylase (HDAC) inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 122145, NDA 22393 (Istodax)

2.3 Drug Formulation

Romidepsin Injection is a ready-to-use solution for intravenous administration supplied as a sterile, clear, colorless to pale yellow solution in (b) (4) glass vials containing 10 mg of romidepsin as a 10 mg/2 mL (5 mg/mL) solution. Each mL contains 5 mg romidepsin, 10 mg povidone, 0.05 mg DL- α -tocopherol, 157.8 mg dehydrated alcohol, and 828.8 mg propylene glycol.

Composition for Romidepsin Injection, 10 mg/vial (5 mg/mL) (excerpted from Applicant's submission)

Ingredients	Function of Components	Concentration (mg/mL)	Content (mg/vial) ^a
Romidepsin ^b	Active Pharmaceutical Ingredient	5.0	(b) (4)
Povidone USP	(b) (4)	10	(b) (4)
DL-Alpha – tocopherol USP ^c	(b) (4)	0.05	(b) (4)
Dehydrated Alcohol, USP	(b) (4)	157.8	(b) (4)
Propylene Glycol, USP	(b) (4)	(b) (4)	(b) (4)
(b) (4)			
(b) (4)			

Component of the proposed container closure system
(excerpted from Applicant's submission)

COMPONENT	DESCRIPTION	COMPONENT SUPPLIER	ADDRESS OF SUPPLIER
Vial	(b) (4) clear type glass vial	(b) (4)	(b) (4)
Stopper	13 mm (b) (4) stopper with (b) (4)		
Cap	13 mm grey aluminum cap (b) (4)		

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

CMC has consulted pharmacology/toxicology to determine the safety of extractable and leachable impurities from the container closure system of the Romidepsin Injection drug product. Based on the proposed indication for the treatment of cutaneous T-cell lymphoma, the qualification thresholds for impurities for drug products in ICHQ3B were used to assess the safety of the extractable and leachable impurities for the Romidepsin Injection drug product. For a maximum daily dose of (b) (4) mg ($14 \text{ mg/m}^2 \times \text{human body surface area of } 1.7 \text{ m}^2$), the qualification threshold in ICHQ3B is 0.5% ((b) (4) μg) or (b) (4) μg total daily intake, whichever is lower. Since each vial contains 10 mg in 2 mL, (b) (4) vials containing (b) (4) mL of solution are needed to administer the maximum daily dose; this information was also used in the calculations.

Extractables

Controlled extraction studies were performed on vials and (b) (4) stoppers. The following compounds were present at higher levels in both solvents tested ((b) (4)). The maximum daily dose for each compound/impurity based on the highest amount detected in μg /stopper and the need for (b) (4) vials of drug product is presented in the table below.

Compound	Highest amount detected (ug/stopper)	Solvent used	Maximum daily dose (µg)
(b) (4)			

Based on the following, there are no pharmacology/toxicology concerns with the maximum daily doses of the extractable impurities:

- The maximum daily doses of (b) (4) are below the 0.5% qualification threshold of (b) (4) µg.
- (b) (4) are both present in the diet. The calculated maximum daily doses of (b) (4) in the proposed Romidepsin Injection drug product are more than 1000-fold lower than dietary levels.
- The maximum daily dose of the (b) (4) (b) (4) µg) is above the 0.5% qualification threshold of (b) (4) µg; however, it is lower than the alternative level of (b) (4) µg.

Leachables

The leachables from the container closure system for the Romidepsin Injection drug product were also investigated. The following compounds were present at levels at or above the set analytical evaluation threshold of (b) (4) µg/mL. The maximum daily dose for each compound/impurity based on the amount detected in µg/mL and the presence of (b) (4) mL of drug product in the (b) (4) vials needed is presented in the table below. Since the maximum daily doses for the leachable impurities are below the 0.5% qualification threshold of (b) (4) µg, there are no pharmacology/toxicology concerns.

Compound	Amount detected (µg/mL)	Maximum daily dose (µg)
(b) (4)		

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indication for Romidepsin Injection is the treatment of cutaneous T-cell lymphoma in patients who have received at least one prior systemic therapy. This indication is one of the approved indications for the listed drug Istodax. The recommended dose for Romidepsin Injection is 14 mg/m² administered intravenously over a 4-hour period on Days 1, 8, and 15 of a 28-day cycle.

2.7 Regulatory Background

Romidepsin is currently available as Istodax for injection marketed by Celgene Corporation under NDA 22393, and was initially approved by the FDA in November 2009. Teva Pharmaceuticals USA has developed a ready-to-use liquid formulation of romidepsin (Romidepsin Injection). Meetings held with the FDA under IND 122145 include a pre-IND meeting in May 2014 and a pre-NDA meeting in August 2015. NDA 208574 was submitted on August 18, 2015.

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/s/

BRENDA J GEHRKE
04/28/2016

CHRISTOPHER M SHETH
04/28/2016
I concur.