CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208574Orig1s000
208574Orig2s000

CLINICAL REVIEW(S)

Division Director Summary Review

Date	March 13, 2020
From	Nicole Gormley, MD
Subject	Division Director Summary Review
NDA/BLA # and Supplement #	208574, Resubmission
Applicant	Teva Pharmaceuticals, USA
Date of Submission	November 22, 2019
PDUFA Goal Date	May 22, 2020
Proprietary Name	Romidepsin Injection
Dosage Form(s)/Strength	Injection/ 5 mg/mL
Applicant Proposed Indication(s)	• Treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy. • Treatment of peripheral T-cell lymphoma (PTCL) in adult patients who have received at least one prior therapy*.
Action or Recommended Action:	Approval

*This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

This Division Director Summary Review is based on review of the following materials:

- CDTL Review by Sherita McLamore, PhD
- Clinical Review by Yvette Kasamon, MD

Summary: On November 22, 2019, Teva Pharmaceuticals resubmitted this 505(b)(2) application for romidepsin. The application was deemed a Class 2 Resubmission. The proposed indications are the same as those of the listed drug (LD), Istodax. Istodax was originally approved on 11/05/2009 for the treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy, and later received accelerated approval for the treatment of peripheral T-cell lymphoma (PTCL) in adult patients who have received at least one prior therapy (6/16/11). This application has previously been issued 3 complete responses (CRs) due to issues related to product quality.

The proposed product has the same active ingredient, concentration of the active ingredient, indications, and route of administration as the LD. The proposed drug product differs from the LD in the following manners:

- The proposed product is supplied as a sterile, clear solution while the LD is supplied as a lyophilized powder for reconstitution and as a part of a kit.
- The proposed product will include a 10 mg/2 mL and a 27.5 mg/5.5 mL presentation.

- The proposed product contains an additional inactive ingredient, α-tocopherol, (b) (4)

No clinical studies were performed as part of this application.

The proposed product is relying on FDA's findings of safety and effectiveness for Istodax for both the CTCL and the PTCL indications. At this time, Istodax is approved for the PTCL indication under the accelerated approval pathway. Because Teva's 505(b)(2) application, like all NDAs, is required to demonstrate safety and effectiveness, and the application relies on a finding for the PTCL indication based on a surrogate endpoint deemed reasonably likely to predict clinical benefit, it is appropriate for Teva's application to be approved under the accelerated approval pathway with a postmarketing requirement (PMR) to verify and describe its clinical benefit in confirmatory clinical trials. Thus, the proposed application will be approved with labeling describing the PTCL indication as based on response rate and continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. A PMR for the PTCL indication will be included in the approval letter to fulfill accelerated approval requirements to verify and describe the product's clinical benefit in that indication. Refer to the action letter for final wording of the PMR and for milestone dates. The clinical review and CDTL both recommend that the PMR include a statement that information to comply with the PMR can be based on the Agency's findings of safety and effectiveness with respect to the listed drug relied upon. I have decided not to include this statement in the PMR. I want to avoid implying that the PMR for Teva's product is somehow dependent on fulfillment of the PMR for Istodax. I note, however, that if Istodax verifies clinical benefit for the PTCL indication prior to the Final Report submission date for Teva's PMR, this application may be able to fulfill its PMR by relying on the Agency's finding of safety and effectiveness for Istodax with respect to confirmation of clinical benefit for the PTCL indication. If Istodax does not confirm clinical benefit for the PTCL indication, this application continues to have a PMR that imposes an independent obligation on Teva to do so.

All review disciplines recommend approval of this application.

Regulatory Recommendation: Approval for the CTCL indication and Accelerated Approval for the PTCL indication.

Nicole Gormley, MD

Division Director (acting), DHMII

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/s/

NICOLE J GORMLEY
03/13/2020 09:50:32 AM

MEMORANDUM

NDA:	208574
Drug:	Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL) in (b) (4) vials
Sponsor:	Teva Pharmaceuticals USA, Inc.
Receipt Date:	November 22, 2019
PDUFA Date:	May 22, 2020
Memo Date:	March 9, 2020
From:	Yvette Kasamon, clinical reviewer, DHMII
Through:	Nicholas Richardson, clinical team leader (acting), DHMII
Subject:	NDA clinical review

Overview of Submission: This is a Class 2 resubmission of a 505(b)(2) application for Romidepsin Injection by Teva Pharmaceuticals. A proprietary name was not proposed. The relied-upon listed drug is Istodax (romidepsin) for injection (Celgene Corporation; NDA 022393). The proposed indications are the same as for Istodax, namely:

- Treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy (regular approval)
- Treatment of peripheral T-cell lymphoma (PTCL) in adult patients who have received at least one prior therapy (accelerated approval)

Drug product: Teva's proposed drug product has the same amount of active ingredient and route of administration as Istodax. The drug products differ in that:

- Whereas the reference drug product is supplied as a lyophilized powder for reconstitution, Teva's product is supplied as a sterile, ready-to-use solution that requires no reconstitution.
- Teva's product contains an additional inactive ingredient, α-tocopherol, (b) (4)
- In addition to a 10 mg/2 mL (5 mg/mL) vial, Teva's product will be supplied as a 27.5 mg/5.5 mL (5 mg/mL) vial.

Regulatory history: This is the fourth submission of the NDA, with three prior Complete Responses due to CMC issues for the applications received 8/18/2015, 12/29/2016, and 5/9/2019. Teva originally submitted their NDA for the CTCL indication. In its May 2019 submission, Teva proposed to add the PTCL indication approved under accelerated approval and the 27.5 mg/5.5 mL (b) (4) vial. The Applicant requested a waiver of in-vivo bioavailability studies.

Per the Orange Book, there is no unexpired exclusivity for romidepsin. Celgene's Orphan Drug Exclusivities for Istodax expired on 11/05/2016 (CTCL) and 6/16/2018 (PTCL), and the New Chemical Entity exclusivity expired on 11/5/2014.

Data: No clinical safety or efficacy data were submitted in this NDA. The current application is approvable from a CMC perspective.

Clinical: The clinical team agrees with granting regular approval of Teva's drug for the CTCL indication, and accelerated approval for the PTCL indication, as worded in Istodax USPI and above. The proposed labeling was reviewed for consistency with the Istodax USPI.

For accelerated approval of the PTCL indication, we are relying on the Agency's previous finding of safety and effectiveness for Istodax, which included in this case, the reliance on a surrogate endpoint likely to predict clinical benefit for the PTCL indication. Given the reliance on a finding that was based on a surrogate endpoint, it is appropriate to require a postmarketing requirement (PMR) for the PTCL indication to fulfill the accelerated approval requirements to verify and describe the clinical benefit for that indication. The draft PMR language is as follows. Refer to the action letter for final wording of the PMR and for milestone dates.

PMR: Submit the final report from a randomized, controlled trial confirming the clinical benefit of romidepsin in patients with peripheral T-cell lymphoma, with progression free survival as the primary efficacy endpoint. Include an interim analysis of overall survival in the final study report. The required information to be submitted can be based on the Agency's previous findings of safety and effectiveness with the reference drug product or on a trial conducted by Teva Pharmaceuticals.

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/s/

YVETTE L KASAMON
03/09/2020 11:32:59 AM

NICHOLAS C RICHARDSON
03/12/2020 02:25:29 PM

Cross-Discipline Team Leader Review

Date	04-Nov-2019
From	Sherita D. McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	208574
Type of Application	505(b)(2)
Applicant	Teva Pharmaceuticals
Date of Receipt	29-May-2019
PDUFA Goal Date	29-Nov-2019
Proposed Proprietary/Established Names	Romidepsin Injection
Dosage forms / Strength	Injection/ 5 mg/mL
Route of Administration	Intravenous
Proposed Indication(s)	• Treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy. • Treatment of peripheral T-cell lymphoma (PTCL) in adult patients who have received at least one prior therapy*.
Recommended:	**COMPLETE RESPONSE**

*This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials

This CDTL review is based on the primary reviews, memos and documented review input of:

- Clinical (Yvette Kasamon, M.D.)
- Drug Product (Anamitro Banerjee, Ph.D.)
- Microbiology (David Bateman, Ph.D.)
- Manufacturing Process and Facilities (Kumar Janoria, Ph.D.)

1. Introduction

NDA 208574 was submitted by Teva Pharmaceuticals as a 505(b)(2) NDA under the Federal Food, Drug and Cosmetic Act for Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL). Romidepsin is histone deacetylase (HDAC) inhibitor that was originally approved for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy. Romidepsin was later granted a new indication under accelerated approval for the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy

This application presents a new formulation of Romidepsin. Romidepsin is a small molecule, bicyclic depsipeptide that was isolated from the bacterium Chromobacterium violaceum. Istodax (romidepsin) for Injection, 10 mg manufactured by Celgene and approved under NDA 22393 is the

listed drug (LD) for this NDA. Istodax was initially granted regular approval on 11/05/2009 for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy and was later granted a new indication under accelerated approval for the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy.

The proposed drug product has the same active ingredient and dosage form as the LD but differs in all other aspects. The proposed product is presented as a sterile, clear, colorless to pale yellow solution containing povidone, DL-alpha-tocopherol, dehydrated alcohol and propylene glycol. The proposed product is supplied in single-dose vials and is intended for intravenous infusion. The LD presented as a sterile, lyophilized powder in a 10 mg single-dose vial containing 11 mg of romidepsin and povidone. It is packaged as a part of a kit which includes the lyophilized powder together with a single-dose sterile diluent vial containing propylene glycol and dehydrated alcohol.

The primary differences between the Teva product and LD are:

- The Teva product is supplied as a sterile, clear solution while the LD is supplied as a lyophilized powder for reconstitution and as a part of a kit.
- The Teva product will include a 10 mg/2 mL and a 27.5 mg/5.5 mL presentation.

No clinical studies were performed with the Teva formulation. Instead, this NDA relies on Istodax (romidepsin) for Injection, 10 mg manufactured by Celgene (NDA 22393) for safety and efficacy.

2. Background

NDA 208574 was originally submitted to the Agency in October of 2015. This submission was not approved but was issued a Complete Response on June 1, 2016 for issues related to product quality (specifically extractables/leachables from the (b) (4)). The applicant responded to the June 2016 Complete Response in December 2016. The December 2016 resubmission was issued a Complete Response in June of 2017 as a result of a withhold recommendation from facilities. This submission (May 29, 2019) represents the response to the Agency's June 2017 Complete Response Letter. In this submission, the Applicant addressed the issues identified in the June 2017 Complete Response and proposed the following changes:

1. Transferring the manufacture of the 2 mL configuration from the Teva facility in Gödöllő, Hungary site to the Teva facility in Irvine, CA (this change addressed the December 2016 CR issue as the Irvine, CA site replaced the Gödöllő, Hungary site).
2. Addition of a new drug product configuration, 27.5 mg/ 5.5 mL. The 5.5 mL configuration has the same concentration (i.e. 5 mg/mL) as the 2 mL configuration.
3. Addition of the PTCL indication (previous submissions on NDA 208574 only requested the CTCL indication)

No other changes were proposed or included in this re-submission.

3. Product Quality

NDA 208574 has been previously been issued two Complete Responses due to issues related to product quality. This submission is the response to the Agency's June 2017 CR Letter. In this submission the Applicant addressed the June 2017 CR deficiency by transferring the manufacture of the 2 mL configuration from the Teva facility in Gödöllő, Hungary site (which was issued a WITHHOLD recommendation during the last review cycle) to the Teva facility in Irvine, CA. In addition to the site transfer, the applicant added a new drug product configuration, 27.5 mg/ 5.5 mL. The 5.5 mL configuration has the same concentration (i.e. 5 mg/mL) as the 2 mL configuration.

New Packaging Configuration:
The new packaging configuration was reviewed by the product quality review team and it was conlcuded that the differences in the analytical methods, specifications and container closure between the 2 mL packaging configuration and 5.5 mL packaging configuration were negligible. No changes were proposed for the API, the drug product formulation or the (b) (4) ; however, there were differences noted in the vial and stopper (b) (4) and in the headspace to volume ratio (higher for the 2 mL form). The new packaging configuration was reviewed and deemed acceptable by all product quality review disciplines.

Transfer of Drug Product Manufacturing Site:
The applicant proposed to transfer drug product manufacturing from the Teva facility in Gödöllő, Hungary site to the Teva facility in Irvine, CA. This change was made in an effort to address the December 2016 CR issue; however, a PAI inspection of the Teva Irvine site resulted in a Withhold recommendation for GMP reasons. Accordingly, this facility is not acceptable to support the approval of NDA 208574, hence this application is deemed inadequate from a compliance perspective. A satisfactory resolution of all deficiencies is required before this NDA may be recommended for approval from the CMC perspective.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality recommends a **COMPLETE RESPONSE** for NDA 208574.

6. Clinical Pharmacology
No new clinical/pharmacology information was included in the resubmission

7. Non-Clinical Pharmacology/Toxicology
n/a

8. Clinical/Statistical-Efficacy
Efficacy was initially based on the Prescribing Information for the Listed Drug and no new information was included in this resubmission.

9. Safety
Safety was initially based on the Prescribing Information for the Listed Drug and no new information was included in this resubmission.

10. Advisory Committee Meeting **N/A**

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

Overall Labeling Recommendation:
The review of the label was completed by the Associate Director for Labeling (see review dated 11/1/2019); however, as a result of the anticipated CR recommendation, labeling reviews were suspended and a final labeling recommendation was not made during this review cycle. Labeling reviews will resume once the sponsor provides an adequate response to this Complete Response. Accordingly, the overall labeling recommendation pending at this time.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the Listed Drug and there were no new clinical or nonclinical studies conducted for this 505(b)(2) application.

With the exception of Facilities (OPF), all disciplines recommended approval of this NDA. The Facilities reviewer entered a withhold recommendation for this NDA because it was determined that the drug product manufacturing site is not in compliance with cGMPs. Accordingly, the CDTL recommendation for this NDA is a **COMPLETE RESPONSE.** The applicant must address all the facility related deficiencies before this NDA may be recommended for approval.

CR Comment to be Conveyed to the applicant:
During a recent inspection of the TEVA PARENTERAL MEDICINES, INC. (FEI 2027158) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

- **Risk Benefit Assessment**

Please refer to NDA 22393.

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/s/

SHERITA D MCLAMORE
11/04/2019 08:34:52 AM

MEMORANDUM

NDA:	208574
Drug:	Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL) in (b) (4) vials
Sponsor:	Teva Pharmaceuticals USA, Inc.
Receipt Date:	May 29, 2019
PDUFA Date:	November 29, 2019
Memo Date:	October 23, 2019
From:	Yvette Kasamon, MD, clinical reviewer, DHP
Through:	R. Angelo de Claro, clinical team leader, DHP
Subject:	NDA clinical review

Summary of Review Findings: No clinical safety or efficacy data were submitted in this NDA application. For recommendations regarding this NDA, please refer to reviews by other disciplines.

Overview of Submission: This is a Class 2 resubmission of a 505(b)(2) application for Romidepsin Injection by Teva Pharmaceuticals. A proprietary name was not proposed. The reference drug product is Istodax (romidepsin) for injection (Celgene Corporation; NDA 022393). The proposed indications are the same as for Istodax, namely:

- Treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy (regular approval)
- Treatment of peripheral T-cell lymphoma (PTCL) in adult patients who have received at least one prior therapy (accelerated approval)

Drug product: Teva's proposed drug product has the same amount of active ingredient and route of administration as Istodax. The drug products differ in that:

- Whereas the reference drug product is supplied as a lyophilized powder for reconstitution, Teva's product is supplied as a sterile, ready-to-use solution that requires no reconstitution.
- Teva's product contains an additional inactive ingredient, α-tocopherol, (b) (4) .
- In addition to a 10 mg/2 mL (5 mg/mL) vial, Teva's product will be supplied as a 27.5 mg/5.5 mL (5 mg/mL) vial.

Regulatory history: Teva originally submitted their NDA on August 18, 2015 for the CTCL indication. It received a Complete Response due to CMC issues, specifically because of concerns regarding potential extractables/leachables from the (b) (4). The application was resubmitted December 29, 2016 but received a Complete Response due to CMC issues, specifically a withhold recommendation from the Office of Process and Facilities reviewer.

The current application adds the PTCL indication and the 27.5 mg/5.5 mL (b) (4) vial. The Applicant requests a waiver of in-vivo bioavailability studies.

According to the Orange Book database, there is no unexpired exclusivity for Istodax. Celgene's Orphan Drug Exclusivities for Istodax expired on 11/05/16 (CTCL) and 06/16/18 (PTCL), and the New Chemical Entity exclusivity expired on 11/05/14."

The proposed labeling was reviewed for consistency with the reference listed drug.

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/s/

YVETTE L KASAMON
10/23/2019 11:32:05 AM

ROMEO A DE CLARO
10/30/2019 03:13:46 PM

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Edvardas Kaminskas, M.D.
Subject	Deputy Division Director Summary Review
NDA# **Supplement #**	208574 Resubmission
Applicant Name	Teva Pharmaceuticals USA
Date of Submission	December 29, 2016
PDUFA Goal Date	June 29, 2017
Established (USAN) Name	Romidepsin Injection
Dosage Forms / Strength	Solution, 10 mg/2 mL vial (5 mg/mL)
Proposed Indications	Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy
Action:	**Complete Response**

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Hyon-Zu Lee, Pharm.D./Virginia E. Kwitkowski, M.S., ACNP-BC
Pharmacology Toxicology Review	Brenda J. Gehrke, Ph.D./Christopher M. Sheth, Ph.D.
CMC Review	Haripada Sarker, Ph.D. (Drug Substance) Paresma Patel, Ph.D. (Drug Product) Kumar Janoria, Ph.D./Maotand Zhou, Ph.D. (Process) David Bateman, Ph.D. (Microbiology) Christina Capacci-Daniel, Ph.D./Derek S. Smith, Ph.D. (Facility) Om Anand, Ph.D. (Biopharmaceutics)
CDTL Review	Anamitro Banerjee, Ph.D.
OMPI/DMPP Review	Shawna Hutchins, BSN, M.P.H./Rowell Medina, Pharm.D./LaShawn Griffiths, MSHS-PH, BSN/Barbara Fuller, MSN, CWOCN
OPDP Review	Rachael Conklin, M.S./Kathleen Davis, BSN, M.S.
OSE/OMPRM/DMEPA Review	Leeza Rahimi, Pharm.D./Hina Mehta, Pharm.D.

OND=Office of New Drugs
OMPRM=Office of Medication Error Prevention and Risk Management
OMPI=Office of Medical Policy Initiatives
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This is a 505(b)(2) application by Teva Pharmaceuticals. Teva is not proposing a proprietary name for their product. The reference drug product (RLD) is Celgene's Istodax® (romidepsin) for injection (NDA 022393). Istodax was initially granted regular approval on 11/05/2009 for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy. On 6/16/2011 Istodax was granted a new indication under accelerated approval for the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy. The Sponsor is seeking only the CTCL indication for its romidepsin product. The orphan drug exclusivity (ODE) for Istodax for the CTCL indication expired on 11/05/2016; the exclusivity for the PTCL indication will expire on 6/16/2018.

Teva's proposed drug product has the same amount of active ingredient and the same route of administration. The main difference between Teva's proposed drug product and the RLD Istodax is that Istodax is supplied as a kit that includes a sterile, lyophilized powder vial and a sterile diluent vial for use in reconstitution before use, while Teva's product will be supplied as a sterile solution that requires no reconstitution prior to use. The drug should be diluted in 500 mL of 0.9% saline injection, USP prior to administration. In addition, Teva's drug product formulation contains α-tocopherol (b) (4)

2. Background

Teva Pharmaceuticals originally submitted this application on August 18, 2015. The application was not approved; it received a Complete Response on the basis that the rationale used to support potential extractables/leachables from the (b) (4) . The sponsor committed to provide study reports regarding potential leachables from the (b) (4) by September, 2016.

3. CMC/Device

Drug Substance: No new information was submitted in the resubmission. The NDA remains acceptable for Drug Substance.

Drug Product: No new information was submitted in the resubmission. The NDA remains acceptable for Drug Product.

Process: The Process Reviewer acknowledged the receipt of a study report by the sponsor regarding potential leachables from the (b) (4). The study design was found acceptable. The study showed several extractable compounds above the Analytical Evaluation Threshold (AET) limit, the majority being (b) (4). Pharmacology/ Toxicology Division was consulted; their recommendations was "There are no P/T issues for NDA 208574 to preclude approval of the drug for the proposed indication". In summary, "The application is recommended for approval from the process perspective".

Facility: Significant CGMP and product specific deficiencies were observed at the drug product manufacturing facility proposed in this NDA. A Complete Response is recommended. The following language should be used:

During a recent inspection of the Teva Pharmaceutical Works Private Limited Company, Gödöllö, Hungary (FEI 3002875215) manufacturing facility for this application, FDA field investigators conveyed deficiencies to the representatives of this facility. **A Complete Response action is recommended due to a withhold recommendation from the Office of Process and Facilities reviewer.** Satisfactory resolution of these deficiencies is required before this application may be approved.

Biopharmaceutics: No new information was submitted in the resubmission. The NDA remains acceptable for biopharmaceutics.

Microbiology: No new information was submitted in the resubmission. The NDA remains acceptable for Microbiology.

Assessment of Environmental Analysis: No new information was submitted in the resubmission.

Overall CMC Recommendation: The Office of Pharmaceutical Quality recommends a COMPLETE RESPONSE ACTION for NDA 208754 from the CMC perspective.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance."

4. Nonclinical Pharmacology/Toxicology

In this resubmission, the applicant provided results from a study to identify the extractables and potential leachables from the (b) (4) of the romidepsin ready-to-use drug product. The Pharmacology/Toxicology reviewers concluded that there are no pharmacology/toxicology concerns (b) (4) (b) (4)

[redacted] (b) (4). The Non-Clinical Pharmacology/Toxicology reviewers recommended approval of this NDA.

"I concur with the conclusions reached by the non-clinical pharmacology/toxicology reviewers that there are no outstanding pharmacology/toxicology issues that preclude approval."

5. Clinical Pharmacology/Biopharmaceutics

N/A. The applicant did not submit any clinical pharmacology data.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical-Efficacy

N/A. The applicant did not submit any new clinical efficacy data in this NDA.

8. Safety

N/A. The applicant did not submit any new clinical safety data in this NDA.

9. Advisory Committee Meeting

This 505(b)(2) NDA was not presented to an Advisory Committee.

10. Pediatrics

N/A.

11. Other Relevant Regulatory Issues

"There are no other unresolved relevant regulatory issues"

12. Labeling

The proposed labeling was to be reviewed for consistency with RLD and ensuring that the labeling with PTCL information removed allows for safe use of this product. Reviewers from ODPD, DMPP, and DMEPA reviewed the proposed labeling, but final recommendations were deferred because of the anticipated CR action and were not conveyed to the sponsor.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: **Complete Response** due to a withhold recommendation from the Office of Process and Facilities on the basis of deficiencies in the drug product manufacturing site.

- Risk Benefit Assessment
  Refer to NDA 022393.

- Recommendation for Postmarketing Risk Management Activities
  Refer to NDA 022393.
- Recommendation for other Postmarketing Study Commitments
  Refer to NDA 022393.

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/s/

EDVARDAS KAMINSKAS
05/24/2017

FILE MEMORANDUM

Memo Date:	February 4, 2016
To NDA:	208574
Submission Date:	August 18, 2015
FDA Received Date:	August 18, 2015
EDR Location:	\\CDSESUB1\evsprod\NDA208574\0000
From:	Hyon-Zu Lee, Pharm.D., Clinical Reviewer; Division of Hematology Products (DHP)
Subject:	Romidepsin Injection, 10 mg/2 mL
Via:	Virginia Kwitkowski, MS, ACNP-BC, Clinical Team Leader, DHP

ISSUE: N/A

ACTIONS RECOMMENDED: Tentative approval

Summary of Review Findings: No clinical safety or efficacy data were submitted in this NDA application. For recommendations regarding this NDA, please refer to reviews by other disciplines.

Background:
This is a 505(b)(2) application by Teva Pharmaceuticals. Teva is not proposing a proprietary name for their product. The reference drug product is Celgene's Istodax® (romidepsin) for injection (NDA 022393). Istodax was initially granted traditional approval on 11/05/09 for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy. On 06/16/11, Istodax was granted a new indication under accelerated approval for the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy. With this approval, a Post-Marketing Requirement was issued (#1775-1) under Subpart H where the Applicant is required to perform a randomized trial in previously untreated patients with PTCL randomized to CHOP ± romidepsin with PFS as the primary endpoint.

According to the Orange Book, Celgene has existing exclusivities for its Istodax product. It has two Orphan Drug Exclusivities (ODE) that expire on 11/05/16 (CTCL) and 06/16/18 (PTCL). The New Chemical Entity exclusivity expired on 11/05/14.

This application seeks the CTCL indication and not the PTCL indication, because the ODE for the CTCL indication expires sooner (on 11/05/16). Teva stated in their Exclusivity Request that they will not seek final approval for their product prior to 11/05/16. They also stated that they omitted the PTCL indication from their proposed labeling and will continue to do so until the ODE expires on 06/16/18.

Teva's proposed drug product has the same amount of active ingredient and route of administration. The main difference between Teva's proposed drug product and Celgene Corporation's product is that Istodax® is supplied as a kit that includes a sterile, lyophilized powder vial and a sterile diluent vial that have to be reconstituted prior to administration, while Teva's product will be supplied as a sterile solution that requires no reconstitution prior to

dilution. The drug product should be diluted in 500 mL of 0.9% saline injection, USP prior to administration.

In addition, Teva's proposed drug product differs from the reference listed drug in the inactive ingredients. Specifically, Teva's drug product formulation contains an additional inactive ingredient, α-tocopherol, (b) (4) that the reference listed drug does not contain. (b) (4)

Teva requests a biowaiver (a waiver of the requirement for the submission of evidence demonstrating the bioequivalence of the drug product).

The proposed labeling will be reviewed for consistency with the RLD and ensuring that the labeling with PTCL information removed allows for safe use of this product.

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/s/

HYON-ZU LEE
02/04/2016

VIRGINIA E KWITKOWSKI
02/04/2016