CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208574Orig1s000
208574Orig2s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	17-Feb-2020
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	22-Nov-2019
PDUFA Goal Date	22-May-2020
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:	**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 CDTL review is based on the primary reviews, memos and documented review input of:

- Clinical (Yvette Kasamon, M.D.)
- Pharmacology/Toxicology (Brenda Gehrke, Ph.D.)
- Drug Product (Anamitro Banerjee, 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 a 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 is a small molecule, bicyclic depsipeptide 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 originally approved 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 approval for the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy under accelerated approval (6/16/11). Istodax's current approved labeling contains the following statements after the PTCL indication to reflect the accelerated approval status: "This indication is approved under accelerated approval based on response rate [see Clinical Studies (14.2)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials." Compared to Istodax, Teva's application presents a new dosage form and presentation of Romidepsin.

The proposed drug product is seeking approval for the same active ingredient, route of administration, concentration of active ingredient, and indications as the LD but differs in its dosage form and presentation. Teva's original NDA submission sought approval of only the CTCL indication; in its May 29, 2019 resubmission, Teva proposed to add the PTCL indication. 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 FDA's finding of safety and effectiveness for Istodax (romidepsin) for Injection, 10 mg manufactured by Celgene (NDA 22393) for safety and efficacy.

2. Background

NDA 208574 has been issued three Complete Responses (CRs) due to issues related to product quality.

1st Review Cycle: October 18, 2015

NDA 208574 was originally submitted to the Agency in October of 2015 (PDUFA Date: 6/18/2016). This submission was issued a Complete Response on June 1, 2016 for matters related to product quality (specifically extractables/leachables from the (b) (4)).

2nd Review Cycle: December 29, 2016

This submission represents the Applicant's response to the Agency's June 2016 Complete Response (PDUFA Date: 6/29/2017). In this submission, the Applicant responded to the extractables and leachables concerns; however, this submission was issued a Complete Response in June of 2017 as a result of a WITHHOLD recommendation from OPF for the Teva Pharmaceutical Works Private Limited manufacturing facility in Gödöllő, Hungary.

3rd Review Cycle: May 29, 2019

This submission represents the Applicant's response to the Agency's June 2017 Complete Response Letter (PDUFA Date: 11/29/19). 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).

The addition of the new 5.5 mL configuration was considered acceptable; however, a PAI inspection of the Teva Irvine site (FEI: 2027158) resulted in 483 observations and a subsequent a WITHHOLD recommendation from ORA for GMP reasons. The WITHHOLD recommendation resulted in the issuance of a Complete Response (November 4, 2019) for this May 2019 resubmission. Of note, the addition of the PTCL indication was not addressed during this review cycle.

4th Review Cycle: November 22, 2019

This submission represents the Applicant's response to the Agency's November 18, 2019 Complete Response Letter (PDUFA Date: 5/22/2020). Due to the Complete Response action in the last review cycle based on a non-GMP compliant facility, the response was classified as a Class 2 resubmission. The applicant disagreed with the submission being designated as Class 2 and filed a Formal Dispute Resolution Request (FDRR) with the agency on January 7, 2020, wherein the Applicant asserted that the agency took action prematurely in the previous review cycle as the facilities deficiencies were resolved by November 18, 2019. In the FDRR, the Applicant requested that the Agency reclassify the November 22, 2019 response as a Class 1 resubmission, which would have resulted in a PDUFA goal date of January 22, 2020. On February 7, 2020, the agency responded to the FDRR and denied the appeal (see appended correspondence), retaining the original Class 2 resubmission designation and associated 6-month review clock.

3. Product Quality

A Prior Approval Inspection (PAI) of the Teva Irvine site (FEI: 2027158) resulted in 483 observations and a subsequent a WITHHOLD recommendation from ORA for GMP reasons. Accordingly, this facility was not considered acceptable to support the approval of NDA 208574 and the recommendation from OPF was WITHHOLD. This submission is the response to the Agency's November 4, 2019 CR Letter. In this submission, the Applicant addressed the November 4, 2019 CR deficiency. During the current review cycle, the Teva Irvine site (FEI: 2027158) was again assessed for GMP compliance status by OPF. Based on the assessment, the recommended action for the site was downgraded from WITHHOLD to Voluntary Action Indicated (VAI) on November 18, 2019. The compliance status of the Teva Irvine site is now considered acceptable. There are no other deficiencies and NDA 208574 is recommended for APPROVAL from a product quality perspective.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality recommends **APPROVAL** for NDA 208574.

6. Clinical Pharmacology

The Teva product is a reformulation of the Listed Drug, Istodax (romidepsin) for Injection, and the applicant is relying on the Agency's previous finding of safety and effectiveness for Istodax, as described in the approved labeling for the LD. The clinical pharmacology team confirms that there was no new clinical pharmacology information included in this application.

7. Non-Clinical Pharmacology/Toxicology

There were no pharmacology/toxicology concerns with the application; however, the June 2016 CR included a quality deficiency related to extractables/leachables. To address this deficiency, the Applicant included a report entitled (b) (4) .

The pharmacology/toxicology team reviewed the information provided and concluded that there were no concerns with the levels of the compounds that could potentially leach from the (b) (4) (b) (4) and therefore recommends APPROVAL for NDA 208574.

8. Clinical/Statistical-Efficacy

Teva did not conduct human clinical studies, and therefore efficacy was based on the Prescribing Information for Istodax (romidepsin) for Injection, the relied-upon listed drug. The clinical team recommends granting approval of NDA 208574 for the CTCL indication and accelerated approval for the PTCL indication with the following PMR to be conveyed in the agency's APPROVAL Letter:

> PMR: Submit the final results from a randomized, controlled trial that verifies the clinical benefit of romidepsin in patients with peripheral T-cell lymphoma. Progression free survival will be the primary efficacy endpoint. An interim analysis of overall survival will be included in the study report. The results 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.

Refer to the action letter for final wording of the PMR and for milestone dates.

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:

Labeling negotiations are ongoing at the time of this review.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and effectiveness for the Listed Drug, Istodax (romidepsin) for Injection, as there were no new clinical or nonclinical studies conducted for this 505(b)(2) application. The Teva product differs from the listed drug in that it 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 and the Teva product will include a 10 mg/2 mL and a 27.5 mg/5.5 mL presentation.

Istodax (romidepsin) was originally approved for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy and subsequently received accelerated approval for the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy. Products approved under accelerated approval require additional adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. At this time, Celgene Corporation, the NDA holder of Istodax, has not submitted the necessary confirmatory trial data to verify and describe its clinical benefit for the Agency's consideration for the PTCL indication to convert that indication to traditional approval. Teva's Romidepsin Injection 505(b)(2) NDA is relying on FDA's finding of safety and effectiveness for Istodax for the PTCL indication. As indicated in the Istodax labeling, Istodax remains approved for the PTCL indication under the accelerated approval pathway on the basis of a surrogate endpoint. Because Teva's 505(b)(2) application has an independent requirement to demonstrate safety and effectiveness, and Teva's application relies on a finding based on a surrogate endpoint, it is appropriate for Teva's application to be approved under the accelerated approval pathway. Accordingly, for NDA 208574, the CTCL indication (Original 1) is recommended for traditional approval and the PTCL indication (Original 2) is recommended for Accelerated Approval with the following postmarketing requirement (PMR):

> *PMR: Submit the final results from a randomized, controlled trial that verifies the clinical benefit of romidepsin in patients with peripheral T-cell lymphoma. Progression free survival will be the primary efficacy endpoint. An interim analysis of overall survival will be included in the study report. The results 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.*

As there are no outstanding issues precluding the approval of this application and based on the recommendations from all review disciplines, the CDTL recommends **APPROVAL** of NDA 208574 Original 1 for Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL) for the treatment of CTCL in adult patients who have received at least one prior therapy and **ACCELERATED APPROVAL** of NDA 208574 Original 2 for Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL) for the treatment of PTCL in adult patients who have received at least one prior therapy**.**

- **Risk Benefit Assessment**

Please refer to NDA 22393.

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

/s/

SHERITA D MCLAMORE
03/13/2020 09:31:04 AM

Cross-Discipline Team Leader Review

Date	17-Feb-2020
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	22-Nov-2019
PDUFA Goal Date	22-May-2020
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:	**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 CDTL review is based on the primary reviews, memos and documented review input of:

- Clinical (Yvette Kasamon, M.D.)
- Pharmacology/Toxicology (Brenda Gehrke, Ph.D.)
- Drug Product (Anamitro Banerjee, 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 a 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 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 approval for the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy under accelerated approval (6/16/11).

The proposed drug product has the same active ingredient and route of administration 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 has been issued three Complete Responses (CRs) due to issues related to product quality.

1st Review Cycle: October 18, 2015

NDA 208574 was originally submitted to the Agency in October of 2015 (PDUFA Date: 6/18/2016). This submission was issued a Complete Response on June 1, 2016 for matters related to product quality (specifically extractables/leachables from the (b) (4)).

2nd Review Cycle: December 29, 2016

This submission represents the Applicant's response to the Agency's June 2016 Complete Response (PDUFA Date: 6/29/2017). In this submission, the Applicant responded to the extractables and leachables concerns; however, this submission was issued a Complete Response in June of 2017 as a result of a WITHHOLD recommendation from OPF for the Teva Pharmaceutical Works Private Limited manufacturing facility in Gödöllő, Hungary.

3rd Review Cycle: May 29, 2019

This submission represents the Applicant's response to the Agency's June 2017 Complete Response Letter (PDUFA Date: 11/29/19). 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)

The addition of the new 2 mL configuration was considered acceptable; however, a PAI inspection of the Teva Irvine site (FEI: 2027158) resulted in 483 observations and a subsequent a WITHHOLD recommendation from ORA for GMP reasons. The WITHHOLD recommendation resulted in the issuance of a Complete Response (November 4, 2019) for this May 2019 resubmission. Of note, the addition of the PTCL indication was not addressed during this review cycle.

4th Review Cycle: November 22, 2019

This submission represents the Applicant's response to the Agency's November 18, 2019 Complete Response Letter (PDUFA Date: 5/22/2020). Due to the Complete Response action in the last review cycle based on a non-GMP compliant facility, the response was classified as a Class 2 resubmission. The applicant disagreed with the submission being designated as Class 2 and filed a Formal Dispute Resolution Request (FDRR) with the agency on January 7, 2020 wherein the Applicant asserted that the agency took action prematurely in the previous review cycle as the facilities deficiencies were resolved by November 18, 2019. In the FDRR the Applicant requested that the Agency reclassify the November 22, 2019 response as a Class 1 resubmission which would have resulted in a PDUFA goal date of January 22, 2020. On January 7, 2020 the agency responded to the FDRR and denied the appeal (see appended correspondence), retaining the original Class 2 resubmission designation and associated 6-month review clock.

3. Product Quality

A Prior Approval Inspection (PAI) of the Teva Irvine site (FEI: 2027158) on DATE resulted in 483 observations and a subsequent a WITHHOLD recommendation from ORA for GMP reasons. Accordingly, this facility was not considered acceptable to support the approval of NDA 208574 and the recommendation from OPF was WITHHOLD. This submission is the response to the Agency's November 4, 2019 CR Letter. In this submission the Applicant addressed the November 4, 2019 CR deficiency. During the current review cycle, the Teva Irvine site (FEI: 2027158) was again assessed for GMP compliance status by OPF. Based on the assessment, the recommended action for the site was downgraded from WITHHOLD to Voluntary Action Indicated (VAI) on November 18, 2019. The compliance status of the Teva Irvine site is now considered acceptable. There are no other deficiencies and NDA 208574 is recommended for APPROVAL from a product quality perspective.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality recommends **APPROVAL** for NDA 208574.

6. Clinical Pharmacology

The Teva product is a reformulation of the Listed Drug, Istodax (romidepsin) for Injection, and the applicant is relying on the Agency's previous findings of safety and efficacy as described in the approved labeling for the LD. The clinical pharmacology team confirms that there was no new clinical pharmacology information included in this application.

7. Non-Clinical Pharmacology/Toxicology

There were no pharmacology/toxicology concerns with the application; however, the June 2016 CR included a quality deficiency related to extractables/leachables. To address this deficiency, the Applicant included a report entitled (b) (4) .

The pharmacology/toxicology team reviewed the information provided and concluded that there were no concerns with the levels of the compounds that could potentially leach from the (b) (4) (b) (4) and therefore recommends APPROVAL for NDA 208574.

8. Clinical/Statistical-Efficacy

Teva did not conduct human clinical studies and therefore efficacy was based on the Prescribing Information for Istodax (romidepsin) for Injection. The clinical team recommends granting approval of NDA 208574 for the CTCL indication and accelerated approval for the PTCL indication with the following PMR to be conveyed in the agency's APPROVAL Letter:

> PMR: Submit the final results from a randomized, controlled trial that verifies the clinical benefit of romidepsin in patients with peripheral T-cell lymphoma. Progression free survival will be the primary efficacy endpoint. An interim analysis of overall survival will be included in the study report. The results 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.

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:

Labeling negotiations are ongoing at the time of this review.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the Listed Drug, Istodax (romidepsin) for Injection as there were no new clinical or nonclinical studies conducted for this 505(b)(2) application. The Teva product differs from the listed drug in that it 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 and the Teva product will include a 10 mg/2 mL and a 27.5 mg/5.5 mL presentation.

Romidepsin was received regular approval for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy and was approved for the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy under the FDA Accelerated Approval Program. Products approved under the accelerated approval regulations require additional adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. Accordingly, the addition of the PTCL indication presented a policy issue within OND as the PTCL indication relied on a use of a surrogate endpoint and the indication has not yet been converted to full approval. After discussions at CDER's Medical Policy, at the OND Program review Council Meeting, with the B2 committee and with the Agency's attorneys, it NDA 208574 was administratively split (Original 1 and Original 2). The CTCL indication (Original 1) is recommended for full regular approval and the PTCL indication (Original 2) is recommended for Accelerated Approval with the following postmarketing requirement (PMR):

> *PMR: Submit the final results from a randomized, controlled trial that verifies the clinical benefit of romidepsin in patients with peripheral T-cell lymphoma. Progression free survival will be the primary efficacy endpoint. An interim analysis of overall survival will be included in the study report. The results 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.*

As there are no outstanding issues precluding the approval of this application and based on the recommendations form all review disciplines, the CDTL recommends **APPROVAL** of NDA 208574 Original 1 for Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL) for the treatment of CTCL in adult patients who have received at least one prior therapy and **APPROVAL** under the FDA Accelerated Approval Program of NDA 208574 Original 2 for Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL) for the treatment of PTCL in adult patients who have received at least one prior therapy**.**

- **Risk Benefit Assessment**

Please refer to NDA 22393.

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

/s/

SHERITA D MCLAMORE
02/18/2020 11:18:23 AM