CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208574Orig1s000
208574Orig2s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 208574

Drug Name/Dosage Form	Romidepsin Injection,
Strength	10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL
Route of Administration	IV
Rx/OTC Dispensed	R_x
Applicant	Teva Pharmaceuticals
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Re-Submission	22-Nov-19	All

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	n/a	n/a
Drug Product	Anamitro Banerjee	Thomas Oliver
Process/Faclilty	Kumar Janoria	Pei-I Chu
Microbiology	n/a	n/a
Biopharmaceutics	n/a	n/a
Regulatory Business Process Manager	Rabiya Hadier	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	n/a	n/a

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	n/a	No Review	Adequate information provided in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22393	Listed Drug

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 208574 for Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL). As part of this action, OPQ grants a 24-month drug product expiration period for the drug product when stored at USP controlled room temperature conditions 20°C to 25°C (68°F to 77°F). There are no outstanding issues and no post-approval quality agreement to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

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.

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. The proposed drug product has the same active ingredient and dosage form as the LD but differs in every other aspect. 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 after dilution with 0.9% Sodium Chloride. The LD presented as a sterile, lyophilized powder in a 10 mg single-dose vial containing 11 mg of romidepsin and 22 mg of povidone, USP. The LD is supplied in a kit which includes the lyophilized powder together with a single-dose sterile diluent vial containing 2.4 mL of 80% propylene glycol, USP and 20% dehydrated alcohol, USP.

The recommended dose of romidepsin is 14 mg/m^2 administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 208574 and grants a 24-month expiration period for the drug product when stored under controlled room temperature in the commercial packaging.

Proposed Indication(s) including Intended Patient Population	• indicated for the treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy • indicated for the treatment of peripheral T-cell lymphoma (PTCL) in adult patients who have received at least one prior therapy
Duration of Treatment	Undefined (Cycles should be repeated every 28 days provided that the patient continues to benefit from and tolerates the drug)
Alternative Methods of Administration	None

B. Quality Assessment Overview

NDA 208574 was originally submitted to the Agency in October of 2015 and was issued a Complete Response on June 1, 2016 for issues related to product quality (see CR comment below):

> *We acknowledge your March 28, 2016 response to the information request dated March 14, 2106. However, the rationale used to support potential extractables/ leachables from* (b) (4) (b) (4)
>
> *Address this concern as it relates to the proposed manufacturing conditions, taking into consideration any worst case scenarios* (b) (4). *Please include data and/or study results to support your conclusions* (b) (4) .

The applicant submitted a response to the June 2016 CR in December 2016 and the December 2016 submission was issued complete response in June of 2017 (see CR comment below):

> *During a recent inspection of the Teva Pharmaceutical Works Private Limited Company, Gödöllő, Hungary (FEI 3002875215) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility.*

The applicant responded to the Agency's June 2017 CR Letter on May 29, 2019. In this response, the Applicant addressed the aforementioned June 2017 CR comment and proposed the following two unsolicited changes:

1. A new drug product configuration, 27.5 mg/ 5.5 mL. This 5.5 mL configuration has the same concentration (i.e. 5 mg/mL) as the 2 mL configuration.
2. 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).

Both changes were evaluated by the product quality review team. A summary of the findings from the review is included below.

Regarding the new 5.5 mL product configuration: It was concluded that the differences in the analytical methods, specifications and container closure between the 2 mL packaging configuration and 5.5 mL packaging configuration are negligible. There were no changes to the drug product formulation or to the (b) (4) ; however, there were differences in the vial and stopper (b) (4) (b) (4) and in the headspace to volume ratio (b) (4) The addition of the new packaging configuration was reviewed and deemed acceptable by all product quality review disciplines; accordingly, the addition of the new packaging configuration was considered acceptable.

Regarding the transfer of the 2 mL from Teva facility in Gödöllő, Hungary site to Teva facility in Irvine, CA: 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. Accordingly, this facility was not considered acceptable support the approval of NDA 208574. The WITHHOLD recommendation resulted in the issuance of a Complete Response (November 4, 2019) and the following comment was included in the CR letter:

> *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*

The applicant responded to the Agency's November 4, 2019 CR Letter on November 22, 2019. At the time of submission, the Teva Irvine site (FEI: 2027158) was downgraded to VAI by CDER OMQ. Accordingly, the facility is considered acceptable to perform the proposed functions listed in current 356h form and outline in this application (see Process and Facility review dated 1/22/2020).

In support of the proposed 24-month expiry for the 10 mg/2 mL and 27.5 mg/5.5 mL drug products, the applicant provided up to 36 months of long-term stability data (see previous drug product review #3 dated 10/22/2019). As noted in the previous review, the available stability data showed consistency over time and supports the proposed expiry. Accordingly, based on the stability data included in this application, **Teva Pharmaceuticals proposed and the FDA accepts the expiration dating period of 24 months** for the drug product when stored at stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment

n/a

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Pei-I Chu

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Date: 1/22/2020 09:28:54AM
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Kumar Janoria

Digitally signed by Kumar Janoria
Date: 1/22/2020 09:14:42AM
GUID: 53160a1a0000844db16f58dfff6949ed

Sherita McLamore

Digitally signed by Sherita McLamore
Date: 2/19/2020 10:34:53AM
GUID: 503257950000415755492db5bb8b1a5c

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/s/

SHERITA D MCLAMORE
02/19/2020 10:41:20 AM

Recommendation: APPROVAL

NDA 208574

Drug Name/Dosage Form	Romidepsin Injection,
Strength	10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL
Route of Administration	IV
Rx/OTC Dispensed	R_x
Applicant	Teva Pharmaceuticals
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Re-Submission	22-Nov-19	All

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	n/a	n/a
Drug Product	Anamitro Banerjee	Thomas Oliver
Process/Faclilty	Kumar Janoria	Pei-I Chu
Microbiology	n/a	n/a
Biopharmaceutics	n/a	n/a
Regulatory Business Process Manager	Rabiya Hadier	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	n/a	n/a

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III	(b) (4)		n/a	No Review	Adequate information provided in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22393	Listed Drug

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 208574 for (b) (4) for Injection, 10 mg/2mL and 27.5 mg/5.5 mL. As part of this action, OPQ grants a 24-month drug product expiration period for the drug product when stored at USP controlled room temperature conditions 20°C to 25°C (68°F to 77°F). There are no outstanding issues and no post-approval quality agreement to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

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.

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. The proposed drug product has the same active ingredient and dosage form as the LD but differs in every other aspect. 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 after dilution with 0.9% Sodium Chloride. The LD presented as a sterile, lyophilized powder in a 10 mg single-dose vial containing 11 mg of romidepsin and 22 mg of povidone, USP. The LD is supplied in a kit which includes the lyophilized powder together with a single-dose sterile diluent vial containing 2.4 mL of 80% propylene glycol, USP and 20% dehydrated alcohol, USP.

The recommended dose of romidepsin is 14 mg/m^2 administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 208574 and grants a 24-month expiration period for the drug product when stored under controlled room temperature in the commercial packaging.

Proposed Indication(s) including Intended Patient Population	• indicated for the treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy • indicated for the treatment of peripheral T-cell lymphoma (PTCL) in adult patients who have received at least one prior therapy
Duration of Treatment	Undefined (Cycles should be repeated every 28 days provided that the patient continues to benefit from and tolerates the drug)
Alternative Methods of Administration	None

B. Quality Assessment Overview

NDA 208574 was originally submitted to the Agency in October of 2015 and was issued a Complete Response on June 1, 2016 for issues related to product quality (see CR comment below):

> *We acknowledge your March 28, 2016 response to the information request dated March 14, 2106. However, the rationale used to support potential extractables/ leachables from* (b) (4) (b) (4)
>
> *Address this concern as it relates to the proposed manufacturing conditions, taking into consideration any worst case scenarios* (b) (4)*. Please include data and/or study results to support your conclusions* (b) (4) .

The applicant submitted a response to the June 2016 CR in December 2016 and the December 2016 submission was issued complete response in June of 2017 (see CR comment below):

> *During a recent inspection of the Teva Pharmaceutical Works Private Limited Company, Gödöllő, Hungary (FEI 3002875215) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility.*

The applicant responded to the Agency's June 2017 CR Letter on May 29, 2019. In this response, the Applicant addressed the aforementioned June 2017 CR comment and proposed the following two unsolicited changes:

1. A new drug product configuration, 27.5 mg/ 5.5 mL. This 5.5 mL configuration has the same concentration (i.e. 5 mg/mL) as the 2 mL configuration.
2. 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).

Both changes were evaluated by the product quality review team. A summary of the findings from the review is included below.

Regarding the new 5.5 mL product configuration: It was concluded that the differences in the analytical methods, specifications and container closure between the 2 mL packaging configuration and 5.5 mL packaging configuration are negligible. There were no changes to the drug product formulation or to the (b) (4) ; however, there were differences in the vial and stopper (b) (4) (b) (4) and in the headspace to volume ratio (b) (4) The addition of the new packaging configuration was reviewed and deemed acceptable by all product quality review disciplines; accordingly, the addition of the new packaging configuration was considered acceptable.

Regarding the transfer of the 2 mL from Teva facility in Gödöllő, Hungary site to Teva facility in Irvine, CA: 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. Accordingly, this facility was not considered acceptable support the approval of NDA 208574. The WITHHOLD recommendation resulted in the issuance of a Complete Response (November 4, 2019) and the following comment was included in the CR letter:

> *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*

The applicant responded to the Agency's November 4, 2019 CR Letter on November 22, 2019. At the time of submission, the Teva Irvine site (FEI: 2027158) was downgraded to VAI by CDER OMQ. Accordingly, the facility is considered acceptable to perform the proposed functions listed in current 356h form and outline in this application (see Process and Facility review dated 1/22/2020).

In support of the proposed 24-month expiry for the 10 mg/2 mL and 27.5 mg/5.5 mL drug products, the applicant provided up to 36 months of long-term stability data (see previous drug product review #3 dated 10/22/2019). As noted in the previous review, the available stability data showed consistency over time and supports the proposed expiry. Accordingly, based on the stability data included in this application, **Teva Pharmaceuticals proposed and the FDA accepts the expiration dating period of 24 months** for the drug product when stored at stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment

n/a

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Pei-I Chu

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Kumar Janoria

Digitally signed by Kumar Janoria
Date: 1/22/2020 09:14:42AM
GUID: 53160a1a0000844db16f58dfff6949ed

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
02/12/2020 07:00:06 PM

QUALITY ASSESSMENT

Recommendation: APPROVAL

NDA 208574

Drug Name/Dosage Form	Romidepsin Injection,
Strength	10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL
Route of Administration	IV
Rx/OTC Dispensed	R_x
Applicant	Teva Pharmaceuticals
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Re-Submission	29-May-19	All
Amendment (SD 0018)	13-Sept-19	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	n/a	n/a
Drug Product	Anamitro Banerjee	Thomas Oliver
Process/Facility	Kumar Janoria	Pei-I Chu
Microbiology	David Bateman	John Metcalfe
Biopharmaceutics	n/a	n/a
Regulatory Business Process Manager	Rabiya Hadier	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	n/a	n/a

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III	(b) (4)		n/a	No Review	Adequate information provided in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22393	Listed Drug

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **COMPETE RESPONSE** for the resubmission of NDA 208574 Romidepsin Injection, 10 mg/2 mL (5 mg/mL) and 27.5 mg/5.5 mL (5 mg/mL) as a result of a WITHOLD recommendation from the Office of Compliance. The following deficiency will be included in the Agency's Compete Response (CR) letter:

> *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.*

II. Summary of Quality Assessments

A. Product Overview

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.

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. The proposed drug product has the same active ingredient and dosage form as the LD but differs in every other aspect. 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 after dilution with 0.9% Sodium Chloride. The LD presented as a sterile, lyophilized powder in a 10 mg single-dose vial containing 11 mg of romidepsin and 22 mg of povidone, USP. The LD is supplied in a kit which includes the lyophilized powder together with a single-dose sterile diluent vial containing 2.4 mL of 80% propylene glycol, USP and 20% dehydrated alcohol, USP.

The recommended dose of romidepsin is 14 mg/m^2 administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle. Cycles should be repeated every 28 days provided that the patient continues to benefit from and tolerates the drug.

Based on the information provided in this application (original submission and in responses to information requests), OPQ recommends issuing a COMPLETE RESPONSE for the 5/29/19 resubmission of NDA 208574.

Proposed Indication(s) including Intended Patient Population	• indicated for the treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy • indicated for the treatment of peripheral T-cell lymphoma (PTCL) in adult patients who have received at least one prior therapy
Duration of Treatment	Undefined
Alternative Methods of Administration	None

B. Quality Assessment Overview

NDA 208574 was originally submitted to the Agency in October of 2015 and was issued a Complete Response on June 1, 2016 for issues related to product quality (see CR comment below):

> *We acknowledge your March 28, 2016 response to the information request dated March 14, 2106. However, the rationale used to support potential extractables/ leachables from the* (b) (4) (b) (4) (b) (4)*. Address this concern as it relates to the proposed manufacturing conditions, taking into consideration any worst case scenario* (b) (4)*. Please include data and/or study results to support your conclusions* (b) (4)*.*

The applicant submitted a response to the June 2016 CR in December 2016 and the December 2016 submission was issued complete response in June of 2017 (see CR comment below):

> *During a recent inspection of the Teva Pharmaceutical Works Private Limited Company, Gödöllő, Hungary (FEI 3002875215) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility.*

This submission (May 29, 2019) is the response to the Agency's June 2017 CR Letter. In this submission the Applicant addressed the aforementioned June 2017 CR comment and proposed the following two unsolicited 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. A new drug product configuration, 27.5 mg/ 5.5 mL. This 5.5 mL configuration has the same concentration (i.e. 5 mg/mL) as the 2 mL configuration.

Both changes were evaluated by the review team (drug product, microbiology, drug process and facilities). Review of the application revealed that the differences in the analytical methods, specifications and container closure between the 2 mL packaging configuration and 5.5 mL packaging configuration are negligible. Moreover, there were no changes to the drug product formulation or to the (b) (4) ; however, there were differences in the vial and stopper (b) (4) and in the headspace to volume ratio (b) (4) The addition of the new packaging configuration was reviewed and deemed acceptable by all product quality review disciplines; accordingly, the addition of the new packaging configuration is considered acceptable.

In support of the proposed 24 month expiry for the 10 mg/2 mL and 27.5 mg/5.5 mL drug products, the applicant provided 36 months stability data for three batches of the 2 mL presentation (this data was included in the original submission) and 9 months data for three batches each of 10 mg/2 mL and 27.5 mg/5.5 mL manufactured at the Irvine, CA site. All batches were manufactured according to the commercial process and packaged in the proposed commercial packaging and stored under the long-term (25°C/60% RH) and accelerated (40°C/75% RH) conditions. Additionally, the applicant provided in-use data for the admixture (0.9% sodium chloride USP in PVC and PE infusion bags) and compared this data to ISTODAX kit (LD). Data was collected at t=0 and at t=24h.

The stability studies were executed in accordance with the ICH 1A and Q1B and at the time tested there were no significant changes observed under any condition (long term, accelerated or in-use). The available stability data shows consistency over time and supports the proposed expiry. Accordingly, based on the stability data included in this application, Teva Pharmaceuticals proposed and the FDA accepts the expiration dating period of **24 months** for the drug product when stored at stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

Facilities:

The following sites were included as a part of the May 2019 resubmission of NDA 208574:

Establishment name	*FEI Number*	*Responsibilities*	*Current status*	*Final Recommendation*
		(b) (4)	**Acceptable** during last review cycle, no change in recommendation	Acceptable, did not include in panorama as no changes that are to be documented were found since last review.

		(b) (4)	**Acceptable** during last review cycle, no change in recommendation	Acceptable, did not include in panorama as no changes that are to be documented were found since last review.
Teva Parenteral Medicines, Irvine, Ca	2027158	Drug product manufacture, release & stability testing, packaging & labeling	**Withhold**	**Withhold**
Teva Pharmaceutical Works Private Ltd. Gödöllő, Hungary	3002875215	Drug product manufacture, release & stability testing, packaging & labeling	Removed from the NDA as part of the 05/29/2019 resubmission	Withdrawn
		(b) (4)	Removed from the NDA as part of the 05/29/2019 resubmission	Withdrawn
			No Evaluation Necessary	No Evaluation Necessary

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 (FEI: 2027158) resulted in a Withhold recommendation for GMP reasons. Accordingly, this facility is not acceptable support the approval of NDA 208574 and the overall recommendation from facilities is **Withhold Approval.** A satisfactory resolution of all deficiencies is required before this NDA may be recommended for approval.

The following deficiency will be included in the Agency's CR letter:

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.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

n/a

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Anamitro Banerjee

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Thomas Oliver

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Date: 10/22/2019 08:00:48AM
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Comments: Just signed

Recommendation: Inadequate

NDA 208574
Process Review #3

Kumar Janoria

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Date: 10/30/2019 01:32:39PM
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Pei-I Chu

Digitally signed by Pei-I Chu
Date: 10/30/2019 01:36:12PM
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MICROBIOLOGY

Product Background:

NDA: 208574

Drug Product Name / Strength: Romidepsin Injection, 10 mg/2mL and 27.5 mg/5.5 mL Single dose

Route of Administration: Intravenous infusion

Applicant Name: Teva Pharmaceuticals USA Inc.

Manufacturing Site:
Previous site:
Teva Pharmaceutical Works Private Limited Company
Tancsics Mihaly ut 82, H-2100, Godollo, Hungary

New site:
Teva Parenteral Medicines
19 Hughes
Irvine, CA 92618

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary: The drug product is (b) (4) filled into (b) (4) vials.

List Submissions Being Reviewed: May 29, 2019 (resubmission), September 24, 2019 (Microbiology IR response).

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The May 29, 2019 submission was a response to the agency complete response letter dated June 2, 2017. Within the response to the facility inspection deficiency, the applicant indicated that commercial manufacturing of the drug product will be transferred from Hungary to Irvine CA. Also that an 8 mL vial configuration

filled to 5.5 mL will be added. This gratuitous amendment was assigned for Microbiology review on September 5, 2019.

Concise Description Outstanding Issues Remaining: None.

Supporting Documents: None.

The applicant provided a gratuitous amendment on May 29, 2019, which includes transferring the manufacturing of the drug product from the Hungary location to Irvine California. The applicant also added an 8 mL vial configuration. This application does not propose any changes to the drug product formulation or to the (b) (4) .

P.1 Description of the Composition of the Drug Product

The applicant does not propose any changes to the formulation of the drug product. However, the applicant has added an additional vial configuration which will be filled with the same 5 mg/mL drug product concentration.

- **Description of previous microbiology reviewed container closure system:**

Component	Description	Manufacturer
Vial	(b) (4) type (b) (4) glass vial with 13mm neck	(b) (4)
Stopper	13 mm (b) (4) (b) (4) stopper	
Cap	13 mm (b) (4) (b) (4)	

- **Description of new container closure system:**

Component	Description	Manufacturer
Vial	(b) (4) type (b) (4) glass vial **(No change)**	(b) (4)
Stopper	13 mm (b) (4) (b) (4) stopper **(No change)**	
Cap	13 mm (b) (4) aluminum cap (b) (4)	
Vial	8 mL clear Type (b) (4) glass vial	
Stopper	20 mm (b) (4) (b) (4) (b) (4) (b) (4) stopper	
Cap	20 mm (b) (4) aluminum cap (b) (4)	

Adequate

Reviewer's Assessment:
The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2 Pharmaceutical Development

(b) (4)

[redacted]

Adequate

Reviewer's Assessment:
The applicant provided an acceptable description of the container closure integrity test.

P.3 Manufacture

(b) (4)

[redacted]

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R Regional Information

Executed Batch Records

The batch records confirm that validated (b) (4) (b) (4) were used for the manufacture of the exhibit batches.

Adequate

Reviewer's Assessment:
The applicant provided detailed batch records for batches 31325360B, 331325363, 31325366 using the 27.5mg/5.5 mL configuration and batches 31325350, 31325353, and 31325356 for the 10 mg/2 mL configuration, which used the described manufacturing processes.

Comparability Protocols

None Provided

Not Applicable

Reviewer's Assessment:
The applicant did not provide any comparability protocols.

Deficiencies to be sent to the applicant:

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

The applicant does not propose any changes to the drug package insert that require microbiological review.

Not Applicable

Reviewer's Assessment:
The applicant does not propose any changes to the package insert that require additional microbiological review.

Post-Approval Commitments:

Not Applicable

Reviewer's Assessment:

List of Deficiencies: *None*

Primary Microbiology Reviewer Name and Date:

David Bateman, Ph.D.
September 25, 2019

Secondary Reviewer Name and Date:
John Metcalfe, Ph.D.
I concur. September 25, 2019

David Bateman

Digitally signed by David Bateman
Date: 9/25/2019 04:38:07PM
GUID: 5463e4f2002198d458a8bff3d150a8ed

John Metcalfe

Digitally signed by John Metcalfe
Date: 9/25/2019 04:37:28PM
GUID: 503451f000004f68b7145543c615dbba
Comments: I concur with the primary reviewer's assessment.

Sherita McLamore

Digitally signed by Sherita McLamore
Date: 11/04/2019 09:04:22AM
GUID: 503257950000415755492db5bb8b1a5c

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/s/

SHERITA D MCLAMORE
11/04/2019 09:11:47 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VERIFICATION REPORT SUMMARY

TO: Janice Brown, CMC Lead
Olen Stephens, Branch Chief
Rabiya Laiq, Methods Validation Project Manager
Office Name: ONDP
E-mail Address: Janice.Brown@fda.hhs.gov
Phone: (301)-796-1652

FROM: FDA
Division of Pharmaceutical Analysis
Laura C. Pogue, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-2155

Through: David Keire, Lab Chief, Branch I
Phone: (314) 539-3850

SUBJECT: Methods Verification Report Summary

Application Number: NDA 208574

Name of Product: N/A (Romidepsin Injection) Solution, 10mg/2mL (5mg/mL)

Applicant: Teva Pharmaceuticals USA

Applicant's Contact Person: Cory Wohlbach, Director, Regulatory Affairs, US Generics

Address: 425 Privet Road, Horsham, PA USA 19044

Telephone: 215-293-6519 Email: cory.wohlbach@tevapharm.com

Date Methods Validation Consult Request Form Received by DPA: 9/3/2015

Date Methods Validation Package Received by DPA: 10/8/2015

Date Samples Received by DPA: 10/8/2015

Date Analytical Completed by DPA: 1/21/2016

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments: See attached summary for analyst comments and results.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis, Missouri 63110
Telephone (314) 539-2135
FAX (314) 539-2113

Date: January 21, 2016

To: Janice Brown, CMC Lead
Olen Stephens, Branch Chief
Rabiya Laiq, Methods Validation Project Manager

Through: David Keire, Ph.D., CDER/OPQ/OTR/DPA, Lab Chief, Branch I

From: Anjanette Smith, Chemist, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 208574: Romidepsin Injection Solution, 10mg/2mL (5mg/mL), TEVA Pharmaceuticals USA

The following methods were verified and are acceptable for quality control and regulatory purposes:

- Assay and Impurities determination for Romidepsin injection
- Alpha-Tocopherol content determination in Romidepsin Injection (paper review)

Analyst worksheets can be viewed using the following ECMS link:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880c639a9

Assay and Impurities determination for Romidepsin injection

%Assay and %Impurity for Romidepsin injection

%Assay, Romidepsin	Avg (2) %Assay	Specification		Results	
(b) (4)		(b) (4)		Fail	
Impurity	**RRT**	**%Impurity**	**Avg(2) %Impurity**		**Specifications**
(b) (4)			(b) (4)	Pass	NMT (b) (4) %
					NMT (b) (4) %
					(b) (4)

Alpha-Tocopherol content determination in Romidepsin Injection

The method was completed by paper review. The representative chromatograms in the method and the validation report show that alpha-tocopherol is (b) (4) The peak shape is sufficient with a tailing factor about (b) (4). The diluent (b) (4) had a % recovery of (b) (4) %.

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/s/

LAURA POGUE
01/22/2016

DAVID A KEIRE
01/22/2016