

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210064Orig1s000

PRODUCT QUALITY REVIEW(S)



QUALITY ASSESSMENT



Recommendation: This 505 (b)(2) NDA is recommended for Approval

NDA 210064 Review #2

Drug Name/Dosage Form	Fosaprepitant for injection
Strength	150 mg Fosaprepitant/vial
Route of Administration	Injection for intravenous use
Rx/OTC Dispensed	Rx
Applicant	Teva Pharmaceuticals USA, Inc.; Parsippany, NJ USA
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Amendment - Resubmission	March 5, 2019	OPQ
Amendment - Labeling	May 31, 2019	ONDP
Amendment - Labeling	July 22, 2019	ONDP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Friedrich Burnett	CDER/OPQ/ONDP/ DNDAP/NDPBI
Drug Product and Labeling	Hailin Wang	CDER/OPQ/ONDP/ DNDP/NDPBI
Process/Facilities	Li-Shan Hsieh	CDER/OPQ/OPF/ DPAP/NDPBI
Microbiology	Yuansha Chen	OMPT/CDER/OPQ/OPF/ DMA/MABII
Regulatory Business Process Manager	Oumou Barry	OMPT/CDER/OPQ/OPRO/DR BP/NDPBI
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDP/NDPBI

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Fosaprepitant Dimeglumine	Active	Adequate, Apr 29, 2019	LoA Nov 10, 2016
	Type III	(b) (4)	(b) (4)	Active	Adequate, May 21, 2019	Nov 22, 2016
	Type III	(b) (4)	(b) (4)	Active	Adequate, Oct 28, 2014	Nov 22, 2016
	Type V	(b) (4)	(b) (4)	Active	Adequate, Aug 2, 2016	Dec 15, 2016

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None	None	None

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of Process and Facilities (OPF) has made a final overall “Approval” recommendation for the facilities involved in this application as of this review.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling issues have been satisfactorily resolved.

Therefore, from the OPQ perspective, this NDA is recommended for approval.

II. Summary of Quality Assessments

- This NDA was originally submitted on December 16, 2016 and it was recommended for approval from OPQ perspective. However, due to the unexpired patent for Emend, a tentative approval was recommended. The earliest possible approval date was being expected on March 4, 2019 when US Patent No. 5691336 is expired.

On March 5, 2019 Teva submitted an amendment to the Tentative Approval letter including the following new information:

- Analytical method for (b) (4) test in the drug substance was transferred from Sindan to Actavis, Italy.
- Analytical procedure for Bacterial Endotoxin and Degradation Products
- The drug product specification for Elemental Impurities with being revised.
- The master batch records from Sindan-Pharma SRL were revised.
- Process validation was revised.
- The drug product stability data up to 36 months
- Revised labeling (PI, PIL and SPL)
- The site contact information for the applicant was revised in Form 356h
- A new patent certification to include the pediatric extension and certification for the newly added Exclusivity.

A. Product Overview

Fosaprepitant for injection is supplied as a single-dose glass vial containing 150 mg of fosaprepitant (equivalent to 245 mg of fosaprepitant dimeglumine salt), sterile white to off-white lyophilized powder. The drug product is reconstituted with 5 mL of 0.9% Sodium Chloride Injection, USP. The reconstituted solution is then added to aseptically prepared infusion bag filled with 145 mL of 0.9% Sodium Chloride Injection, USP and administered intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy.

Proposed Indication(s) including Intended Patient Population	Fosaprepitant Dimeglumine for Injection is a substance P/neurokinin-1 (NK1) receptor antagonist, indicated in adults, in combination with other antiemetic agents, for the prevention of: - acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin - delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)
Duration of Treatment	As needed
Maximum Daily Dose	Recommended dosage in adults is 150 mg on Day 1 as an intravenous infusion over 20 to 30 minutes approximately 30 minutes prior to chemotherapy.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

The analytical method for the determination of (b) (4) and the Analytical Methods Transfer Exercise and the revised drug substance specification were reviewed by Dr. Friedrich Burnett and deemed adequate. (See **Drug Substance Review dated May 21, 2019**)

Drug Product:

The revised drug product specification now includes tests for Elemental Impurities per USP <233> and ICH Q3D as well as Product Quality Tests for Parenteral Dosage Forms per USP <1>. The applicant also submitted up to 36 months of long-term drug product stability data to support proposed 24-month shelf life as the RLD. The revised drug product specification and the stability data were reviewed by Dr. Hailing Wang and deemed adequate. The drug product shelf-life of 24-month at 5°C ± 3°C was granted. (See **Drug Product Review #2 dated July 17, 2019**)

The drug product manufacturing process related information including manufacturing process validation reports and validation of holding times were reviewed by the Process reviewer, Li-Shan, and deemed adequate. (see **Memorandum to File dated June 12, 2019**)

The drug product specification for Bacterial Endotoxins and Sterility were reviewed by the microbiology reviewer, Yuansha Chen, and deemed adequate. (see **Microbiology Review dated May 9, 2019**)

Facilities and Process:

All manufacturing and testing facilities in connection with this NDA were now found **Acceptable**. (see **Memorandum to File dated June 12, 2019**)

Labels and Labeling:

The labels and labeling issues have been satisfactorily resolved. (see **Labeling Review dated July 22, 2019**)

Special Product Quality Labeling Recommendations: None

Final Risk Assessment (see Attachment I)

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
July 29, 2019



Hitesh
Shroff

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CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION: Adequate per ONDPV Labeling Review #1 by Sarah Ibrahim

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION): Adequate per ONDPV Labeling Review #1 by Sarah Ibrahim

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS): Adequate per ONDPV Labeling Review #1 by Sarah Ibrahim

1.2.3 Section 11 (DESCRIPTION): Adequate per ONDPV Labeling Review #1 by Sarah Ibrahim

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

The following amendment to the PI is provided in SD#13 on 7/22/2019

Item	Information Provided in the NDA	Assessor's Comments
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	(b) (4)	

Other sections are Adequate per ONDPV Labeling Review #1 by Sarah Ibrahim

1.2.5 Other Sections of Labeling: Adequate per ONDPV Labeling Review #1 by Sarah Ibrahim

1.2.6 Manufacturing Information After Section 17 (for drug products): Adequate per ONDPV Labeling Review #1 by Sarah Ibrahim

2.0 PATIENT LABELING: Adequate per ONDPV Labeling Review #1 by Sarah Ibrahim

3.0 CARTON AND CONTAINER LABELING: Adequate per ONDPV Labeling Review #1 by Sarah Ibrahim

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: Hailin (Sheena) Wang, Ph.D. 07/22/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed):

I agree with Dr. Wang's assessment on the final labeling/labels, and therefore, I recommend approval of this application from the drug product labeling perspective.

Moo-Jhong Rhee, Ph.D.

Chief, Branch V

DNDP II/ONDP/OPQ

7/22/2019



Moo Jhong
Rhee

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Sheena Hailin
Wang

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MICROBIOLOGY**Product Background:**

NDA: 210064

Drug Product Name / Strength: Fosaprepitant Dimeglumine for Injection, 150 mg/vial, single dose

Route of Administration: IV

Applicant Name: Teva Pharmaceuticals USA, Inc.

Manufacturing Sites:

Actavis Italy S.p.A. – Nerviano Plant

Via Pasteur 10

20014 Nerviano (Milan)

Italy

S.C. SINDAN-PHARMA S.R.L.

11th Ion Mihalache Boulevard

011171, Bucharest 1,

Romania

Method of Sterilization: (b) (4)

Review Summary:

The application is recommended for approval on the basis of sterility assurance.

List Submissions being reviewed (table):

Submitted	Received	Assigned to Reviewer
12/16/2016	12/16/2016	1/25/2017
5/31/2017	5/31/2017	6/1/2017 (IR response)
3/5/2019	3/5/2019	3/20/2019 (resubmission for final approval)

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: DMF (b) (4) and the associated microbiology review (b) (4) mic35.doc (adequate) dated 5/18/2016 by Y. Smith are referenced for the depyrogenation information of the stoppers.

(b) (4)

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – The drug product is a sterile, white to off-white lyophilized powder in a single-dose glass vial.

- **Drug product composition** –

Components	Function	Amount/Unit
Fosaprepitant Dimeglumine	API	245.3 mg
Edetate disodium (b) (4)	(b) (4)	(b) (4) mg
Kollidon 12 PF		600.0 mg
Meglumine		75.0 mg
Hydrochloric acid (b) (4) / Meglumine (b) (4)		pH adjusters Up to (b) (4)
WFI	(b) (4)	(b) (4)

- **Description of container closure system** –

Component	Description	Manufacturer
Vials	(b) (4) clear glass vials, 10 mL	(b) (4) (b) (4) Or (b) (4) (b) (4) (b) (4)
Stoppers	Rubber stopper, (b) (4)	(b) (4)
Seals	(b) (4) cap with (b) (4) disk	(b) (4)

Note to reviewer: Stoppers used in the two facilities are identical (product code (b) (4)). Vials used in the two facilities are from the same suppliers. However, specifications for vials by the two facilities are not identical. The inner neck diameter is specified as (b) (4) by the Actavis facility and (b) (4) by the Sindan facility. Clarification will be requested.

Information Request: An IR letter dated 5/8/2017 was conveyed to the NDA holder. The applicant's response was received in 5/31/2017. The original comments followed by the IR response are included below.

It is noted that the provided specifications for the glass vials used for drug product manufacturing at the Actavis facility and Sindan facility appear to be different. For example “(b) (4)” is indicated on the Actavis facility vial specification (spec-(b) (4).pdf) while “(b) (4)” is listed on the Sindan facility vial specification (spec-(b) (4).pdf). Please clarify whether the drug product container/closure systems used at the Actavis and Sindan facilities are identical.

Response: *Although the 10-mL glass vials used for drug product at the Actavis facility and Sindan facility are supplied by the same supplier, (b) (4) they are slightly different in some dimensional parameters. Dimensions for vials proposed for both facilities are provided.*

Reviewer's Assessment: ADEQUATE

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity -**
Container closure integrity test is provided by the Actavis facility.

Actavis

(P.3.5. container-closure-integ.pdf)

Vial: (b) (4)

Stopper: (b) (4)

The container/closure system used for validation was: Same as the drug product

Test method: microbial immersion

Brief description: Study was performed in Nov. 2016. Test vials are submerged inverted in a container that contains *B. diminuta* culture. The entire system (container with test vials) was incubated at 30-35°C for 14 days.

Challenge organism: *B. diminuta*

Challenge level: (b) (4)

Results:

Sample	# Positive/ # Tested
Test Units	0/300
Growth Promotion	2/2
Negative Control	0/2

Sindan

(P.3.3. facility-process-description-sindan.pdf, p47/68; P.3.5. (b) (4))

CCIT was performed with both the dye ingress method and microbial immersion method. Test procedure is not described for either method. Data provided for microbial immersion method is summarized below.

Container/Closure system:

Component	Production	CCIT
Vial	10 mL vials (b) (4) (b) (4) (b) (4)	10 mL vials (b) (4)
Stopper	(b) (4)	(b) (4)

It is indicated that stoppers for production and for CCIT have the same diameters.

Test method: microbial immersion

Brief description: Test vials are filled with TSB. After testing, vials were incubated at 30-35°C for 14 days. Positive control vials had a 0.45 mm diameter needle fragment inserted into the stoppers.

Challenge organism: B. diminuta

Challenge level: (b) (4)

Results:

Sample	# Positive/ # Tested
Test Units	0/20
Positive control	5/5
Negative Control	0/2

Note to reviewer: Container closure integrity test is performed as part of the performance qualification for the filling and capping machine in the Sindan facility. Stoppers tested in the CCIT (product code (b) (4)) were different from stoppers used for production (product code (b) (4)). However, diameters for the two stoppers are identical (P.3.3. facility-process-description-sindan.pdf, p47/68). Description of vials used in the CCIT is not clear and clarification will be requested. If container/closures for the drug product are the same for both the Actavis and Sindan facilities, the CCIT performed in the Actavis facility is adequate.

Information Request: An IR letter dated 5/8/2017 was conveyed to the NDA holder. The applicant's response was received in 5/31/2017. The original comments followed by the IR response are included below.

With regard to the container closure integrity test (CCIT) information provided for product manufactured at the Sindan facility:

- Clarify whether vials tested in the CCIT are identical or have identical diameters to the vials proposed for the drug product. If not, provide new CCIT data for the container/closure system proposed for the drug product.*

- b) Describe the test procedure for the microbial immersion test, including the duration that the vials were immersed in the microbial culture, and whether the challenge incorporates vacuum/pressure exposure.

Response:

- a) The vials tested in the CCIT are identical to the vials proposed for the drug product. The stoppers are different. The stopper used in CCIT was (b) (4)) while the one proposed was (b) (4) . However diameters of the closure foots are the same for the stoppers used in the CCIT and for the stoppers proposed for drug product, both are (b) (4) mm.
- b) Test method: microbial immersion. Test vials filled with TSB were placed into a desiccator which contained the microorganism suspension. A pressure drop up to -700 mbar in the interior of the desiccator was achieved by using a vacuum pump. The vials were kept for 10 minutes in the vessel, and then the vessel was decompensated. The immersed vials were left for 30 minutes, after which they were removed and decontaminated using a disinfectant solution for 3 minutes. After testing, vials were incubated at 30-35°C for 14 days. Positive control vials had a 0.45 mm diameter needle fragment inserted into the stoppers and subjected to immersion and vacuum. However once the -700 mbar was achieved in the desiccator, the vessel was decompensated immediately and the vials were removed and decontaminated.

Reviewer's Assessment: ADEQUATE

- **Antimicrobial Effectiveness Testing -**

N/A. The subject drug product is a single dose; antimicrobial effectiveness testing is not required.

Reviewer's Assessment: ADEQUATE

P.3 Manufacture

P.3.1 Manufacturers

Two manufacturing facilities are proposed. Both facilities will be responsible for manufacture, packaging, labeling, release and stability testing of the drug product.

Actavis Italy S.p.A. – Nerviano Plant
Via Pasteur 10
20014 Nerviano (Milan)
Italy

S.C. SINDAN-PHARMA S.R.L.
11th Ion Mihalache Boulevard
011171, Bucharest 1,

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date:

Yuansha Chen, Ph.D.

CDER/OPQ/OPF/DMA

5/9/2019

Secondary Reviewer Name and Date:

Neal J. Sweeney, Ph.D.

CDER/OPQ/OPF/DMA

5/9/2019



Yuansha
Chen

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Neal
Sweeney

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 210064

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Assay	Formulation, Raw materials, Process Parameters, Scale/equipment	L	Assay is determined by a validated HPLC method. Critical manufacturing process steps were identified and controlled. The long term and accelerated stability studies show that the assay is consistent during the time tested.	The dose strength of the drug product is expected to be within the specification during the entire shelf life from product quality perspective. None	None
Impurities	Raw materials, process parameters,	M	The degradants/ impurities are fully characterized and controlled by DS specification and DP specification. The test results during the stability studies are within the specification. The impurities are assessed by validated HPLC methods.	The degradants/impurities of the drug product are expected to be controlled and the drug product is safe for IV administration during the entire shelf life from product quality perspective. Low	None
Bioburden	Manufacturing environment and processes	M	Applicant's environmental monitoring program is consistent with regulatory requirement for aseptic processing.	Bioburden is controlled in the drug product at release and stability. Low	None
Sterility	Sterilization	M	(b) (4)	Sterility is controlled in drug product at release and stability. Low	None

Document History

Document History		
Author: Integrated Quality Assessment Team, and Don Henry.		
Clearance Statement: This document is sponsored by the Integrated Quality Assessment Team. Jorge Rondon (OPRO/OE), Don Henry (OPRP/OE), and the Integrated Quality Assessment Team have cleared this template for use.	This process (CDER OPQ Integrated Quality Assessment Template) will be reviewed at the following intervals and changes to the work aid will be captured as needed: This process will be reviewed approximately 150 days from date issued (February 18, 2016).	
Version	Summary of Changes	Date Issued
03	Content update	02/18/2016

Memorandum

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

Date: October 10, 2017
From: Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II Office
of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: CMC Review #1 of NDA 210064

Subject: Final Recommendation for NDA 210064

At the time when the CMC Review #1 was completed on September 11, 2017, it had noted the following pending issues:

- Final “Acceptable” recommendation from the Office of Process and Facilities was not issued.
- The label/labeling issues were not resolved.

Because of these deficiencies, this NDA was not recommended for approval from the ONDP perspective.

On October 10, 2017 the Office of Process and Facilities issued the overall “Approval” recommendation for the facilities involved in this NDA (see Facilities review).

The immediate container labels, carton labels and package insert were revised and submitted on September 18, 2017, October 4, 2017 and October 5, 2017. The CMC sections of the immediate container label, carton label and package insert, were reviewed by Dr. Sarah Ibrahim and found acceptable (see Labeling Review).

Recommendation:

This NDA is now recommended for Approval from the ONDP perspective.

Application Technical Lead’s Assessment and Signature

The NDA is recommended for Approval from quality perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II

FACILITIES[IQA Review Guide Reference](#)

Product Background: The drug product is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

NDA: 210064

Drug Product Name / Strength: Fosaprepitant Dimeglumine (EMEND) Powder For Injection, Eq 150 mg base / vial

Route of Administration: Intravenous

Applicant Name: Teva Pharmaceuticals USA, Inc.

Review Recommendation: *OPF/DIA assessed all facilities as acceptable to support this application.*

Review Summary: Following a review of the application and inspectional documents, there are significant outstanding, manufacturing or facility risks that prevent approval of this application. No preapproval inspection requests were made during the review cycle. The manufacturing facilities listed for NDA 210064 are acceptable at this time.

List Submissions being reviewed (table):

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original –0000 (1)	12/16/2016
Original –0001 (2)	02/08/2017
Original –0002 (3)	02/09/2017
Original –0003 (4)	03/10/2017
Original –0004 (5)	03/17/2017
Original –0006 (7)	05/31/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

List Number of Comparability Protocols (ANDA only): N/A

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Aldridge

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Vidya
Pai

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Memorandum

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

Date: October 6, 2017

From: Sarah Ibrahim, Ph.D.
Reviewer
Division of New Drug Products II
Office of New drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New drug Products

To: Labeling Review #1 of NDA 210064

Subject: Final Recommendation

The Labeling review #1 has noted the following pending issues:

A. Regarding PI

a) Highlight Section

- The established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for Injection” in the Title and Dosage and Strength sections.

b) Full Prescribing Information

#3: Dosage Forms and Strengths

- The established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for Injection”

#11: Description

- The established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for Injection”

#16: How Supplied/Storage and Handling

- The established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for Injection”

B. Regarding of the Container/Carton Labels:

- Established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for injection”.

And because of these deficiencies, in the Labeling Review #1, this NDA was not recommended for approval from the labeling perspective.

On September 18, 2017 (container label), October 4, 2017 (carton label), October 5, 2017 (PI), the applicant amended the labels and labeling, and the above issues are satisfactorily resolved (see the **Attachment**).

Recommendation:

This NDA is **now** recommended for approval from the labeling perspective.

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Sarah
Ibrahim

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Comments: Final one with facility status change



Moo Jhong
Rhee

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Hitesh
Shroff

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Recommendation: As of this review this 505 (b)(2) NDA is *not* ready for Approval in its present form per 21 CFR 314.125(b)(13)

NDA 210064 Review 1

Drug Name/Dosage Form	Fosaprepitant for injection
Strength	150 mg Fosaprepitant/vial
Route of Administration	Injection for intravenous use
Rx/OTC Dispensed	Rx
Applicant	Teva Pharmaceuticals USA, Inc.; Parsippany, NJ USA
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	12/16/2016	OPQ
Amendment	02/08/2017	OPF
Amendment	02/09/2017	OPQ
Amendment	03/10/2017	OPQ
Amendment	03/17/2017	ONDP/DNDAPI ONDP/DB
Amendment	05/31/2017	OPF ONDP OPF/DMA

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Friedrich Burnett	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product and Labeling	Sarah Ibrahim	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process	Li-Shan Hsieh	CDER/OPQ/OPF/ DPAIII/PABVIII
Microbiology	Yuansha Chen	OMPT/CDER/OPQ/OPF/DM A/MABIII
Facility	Allison Aldridge	CDER/OPQ/OPF/DIA/IABIII
Biopharmaceutics	Kelly Kitchens	CDER/OPQ/ONDP/ DB/BBII
Regulatory Business Process Manager	Oumou Barry	OMPT/CDER/OPQ/OPRO/DR BPMI/RBPMBI
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV
Laboratory (OTR)	N/A	N/A
ORA Lead	Paul Perdue Jr.	ORA/OO/OMPTO/ DMPTPO/MDTP
Environmental Analysis (EA)	Sarah Ibrahim	CDER/OPQ/ONDP/ DNDPII/NDPBV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Fosaprepitant Dimeglumine	Active	Adequate, Jan 01/2017	LoA Nov 10, 2016
	Type III	(b) (4)		Active	Adequate, Aug 5, 2016	Nov 22, 2016
	Type III			Active	Adequate, Oct 28, 2014	Nov 22, 2016
	Type V			Active	Adequate, Aug 2, 2016	Dec 15, 2016

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None	None	None

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of Process and Facilities (OPF) has **not** made a final overall “Approval” recommendation for the facilities involved in this application as of this review.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling issues have been satisfactorily resolved.

Therefore, from the OPQ perspective, this NDA is **not** deemed ready for approval in its present form per 21 CFR 314.125(b)(13).

II. Summary of Quality Assessments

A. Product Overview

Fosaprepitant for injection is a substance P/neurokinin-1 (NK₁) receptor antagonist. It is supplied as a single-dose glass vial containing 150 mg of fosaprepitant (equivalent to 245 mg of fosaprepitant dimeglumine salt) sterile white to off-white lyophilized powder. The drug product is reconstituted with 5 mL of 0.9% Sodium Chloride Injection, USP. The reconstituted solution is then added to aseptically prepared infusion bag filled with 145 mL of 0.9% Sodium Chloride Injection, USP and administered intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy.

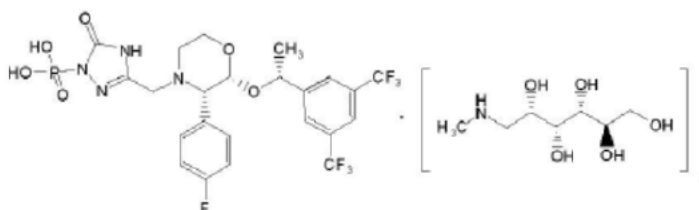
Proposed Indication(s) including Intended Patient Population	Fosaprepitant Dimeglumine for Injection is a substance P/neurokinin-1 (NK ₁) receptor antagonist, indicated in adults, in combination with other antiemetic agents, for the prevention of: - acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin - delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)
Duration of Treatment	As needed
Maximum Daily Dose	Recommended dosage in adults is 150 mg on Day 1 as an intravenous infusion over 20 to 30 minutes approximately 30 minutes prior to chemotherapy.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

The active pharmaceutical ingredient (API) in the drug product is fosaprepitant dimeglumine. Fosaprepitant dimeglumine is a prodrug of aprepitant. It is rapidly converted *in vivo* to the aprepitant. It is manufactured by (b) (4). The complete CMC information for the drug substance is provided in DMF (b) (4). A Letter of Authorization to reference the DMF (b) (4) in support of this NDA was provided. The DMF was reviewed by Dr. Friedrich Burnett on January 01, 2017 and was deemed adequate. There are no CMC related significant updates since the last review.

Its chemical name is 1-Deoxy-1-(methylamino)-D-glucitol [3-[[[(2R,3S)-2-(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinylmethyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]phosphonate (2:1). Its molecular formula is $C_{23}H_{22}F_7N_4O_6P \cdot 2(C_7H_{17}NO_5)$ and its molecular weight is 1004.83. Its structural formula is the following:



Fosaprepitant dimeglumine is a white to off-white hygroscopic powder that is freely soluble in water and methanol. It is a chiral compound with a specific rotation of +28° to +33° in methanol. The X-ray diffraction analysis shows that it is amorphous. It is freely soluble in water and methanol, practically insoluble in absolute ethanol. The pH of the aqueous solution is between (b) (4).

The quality of fosaprepitant dimeglumine is controlled by its specification which includes identification by infrared spectroscopy and HPLC; purity by HPLC, heavy metals per UPS <231> Method II, impurities by HPLC and residual solvents etc.

(b) (4) during the drug product manufacturing process (b) (4). The API specification deemed adequate per drug substance reviewer Dr. Friedrich Burnett. (See the **Drug Substance** review)

The information regarding container closure and stability is provided in DMF (b) (4). Based on the stability data, the API re-test period of (b) (4) months was established.

The Office of Process and Facilities (OPF) reviewer, Dr. Allison Aldridge, has made an “Adequate” recommendation for the drug substance manufacturing and testing facility (See the **Facilities** review).

(b) (4) is manufactured and controlled according to the procedure described in DMF (b) (4) from (b) (4). (b) (4) conforms to the requirements (specification) for drug product formulation of fosaprepitant for injection.

Drug Product:

Fosaprepitant for injection is supplied in single-dose 10mL (b) (4) clear glass vials as a white to-off white sterile lyophilized powder for reconstitution. The vials are stoppered with dark grey rubber stoppers and capped with (b) (4) caps with (b) (4) disks.

Each vial contains 245.3 mg of fosaprepitant equivalent to 150 mg of fosaprepitant dimeglumine and the following inactive ingredients: edetate disodium (18.8 mg), meglumine (75 mg), povidone K12 (600 mg), and water for injection. Hydrochloric acid and/or meglumine may have been added to adjust the pH up to (b) (4). The drug product formulation does not contain any preservatives or antioxidants.

Both fosaprepitant for injection and the reference listed drug, Emend for injection, contain 18.8 mg of edetate disodium as chelating agent. However, the new Emend for injection formulation approved in December 2, 2016 contains 5.4 mg of edetate disodium.

The drug product is manufactured, tested and released by Actavis Italy S.p.A., Milan, Italy and S. C. Sindan-Pharma S.R.L., Rumania. The manufacturing process involves (b) (4)

(b) (4). These two manufacturing sites appear to have the same manufacturing principles and controls with different manufacturing processing scales and time required for each step. The final drug product controls are the same, test results meet the specification. The manufacturing processes at Actavis and Sindan were reviewed by Dr. Li-Shan Hsieh and deemed acceptable. (See **Process** review)

The overall control strategy for the drug product is deemed adequate based on raw material controls, drug product specification including appearance, identity, assay, impurities, water content, content uniformity, heavy metals and microbial and endotoxin limits, and also stability data assuring the identity, strength, purity, and quality during the 24-month of expiration dating period when stored at refrigerated temperature ($5 \pm 3^{\circ}\text{C}$) in the proposed container closure system according to drug product reviewer, Dr. Sarah Ibrahim (see the **Drug Product** review).

The microbiology reviewer, Dr. Yuansha Chen, reviewed the manufacturing steps involving environmental monitoring, (b) (4) bioburden and endotoxin in drug product specification, etc., and concluded that the applicant has met regulatory expectations for the product release (See the **Microbiology** review).

The Office of Process and Facilities (OPF) reviewer, Dr. Allison Aldridge, has *not* made an “Adequate” recommendation for the drug product manufacturing and testing facilities (See the **Facility** review).

Based on the stability data provided, a 24-month of expiration dating period for the drug product is granted when stored at $5 \pm 3^{\circ}\text{C}$ in the proposed container closure system.

The applicant claimed a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31(a) and a statement of no extraordinary circumstances existed was included. The claim was reviewed and found to be acceptable.

The Biopharmaceutics reviewer, Dr. Kelly Kitchens, concluded that in accordance with 21 CFR 320.24(b)(6) the applicant has provided adequate information to establish a biobridge between the relative bioavailability of the drug product and Agency's finding of safety and efficacy of the Reference Listed Drug, Emend for injection, 150 mg. Therefore, additional in vivo bioequivalence (BE) bridging study is not needed. (See the **Biopharmaceutics** review)

The proposed labels and labeling are deemed adequate from the CMC perspective according to Dr. Sarah Ibrahim (see **Labeling** review).

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (see Attachment)

E. List of Deficiencies:

Regarding Facilities

There has not been a recommendation from the facility reviewer as of this review.

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II

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R Regional Information

Environmental Analysis

The applicant has submitted categorical exclusion for manufacturing of the API from the requirements to prepare an Environmental Assessment or an Environmental Impact Statement under 21 CFR 25.31.

The drug product Fosaprepitant Dimeglumine for Injection, Eq. 150 mg base/vial c is not expected to increase the use of the active moiety because will not be administered at higher dosage levels, for longer duration, or for different indications, than were previously in effect. The applicant therefore submitted a Exemption from the requirement of an environmental assessment is warranted under Title 21 CFR, Section 25.31(a).

Reviewer's Assessment:

The applicant has submitted a claim of categorical exclusion. The categorical exclusion cited at 21 CFR 25.31 is appropriate for the estimated amount of drug to be produced for direct use, and a statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.

Methods Verification Package

Reviewer's Assessment:

Not Applicable.

Comparability Protocols

Reviewer's Assessment:

Not Applicable

Post-Approval Commitments

Reviewer's Assessment:

The post-approval commitments with regard to stability update, annual reports and compliance with 21 CFR §314.81 is deemed Adequate.

This section is Satisfactory.

Lifecycle Management Considerations

Reviewer's Assessment:

Not applicable.

List of Deficiencies

None.

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:

- Fosaprepitant Dimeglumine for Injection, Eq. 150 mg base/vial in combination with other antiemetic agents, is indicated in adults for the prevention of - acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).
- The drug product containing 150 mg fosaprepitant (free acid)/vial that gives a 1 mg/ml solution for infusion after reconstitution with 0.9% Sodium Chloride and further dilution with 0.9% Sodium Chloride.

- The inactive ingredients are compendial, with justified functions and the amount administered intravenously is within the limit listed in the IIG with the exception of Kollidon K12 (Povidone K12). When concentration of povidone K12 was calculated based on daily exposure it was found to be within range of other approved IV products and was therefore deemed acceptable.
- Although composition table indicates 75mg of meglumine, the drug product contains a total of (b) (4) mg/ml after reconstitution due to the extra meglumine contributed by the drug substance. Since this will be further diluted to 150 ml before infusion, its potency will be (b) (4) % which is far below 5.7% for IV in IIG. Furthermore, povidone K12 (600mg) will be also diluted to 150ml before infusion, and its concentration will be 4mg/ml (0.4%) which is less than IV limit 2% in IIG).
- The applicant has provided sufficient information on the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product.
- The finished drug product is packaged in glass vial (b) (4) -colorless- with a nominal filling capacity of 10 ml, sealed with a rubber stopper and (b) (4) (b) (4) cap with (b) (4) disk and is suitable for the dosage form and intended patient population and conditions of use by patient/provider.
- The applicant lists identity, assay, apparent viscosity, related substance, reconstitution time and uniformity in containers in the drug product specification, which is adequate to assure the identity, strength, quality, and potency of the product.
- The applicant has validated the analytical procedures to demonstrate their suitability in order to ensure the identity, strength, quality, purity and potency of the drug product so that future commercial production batches are comparable to the pivotal clinical batches for the clinical performance.
- The registration stability studies were conducted in accordance with ICH Q1A R2 at $5 \pm 3^{\circ}\text{C}$ and $25 \pm 2^{\circ}\text{C}$ with results showing no evidence of any significant changes with proposed package configuration. The stability data submitted is sufficient to justify the proposed expiration dating of 24 months when stored at $5 \pm 3^{\circ}\text{C}$.

Overall Recommendation:

This NDA is recommended for **Approval** from the Drug Product perspective.

Sarah Ibrahim, PhD

DNDP II/ONDP

Branch V

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Supervisor Comments and Concurrence:

Nausea and vomiting are common complications of cancer chemotherapy (CINV) and for this, an oral dosage form of neurokinin 1 receptor antagonist, Emend (aprepitant) capsules, was approved. However, sometimes due to complication from CINV, an IV formulation is preferred to the oral capsule dosage form. To meet this medical need, a water soluble form of aprepitant, fosaprepitant dimeglumine, was developed, which is a prodrug and undergoes to form aprepitant in-vivo. It was approved as Emend (fosaprepitant dimeglumine) for Injection in 2008.

However, when the Emend (fosaprepitant dimeglumine) undergoes degradation, it produces aprepitant which will precipitate due to its low solubility in water, and to prevent it from precipitation, (b) (4)

One salient feature of this product purported by the applicant is to mitigate the reported hypersensitivity caused by the polysorbate 80 in the Emend formulation, and, through extensive developmental studies, they claim that povidone K12 is a suitable (b) (4)

Whether that claim is valid or not is beyond the purview of this review.

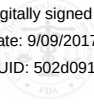
I agree with Dr. Ibrahim's assessment on the overall control strategy for the production of the drug product and therefore, from the drug product perspective, I concur with her recommendation of **Approval** of this application with a 24-month of expiration dating period.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP



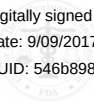
Moo Jhong
Rhee

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Sarah
Ibrahim

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LABELING

R. Regional Information

1.14 Labeling

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

FOSAPREPITANT DIMEGLUMINE for injection, for intravenous use
Initial U.S. Approval: 2008

2) DOSAGE FORMS AND STRENGTHS

Fosaprepitant Dimeglumine for Injection: 150 mg, lyophilized powder in single-dose vial for reconstitution (3)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	fosaprepitant dimeglumine for injection	No Proprietary name is proposed, but is acceptable. The established name should be presented as "Fosaprepitant for Injection" Not Satisfactory.
Dosage form, route of administration	for injection, for intravenous use	The dosage form, for injection, is described adequately. Route of administration is presented correctly. Satisfactory.
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))	Fosaprepitant Dimeglumine for Injection: 150 mg, lyophilized powder in single-dose vial for reconstitution	The dosage form, for injection, is described correctly. The strength, 150mg, is based on free base and is described correctly Satisfactory.
Whether the drug product is scored		

2. "FULL PRESCRIBING INFORMATION

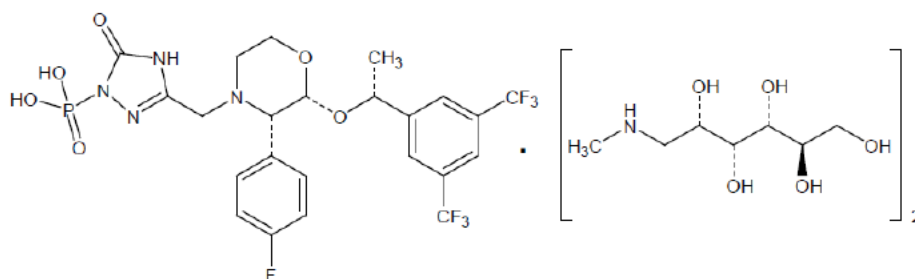
1) #3: DOSAGE FORM AND STRENGTHS

Fosaprepitant Dimeglumine for Injection: 150 mg, white to off-white lyophilized powder in single-dose glass vial for reconstitution.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	Fosaprepitant Dimeglumine for Injection	"Fosaprepitant Dimeglumine for Injection" should be revised to "Fosaprepitant for Injection" Not Satisfactory.
Strengths: in metric system	150 mg	The strength, 150mg, is based on free base and presented correctly. Satisfactory.
Active moiety expression of strength with equivalence statement (if applicable)		See #11 Description section
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	lyophilized powder in single-dose vial for reconstitution	The description is correctly expressed. Satisfactory.

2) #11: DESCRIPTION

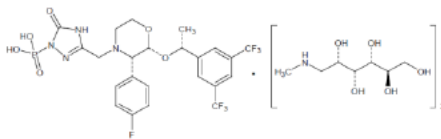
Fosaprepitant Dimeglumine for Injection is a sterile, lyophilized prodrug of aprepitant, a substance P/neurokinin-1 (NK₁) receptor antagonist, an antiemetic agent, chemically described as 1-Deoxy-1- (methylamino)-D-glucitol[3-[[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4- morpholinyl]methyl]-2,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]phosphonate (2:1) (salt).



Its empirical formula is $C_{23}H_{22}F_7N_4O_6P \cdot 2(C_7H_{17}NO_5)$ and its structural formula is:

Fosaprepitant dimeglumine is a white to off-white amorphous powder with a molecular weight of 1004.83. It is freely soluble in water.

Each vial of Fosaprepitant Dimeglumine for Injection for administration as an intravenous infusion contains 245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg of fosaprepitant free acid and the following inactive ingredients: edetate disodium (18.8 mg), meglumine (75 mg), povidone k12 (600 mg), and water for injection. Hydrochloric acid and/or meglumine may have been added for pH adjustment.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	No proprietary name is proposed. Fosaprepitant dimeglumine for injection	The drug name, "Fosaprepitant Dimeglumine for Injection", should be revised to "Fosaprepitant for Injection". Not Satisfactory.
Dosage form and route of administration	For Injection for administration as an intravenous infusion	The dosage form, for injection, and route of administration, intravenous infusion, are expressed correctly. Satisfactory.
Active moiety expression of strength with equivalence statement (if applicable)	245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg of fosaprepitant free acid	The equivalence statement is expressed correctly. Satisfactory.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	edetate disodium (18.8 mg), meglumine (75 mg), povidone k12 (600 mg), and water for Injection. Hydrochloric acid and/or meglumine may have been added for pH adjustment.	The inactive ingredients information is presented correctly with their composition. Satisfactory.
Statement of being sterile (if applicable)	sterile	Satisfactory
Pharmacological/ therapeutic class	P/neurokinin-1 (NK1) receptor antagonist	Satisfactory
Chemical name, structural formula, molecular weight	1-Deoxy-1- (methylamino)-D-glucitol[3-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4- fluorophenyl)-4- morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]phosphonate (2:1) (salt) Its empirical formula is C ₂₃ H ₂₂ F ₇ N ₄ O ₆ P • 2(C ₇ H ₁₇ NO ₅) and its structural formula is:  Fosaprepitant dimeglumine is a white to off-white amorphous powder with a molecular weight of 1004.83.	The chemical names and the structural formula are correctly presented. The molecular weight is included. Satisfactory.
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	NA	NA

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

One 150 mg, sterile, white to off-white lyophilized powder in single-dose glass vial, for reconstitution.

Supplied as follows:

NDC 0591-4385-79 1 vial per carton.

Storage

Fosaprepitant Dimeglumine for Injection vials must be refrigerated, store at 2° to 8°C (36° to 46°F).

The reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25°C (77°F)].

Sterile, Nonpyrogenic, Preservative-free.

The vial stopper is not made with natural rubber latex.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	One 150 mg	Satisfactory.
Available units (e.g., bottles of 100 tablets)	1 vial per carton	The information provided is Adequate. Satisfactory.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white to off-white lyophilized powder in single-dose glass vial, for reconstitution: NDC 0591-4385-79	The information provided is Adequate. Satisfactory.
Special handling (e.g., protect from light)	vials must be refrigerated	The information provided is Adequate. Satisfactory.
Storage conditions	Fosaprepitant Dimeglumine for Injection vials must be refrigerated, store at 2° to 8°C (36° to 46°F). The reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25°C (77°F)].	The information provided is Adequate. Satisfactory.
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Not included in this section but displayed in the #17.	Satisfactory.

II. Labels

1. IMMEDIATE CONTAINER

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Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Fosaprepitant Dimeglumine for injection	No proprietary name is not presented. Established name, "fosaprepitant dimeglumine for injection", should be revised to "fosaprepitant for injection". Not Satisfactory.
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	150 mg/vial	Equivalency statement is missing. However, since the statement is presented in the carton label, it is acceptable in consideration of limited space. Satisfactory.
Net contents	150mg	Satisfactory
"Rx only" displayed prominently on the main panel	Displayed	Satisfactory.
NDC number (21 CFR 207.35(b)(3)(i))	Displayed	Satisfactory.
Lot number and expiration date (21 CFR 201.17)	Displayed	Satisfactory.
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Displayed	Satisfactory.
Bar code (21CFR 201.25)	Displayed	Satisfactory.
Name of manufacturer/distributor	Displayed	Satisfactory.
And others, if space is available		

2. CARTON LABELS:

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Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	No proprietary name is proposed. Established name is presented as "Fosaprepitant Dimeglumine for Injection"	No proprietary name is proposed but that is acceptable. Established name should be revised to "Fosaprepitant for injection". Not Satisfactory.
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	150 mg/vial Each vial contains 245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg of fosaprepitant	Satisfactory.
Net quantity of dosage form	Not displayed.	
"Rx only" displayed prominently on the main panel	Displayed	Satisfactory.
Lot number and expiration date	Displayed	Satisfactory.
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Displayed	Satisfactory.
Bar code (21CFR 201.25)	Displayed	Satisfactory.
NDC number (21 CFR 207.35(b)(3)(i))	Displayed	Satisfactory.
Manufacturer/distributor's name	Displayed	Satisfactory.
Quantitative ingredient information (injectables)	Displayed	Satisfactory.
Statement of being sterile (if applicable)	Displayed	Satisfactory.
"See package insert for dosage information"	Displayed	Satisfactory.
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	N/A	N/A

III. LIST OF DEFICIENCIES:

A. Regarding PI

a) Highlight Section

- The established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for Injection” in the Title and Dosage and Strength sections.

b) Full Prescribing Information**#3: Dosage Forms and Strengths**

- The established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for Injection”

#11: Description

- The established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for Injection”

#16: How Supplied/Storage and Handling

- The established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for Injection”

B. Regarding of the Container/Carton Labels:

- Established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for injection”.

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

Overall, labeling and labels have required information, except for the established name, which should be revised to comply with CDER’s Salt policy as delineated in the **List of Deficiencies**.

Recommendation:

From the ONDP perspective, this application is *not* recommended for approval per (314.1259b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:***Secondary Reviewer Name and Date (and Secondary Summary, as needed):***

The RLD, EMEND (fosaprepitant dimeglumine) for Injection, was approved with salt name before the “Salt Policy” was implemented in 2013, however, this RLD product has recently changed the established name to comply with the salt policy.

Therefore, this application should revise the established name without salt to mitigate any medication error with the already approved product.

I, therefore, agree with Dr. Ibrahim's assessment on the labels/labeling and her recommendation of removal of salt from the established name, and concur with her recommendation for delaying approval of this application until revision of the labels and labeling is made with the correct established name.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP



Sarah
Ibrahim

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Moo Jong
Rhee

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Date: 8/22/2017 10:19:04AM
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Memorandum

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

Date: September 11, 2017

From: Sarah Ibrahim, Ph.D.
Reviewer, Branch V
Division of New Drug Products II
Office of New drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New drug Products

To: Labeling Review #1 of NDA 210064

Subject: Final Recommendation

The Labeling review #1 has noted the following pending issues:

A. Regarding PI

a) Highlight Section

- The established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for Injection” in the Title and Dosage and Strength sections.

b) Full Prescribing Information

#3: Dosage Forms and Strengths

- The established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for Injection”

#11: Description

- The established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for Injection”

#16: How Supplied/Storage and Handling

- The established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for Injection”

B. Regarding of the Container/Carton Labels:

- Established name, “Fosaprepitant Dimeglumine for Injection” should be revised to “Fosaprepitant for injection”.

And because of these deficiencies, in the Labeling Review #1, this NDA was not recommended for approval from the labeling perspective.

On August 23, 2017, the applicant amended the labeling and the above issues are satisfactorily resolved (see the **Attachment**).

Recommendation:

This NDA is **now** recommended for approval from the labeling perspective.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page



Sarah
Ibrahim

Digitally signed by Sarah Ibrahim
Date: 9/11/2017 01:28:04PM
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Moo Jong
Rhee

Digitally signed by Moo Jong Rhee
Date: 9/11/2017 01:32:44PM
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BIOPHARMACEUTICS

Product Background: The Applicant is seeking approval of Fosaprepitant Dimeglumine for Injection, Eq. 150 mg base/vial under the 505(b)(2) path. The approval is based on the previous findings of safety and efficacy for the reference listed drug (RLD), Emend® (fosaprepitant dimeglumine) for injection, under NDA 22023. The drug product is indicated in adults, in combination with other antiemetic agents, for the prevention of:

- Acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin; and,
- Delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

NDA: 210064

Drug Product Name / Strength: Fosaprepitant Dimeglumine for Injection / Eq. 150 mg base/vial

Route of Administration: Intravenous

Applicant Name: Teva Pharmaceuticals USA, Inc.

Review Summary:

The Applicant requests a biowaiver for Fosaprepitant Dimeglumine for Injection per 21 CFR 320.24 (b)(6) since their proposed product contains the same active ingredient in the same concentration as the approved reference product, Emend® (fosaprepitant dimeglumine) Injection; however, the inactive ingredients of the proposed and reference products are not qualitatively and quantitatively (Q1/Q2) the same.

The Applicant provided adequate justification for the differences in the inactive ingredients, and in the physiochemical properties between the proposed and listed drug products. Consistent with 21 CFR 320.24 (b)(6), FDA deemed the information supporting the relative bioavailability of Teva's proposed drug product to the listed drug to be adequate, and a *biobridge* has been established to the Agency's finding of safety and effectiveness for the listed drug. Thus, an additional in vivo bioequivalence (BE) bridging study is not needed.

From the Biopharmaceutics perspective, NDA 210064 for Fosaprepitant Dimeglumine for Injection, Eq. 150 mg base/vial is recommended for **approval**.

List Submissions being reviewed:

Submission Date	Purpose of Submission
December 13, 2016	Original
March 17, 2017	Amendment – Information Request

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

BCS Designation

Reviewer's Assessment: N/A for intravenous product

Solubility:

Permeability:

Dissolution:

Biowaiver Request

Reviewer's Assessment:

- The proposed Fosaprepitant Dimeglumine for Injection product contains the same active ingredient in the same concentration as the approved reference product, Emend® (fosaprepitant dimeglumine) Injection. However, the inactive ingredients of the proposed and reference products are not qualitatively and quantitatively (Q1/Q2) the same.
- The following tables compare the proposed product and the reference product:

	Listed Drug	Proposed Teva Drug
	Emend® (Fosaprepitant Dimeglumine for injection)	Fosaprepitant Dimeglumine for Injection
<i>Conditions of use</i>	EMEND® for injection, in combination with other antiemetic agents, is indicated in adults for the prevention of: - acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin - delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) <u>Limitations of Use</u> - EMEND® has not been studied for treatment of established nausea and vomiting.	Fosaprepitant dimeglumine for injection, in combination with other antiemetic agents, is indicated in adults for the prevention of: - acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin - delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) <u>Limitations of Use</u> - Fosaprepitant dimeglumine for injection has not been studied for treatment of established nausea and vomiting.
<i>Active Ingredient</i>	FOSAPREPITANT DIMEGLUMINE	FOSAPREPITANT DIMEGLUMINE
<i>Inactive Ingredients</i>	Edetate disodium Polysorbate 80 Lactose anhydrous Sodium hydroxide and/or hydrochloric acid (for pH adjustment)	Edetate disodium Povidone K12 Meglumine Hydrochloric acid (b) (4) Meglumine (b) (4)
<i>Route of administration</i>	Intravenous use	Intravenous use
<i>Dosage form</i>	Lyophilized powder	Lyophilized powder
<i>Strength (s)</i>	EQ 150MG BASE/VIAL	EQ 150MG BASE/VIAL

Components	EMEND® for Injection 150 mg	Fosaprepitant Dimeglumine for Injection 150 mg	Role in formulation
	Formula/ unit dose	Formula/ unit dose	
	Powder; Intravenous mg/vial	Powder; Intravenous mg/vial	
Fosaprepitant dimeglumine (corresponding to fosaprepitant free acid)	245.3 (150.0)	245.3 (150.0)	Active substance
EDTA (b) (4)	18.8*	(b) (4) (18.8)	(b) (4)
Polysorbate 80	75	--	
Lactose anhydrous	375	--	
Povidone K12	--	600.0	
Meglumine	--	75.0	
Sodium hydroxide/Hydrochloric acid	pH adjustment	--	pH adjusters
Hydrochloric acid (b) (4) Meglumine (b) (4)	-	(b) (4)	pH adjusters

*EMEND® labeling provides no details if the EDTA is anhydrous or dihydrate

- The proposed product is meant to be reconstituted and diluted in the same way as Emend. The product is reconstituted with 0.9% sodium chloride and the resulting solution of 30 mg/mL Fosaprepitant is further diluted in 0.9% sodium chloride to a concentration of 1 mg/mL.
- The excipients were selected to provide a physically and chemically stable formulation. Since hypersensitivity reactions with polysorbate 80 have been documented in literature, the Teva proposed formulation avoids the use of polysorbate 80.
 - (b) (4)
- Povidone K12 was tested and found to be adequate to (b) (4)
 - Lower molecular weight povidone, such as K12 (b) (4), are regarded as safe for parenteral formulations.^{1,2} The toxicity profile reportedly is expected to be low due to easy elimination through glomerular filtration and reduced reticuloendothelial system uptake.
 - The daily exposure level of povidone K12 used in the proposed drug product formulation (600 mg) is below the amount used in other marketed products as shown below, such as FDA-approved Docetaxel Injection Concentrate Intravenous Infusion (NDA 203551):

¹ Bee T, 2010

² Schulte S, 1999

Table 3: Povidone in Marketed Products Summary:

IV drugs containing Povidone as excipient	Povidone details	Povidone content	Human povidone dose/day (mg) ¹	Comments
Actavis [®] Docetaxel (NDA # 203551) (Docetaxel PI) ¹	Povidone K12	100 mg povidone/mL	900 mg	Based on the maximum infusion dose of 100 mg docetaxel/m ² /day administered as a one-hour infusion every three weeks
Alkeran [®] (Alkeran [®] PI) ²	Povidone K12	20 mg povidone/vial	172.8 mg	Based on the usual IV dose of 16 mg melphalan/m ² /day administered as a single infusion over 15 to 20 minute
Istodax [®] (Istodax [®] PI) ³	No data	20 mg povidone/vial	50.4 mg	Based on the recommended dose of romidepsin of 14 mg/m ² administered intravenously over a 4-hour period on days 1, 8 and 15 of a 28-day cycle.
Bexxar [®] (Bexxar [®] PI) ⁴	No data	5.0-6.0% povidone (w/v)	1900 mg	Based on prescribed therapeutic dose of Iodine ¹³¹ I Tositumomab (35 mg) over 20 minutes supplied at nominal protein and activity concentrations of 1.1 mg/mL and 55 5.6 mCi/mL (at date of calibration), respectively

¹ Assuming a 70 kg person with body surface area of 1.8 m²¹ http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/203551s002lbl.pdf² http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/20207s1r007_alkeran_lbl.pdf³ http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022393s014lbl.pdf

- The Drug Product reviewer, Dr. Sarah Ibrahim, and Pharmacology/Toxicology reviewer, Dr. Sushanta Chakder, have no quality or safety concerns with the amount of povidone K12 in the proposed drug product formulation.
- Due to the low toxicity profile of povidone K12, similar to lower povidone K12 levels compared to other marketed injectable products, similar physicochemical properties as the reference product (see the following physicochemical data tables), and satisfactory quality and safety assessment of the amount of povidone K12, the use of povidone K12 in the proposed drug product formulation is not expected to affect the in vivo performance of the drug product.
- Edetate disodium was added to the formulation in the same quantity as added to the Emend formulation.
- Meglumine was added to the formulation^{(b) (4)} [REDACTED].
- The amount of meglumine used in the proposed drug product formulation (75 mg meglumine as inactive ingredient and ^{(b) (4)} [REDACTED]) is below the amount used in other marketed injectable drug products, such as the following FDA-approved products (except Urografin[®] 150[®]):

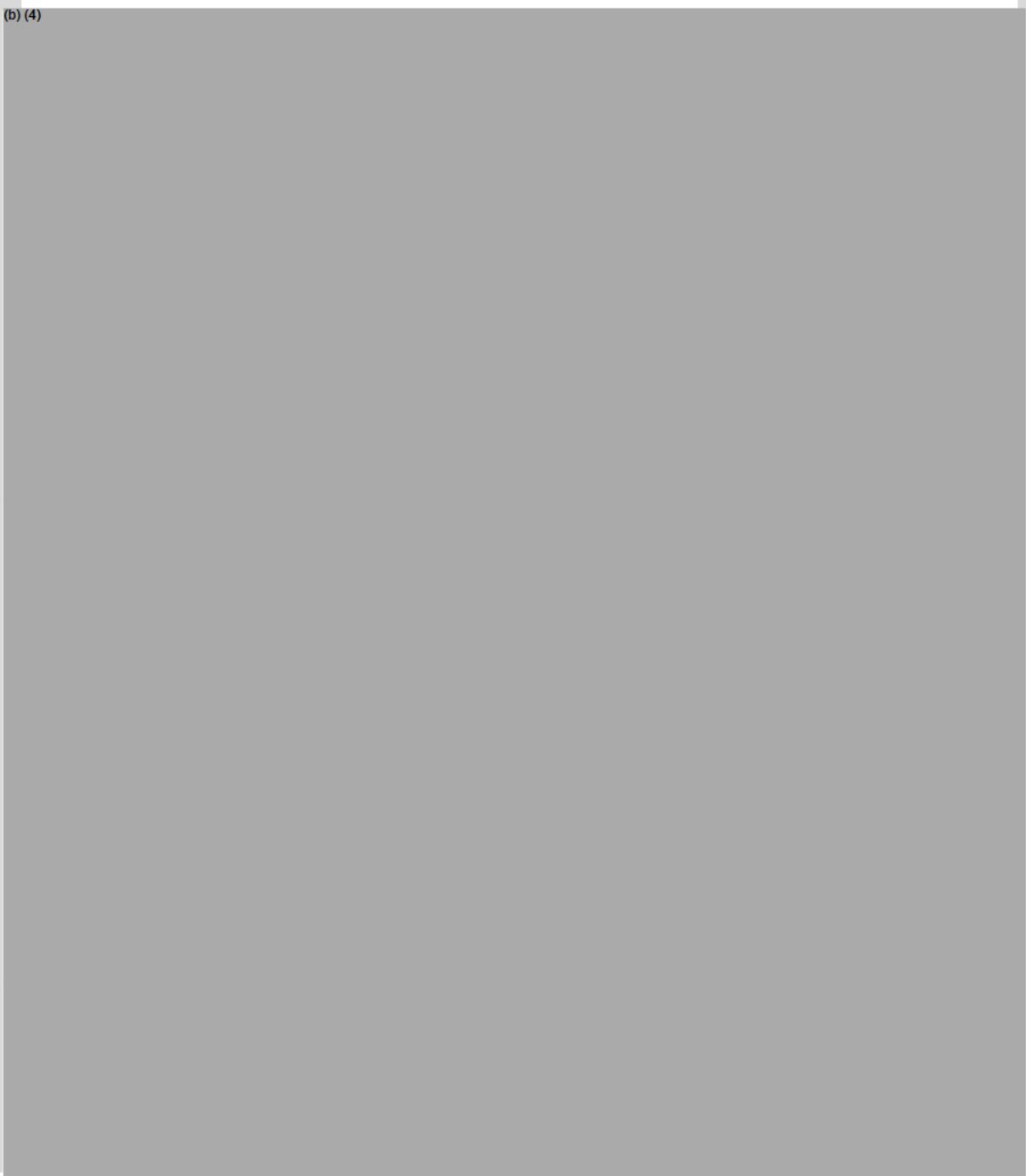
Table 4: Meglumine in Marketed Products Summary:

DRUGS CONTAINING MEGLOMIN	AMOUNT PER VIAL	DAILY EXPOSURE
Conray™ 43% injection ⁵	430 mg/mL of iohalamate meglumine (mw= 809.13); this means 103.6 mg/mL of meglumine (mw= 195)	100 mL solution of Conray™; this means up to 10.3 grams of meglumine per administration
Magnevist® ⁶	469 mg/mL of gadopentetate dimeglumine (mw= 938); this means 195 mg/mL of meglumine (mw= 195)	14 mL solution of Magnevist®; this means 2.73 grams of meglumine per administration
Dotarem® ⁷	376.9 mg/mL of gadoterate meglumine (mw=753.9); this means 97.5 mg/mL of meglumine (mw= 195)	14 mL solution of Dotarem®; this means 1.36 grams of meglumine per administration
Multihance® ⁸	529 mg/mL of gadobenate dimeglumine (mw=1058.2); this means 195 mg/mL mg of meglumine (mw= 195)	14 mL solution of Multihance®; this means 2.73 grams of meglumine per administration
Urografin® 150 ⁹ (not in US)	1 mL contains 260 mg meglumine diatrizoate (mw= 809.1); this means 62.6 mg/mL	2-4 mL/kg body weight, up to 250 mL; this means 15.6 grams of meglumine per administration
Hexabrix™ ¹⁰	393 mg/mL of ioxaglate meglumine (mw= 1268.8+195), 196 mg/mL of ioxaglate sodium; this means 52.3 mg/mL mg of meglumine (mw= 195)	50 mL solution of Hexabrix™; this means 2.61 grams of meglumine per administration

- The Drug Product reviewer, Dr. Sarah Ibrahim, and Pharmacology/Toxicology reviewer, Dr. Sushanta Chakder, have no quality or safety concerns with the amount of meglumine in the proposed drug product formulation.
- Due to lower meglumine levels compared to other marketed injectable products, similar physicochemical properties as the reference product (see the following tables), and satisfactory quality and safety assessment of the amount of meglumine, the use of meglumine in the proposed drug product formulation is not expected to affect the in vivo performance of the drug product.
- The pH is adjusted to (b) (4) using HCl (b) (4) meglumine (b) (4) which is within acceptable pH range for Fosaprepitant Dimeglumine for Injection (pH (b) (4)).
- The Applicant requests a waiver of the requirement for in vivo bioavailability testing of the proposed drug product per 21 CFR 20.24 (b)(6) – *Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence*, and submitted the following information to justify the differences in the inactive ingredients between the proposed product and the reference product.
 - Comparative physicochemical data showing that proposed product has similar potency and impurity/degradation profile when compared to Emend.

Annex 1: Comparative physico-chemical data showing that Teva product has similar potency and impurity/degradation profile when compared to LD, EMEND®:

(b) (4)



Reviewer's Note: The above potency and impurity/degradation profile will be reviewed by the CMC reviewers.

- Comparative physicochemical data showing similarity between the proposed product and Emend when reconstituted and diluted in 0.9% NaCl solution (as per the package insert). The following tests have been performed in order to

demonstrate the sameness with Emend: pH, osmolality, surface tension, viscosity, and specific gravity.

Annex 2: Comparative physico-chemical data showing similarity between the Teva product and the listed drug, Emend® for Injection when reconstituted and diluted in 0.9% NaCl solution (as per the package insert):

(b) (4)

- A comparative dilution study showing that the relative performance and impurity profile of the proposed product and Emend is comparable, when reconstituted and diluted in 0.9% NaCl solution, as per the package insert.

Annex 3: Comparative results obtained for diluted solutions in 0.9% Sodium Chloride Injection:

(b) (4)

The following comments were conveyed to the Applicant in the 74-day letter dated March 3, 2017:

In order to conclude that adequate bridging information is provided according to 21 CFR 320.24 (b)(6), you need to provide the following for review:

A rationale with supporting data/information to demonstrate that any differences between your proposed drug product and the reference product, in terms of pH (buffer capacity), viscosity, and osmolality are considered minor and will not affect the pharmacokinetic performance and/or the

clinical safety and efficacy outcome of your proposed drug product compared to those of the reference product.

A summary of the firm's March 17, 2017 response is as follows:

When ready for administration (at final concentration of 1 mg/mL), the evaluated physicochemical parameters of the injectable solution (pH, viscosity and osmolality) are very similar between test and reference product. Therefore, there are no differences that could affect the pharmacokinetic performance and/or the clinical safety and efficacy outcome of proposed drug product when compared with those of the reference product.

The minor differences noted for the reconstituted solution (at 30 mg/mL) in terms of osmolality and viscosity are considered to have very limited clinical relevance, since the label precludes direct administration of the undiluted solution to the patient (it recommends dilution to 1 mg/mL final concentration before administration).

From a biowaiver perspective alone, the minor differences in osmolality and viscosity of the injectable solution are not expected to influence the pharmacokinetic performance of the product, as long as the bioavailability of fosaprepitant after IV administration is always 100%.

In conclusion, from a clinical perspective, the minor differences in osmolality and viscosity values for the reconstituted solution are not expected to affect the pharmacokinetic performance and/or the clinical safety and efficacy outcome of proposed drug product compared with those of the reference product.

Reviewer's comments:

- This reviewer agrees that the differences in pH, osmolality and viscosity of the final proposed and reference drug products (i.e. reconstituted and diluted to a final concentration of 1 mg/mL with 0.9% sodium chloride) are minor, and therefore the differences will not possibly affect the pharmacokinetic performance or clinical safety and efficacy outcomes of the proposed drug product when compared to the reference product. The following table highlights that these physiochemical properties are similar:

	Fosaprepitant Dimeglumine for Injection Batch GF15001A	Fosaprepitant Dimeglumine for Injection Batch 5ZD502	Emend (fosaprepitant dimeglumine) for Injection Batch L051112
pH	8.29	8.32	8.22
Osmolality (mOsm/kg)	306	306	305
Viscosity (mm ² /s)	0.99	0.99	0.98

- Based on the information provided, as it is consistent with 21 CFR 320.24.(b)(6), FDA deemed the information supporting the relative bioavailability of Teva's proposed drug product to the listed drug to be adequate, and a *biobridge* has been established to the Agency's finding of safety and effectiveness for the listed drug. Thus, an additional in vivo bioequivalence (BE) bridging study is not needed.

APPEARS THIS WAY ON ORIGINAL

List of Deficiencies: N/A

Primary Biopharmaceutics Reviewer Name and Date:

Kelly M. Kitchens, Ph.D., April 21, 2017

Secondary Reviewer Name and Date:

I concur. 04/24/17

Tien-Mien Chen, Ph.D.

Acting Biopharmaceutics Lead

DB/ONDP/OPQ



Tien Mien
Chen

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Kelly
Kitchens

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MICROBIOLOGY**Product Background:**

NDA: 210064

Drug Product Name / Strength: Fosaprepitant Dimeglumine for Injection, 150 mg/vial, single dose

Route of Administration: IV

Applicant Name: Teva Pharmaceuticals USA, Inc.

Manufacturing Sites:

Actavis Italy S.p.A. – Nerviano Plant

Via Pasteur 10

20014 Nerviano (Milan)

Italy

S.C. SINDAN-PHARMA S.R.L.

11th Ion Mihalache Boulevard

011171, Bucharest 1,

Romania

Method of Sterilization:

(b) (4)

Review Summary:

The application is recommended for approval on the basis of sterility assurance.

List Submissions being reviewed (table):

Submitted	Received	Assigned to Reviewer
12/16/2016	12/16/2016	1/25/2017
5/31/2017 *	5/31/2017	6/1/2017
*IR response		

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: DMF (b) (4) and the associated microbiology review (b) (4) mic35.doc (adequate) dated 5/18/2016 by Y. Smith are referenced for the depyrogenation information of the stoppers.

(b) (4)

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – The drug product is a sterile, white to off-white lyophilized powder in a single-dose glass vial.
- **Drug product composition** –

Components	Function	Amount/Unit
Fosaprepitant Dimeglumine	API	245.3 mg
Edetate disodium (b) (4)	(b) (4)	(b) (4)
Kollidon 12 PF		600.0 mg
Meglumine		75.0 mg
Hydrochloric acid (b) (4) / Meglumine (b) (4)	pH adjusters	Up to (b) (4)
WFI	(b) (4)	

- **Description of container closure system** –

Component	Description	Manufacturer
Vials	(b) (4) clear glass vials, 10 mL	(b) (4) (u) (4) Or (b) (4) (u) (4) (b) (4)
Stoppers	Rubber stopper, (b) (4)	(b) (4)
Seals	(b) (4) (b) (4) cap with (u) (4) disk	(b) (4)

Note to reviewer: Stoppers used in the two facilities are identical (product code (b) (4)). Vials used in the two facilities are from the same suppliers. However, specifications for vials by the two facilities are not identical. The inner neck diameter is specified as (b) (4) by the Actavis facility and (b) (4) by the Sindan facility. Clarification will be requested.

Information Request: An IR letter dated 5/8/2017 was conveyed to the NDA holder. The applicant's response was received in 5/31/2017. The original comments followed by the IR response are included below.

It is noted that the provided specifications for the glass vials used for drug product manufacturing at the Actavis facility and Sindan facility appear to be different. For example “(b) (4)” is indicated on the Actavis facility vial specification (spec (b) (4).pdf) while “(b) (4)” is listed on the Sindan facility vial specification ((b) (4).pdf). Please clarify whether the drug product container/closure systems used at the Actavis and Sindan facilities are identical.

Response: Although the 10-mL glass vials used for drug product at the Actavis facility and Sindan facility are supplied by the same supplier, (b) (4) they are slightly different in some dimensional parameters. Dimensions for vials proposed for both facilities are provided.

Reviewer's Assessment: ADEQUATE

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity -**
Container closure integrity test is provided by the Actavis facility.

Actavis

(P.3.5. container-closure-integ.pdf)

Vial: diameter (b) (4)

Stopper: (b) (4)

The container/closure system used for validation was: Same as the drug product

Test method: microbial immersion

Brief description: Study was performed in Nov. 2016. Test vials are submerged inverted in a container that contains *B. diminuta* culture. The entire system (container with test vials) was incubated at 30-35°C for 14 days.

Challenge organism: *B. diminuta*

Challenge level: (b) (4)

Results:

Sample	# Positive/ # Tested
Test Units	0/300
Growth Promotion	2/2
Negative Control	0/2

Sindan

(P.3.3. facility-process-description-sindan.pdf, p47/68; P.3.5. (b) (4)

CCIT was performed with both the dye ingress method and microbial immersion method. Test procedure is not described for either method. Data provided for microbial immersion method is summarized below.

Container/Closure system:

Component	Production	CCIT
Vial	10 mL vials (b) (4) group (b) (4)	10 mL vials (b) (4)
Stopper	FM457/0	(b) (4)

It is indicated that stoppers for production and for CCIT have the same diameters.

Test method: microbial immersion

Brief description: Test vials are filled with TSB. After testing, vials were incubated at 30-35°C for 14 days. Positive control vials had a 0.45 mm diameter needle fragment inserted into the stoppers.

Challenge organism: *B. diminuta*

Challenge level: (b) (4)

Results:

Sample	# Positive/ # Tested
Test Units	0/20
Positive control	5/5
Negative Control	0/2

Note to reviewer: Container closure integrity test is performed as part of the performance qualification for the filling and capping machine in the Sindan facility. Stoppers tested in the CCIT (product code (b) (4)) were different from stoppers used for production (product code (b) (4)). However, diameters for the two stoppers are identical (P.3.3. facility-process-description-sindan.pdf, p47/68). Description of vials used in the CCIT is not clear and clarification will be requested. If container/closures for the drug product are the same for both the Actavis and Sindan facilities, the CCIT performed in the Actavis facility is adequate.

Information Request: An IR letter dated 5/8/2017 was conveyed to the NDA holder. The applicant's response was received in 5/31/2017. The original comments followed by the IR response are included below.

With regard to the container closure integrity test (CCIT) information provided for product manufactured at the Sindan facility:

- Clarify whether vials tested in the CCIT are identical or have identical diameters to the vials proposed for the drug product. If not, provide new CCIT data for the container/closure system proposed for the drug product.*

- b) Describe the test procedure for the microbial immersion test, including the duration that the vials were immersed in the microbial culture, and whether the challenge incorporates vacuum/pressure exposure.

Response:

- a) The vials tested in the CCIT are identical to the vials proposed for the drug product. The stoppers are different. The stopper used in CCIT was (b) (4) while the one proposed was (b) (4). However diameters of the closure foots are the same for the stoppers used in the CCIT and for the stoppers proposed for drug product, both are (b) (4) mm.
- b) Test method: microbial immersion. Test vials filled with TSB were placed into a desiccator which contained the microorganism suspension. A pressure drop up to -700 mbar in the interior of the desiccator was achieved by using a vacuum pump. The vials were kept for 10 minutes in the vessel, and then the vessel was decompensated. The immersed vials were left for 30 minutes, after which they were removed and decontaminated using a disinfectant solution for 3 minutes. After testing, vials were incubated at 30-35°C for 14 days. Positive control vials had a 0.45 mm diameter needle fragment inserted into the stoppers and subjected to immersion and vacuum. However once the -700 mbar was achieved in the desiccator, the vessel was decompensated immediately and the vials were removed and decontaminated.

Reviewer's Assessment: ADEQUATE

- **Antimicrobial Effectiveness Testing -**

N/A. The subject drug product is a single dose; antimicrobial effectiveness testing is not required.

Reviewer's Assessment: ADEQUATE

P.3 Manufacture

P.3.1 Manufacturers

Two manufacturing facilities are proposed. Both facilities will be responsible for manufacture, packaging, labeling, release and stability testing of the drug product.

Actavis Italy S.p.A. – Nerviano Plant
Via Pasteur 10
20014 Nerviano (Milan)
Italy

S.C. SINDAN-PHARMA S.R.L.
11th Ion Mihalache Boulevard
011171, Bucharest 1,

R.2 Comparability Protocol – No CP was included in the application.

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

A. PACKAGE INSERT

(P. 1.14; P.8.3. Microbial Stability Testing Report - cm-012-16r.pdf)

Storage temperature: 2° to 8°C; Route of administration: IV; Container: Single dose

Reconstituted/Further Diluted Drug Product

The product is first reconstituted with 5 mL of 0.9% sodium chloride, and then is added to an infusion bag of 145 mL 0.9% sodium chloride for a final concentration of 1 mg/mL.

The reconstituted final drug solution is stable for 24 hours at ambient room temperature (at or below 25°C).

Post-reconstitution stability study for microbiology was performed.

Report number: REPORT CM-012-16/R.

Product was diluted to 1mg/mL with sodium chloride. Microorganisms were spiked into the drug solution and incubated at 15-30°C for 48 hours. Microorganisms were counted at initial, 24 hours and 48 hours.

Results:

Microorganism	Initial count (cfu/mL)	24 hours log increase	48 hours log increase
<i>S. epidermidis</i>	98	-1.99	-1.99
<i>St. aureus</i>	60	0.29	0.32
<i>P. aeruginosa</i>	114	0.14	-0.42
<i>B. subtilis</i>	111	-2.04	-2.04
<i>A. niger</i>	32	-0.04	-0.16
<i>C. albicans</i>	131	-0.33	-0.77

Growth was less than 0.5 log increase at the proposed storage condition and duration.

Reviewer's Assessment: ADEQUATE

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date:



Yuansha Chen, Ph.D.

CDER/OPQ/OPF/DMA

6/19/2017

Secondary Reviewer Name and Date:

Neal J. Sweeney, Ph.D.

CDER/OPQ/OPF/DMA

6/20/2017



Yuansha
Chen

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Neal
Sweeney

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 210064

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Assay	Formulation, Raw materials, Process Parameters, Scale/equipment	L	Assay is determined by a validated HPLC method. Critical manufacturing process steps were identified and controlled. The long term and accelerated stability studies show that the assay is consistent during the time tested.	The dose strength of the drug product is expected to be within the specification during the entire shelf life from product quality perspective. None	None
Impurities	Raw materials, process parameters,	M	The degradants/ impurities are fully characterized and controlled by DS specification and DP specification. The test results during the stability studies are within the specification. The impurities are assessed by validated HPLC methods.	The degradants/impurities of the drug product are expected to be controlled and the drug product is safe for IV administration during the entire shelf life from product quality perspective. Low	None
Bioburden	Manufacturing environment and processes	M	Applicant's environmental monitoring program is consistent with regulatory requirement for aseptic processing.	Bioburden is controlled in the drug product at release and stability. Low	None
Sterility	Sterilization	M	(b) (4)	Sterility is controlled in drug product at release and stability. Low	None

Document History

Document History		
Author: Integrated Quality Assessment Team, and Don Henry.		
Clearance Statement: This document is sponsored by the Integrated Quality Assessment Team. Jorge Rondon (OPRO/OE), Don Henry (OPRP/OE), and the Integrated Quality Assessment Team have cleared this template for use.	This process (CDER OPQ Integrated Quality Assessment Template) will be reviewed at the following intervals and changes to the work aid will be captured as needed: This process will be reviewed approximately 150 days from date issued (February 18, 2016).	
Version	Summary of Changes	Date Issued
03	Content update	02/18/2016



Hitesh
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