CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209296Orig1s000

PRODUCT QUALITY REVIEW(S)

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 209296**

Subject: Final Recommendation for NDA 209296

At the time when the CMC Review #1 was completed on October 10, 2017, it had noted the following pending issues:

- The label/labeling issues were not resolved.

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

The applicant submitted updated labeling on October 6, 2017. The CMC sections of the immediate container label, carton label and package insert, were reviewed by Dr. Caroline Strassinger 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

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
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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 9, 2017**

From: **Caroline Strasinger, 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 209296**

Subject: **Final Recommendation**

Labeling Review #1 had noted the following pending issues:

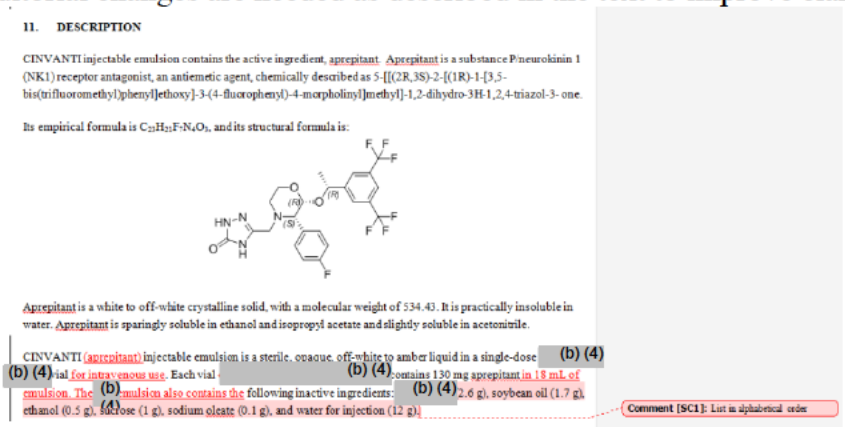
Full Prescribing Information

#3: Dosage Forms and Strengths

- Include opaque, off-white to amber in description
- (b) (4)

#11: Description

- List the inactive ingredients in alphabetical order
- Editorial changes are needed as described in the text to improve clarity.



11. DESCRIPTION

CINVANTI injectable emulsion contains the active ingredient, aprepitant. Aprepitant is a substance P/neurokinin 1 (NK1) receptor antagonist, an antiemetic agent, chemically described as 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3- one.

Its empirical formula is $C_{23}H_{21}F_7N_4O_3$, and its structural formula is:

Aprepitant is a white to off-white crystalline solid, with a molecular weight of 534.43. It is practically insoluble in water. Aprepitant is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile.

CINVANTI (aprepitant) injectable emulsion is a sterile, opaque, off-white to amber liquid in a single-dose (b) (4) vial for intravenous use. Each vial (b) (4) contains 130 mg aprepitant in 18 mL of emulsion. The (b) (4) emulsion also contains the following inactive ingredients: (b) (4) 2.6 g), soybean oil (1.7 g), ethanol (0.5 g), sucrose (1 g), sodium oleate (0.1 g), and water for injection (12 g).

Comment [SC1]: List in alphabetical order

#16: How Supplied/Storage and Handling

- Include opaque, off-white to amber in description

- Present as 1 single dose vial per (b) (4)
- Delete the (b) (4) as this is covered in administration sections.

Container/Carton Labels:

- There were no deficiencies communicated with the Container/Carton from the CMC perspective.

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

On October 6, 2017 the Applicant submitted updated labeling satisfactorily addressing all previous deficiencies (see the Attachment).

OVERALL ASSESSMENT AND RECOMMENDATION:

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

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Caroline Strasinger

Digitally signed by Caroline Strasinger
Date: 10/10/2017 12:07:02PM
GUID: 5051dfdd000013b995075b4d54108ed8

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 10/10/2017 12:08:33PM
GUID: 502d0913000029f9798ca689a802fa55

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)(6).

NDA 209296
OPQ Review #1

Drug Name/Dosage Form	Aprepitant Injectable Emulsion
Strength	130 mg/18 mL (7.2 mg/mL)
Route of Administration	Intravenous use
Rx/OTC Dispensed	Rx
Applicant	Heron Therapeutics, Inc.; San Diego, CA
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	1/12/2017	OPQ
Amendment	3/03/2017	OPQ//ONDP/DB/BBIII
Amendment	4/21/2017	ONDP/DNDAPI/NDBII
Amendment	5/01/2017	ONDP/DNDAPI/NDBII
Amendment	5/12/2017	OPQ/OPF/DMA/MAB
Amendment	5/24/2017	ONDP/DNDAPI/NDBII
Amendment	7/03/2017	ONDP
Amendment	7/31/2017	ONDP/DNDAPI/NDBII
Amendment	8/14/2017	ONDP
Amendment	8/28/2017	ONDP
Amendment	9/13/2017	ONDP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Friedrich Burnett	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product and Labeling	Caroline Strasinger	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process	Peter Krommenhoek	CDER/OPQ/OPF/ DPAIII/PABVIII
Microbiology	Helen Ngai	OMPT/CDER/OPQ/OPF/DM A/MABI
Facility	Allison Aldridge	CDER/OPQ/OPF/DIA/IABIII
Biopharmaceutics	Sandra Suarez	CDER/OPQ/ONDP/DB/BBIII
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
Environmental Analysis (EA)	Caroline Strasinger	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)	(b) (4)	(b) (4)	Drug substance manufacturer	Active	Dr. Xinghua Wu, June 15, 2017, adequate.	LOA March 29, 2017
			Drug substance manufacturer	Active	Dr. Friedrich Burnett, April 26, 2017, adequate	LOA March 25, 2015
			(b) (4)	Active	Sufficient information provided in application	LOA Date October 21, 2015
				Active	November 29, 2016, adequate	LOA November 29, 2016
				Active	April 25, 2017, adequate	LOA November 29, 2016
				Active	June 18, 2017, adequate	LOD June 9, 2016
				Active	September 20, 2012, adequate, no amendments since then	LOA June 9, 2016
				Active	Dr. Helen Ngai, April 19, 2017, adequate	LOA July 21, 2016

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	022023	Emend (fosaprepitnat) for injection Reference listed drug
IND	125926	Aprepitant injectable emulsion bioequivalence study

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

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 label/labeling issues have ***not*** 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)(6).

II. Summary of Quality Assessments

A. Product Overview

Aprepitant is a substance P/neurokinin-1 (NK_1) receptor antagonist. It is supplied in a single-dose glass vial containing 130 mg of aprepitant as 18 mL of a sterile, opaque, and off-white to amber emulsion. For 100 mg aprepitant regimen 14 mL of the drug product is admixed with 101 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection USP, in an infusion bag. For 130 mg aprepitant regimen, 18mL of the drug product is admixed with 132 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP in an infusion bag. The IV solution is administered intravenously over 30 minutes approximately 30 minutes prior to chemotherapy.

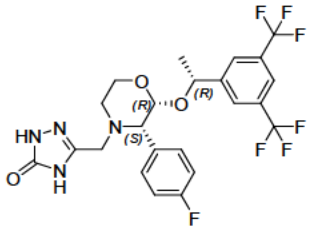
Proposed Indication(s) including Intended Patient Population	Aprepitant (b) (4) is a substance P/neurokinin-1 (NK1) receptor antagonist, indicated in adults, in combination with other antiemetic agents, for prevention of: • acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin • 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 130 mg or 100 mg on Day 1 as an intravenous infusion over 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 aprepitant, USP. It is manufactured by [redacted] (DMF [redacted] (DMF [redacted]. The applicant has provided Letters for Authorization to reference both DMFs in support of this NDA. The complete CMC related information for aprepitant is provided in those DMFs.

DMF [redacted] was reviewed by Dr. Friedrich Burnett on April 26, 2017 and was deemed adequate. DMF [redacted] was reviewed by Dr. Xinghua Wu on June 15, 2017 and was deemed adequate.

Aprepitant is chemically described as 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis (trifluoromethyl) phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3- one. The empirical formula of aprepitant is $C_{23}H_{21}F_7N_4O_3$. Its molecular weight is 534.43 and its structural formula is the following:



Aprepitant is a non-hygroscopic and white to off-white powder. It has a very low solubility in water. It is soluble in [redacted]. It is a chiral compound with 3 chiral centers with specific rotation of [redacted] The pH of the aqueous solution is [redacted] Its partition coefficient (Log P) is 5.2.

Aprepitant polymorphism is not an issue because the applicant has demonstrated that there is no difference in the solubility of aprepitant polymorphs and the drug product is manufactured by [redacted]. Aprepitant is a BCS Class IV drug substance with low solubility and low permeability. Because this drug product is intravenously administered, the BCS class is irrelevant.

The quality of aprepitant is controlled by its specification which includes appearance, identification by infrared spectroscopy and HPLC; purity by HPLC, heavy metals per UPS <231> Method II, impurities by HPLC and residual solvents by GC, etc. The API particle size is not important because during the drug product manufacturing process, it is completely dissolved [redacted]. The API specification deemed adequate per drug substance reviewer, Dr. Friedrich Burnett. (See **the Drug Substance** review)

Based on aprepitant stability data provided in both DMF [redacted] and DMF [redacted] a re-test period of [redacted] were established, respectively.

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).

Aprepitant, USP is manufactured and controlled according to the procedure described in DMF (b) (4) and DMF (b) (4) to conform to the requirements (specification) for the formulation of aprepitant injectable emulsion.

Drug Product:
Aprepitant injectable emulsion is supplied as a sterile, opaque and off-white to amber emulsion in a single-dose glass vial for intravenous use. The vials are stoppered with rubber stoppers and capped with aluminum overseals with plastic flip-off caps.

Each vial contains 130 mg aprepitant and the following inactive ingredients (b) (4) (2.6 g), soybean oil (1.7 g), ethanol (0.5 g), sucrose (1 g), sodium oleate (0.1 g) and water for injection (12 g) in 18 mL of emulsion. The drug product is supplied as a single-dose and single-use vial and it does not contain any preservatives or antioxidants.

The drug product is manufactured by Alcami Corporation, (b) (4) It is manufactured using (b) (4) . The drug product manufacturing process was reviewed by Dr. Peter Krommenhoek 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, dose uniformity, mean particle size, globule size distribution, particulate matter, sterility, pH, heavy metals, container closure integrity and endotoxin limits. When USP methods were not used the applicant used validated in-house methods.

Based on long-term and accelerated stability data of the drug product assuring the identity, strength, purity and quality, a 24-month of expiration dating period when stored at refrigerated temperature ((b) (4) in the proposed container closure system is granted. (See the **Drug Product** review of Dr. Caroline Strasinger).

The microbiology reviewer, Dr. Helen Ngai, reviewed the manufacturing steps involving environmental monitoring, component/equipment sterilization, sterile filtration, (b) (4) . The microbiology related attributes in the drug product specification including endotoxins, sterility and container closure integrity etc., were also reviewed by her and she has recommended for approval on the basis of sterility assurance. (See the **Microbiology** review).

The *in vitro* drug release (IVDR) method using USP Type IV apparatus with filter membrane and its acceptance criteria were reviewed by the Biopharmaceutics reviewer, Dr. Sandra Suarez, and she deemed acceptable because the proposed IVDR method is capable of detecting variation in critical quality attributes of the drug product such as particle size and crystal content, thereby ensuring consistent *in vitro* and *in vivo* performance of the drug product throughout its life cycle. However, during the lifecycle, if any changes are proposed beyond the ranges approved, depending on the impact of the changes on the drug product critical quality attributes (CQA), an *in vitro* BE testing may be needed. (See the **Biopharmaceutics** review)

The Office of Process and Facilities (OPF) reviewer, Dr. Allison Aldridge, has made an "Adequate" recommendation for the drug product manufacturing and testing facilities (See the **Facility** review).

An environmental impact analysis assessment with calculation of estimated entry into aquatic environment, less than 1 ppb, was provided with a statement that no extraordinary circumstances exist. Therefore, claim of a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31 was deemed acceptable.

The labels and labeling issues are ***not*** satisfactorily resolved from the CMC perspective according to the labeling reviewer, Dr. Caroline Strasinger. Therefore, This application is not deemed ready for approval in its present form per 21CFR 314.125(b)(6) from the OPQ perspective until the deficiencies are satisfactorily resolved. (See the **Labeling** review).

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (see Attachment)

E. List of Deficiencies:

The following labeling comments should be resolved with the applicant.

A. **Regarding PI**

a) Full Prescribing Information

#3: Dosage Forms and Strengths

3. DOSAGE FORMS AND STRENGTHS

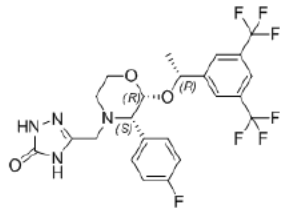
(b) (4) injectable emulsion: 130 mg/18 mL (7.2 mg/mL) aprepitant as an, opaque, off-white to amber emulsion in single-dose (b) (4) vial

#11: Description

11. DESCRIPTION

CINVANTI injectable emulsion contains the active ingredient, aprepitant. Aprepitant is a substance P/neurokinin 1 (NK1) receptor antagonist, an antiemetic agent, chemically described as 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3- one.

Its empirical formula is $C_{23}H_{21}F_7N_4O_2$, and its structural formula is:



Aprepitant is a white to off-white crystalline solid, with a molecular weight of 534.43. It is practically insoluble in water. Aprepitant is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile.

CINVANTI (aprepitant) injectable emulsion is a sterile, opaque, off-white to amber liquid in a single-dose (b) (4) (b) (4) vial for intravenous use. Each vial (b) (4) contains 130 mg aprepitant in 18 mL of emulsion. The (b) (4) emulsion also contains the following inactive ingredients: (b) (4) (2.6 g), soybean oil (1.7 g), ethanol (0.5 g), sucrose (1 g), sodium oleate (0.1 g), and water for injection (12 g).

Comment [SC1]: List in alphabetical order

#16: How Supplied/Storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

CINVANTI injectable emulsion is supplied as an opaque, off-white to amber emulsion in a ~~carton containing~~ single-dose (b) (4) vial of 130 mg aprepitant/18 mL emulsion.

~~(~~NDC 47426-201-01~~)~~ 1 single-dose vial per carton

Storage

CINVANTI injectable emulsion vials must be refrigerated, store at 2°C-8°C (36°F-46°F).
CINVANTI injectable emulsion vials can remain at room temperature up to 60 days.

Do not freeze.

(b) (4)

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
October 4, 2017

Hitesh N. Shroff -S

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Date: 2017.10.10 18:36:55 -04'00'

LABELING

R. Regional Information

1.14 Labeling

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

CINVANTI (aprepitant) injectable emulsion, for intravenous use
Initial U.S. Approval: 2003

2) DOSAGE FORMS AND STRENGTHS

(b) (4) -Injectable emulsion: 130 mg aprepitant, (b) (4) in single-dose (b) (4) vial (3)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: CINVANTI Established Name: aprepitant injectable emulsion	Adequate
Dosage form, route of administration	Dosage: injectable emulsion Route: Intravenous	Adequate
Controlled drug substance symbol (if applicable)		NA
Dosage Forms and Strengths (201.57(a)(8))		
Summary of dosage form and strength	CINVANTI Injectable emulsion: 130 mg emulsion	INADEQAUTE Delete (b) (4) Add "aprepitant" Refer to edits above.

Reviewer Assessment: INADEQUATE

The above information was communicated to OND on September 12th and will be communicated the Applicant on October 12th.

2. "FULL PRESCRIBING INFORMATION

1) #3: DOSAGE FORM AND STRENGTHS

3. DOSAGE FORMS AND STRENGTHS

(b) (4) injectable emulsion: 130 mg/18 mL (7.2 mg/mL) aprepitant as an, opaque, off-white to amber emulsion in single-dose (b) (4) vial

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	Injectable emulsion	Adequate
Strengths: in metric system	130 mg/18 mL	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Emulsion in a single dose (b) (4) vial	INADEQUATE

Reviewer Assessment: Inadequate

- Include opaque, off-white to amber in description
- (b) (4)

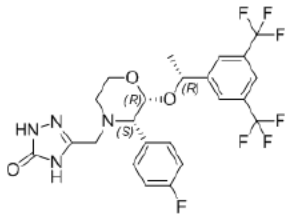
The above information was communicated to OND on September 12th and will be communicated the Applicant on October 12th.

2) #11: DESCRIPTION

11. **DESCRIPTION**

CINVANTI injectable emulsion contains the active ingredient, aprepitant. Aprepitant is a substance P/neurokinin 1 (NK1) receptor antagonist, an antiemetic agent, chemically described as 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3- one.

Its empirical formula is $C_{23}H_{21}F_7N_4O_3$, and its structural formula is:



Aprepitant is a white to off-white crystalline solid, with a molecular weight of 534.43. It is practically insoluble in water. Aprepitant is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile.

CINVANTI (aprepitant) injectable emulsion is a sterile, opaque, off-white to amber liquid in a single-dose (b) (4) vial for intravenous use. Each vial (b) (4) contains 130 mg aprepitant in 18 mL of emulsion. The (b) (4) emulsion also contains the following inactive ingredients: (b) (4) 2.6 g), soybean oil (1.7 g), ethanol (0.5 g), sucrose (1 g), sodium oleate (0.1 g), and water for injection (12 g).]

Comment [SC1]: List in alphabetical order

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	CIVANTI (apreptiant) injectable emulsion	Adequate
Dosage form and route of administration	Injectable emulsion	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	(b) (4) (2.6 g), soybean oil (1.7 g), ethanol (0.5 g), sucrose (1 g), sodium oleate (0.1 g), and water for injection (12 g).	Inadequatel list in alphabetical order
Statement of being sterile (if applicable)	Sterile	Adequate
Pharmacological/ therapeutic class	substance P/neurokinin 1 (NK1) receptor antagonist	Adequate
Chemical name, structural formula, molecular weight	Structure, molecular weight, formula presented	Adequate
If radioactive, statement of important nuclear characteristics.	NA	Adequate
Other important chemical or physical properties (such as pKa or pH)	Solubility	Adequate

Reviewer Assessment: INADEQUATE

- List the inactive ingredients in alphabetical order

- Make the above described editorial comments to improve clarity.

The above information was communicated to OND on September 12th and will be communicated the Applicant on October 12th.

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

16 HOW SUPPLIED/STORAGE AND HANDLING

CINVANTI injectable emulsion is supplied as an opaque, off-white to amber emulsion in a (b) (4) single-dose (b) (4) vial of 130 mg aprepitant/18 mL emulsion.

(NDC 47426-201-01) 1 single-dose vial per carton

Storage

CINVANTI injectable emulsion vials must be refrigerated, store at 2°C-8°C (36°F-46°F).
CINVANTI injectable emulsion vials can remain at room temperature up to 60 days.

Do not freeze.

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	130 mg/18 mL	Adequate
Available units (e.g., bottles of 100 tablets)	Carton containing sing dose vial	INADEQUATE Present as 1 single dose vial per carton
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	single-dose vial;	INADEQUATE Include opaque, off-white to amber emulsion
Special handling (e.g., Dispense in tight and light resisteant container as defined in USP)	Do not freeze	Adequate
Storage conditions	Must be refrigerated, store at 2-8C (36F-46F)	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured by Alcami Corporation, LLC Distributed by Heron Therapeutics, Inc	Adequate

Reviewer Assessment: INADEQUATE

The above information was communicated to OND on September 12th and will be communicated the Applicant on October 12th.

II. Labels (Provided January 12, 2017)

1. IMMEDIATE CONTAINER LABEL

Reviewer Assessment: ADEQUATE

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Cinvanti (aprepitant)	Adequate
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	130 mg/ 18 mL (7.2 mg/ mL)	Adequate
Net contents	single dose vial	Adequate
"Rx only" displayed prominently on the main panel	Rx only	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Presnet	Adequate
lot number and expiration date (21 CFR 201.17)	Location present	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store Cinvanti in refrigerator at 2- 8ºC (36° to 46°F); Do not Freeze Dilute before use Discard Unused Portion	Adequate
Bar code (21CFR 201.25)	Present	Adequate
Name of manufacturer/distributor	Present	Adequate
And others, if space is available		

2. CARTON LABELS:

Reviewer Assessment: **ADEQUATE**


(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	Cinvanti (aprepitant)	Adequate
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	130 mg/ 18 mL (7.2 mg/ mL)	Adequate
Net quantity of dosage form	single dose vial	Adequate
"Rx only" displayed prominently on the main panel	Displayed on front and back panel	Adequate
Lot number and expiration date	Side Panel	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store Cinvanti in refrigerator at 2- 8ºC (36° to 46°F); Do not Freeze Dilute before use Discard Unused Portion	Adequate
Bar code (21CFR 201.25)	Side panel	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Front and back panel	Adequate
Manufacturer/distributor's name	Side panel	Adequate
Quantitative ingredient information (injectables)	(b) (4) (2.6g), soy bean oil (1.7), ethanol (0.5g), sucrose (1 g), sodium oleate (o..1g), and water for injection (12g)	Adequate
Statement of being sterile (if applicable)	Sterile	
"See package insert for dosage information"	Front and back panels	Adequate
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Not applicable	Adequate

III. LIST OF DEFICIENCIES:

A. Regarding PI

a) Highlight Section

b) Full Prescribing Information

#3: Dosage Forms and Strengths

- Include opaque, off-white to amber in description

- (b) (4)

#11: Description

- List the inactive ingredients in alphabetical order
- Editorial changes are needed as described in the text to improve clarity.

#16: How Supplied/Storage and Handling

- Include opaque, off-white to amber in description
- Present as 1 single dose vial per container
- Delete the (b) (4) as this is covered in administration sections.

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

The Label and Labeling of NDA 209296 is inadequate due to the deficiencies noted above for Highlights, Section 3, 11 and 16 of the PI. This information was communicated to OND on September 12, 2017 and will be communicated to the Applicant October 12, 2017. The Container and Carton Labels are adequate.

This application is not deemed ready for approval in its present form per 21CFR 314.125(b)(6) from the label/labeling perspective until the deficiencies noted above are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Caroline Strasinger, PhD 12-SEP-2017
OPQ, ONDP, DNDP II, BV

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

I agree with Dr. Strasinger's assessment on the labeling and labels and concur with her recommendation that this application is ***not*** deemed ready for approval as of this review.

Moo-Jhong Rhee, Ph.D. 12-Sep-2017
Chief, Branch V
DNDP II/ONDP

Caroline Strasinger

Digitally signed by Caroline Strasinger
Date: 9/12/2017 08:15:58PM
GUID: 5051dfdd000013b995075b4d54108ed8

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 9/13/2017 09:28:36AM
GUID: 502d0913000029f9798ca689a802fa55

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BIOPHARMACEUTICS

Product Background:

NDA: 209296 ORIG-1

Drug Product Name / Strength: CINVANTI (aprepitant) injectable emulsion, 130 mg/ 18 mL, emulsion in single-dose glass vial

Route of Administration: Intravenous

Applicant Name: Heron Therapeutics

The Applicant is seeking approval of CINVANTI™ (aprepitant) injectable emulsion, for intravenous (IV) infusion in the treatment of acute and delayed chemotherapy-induced nausea and vomiting. CINVANTI™ (also referred in here as HTX-019) injectable emulsion is a sterile oil-in-water emulsion. Each vial of HTX-019 injectable emulsion contains 130 mg aprepitant/18 mL. The formulation concentration is 7.2 mg aprepitant/mL.

For administration, the 130 mg aprepitant dose (18 mL) is diluted with 13 (b) (4) mL of 0.9% sodium chloride injection, USP or 5% dextrose injection, USP in a 150 mL (b) (4) bag. The 100 mg aprepitant dose (14 mL) is withdrawn and diluted with 10 (b) (4) mL of 0.9% sodium chloride injection, USP or 5% dextrose injection, USP in a 150 mL (b) (4) bag. The emulsion has a target mean particle size of (b) (4) nm at release.

The development program follows the 505(b)(2) path relying, in part, on FDA's previous findings of safety and effectiveness for the reference listed drug (LD), EMEND® (fosaprepitant dimeglumine) for injection, for intravenous use (NDA 22-023). Comparative BA studies against the LD along with clinical data were also submitted in support of this NDA. HTX-019 is manufactured, (b) (4) by Alcami Corporation. Alcami Corporation has a manufacturing facility located in Charleston, South Carolina, (b) (4) The clinical trial formulation and manufacturing site are the same as the TBM formulation.

Review Summary:

This 505b (b)(2) drug product (injectable oil-in water emulsion) containing the drug substance aprepitant is to be administered via intravenous injection for the treatment of chemotherapy-induced nausea and vomiting. Aprepitant has been classified as BCS Class IV drug substance. BCS classification is leveraged in support of biowaiver for orally administered drug products. Therefore, BCS class for this drug product is not relevant since it is to be administered by intravenous injections. CINVANTI™ is to be marketed as an immediate release drug product. The drug product's formulation, in vitro release characteristics and comparative PK profiles of CINVANTI with approved IR drug products support the IR claim.

The drug product's final commercial formulation, manufacturing process and equipment are the same as those tested in pivotal BA/BE studies. In vitro release profiles comparing the drug product manufactured using API from two different vendors (b) (4) were similar indicating that any differences in their attributes did not have a significant impact on the in vitro release performance.

The following in vitro release method and acceptance criterion were agreed upon (refer to submission dated Aug 14, 2017):

Parameters	Description
Apparatus	USP 4 (Flow through cell) setup as closed system
Medium	35% ethanol absolute in USP PBS buffer pH 7.4
Volume	200 mL
Speed rate	4.0 mL/min
Temperature	37°C ± 0.5°C
Sample	1.0mL of suspension of Aprepitant
Filtration	Glass fiber 2.7µm (GF/D) + Aluminum oxide 0.02µm filters
Cells setup	1 spoon of glass beads (GB) in each cell (about 6.5g) Addition of 1.0 mL of suspension
Sampling profile	1mL at sampling time points : 5, 10, 15, 20, 30, 60 and 90 minutes
Quantification	See paragraph HPLC method

This method is the result on extensive investigations that included the study of several in vitro release methods (b) (4) usually considered for this type of dosage form. The approved method, namely USP Type IV apparatus with filter membrane dilutes the emulsion drug product into a solubilizing buffer, remove aliquots at specified time points, and separate the lipid droplets from the released "free" API in the aliquots by filtration using a 20 nm aluminum oxide filter. Data provided demonstrated that the in vitro release method and acceptance criterion are able to reject batches with crystal content above (b) (4) %, degraded (b) (4) and mean particle diameter higher than (b) (4)).

The proposed control strategy (e.g. critical tests that govern aprepitant release from HTX-019 emulsion including mean particle size and globule size distribution to control for particle size, pH, and free fatty acids to control for lipid composition) is acceptable from biopharmaceutics perspective to assure product quality and performance and hence is adequate for lifecycle management of the product for changes within process/formulation ranges tested. However, the adequacy of particulate matter proposed acceptance criterion needs to be evaluated by the CMC review teams in terms of its in vivo impact (safety). During the lifecycle, if the changes are proposed beyond the ranges tested, depending on the criticality of the changes and its effect on drug product CQA and hence on product quality and performance, it would indicate a need of in vitro BE testing (e.g., (b) (4) process change).

List Submissions being reviewed (table):

SUBMISSION(S) DATE	SEQUENCE NO.
1/11/17	0001
3/3/17	0006
4/21/17	0009
05/01/16	0011
08/14/17	0019
08/26/17	0020

Highlight Key Outstanding Issues from Last Cycle: NONE

Concise Description Outstanding Issues Remaining: NONE

From Biopharmaceutics perspective, NDA 209296 CINVANTI (aprepitant) injectable emulsion *is recommended for* ***Approval***.

Drug Product

CINVANTI injectable emulsion is a sterile, opaque, off-white to amber liquid in a single-dose clear glass vial. Each vial of CINVANTI injectable emulsion contains 130 mg aprepitant (7.2 mg aprepitant/mL) and following inactive ingredients: (b) (4) (2.6 g), soybean oil (1.7 g), ethanol (0.5 g), sucrose (1 g), sodium oleate (0.1 g), and water for injection (12 g). The composition of HTX-019 (aprepitant) injectable emulsion is shown below.

Component	Concentration (%w/w)	Concentration (mg/mL)	To Deliver Concentration (g/18 mL)	Function	Reference to Quality Standard
Aprepitant	0.716	7.2	0.13	Drug Substanc	Manufacturer
Egg Lecithin, (b) (4)	(b) (4)				NF
Soybean Oil					USP Ph. Eur.
Ethanol					USP Ph. Eur.
Sucrose					NF Ph. Eur.
Sodium Oleate					NF
Water for Injection					USP Ph. Eur.
Total	**100.00**	**1010.0**	**18.23**	**–**	**–**

BCS Designation

The aprepitant pH solubility profile is summarized on Table 1.

Table 1. Aprepitant pH Solubility Profile (mg/mL)

pH 1.0	0.1171
pH 3.3	0.0002
pH 4.3	< 0.0002
pH 5.5	
pH 6.5	
pH 7.5	
pH 8.7	0.0003
pH 9.7	0.0085
pH 10.7	0.0114

Based on the pH solubility profile table for aprepitant, the highest strength (130 mg) / Lowest solubility (0.0002) = >1000 mL which is much more than 250 mL. Therefore, aprepitant is considered to have very low solubility. Based on reported permeability and solubility study performed over a physiological pH range, as per Biopharmaceutical Classification System (BCS), aprepitant can be considered BCS Class IV compound[1].

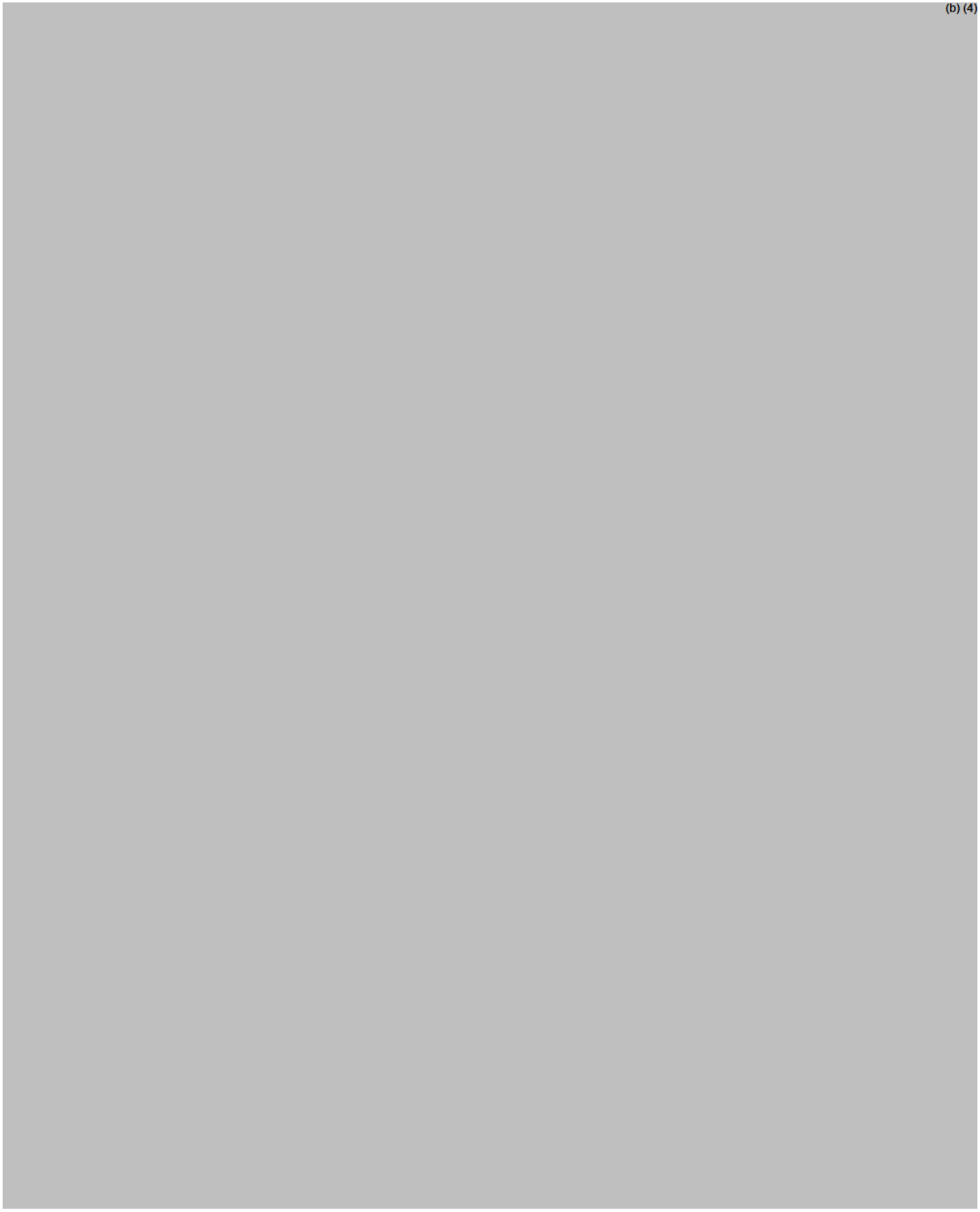
Reviewer's Assessment:

Aprepitant is practically insoluble in water. It belongs to a class IV compound according to the Biopharmaceutics Classification System (BCS). The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. This information is leveraged in support of biowaiver for orally administered drug products. Therefore, BCS class for this drug product is not relevant since it is to be administered by intravenous injection.

(b) (4)

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4845550/ .

(b) (4)



(b) (4)

IVR Method and Acceptance Criterion

IVR Method

The original submission did not include in vitro release testing as part of drug product specification. According to the Applicant, efforts in developing a method (see submission dated 1/11/17 under 32p2), as recommended during the IND stage failed because the rate of diffusion of aprepitant is determined by passage of aprepitant across a membrane, rather than by release from the oil phase. Therefore, the following comments were conveyed to the Applicant during the review cycle:

1. ***It is noted that in vitro release testing is not part of your proposed drug product specifications. As recommended during the IND stage (refer to MM dated 12/14/16) an in vitro release method needs to be developed for drug product quality control and stability testing purposes, i.e., drug performance and drug quality tests.***
   - ***In this regard, we acknowledge your assertion provided during the teleconference dated 12/08/16 that "We have been unable to develop an (b) (4) assay to determine the release rate of aprepitant from the HTX-019 emulsion in human plasma". However, data available to the FDA and literature information indicate the feasibility for developing in vitro release methods for O/W emulsions (i.e. Journal of Pharmaceutics, 66 (1990) 29-37). Therefore, you should develop and implement in vitro release testing for your drug product or submit the developmental data demonstrating that the implementation of an in vitro release method for your drug product is not feasible. Note that the method you developed does not represent a "typical" in vitro release testing for emulsion products since it was coupled with protein binding analysis. Provide your plans for submission of these data/information during the review cycle.***

In response to the FDA's request, the following in vitro release method was developed during the review cycle and it is proposed for release and stability testing:

Parameters	Description
Apparatus	USP 4 (Flow through cell) setup as closed system
Medium	35% ethanol absolute in USP PBS buffer pH 7.4
Volume	200 mL
Speed rate	4.0 mL/min
Temperature	37°C ± 0.5°C
Sample	1.0mL of suspension of Aprepitant
Filtration	Glass fiber 2.7µm (GF/D) + Aluminum oxide 0.02µm filters
Cells setup	1 spoon of glass beads (GB) in each cell (about 6.5g) Addition of 1.0 mL of suspension
Sampling profile	1mL at sampling time points : 5, 10, 15, 20, 30, 60 and 90 minutes

Quantification	See paragraph HPLC method

Method Development

(b) (4)

[redacted]

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(b) (4)

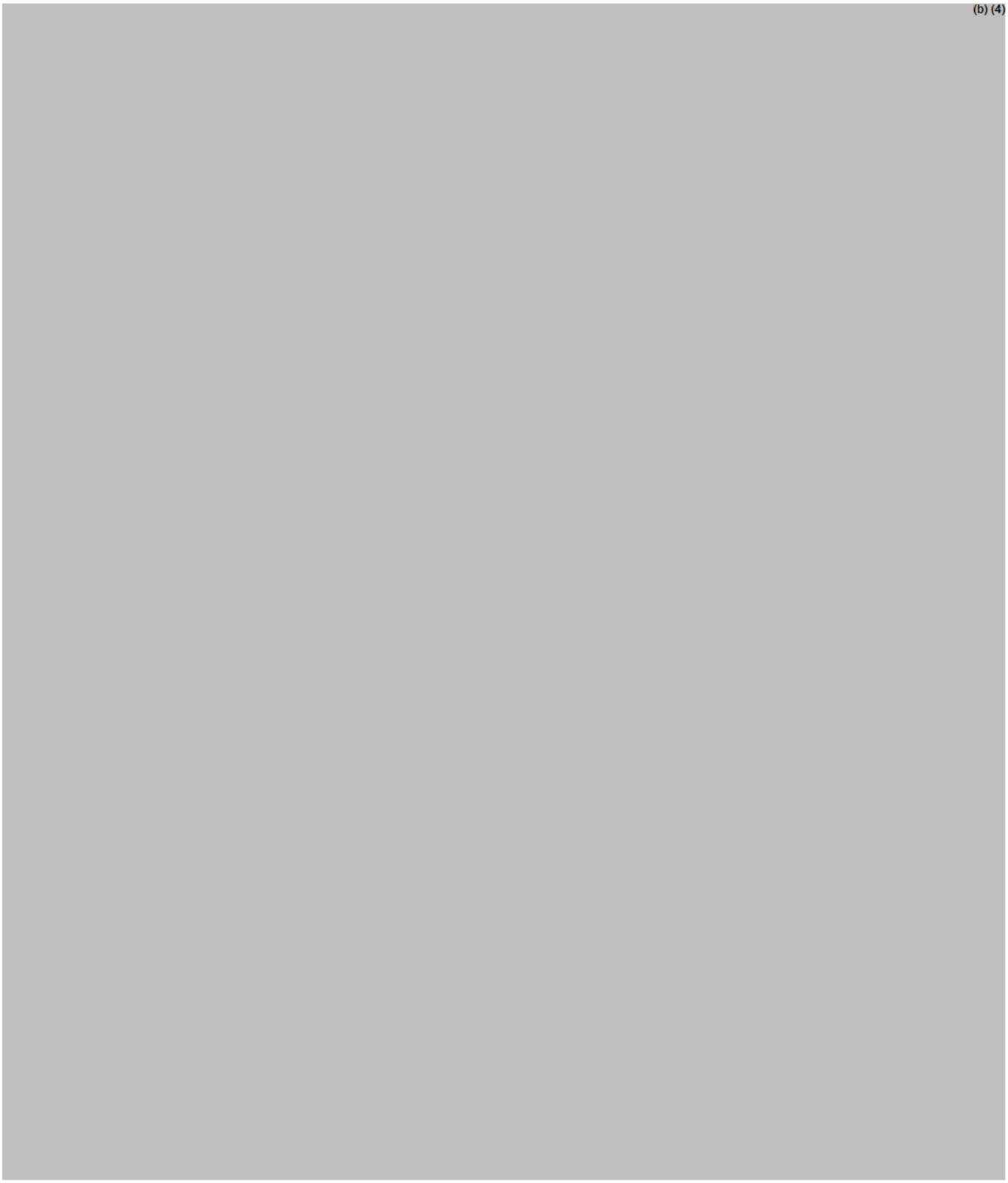


Figure 3. IVR Profiles of Aprepitant from HTX-019 and Various Model Emulsions Measured in USP Apparatus 4.

IVR Acceptance Criterion

The following acceptance criteria were originally proposed for the drug product under review:

NLT (b) (4) % (Q) in (b) (4) min

However, based on the data provided in Figure 3, this criterion is no able to reject batches made with a crude emulsion with a mean particle diameter of (b) (4). Therefore, in order to increase the discriminating ability of the method and based on the performance of several batches tested included the clinical batch (Figure 4), the Applicant was recommended during the review cycle to adopt the following criterion:

1. We acknowledge the responses received on Jun 30, 2017 in terms of in vitro release method. The in vitro release data provided on several batches indicate that more than (b) (4) % of the drug is release within (b) (4) 15 min. In addition, your proposed acceptance criterion of NLT (b) (4) % (Q) in (b) (4) min will not be able to discriminate for batches with large mean particle size (e.g. larger than (b) (4)) and it is not acceptable. Therefore, to increase the discriminating ability of the method and to ensure a better quality control and similar performance to the pivotal

clinical batches we recommend that you implement the following in vitro release acceptance criterion:

NLT (b) (4) % (Q) in 15 min

On a teleconference dated 08/14/17, the Applicant agreed to the recommended acceptance criterion (see also submission dated 8/16/17 with the update table of specification reflecting this recommendation).

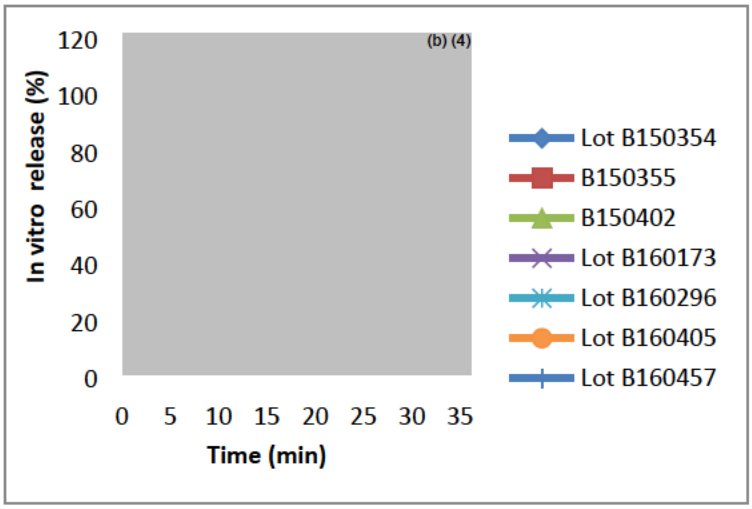


Figure 4. IVR performance for clinical pivotal and registration batches. Originated by the reviewer based on provided data.

Reviewer's Assessment: ADEQUATE

The selected IVR method proposed for release and stability testing, namely USP Type IV apparatus with filter membrane is the result on extensive investigations that included the study of several in vitro release methods (b) (4) usually considered for this type of dosage form. This method, dilutes the emulsion drug product into a solubilizing buffer, remove aliquots at specified time points, and separate the lipid droplets from the released "free" API in the aliquots by filtration using a 20 nm aluminum oxide filter. This method (i.e. along with the recommended acceptance criterion) are deemed acceptable as they are discriminating against critical quality attributes such as particle size and crystal content and will ensure consistent in vitro and in vivo performance of the drug product throughout its life cycle.

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: NA

There are no data relating variations on the critical quality attributes, in vitro release and in vivo performance (e.g. systemic exposure) to evaluate the clinically relevance of the in vitro release specifications (method and criteria). Based on the in vitro data provided, the method will be able to reject for batches with inadequate performance on the critical attributes.

Application of dissolution/IVIVC in QbD

The most critical parameter determining release of aprepitant (b) (4)

(b) (4)

(b) (4)

[redacted]

Reviewer's Assessment: ADEQUATE

From Biopharmaceutics perspective, the proposed control strategy (including the in process controls attributes/parameters) is acceptable to assure product quality and performance. In vitro release testing method and implemented acceptance criterion (b) (4) [redacted] However, the adequacy of particulate matter proposed acceptance criterion needs to be evaluated by the CMC review teams in terms of its in vivo impact (safety).

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: NA

This drug product is to be administered parenterally, and therefore, in vitro alcohol dose-dumping assessment is not applicable.

Bridging of Formulations Across Phases of Development

According to the Applicant, the initial process for the manufacture of HTX-019 injectable emulsion was developed at the laboratory and pilot scales ranging from (b) (4) which laid the foundation for the overall manufacturing process as well as provided initial processing parameters. These initial parameters were further evaluated during the scale-up development from (b) (4).

The clinical development program for HTX-019 included 2 Phase 1 bioequivalence/ bioavailability (BA/BE) trials (HTX-019 C2015-104 and HTX-019-106). Both trials included the same drug product lot (Lot B150402) at the (b) (4) scale. There were no additional clinical trials conducted with HTX-019. Using the processing parameters identified/established during scale-up development, 7 registration lots, 4 lots (B150354, B150355, B150402, B160173) using drug substance from (b) (4) and 3 lots (B160296, B160405, B160457) using drug substance from (b) (4) were manufactured at the proposed commercial scale (b) (4)

Figure 4 above shows similar in vitro performance among all these batches, suggesting that the differences in formulation/process (if any) implemented are not impacting the in vitro performance of the drug product. Lack of implemented manufacturing changes on the biobatch was also confirmed via email communication on 3/22/17 with CMC reviewer Dr. Peter Krommmednhoek who stated that "There are no major differences proposed in the manufacturing process between the intended commercial batches and those used in the BE/BA batch. The process parameters and order of addition for all phases (oil, water, emulsion) are identical, or very similar. So, I concur with the applicant's assertion there are no major changes"

Reviewer's Assessment: ADEQUATE

There are no formulation/manufacturing changes implemented to the biobatch. The data demonstrated that there is no change in in vitro release when changing API vendors (b) (4) In addition, the Applicant claims that differences in some API attributes such as particle size distribution are of no clinical relevance given the lack of effect on the in vitro release of the API in the vehicle (oil). In addition, any changes in the ratio of crystal forms may not be clinically relevant as the drug substance is to be dissolved in the vehicle and the final concentration (NLT (b) (4)) is monitored.

Biowaiver Request

Reviewer's Assessment:

See section above on bridging.

Comparability Protocols

Reviewer's Assessment: NA

Post-Approval Commitments

Reviewer's Assessment: NA

Lifecycle Management Considerations

The proposed control strategy is acceptable from biopharmaceutics perspective to assure product quality and performance and hence is adequate for lifecycle management of the product for changes within process/formulation ranges tested. However, during the lifecycle, if the changes are proposed beyond the ranges tested, depending on the criticality of the changes and its effect on drug product CQA and hence on product quality and performance, it would indicate a need of in vitro BE testing (e.g., (b) (4) process change).

List of Pending Deficiencies

NONE

Primary Biopharmaceutics Reviewer Name and Date:

Sandra Suarez Sharp, Ph.D. (Branch 2DB\ONDP\OPQ), September 13, 2017

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

Tien Men (Albert) Chen, Ph.D., Acting Team Lead (Branch 2\DB\ONDP\OPQ)

I concur. 09/15/17

DB/ONDP/OPQ

APPENDIX

Comments conveyed to the Applicant as part of the 74-day letter:

We are in the process of reviewing your NDA and have identified the lack of some relevant information/data. In order to continue reviewing your submission, provide the following information. Please note that this information is needed by Friday, March 3, 2017:

1. Provide detailed description (e.g. by developmental phase) of all the manufacturing changes implemented to your drug product during the phases of development, especially any manufacturing changes implemented after the conduct of the pivotal BA/BE studies and pivotal phase 3 clinical studies.

2. It is noted that in vitro release testing is not part of your proposed drug product specifications. As recommended during the IND stage (refer to MM dated 12/14/16) an in vitro release method needs to be developed for drug product quality control and stability testing purposes, i.e., drug performance and drug quality tests.

    – In this regard, we acknowledge your assertion provided during the teleconference dated 12/08/16 that "We have been unable to develop an (b) (4) assay to determine the release rate of aprepitant from the HTX-019 emulsion in human plasma". However, data available to the FDA and literature information indicate the feasibility for developing in vitro release methods for O/W emulsions (i.e. Journal of

Pharmaceutics, 66 (1990) 29-37). Therefore, you should develop and implement in vitro release testing for your drug product or submit the developmental data demonstrating that the implementation of an in vitro release method for your drug product is not feasible. Note that the method you developed does not represent a "typical" in vitro release testing for emulsion products since it was coupled with protein binding analysis. Provide your plans for submission of these data/information during the review cycle.

3. Submit detailed information (e.g. dissolution testing conditions, medium and batch employed, etc.) on the In vitro dissolution studies conducted to determine the effect of crystal size on the dissolution of aprepitant. These data should also include the raw data generated in tabular and graphical form.

Comments conveyed to the Applicant as part of the mid-cycle:

Question 1. Does FDA agree that the information that we propose to provide is adequate for the review of the IVR method?

FDA's Response:

The information you plan to provide, as listed below, is appropriate to evaluate the adequacy of your proposed in vitro release method for CINVANTI™ (aprepitant) injectable emulsion 130 mg:

- Background information
- Selection of equipment/apparatus,
- Description of the in vitro release method
- Selection of in vitro release media, temperature, pH, sink condition, flow rate, time points, biorelevance
- Description of the discriminatory power of the method
- Validation parameters for the in vitro release method
- Justification for selection of the specification time point
- Results of testing of the 7 GMP lots

Note that you should also provide the complete dissolution profile data (*individual, mean, SD, profiles*) for the proposed lots of your product.

Question 2. Does the FDA have any comments on the proposed IVR method (attached to the validation protocol) using the Type IV apparatus with filter membrane for batch release and stability testing?

FDA's Response:
The procedure you intent to follow for method validation seems to be in accordance with the recommendations under USP <1092> , <1225> and we do not have any comments at this time.

Question 3. Does the FDA agree that because HTX-019 is an immediate release product, a single point specification of Q = (b)(4)% aprepitant release in (b)(4) minutes is acceptable?

FDA's Response:
The adequacy of the proposed acceptance criterion for your drug product will be determined once the data are provided and reviewed. In general, the acceptance criterion (time point and Q value) are data driven and set based on the performance of the pivotal clinical batches. We acknowledge that data from pivotal clinical batches may not be available, therefore, data from recently manufactured batches produced under the same in process controls as those implemented for the clinical batches will be acceptable.

Question 4. Is the attached validation protocol for the proposed IVR method acceptable?

FDA's Response:
Based on a preliminary assessment the validation protocol seems appropriate to achieve the stated objectives.

The Applicant may consider cancelling the meeting scheduled on June 5, 2017 if the responses given above are sufficient.

Other Biopharmaceutics issues conveyed to the Applicant

We are in the process of reviewing your NDA and have identified some issues and the lack of some relevant information/data as follows. Before we can continue with the review of the biopharmaceutics related data and adequacy of the dissolution acceptance criteria, we request that you consider the following recommendation:

1. We acknowledge the responses received on Jun 30, 2017 in terms of in vitro release method. The in vitro release data provided on several batches indicate that more than (b)(4)% of the drug is release within (b)(4)15 min. In addition, your proposed acceptance criterion of NLT (b)(4)% (Q) in (b)(4)min will not be able to discriminate for batches with large mean particle size (e.g. larger than (b)(4)) and it is not acceptable. Therefore, to

increase the discriminating ability of the method and to ensure a better quality control and similar performance to the pivotal clinical batches we recommend that you implement the following in vitro release acceptance criterion:

- NLT (b) (4) % (Q) in 15 min

2. Please submit and updated table of specifications reflecting these recommended changes.

Tien Mien Chen

Digitally signed by Tien Mien Chen
Date: 9/23/2017 10:16:46AM
GUID: 508da7240002a26723d38018ce005126
Comments: I concur. 09/23/17

Sandra Suarez

Digitally signed by Sandra Suarez
Date: 9/22/2017 10:21:32AM
GUID: 5033874b000046a4a8b9c51d6f5bd8ba

QUALITY ASSESSMENT

MICROBIOLOGY

Product Background: 505(b)(2)

NDA: 209296

Drug Product Name / Strength: Cinvanti (aprepitant) / 130 mg

Route of Administration: Intravenous

Applicant Name: Heron Therapeutics, Inc.

Manufacturing Site: Alcami Corporation, 4221 Faber Pl Dr, North Charleston, SC 29405

Method of Sterilization: Filter sterilization (b) (4)

Review Summary: The submission is recommended for approval on the basis of sterility assurance.

List Submissions being reviewed:

1/12/2017 (submit); 1/12/2017 (receive)
5/12/2017 (submit); 5/12/2017 (receive)
5/26/2017 (submit); 5/26/2017 (receive)

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None identified.

Supporting/Related Documents:

Type V DMF (b) (4) was reviewed in:

(b) (4)
ic1.doc (not adequate) dated 2/9/2012 by S. Donald
ic1a1.doc (adequate) dated 5/29/2012 by J. Wells
ic1a2 (not adequate) dated 7/23/2012 by J. Wells
mic1a3.doc (adequate) dated 10/3/2013 by J. Wells

(b) (4)
D M03R01.doc (not adequate) dated 6/9/2016 by Y. Smith
D M03R02.doc (adequate) dated 3/1/2017 by Y. Smith
D M04R01.doc (not adequate) dated 8/22/2016 by Z. Cusumano
D M04R02.doc (adequate) dated 4/19/2017 by H. Ngai

Type V DMF [redacted]. LOA dated 11/29/2016. Relevant information for the [redacted] stopper [redacted] was reviewed in D[redacted]M33R01.doc (adequate) dated 2/3/2017 by M. Cruz-Fisher.

Remarks Section: eCTD/ Global submit review. Comparability protocols were not provided. Some figures are reproduced from the submission. Micro did not have any comments for the 74 day letter (due 3/9/2017). An IR was sent on 4/20/2017; response received 5/12/2017. A second IR was sent on 5/24/2017; response received 5/26/2017. The goal date is 11/12/2017.

P.1 Description of the Composition of the Drug Product

- Description of drug product – HTX-019 (aprepitant) injectable emulsion is a sterile oil-in-water emulsion for the intravenous injection of aprepitant. Single dose.

- Drug product composition –

Ingredient	Content per mL	Function
Aprepitant	7.2 mg	API
Egg lecithin, [redacted]	[redacted]	[redacted]
Soybean oil		
Ethanol		
Sucrose		
Sodium oleate		
WFI		

Exhibit batch size: [redacted] vials
Maximum proposed commercial batch size: Same; [redacted] vials

- Description of container closure system –

Configuration	Component	Description	Manufacturer
7.2 mg/mL	Vial	20 mL USP [redacted] glass vial, clear with 20 mm opening	[redacted]
	Stopper	20 mm [redacted] rubber stoppers [redacted]	
	Seal	Aluminum overseal with plastic flip-off cap, 20 mm	

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

Acceptable

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

The container/closure system used for validation was: Same as the drug product; (b) (4) 20 mL/ 20 mm glass vial, (b) (4) 20 mm rubber stopper, (b) (4) seal.

Study/Report # and date: Co-validation report for container closure integrity limit test for HTX-019 vials using dye ingress method, signed/ dated 12/9/2016.

Test method: dye ingress
Brief description: Three exhibit batches samples (HTX-019 with 20 mL fill in 20 mL vials) were randomly selected for the ccit validation test. (b) (4)
LOD: (b) (4)
Sensitivity: (b) (4)

Results:

Sample	# Positive/ # Tested
Test Units	(b) (4)
Positive Control	
Negative Control	

Reviewer's Assessment: The data provided demonstrate that the container closure system is capable of maintaining a barrier against microbial ingress.

Acceptable

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

Reviewer's Assessment: N/A

P.3 Manufacture

P.3.1 Manufacturers – Alcami Corporation, 4221 Faber Pl Dr, North Charleston, SC 29405

P.3.3 Description of the Manufacturing Process and Process Controls

Overall Manufacturing Operation

P.8.3 Stability Data

Time points tested: 0, 12 months at 2-8°C. The applicant is being requested to revise the proposed bacterial endotoxins acceptance criteria for stability testing; see comment above.

DP lot #	Endotoxins (EU/mL) A.C.: (b) (4) EU/mL	C/C A.C.: NMT (b) (4)
B150354	(b) (4)	(b) (4)
B150355		
B150402		
B160173	(0, 6 month)	(0, 6 month)
B160296	(0 month)	(0 month)
B160405	(0 month)	(0 month)
B160457	(0 month)	(0 month)

Time points tested: 0, 3, 6 months at 25°C/ 60% RH

DP lot #	Endotoxins (EU/mL) A.C.: (b) (4) EU/mL	C/C A.C.: NMT (b) (4)
B150354	-	(b) (4)
B150355	-	
B150402	-	
B160173	-	(0, 3, 6 month)
B160296	-	(0, 3 month)
B160405	-	(0, 3 month)
B160457	-	(0, 3 month)

The exhibit batches met the stability specifications at the designated time points; results provided.

Reviewer's Assessment: There are no microbiology relevant concerns regarding the stability data for the exhibit batches.

Acceptable

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: N/A

A.2.1 Materials of Biological Origin

Reviewer's Assessment: N/A

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: N/A

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: N/A

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: N/A

R Regional Information

Executed Batch Records

Executed lot #(s): B160405 was manufactured in 6/2016.

The batch records confirm that validated component sterilization/ (b) (4) processes were used for the manufacture of the exhibit batch. (b) (4), respectively, b160405-executed-batch-records-final-scan-attachment.pdf, pg. 65).

Reviewer's Assessment: The batch records confirm that validated component sterilization (b) (4) processes were used for the manufacture of the exhibit batch.

Acceptable

Comparability Protocols

Reviewer's Assessment: N/A; Comparability protocols were not provided.

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

2.A. Package Insert

Cinvanti injectable emulsion is supplied in a carton containing single dose glass vial of 130 mg aprepitant/ 18 mL. Cinvanti injectable emulsion vials must be refrigerated, store at 2°C-8°C (36°F-46°F). Cinvanti injectable emulsion vials can remain at room temperature up to 60 days. Do not freeze.

Preparation as described in the package insert:

- For 130 mg HEC dosing, withdraw 18 mL from the vial and add to an infusion bag filled with 13 (b) (4) mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose for Injection, USP.
- For 100 mg MEC dosing, withdraw 14 mL from the vial and add to an infusion bag filled with 10 (b) (4) mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose for Injection, USP.

After dilution with the appropriate solution, the diluted drug solution is stable at ambient room temperature for 6 hours in 0.9% sodium chloride injection, USP or 12 hours in 5% dextrose injection, USP.

Microbiological hold times for the diluted solution are provided (3.2.P.2, Microbiological attributes.pdf). The study was performed by (b) (4) in duplicate. The drug product was diluted in 0.9% sodium chloride or 5% dextrose per the package insert ((b) (4) final concentration). The admixtures were inoculated with 1 (b) (4) of the challenge organism. The admixtures were incubated at 22.5°C ±2.5°C then sampled for bioburden at 0, 12, 36 and 48 hour time points. The results are reproduced below.

Table 3.2.P.2.5-1: Microbiological Challenge Testing of HTX-019 Injectable Emulsion Admixtures at Ambient Conditions

Challenge Organisms	Hold Time (Hour)	Reference Inoculum (CFU/mL)	Log_{10} Increase	
			Dextrose	Saline
Escherichia coli	0	(b) (4)		
	6			
	8			
	12			
	24			
	36			
	48			
Staphylococcus aureus	0			
	12			
	24			
	36			
	48			
Pseudomonas aeruginosa	0			
	12			
	24			
	36			
	48			
Methicillin-resistant Staphylococcus aureus (MRSA)	0			
	12			
	24			
	36			
	48			
Vancomycin-resistant Enterococcus faecalis (VREF)	0			
	12			
	24			
	36			
	48			
Candida albicans	0			
	12			
	24			
	36			
	48			

Challenge Organisms	Hold Time (Hour)	Reference Inoculum (CFU/mL)	Log_{10} Increase	
			Dextrose	Saline
Aspergillus braziliensis	0	(b) (4)		
	12			
	24			
	36			
	48			

All negative media controls showed no growth (turbidity) and microbiological media passed growth promotion testing. HTX-019 admixtures at room temperature did not show more than 0.5 log growth for the tested organisms for up to 6 hours in saline or 12 hours in dextrose.

Reviewer's Assessment: Microbiological hold time studies for the diluted drug product are provided. The subject drug product met the acceptance criteria at the (b) (4) mg/mL

concentration in 0.9% sodium chloride or 5% dextrose. The hold times are suitable for the subject drug product.

Acceptable

Post-Approval Commitments:

Reviewer's Assessment: N/A

Lifecycle Management Considerations

Reviewer's Assessment: The HTX-019 manufacturing process consists of (b) (4)

List of Deficiencies: None identified.

Primary Microbiology Reviewer Name and Date: Helen Ngai, Ph.D., 6/12/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Jesse Wells, Ph.D., 6/12/2017

Helen Ngai

Digitally signed by Helen Ngai
Date: 6/14/2017 07:45:38AM
GUID: 508da70b00028e6d6f228f597b070551

Jesse Wells

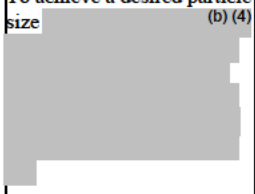
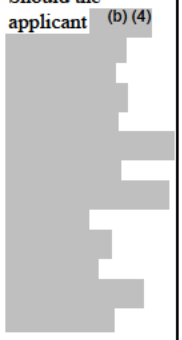
Digitally signed by Jesse Wells
Date: 6/14/2017 07:44:57AM
GUID: 508da70b00028ea901ac6652677f7d00

Attachments:

ATTACHMENT I: Risk Assessment

Initial Risk Assessment for NDA 209296 Aprepitant Injectable Emulsion for Intravenous Use

Product Attribute / CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	LifeCycle consideration/Comments
Emulsion Appearance	Emulsion separation, globules aggregation, precipitation Manufacturing process	M to H	The oil in water emulsion is manufactured by a typical emulsion manufacturing process. At appropriate process steps (b) (4)	The registration batches met the appearance specification. During the stability testing no significant change was observed in the parameters tested. All batches met the proposed specification Low to Medium	If the changes are proposed beyond the ranges tested, depending on the criticality of the changes and its effect on the drug product CQA and hence on product quality and performance, it would indicate a need of in vitro BE testing (e.g. (b) (4) process change) Low to Medium
Assay	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	During manufacturing process development critical steps were identified and in-process controls (IPC) instituted for a robust manufacturing process to consistently produce quality DP. Assay is determined by a validated HPLC method. The long-term and accelerated stability studies of the registration batches demonstrated that there is no significant change in the quality of the DP during the time tested	The drug product is expected to be safe for IV administration during the entire shelf life from product quality perspective. Low to None	None
Sterility	• Process parameters • Container/closure system	L	The bulk drug product is sterilized by a sterile filtration. (b) (4) Sterility is controlled by the drug product specification. The container closure system is adequate to protect the drug product from biological contamination.	Low to None	None

Mean particle size	• Formulation • Process parameters • Scale/equipment	M to H	To achieve a desired particle size (b) (4)  The proposed manufacturing process is capable of making the drug product consistently with mean particle size (b) (4)	The registration batches met the globule size specification. The drug product particle size may have impact on bioavailability. Low to Medium	Should the applicant (b) (4)  Low to Medium

ATTACHMENT II: List of Deficiencies

The following comments regarding PI should be sent to the applicant.

A. Regarding Labeling/Labels:

a) Full Prescribing Information

#3: Dosage Forms and Strengths

- Include opaque, off-white to amber in description
- (b) (4)

#11: Description

- List the inactive ingredients in alphabetical order
- Editorial changes are needed as described in the text to improve clarity.

#16: How Supplied/Storage and Handling

- Include opaque, off-white to amber in description
- Present as 1 single dose vial per container
- Delete th (b) (4) as this is covered in administration sections.

Hitesh Shroff

Digitally signed by Hitesh Shroff
Date: 10/10/2017 06:39:25PM
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Hitesh Shroff

Digitally signed by Hitesh Shroff
Date: 10/10/2017 08:55:41PM
GUID: 502d1ab500002afd219fd67e3b9c99c8