

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209296Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209296 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Cinvanti Established/Proper Name: aprepitant Dosage Form: injection		Applicant: Heron Therapeutics, Inc. Agent for Applicant (if applicable):
RPM: Mary Chung		Division: Division of Gastroenterology and Inborn Errors Products
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>November 12, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|---|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☐ Direct-to-OTC |
| ☐ Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) (link)	☒ Included
Documentation of consent/non-consent by officers/employees (link)	☒ Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) Approval, 11/9/17
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
Most-recent draft labeling	☒ Included
❖ Proprietary Name	
- Acceptability/non-acceptability letter(s) (indicate date(s)) - Review(s) (indicate date(s))	Proprietary name review 2/8/17 Proprietary name granted 2/14/17
❖ Labeling reviews (indicate dates of reviews)	RPM: ☒ None DMEPA: ☐ None 9/20/17 DMPP/PLT (DRISK): ☐ None 9/28/17 OPDP: ☐ None 9/28/17 SEALD: ☒ None CSS: ☒ None Product Quality ☐ None See OPQ review dated 10/10/17 Other: ☐ None DPMH Pediatric 10/3/17, DPMH Maternal 9/20/17
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	3/8/17
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☐ Not a (b)(2) 11/6/17
❖ NDAs/NDA supplements only: Exclusivity Summary (signed by Division Director)	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

- This application is on the AIP - If yes, Center Director's Exception for Review memo <i>(indicate date)</i> - If yes, OC clearance for approval <i>(indicate date of clearance communication)</i>	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics <i>(approvals only)</i> Date reviewed by PeRC September 27, 2017 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i>	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i> <i>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</i>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) <i>(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)</i>	10/18/17, 10/10/17, 10/2/17, 9/5/17, 8/14/17, 8/8/17, 5/24/17, 5/11/17, 5/9/17, 4/20/17, 4/17/17, 3/27/17, 3/7/17, 2/23/17, 2/15/17
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	☒ N/A or no mtg
Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	☐ No mtg 12/8/16
EOP2 meeting <i>(indicate date of mtg)</i>	☒ No mtg
Mid-cycle Communication <i>(indicate date of mtg)</i>	☒ N/A
Late-cycle Meeting <i>(indicate date of mtg)</i>	☒ N/A
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	☒ None
Division Director Summary Review <i>(indicate date for each review)</i>	☐ None 11/8/17
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	☐ None 10/12/17
PMR/PMC Development Templates <i>(indicate total number)</i>	☐ None 11/8/17
Clinical	

❖ Clinical Reviews		
• Clinical Team Leader Review(s) (indicate date for each review)		☒ No separate review
• Clinical review(s) (indicate date for each review)		10/2/17
• Social scientist review(s) (if OTC drug) (indicate date for each review)		☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)		Pages 16-17 of Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵		☐ None DPMH Pediatrics 10/3/17
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)		☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)		☒ None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)		☒ None requested
Clinical Microbiology		☒ None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)		☐ None
Biostatistics		☒ None
❖ Statistical Division Director Review(s) (indicate date for each review)		☐ No separate review
Statistical Team Leader Review(s) (indicate date for each review)		☐ No separate review
Statistical Review(s) (indicate date for each review)		☐ None
Clinical Pharmacology		☐ None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)		☐ None 10/2/17
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)		☐ None requested 8/21/17, 7/14/17

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None 9/28/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	☒ None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	☐ None 10/10/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☒ Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity (Notify CDER OND IO)
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done (Send email to CDER OND IO)
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☐ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

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/s/

MARY H CHUNG
11/09/2017

Chung, Mary

From: Chung, Mary
Sent: Wednesday, October 18, 2017 1:08 PM
To: Kimberly Manhard (Kmanhard@herontx.com)
Cc: Chung, Mary
Subject: NDA 209269 aprepitant inj. emulsion - PI
Attachments: NDA 209296 aprepitant inj. emulsion FDA proposed PI annotated 10-18-17.docx; NDA 209296 aprepitant inj. emulsion FDA proposed PI annotated 10-18-17.pdf; NDA 209296 aprepitant inj. emulsion FDA proposed PI clean 10-18-17.docx; NDA 209296 aprepitant inj. emulsion FDA proposed PI clean 10-18-17.pdf

Hello Kimberly,

Reference is made to your NDA 209296 aprepitant inj. emulsion submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) on January 12, 2017.

On October 6, 2017, we received your proposed labeling submission (PI and PPI) to this application, and have proposed revisions that are included as an enclosure (PI). We request that you resubmit labeling (PI) that addresses these issues to the NDA by 1:00 PM EST October 24, 2017 or before.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,

Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
10/18/2017

From: [Chung, Mary](#)
To: [Kimberly Manhard \(Kmanhard@herontx.com\)](mailto:Kmanhard@herontx.com)
Cc: [Chung, Mary](#)
Subject: NDA 209296 aprepitant inj. emulsion
Date: Tuesday, October 10, 2017 3:36:45 PM

Hello Kimberly,

Reference is made to your NDA 209296 aprepitant inj. emulsion submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) on January 12, 2017.

We have the following proposed Post Marketing Requirement (PMR) for this application. Please confirm your agreement with this requirement, including agreement with the proposed milestone dates. We request that you provide your response by October 16, 2017 or before.

Post Marketing Requirement

A study to evaluate pharmacokinetics, safety, and tolerability of a single dose of Cinvanti (aprepitant) injectable emulsion as part of a 3-day regimen in pediatric patients 0 to 17 years of age.

Utilize modeling and simulation to support the single dose (1-day) regimen in pediatric patients 0 to 17 years of age undergoing treatment with single day emetogenic chemotherapy.

Final Protocol Submission: 07/2020

Study/Trial Completion: 11/2026

Final Report Submission: 05/2027

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
10/11/2017

From: [Chung, Mary](#)
To: [Kimberly Manhard \(Kmanhard@herontx.com\)](#)
Cc: [Chung, Mary](#)
Subject: NDA 209296 Aprepitant inj. emulsion- PI and PPI
Date: Monday, October 02, 2017 11:51:17 AM
Attachments: [N209296 Aprepitant inj emulsion FDA proposed PI tracked changes 10-2-17.pdf](#)
[N209296 Aprepitant inj emulsion FDA proposed PI tracked changes 10-2-17.docx](#)
[N209296 Aprepitant inj emulsion FDA proposed PI clean 10-2-17.pdf](#)
[N209296 Aprepitant inj emulsion FDA proposed PI clean 10-2-17.docx](#)
[NDA209296 Aprepitant inj emulsion FDA proposed PPI annotated 10-2-17.pdf](#)
[NDA209296 Aprepitant inj emulsion FDA proposed PPI annotated 10-2-17.docx](#)
[NDA209296 Aprepitant inj emulsion FDA proposed PPI clean 10-2-17.pdf](#)
[NDA209296 Aprepitant inj emulsion FDA proposed PPI clean 10-2-17.docx](#)

Hello Kimberly,

Reference is made to your NDA 209296 Aprepitant inj. emulsion submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) on January 12, 2017.

On January 12, 2017, we received your proposed labeling submission (PI and PPI) to this application, and have proposed revisions that are included as an enclosure (PI and PPI). We request that you resubmit labeling (PI, PPI) that addresses these issues to the NDA by October 10, 2017 or before.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
10/02/2017

From: [Chung, Mary](#)
To: [Kimberly Manhard \(Kmanhard@herontx.com\)](mailto:Kmanhard@herontx.com)
Cc: [Chung, Mary](#)
Subject: NDA 209296 aprepitant inj. emulsion- carton/container label
Date: Monday, October 02, 2017 12:00:44 PM

Hello Kimberly,

Reference is made to your NDA 209296 aprepitant inj. emulsion submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) on January 12, 2017.

We have the following comments and recommendations for your proposed draft carton/container label submitted September 13, 2017.

A. All Carton Labeling

Revise the excipients presentation on the carton labeling to display the list of excipients in alphabetical order to be consistent with the Prescribing Information.

B. General Comment

Please submit the proposed container label for the Patient Assistance Program for the Agency to review.

We request that you resubmit carton/container labeling that addresses the above to the NDA by October 10, 2017 or before.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
10/02/2017

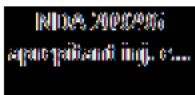
Chung, Mary

From: Chung, Mary
Sent: Tuesday, September 05, 2017 1:53 PM
To: Kimberly Manhard (Kmanhard@herontx.com)
Cc: Chung, Mary
Subject: NDA 209296 aprepitant inj. emulsion- carton/container label

Hello Kimberly,

Reference is made to your NDA 209296 aprepitant inj. emulsion submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) on January 12, 2017.

We have the attached comments and recommendations for your proposed carton/container label.



We request that you resubmit carton/container labeling that addresses these issues by September 18, 2017 or before to the NDA.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0260. Thank you.

A. Carton Label

1. We recommend revising the statement “(b) (4)” to read: **“Must be refrigerated. Store at 2°C-8°C (36°F-46°F). Do Not Freeze.”** Furthermore, we recommend placing the statement on the principal display panel, in addition to its location on the side panel, to emphasize this important information. The statement “See Package Insert for Dosage and Administration Information” can be moved to the side panel to make room.
2. Revise the statement “(b) (4)” to “1 Sterile Single-Dose Vial” to clarify the contents of the carton.

B. Carton and Container Label

1. We recommend revising the statement “(b) (4)” to read as **“For Intravenous Administration Only”** to emphasize this important administration information.
2. We recommend revising the statement “(b) (4)” to read as **“Must Dilute Before Use”** to emphasize this important preparation information.
3. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product barcode to each individual carton and container label as required per 21CFR 201.25(c)(2). Additionally, consider orienting the barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature^a.

C. Container Label

1. We recommend moving the statements (b) (4) and “Must Dilute Before Use” to the principal display panel as this is important preparation and administration information.
2. We recommend revising the statement “(b) (4)” to read: **“Must be refrigerated. Store at 2°C-8°C (36°F-46°F). Do Not Freeze.”**

^a Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

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/s/

MARY H CHUNG
09/05/2017

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

DATE: 8/16/2017

TO: Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance

SUBJECT: **Decline to Conduct Biopharmaceutical Inspection**

RE: NDA 209296

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends that the clinical data for Study HTX-019 C2015-104 be further scrutinized without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected

(b) (4)

It should be noted that Study HTX-019 C2015-105 under NDA 209296 was conducted

(b) (4)

inspection should be taken into consideration by the review division for NDA 209296

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)

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/s/

ANGEL S JOHNSON
08/21/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209296

INFORMATION REQUEST

Heron Therapeutics, Inc.
Attention: Kimberly Manhard
Executive Vice President, Drug Development
4242 Campus Point Court, Suite 200
San Diego, CA 92121

Dear Ms. Manhard:

Please refer to your New Drug Application (NDA) dated January 11, 2017 received January 12, 2017 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CINVANTI™ (aprepitant) injectable emulsion 130 mg.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response by close of business **Monday August 28, 2017** in order to continue our evaluation of your NDA.

Information Request:

Process:

[Redacted content]

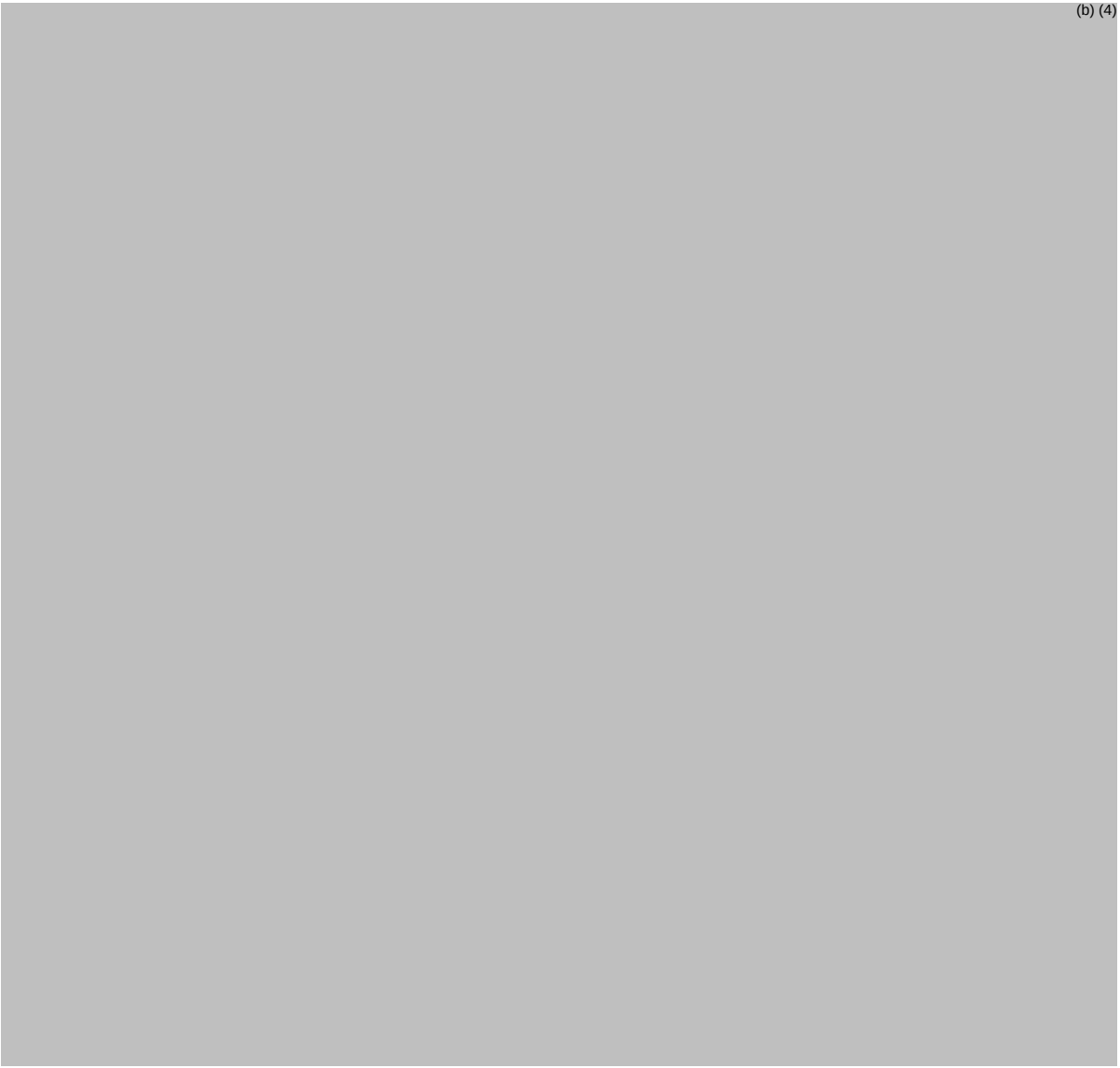
(b) (4)

Drug Product:

[Redacted content]

(b) (4)

(b) (4)



4. Provide all available updated stability data for the 7 registration batches. (b) (4)

If you have any questions, please do not hesitate to contact me at (240) 402-8257 or email me at oumou.barry@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

LCDR Oumou Barry, MT (ASCP), MHA

Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Oumou
Barry

Digitally signed by Oumou Barry
Date: 8/14/2017 02:15:10PM
GUID: 587e5a600171e0f766aa3b48efe5249b





NDA 209296

INFORMATION REQUEST

Heron Therapeutics, Inc.
Attention: Kimberly Manhard
Executive Vice President, Drug Development
4242 Campus Point Court, Suite 200
San Diego, CA 92121

Dear Ms. Manhard:

Please refer to your New Drug Application (NDA) dated January 11, 2017 received January 12, 2017 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CINVANTI™ (aprepitant) injectable emulsion 130 mg.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response by close of business **Friday August 11, 2017** in order to continue our evaluation of your NDA.

Biopharmaceutics:

- In order to continue our 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 (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.

If you have any questions, please do not hesitate to contact me at (240) 402-8257 or email me at oumou.barry@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

LCDR Oumou Barry, MT (ASCP), MHA
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Oumou
Barry

Digitally signed by Oumou Barry
Date: 8/08/2017 08:17:25AM
GUID: 587e5a600171e0f766aa3b48efe5249b



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

DATE: 7/10/2017

TO: Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209296

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

ANGEL S JOHNSON
07/14/2017



NDA 209296

INFORMATION REQUEST

Heron Therapeutics, Inc.
Attention: Kimberly Manhard
Executive Vice President, Drug Development
4242 Campus Point Court, Suite 200
San Diego, CA 92121

Dear Ms. Manhard:

Please refer to your New Drug Application dated January 11, 2017, received January 12, 2017 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CINVANTI™ (aprepitant) injectable emulsion 130 mg.

We are reviewing the Microbiology section of your submission and have the following comment and information request. We request a written response **by Friday June 2, 2017** in order to continue our evaluation of your NDA.

- It is noted that the bacterial endotoxins limit for HTX-019 drug product was revised to (b) (4) also reflected in section 32p54 batch analyses. Please clarify the bacterial endotoxins acceptance criteria proposed for stability studies. If the bacterial endotoxins specification for stability testing is higher than the release specification, please clarify why. Please note that increasing levels of endotoxins from release to stability time points would suggest contamination of the drug product. Please align the stability specification with the release specification and provide stability specification documents reflecting the change.

If you have any questions, please contact me by telephone: 240-402-8257 or via email: Oumou.barry@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

LCDR Oumou Barry, MT (ASCP), MHA

Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Oumou
Barry

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Date: 5/24/2017 11:06:19AM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209296

INFORMATION REQUEST

Heron Therapeutics, Inc.
Attention: Kimberly Manhard
Executive Vice President, Drug Development
4242 Campus Point Court, Suite 200
San Diego, CA 92121

Dear Ms. Manhard:

Please refer to your New Drug Application (NDA) dated January 11, 2017 received January 12, 2017 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CINVANTI™ (aprepitant) injectable emulsion 130 mg.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comment and information request. We request a written response by Wednesday **May 24, 2017** in order to continue our evaluation of your NDA.

- Replace the test for (b) (4) with the test for Elemental Impurities (USP<232> and USP<233>) and follow guidelines for reporting of individual metals.

If you have any questions, please do not hesitate to contact me at, (240) 402-8257 or email me at oumou.barry@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

LCDR Oumou Barry, MT (ASCP), MHA
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Oumou
Barry

Digitally signed by Oumou Barry
Date: 5/11/2017 01:30:16PM
GUID: 587e5a600171e0f766aa3b48efe5249b



From: [Chung, Mary](#)
To: [Kimberly Manhard \(Kmanhard@herontx.com\)](mailto:Kmanhard@herontx.com)
Cc: [Chung, Mary](#)
Subject: NDA 209296 aprepitant inj. emulsion- Information Request
Date: Tuesday, May 09, 2017 12:42:04 PM

Hello Kimberly,

Reference is made to your NDA 209296 aprepitant inj. emulsion submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) on January 12, 2017.

Additional reference is made to our 74 day filing communication- filing review issues identified letter dated March 27, 2017, and your submission dated April 18, 2017.

We have the following comments and request for additional information in response to your April 18, 2017 submission:

You may rely on the discontinued 115 mg strength of Emend IV for the 3-day IV and oral dosing regimen proposed for the 100 mg dose of Cinvanti for the MEC indication. However, you will need to provide a bridge between your proposed product and the 115 mg strength of Emend IV. If there is not a study you conducted to bridge your proposed product and the 115 mg strength of Emend IV, provide your scientific rationale which justifies how your proposed product can be bridged to the 115 mg strength of Emend IV without such study.

We request you provide your response to the above to the NDA May 16, 2017 or before.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
05/09/2017



NDA 209296

INFORMATION REQUEST

Dear Ms. Manhard:

Please refer to your New Drug Application (NDA) dated January 11, 2017 received January 12, 2017 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CINVANTI™ (aprepitant) injectable emulsion 130 mg.

We are reviewing the Microbiology section of your submission and have the following comments and information requests. We request a written response by **Friday May 19, 2017** in order to continue our evaluation of your NDA.

1. Please provide a (b) (4) statement for the subject drug product. Alternatively, please provide the location of the (b) (4) statement in the original submission.
2. In regard to the (b) (4)
(b) (4)
3. It is noted that in section 32p3-manufprocess-validation.pdf, pg. 3, stoppers are obtained (b) (4). Please provide a letter of authorization with submission dates and locations of the requested information from the DMF holder.
4. In regard to the finished drug product proposed specifications, please clarify the bacterial endotoxins acceptance criteria. (b) (4)

If you have any questions, please do not hesitate to contact me at, (240) 402-8257 or email me at oumou.barry@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

LCDR Oumou Barry, MT (ASCP), MHA
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Oumou
Barry

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Date: 4/20/2017 10:38:01AM
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NDA 209296

INFORMATION REQUEST

Heron Therapeutics, Inc.
Attention: Kimberly Manhard
Executive Vice President, Drug Development
4242 Campus Point Court, Suite 200
San Diego, CA 92121

Dear Ms. Manhard:

Please refer to your New Drug Application (NDA) dated January 11, 2017 received January 12, 2017 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CINVANTI™ (aprepitant) injectable emulsion 130 mg.

We are reviewing the Biopharmaceutical section of your submission and have the following comments and information requests. We request a written response by **Monday April 24, 2017** in order to continue our evaluation of your NDA.

- Submit detailed information (e.g. dissolution testing conditions, medium and batch employed, etc.) on the In vitro dissolution studies conducted to determine the (b) (4) dissolution of aprepitant. These data should also include the raw data generated in tabular and graphical form.

If you have any questions, please do not hesitate to contact me at, (240) 402-8257 or email me at oumou.barry@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

LCDR Oumou Barry, MT (ASCP), MHA

Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Oumou
Barry

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Date: 4/17/2017 12:46:07PM
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NDA 209296

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Heron Therapeutics, Inc.
Attention: Kimberly Manhard
Executive Vice President, Drug Development
4242 Campus Point Court, Suite 200
San Diego, CA 92121

Dear Ms. Manhard:

Please refer to your New Drug Application (NDA) dated January 12, 2017, received January 12, 2017, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for aprepitant injectable emulsion.

We also refer to your amendments dated March 8, 2017, March 3, 2017, and February 17, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 12, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 12, 2017. If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug and contains a paragraph IV certification, this filing communication is the "paragraph IV acknowledgment letter" described in 21 CFR 314.52(b) and the "postmark" is 4 calendar days after the date on which this letter is signed. Notice of the paragraph IV certification must be sent to the persons described in 21 CFR 314.52(a) no later than 20 days after the date of the postmark on this paragraph IV acknowledgment letter and must contain the information described in 21 CFR 314.52(c).

During our filing review of your application, we identified the following potential review issues:

We acknowledge that in your pre-NDA meeting background package, you indicated your planned reliance on the prior labeling for Emend IV regarding the 3-day IV and oral dosing regimen for the MEC indication (version dated August 2014). However, FDA's finding of safety and effectiveness is reflected in the current approved labeling of the IV product. Since the current approved labeling for Emend IV does not include information describing the 3-day IV and oral dosing regimen for the MEC indication, there is no information available in the approved labeling for Emend IV that can be relied on for purposes of inclusion of that dosing regimen in your proposed labeling. You will need to provide information derived from another source (e.g., published literature, FDA's finding of safety and effectiveness for oral Emend) to support the 3-day IV and oral dosing regimen for the MEC indication. Alternatively, you may remove the MEC indication with the 3-day IV and oral dosing regimen from your proposed labeling.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug, we recommend that the cover letter for amendments to your unapproved 505(b)(2) application either: 1) state that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or 2) verify that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents

- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DONNA J GRIEBEL
03/27/2017

From: [Chung, Mary](#)
To: [Kimberly Manhard \(Kmanhard@herontx.com\)](mailto:Kimberly.Manhard@herontx.com)
Cc: [Chung, Mary](#)
Subject: NDA 209296 aprepitant inj. emulsion- Clinical Pharmacology Information Request
Date: Tuesday, March 07, 2017 9:51:52 AM

Hello Kimberly,

Reference is made to your NDA 209296 aprepitant inj. emulsion submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) on January 12, 2017.

We have the following request for additional information:

Submit the NONMEM control stream as an electronic file along with the data set used for the analysis. Clarify the data 'pk.xpt' you submitted is which data set among 'Heron106_PopPK_20161122.csv', 'Heron106_PopPK_20161206.csv', and 'Heron106_PopPK_20161206b.csv'. If available, submit all 3 data sets in csv format.

We request to receive your response to the above request to the NDA by 3/8/17, or 12:00 PM Eastern Standard Time 3/9/17.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
03/07/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209296

INFORMATION REQUEST

Heron Therapeutics, Inc.
Attention: Kimberly Manhard
Executive Vice President, Drug Development
4242 Campus Point Court, Suite 200
San Diego, CA 92121

Dear Ms. Manhard:

Please refer to your New Drug Application dated January 12, 2017, received January 12, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CINVANTI™ (aprepitant) injectable emulsion 130mg.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Biopharmaceutics:

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 this data/information during the review cycle.

If you have any questions, please contact me, at (240) 402-6153. Please respond by **Friday, March 3, 2017**.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

**Rabiya
Laiq -S**

Digitally signed by Rabiya Laiq -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Rabiya Laiq -S,
0.9.2342.19200300.100.1.1=20015
55007
Date: 2017.02.23 14:35:43 -05'00'

From: [Chung, Mary](#)
To: [Kimberly Manhard \(Kmanhard@herontx.com\)](mailto:Kmanhard@herontx.com)
Cc: [Chung, Mary](#)
Subject: NDA 209296 aprepitant inj. emulsion- Clinical Pharmacology Information Request
Date: Wednesday, February 15, 2017 2:15:32 PM

Hello Kimberly,

Reference is made to your NDA 209296 aprepitant inj. emulsion submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) on January 12, 2017.

We have the following request for additional information:

The in-study bioanalytical assay report for Study HTX-019-104 could not be located. If the report was submitted, please guide the reviewer to its location. If not, please submit the report by February 21, 2017 to the NDA to facilitate the clinical pharmacology filing review.

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 / Fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
03/07/2017



NDA 209296

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Heron Therapeutics, Inc.
4242 Campus Point Court
Suite 200
San Diego, CA 92121

ATTENTION: Kimberly J. Manhard
Executive Vice President, Drug Development

Dear Ms. Manhard:

Please refer to your New Drug Application (NDA) dated and received January 12, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Aprepitant Emulsion for Injection, 130 mg per vial.

We also refer to your January 16, 2017, correspondence, received January 17, 2017, requesting review of your proposed proprietary name, Cinvanti.

We have completed our review of the proposed proprietary name, Cinvanti, and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your January 16, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nicholas Miles, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-7025. For any other information regarding this application, contact Mary Chung, PharmD, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
02/14/2017



IND 125926

MEETING MINUTES

Heron Therapeutics, Inc.
Attention: Rozalyn Littler
Director, Regulatory Affairs
4242 Campus Point Court, Suite 200
San Diego, CA 92121

Dear Ms. Littler:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for HTX-019 (aprepitant) injectable emulsion.

We also refer to the teleconference between representatives of your firm and the FDA on December 8, 2016. The purpose of the meeting was to discuss your pre-submission plans for your planned NDA.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B, Teleconference
Meeting Category: Pre-NDA

Meeting Date and Time: December 8, 2016 10:00 AM- 11:00 AM EST

Application Number: IND 125926
Product Name: HTX-019 (aprepitant) injectable emulsion
Indication: Prevention of chemotherapy induced nausea and vomiting
Sponsor/Applicant Name: Heron Therapeutics

Meeting Chair: Anil Rajpal, M.D.
Meeting Recorder: Mary Chung, PharmD.

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D.	Director
Shari Targum, M.D.	Deputy Director, Acting
Anil Rajpal, M.D.	Medical Team Lead
Aisha Johnson, M.D.	Medical Reviewer
Sushanta Chakder, Ph.D.	Pharmacology Team Lead
Brian Strongin, R.Ph., M.B.A.	Chief, Project Management Staff

Office of Clinical Pharmacology

Insook Kim, Ph.D.	Team Lead, Acting
Dilara Jappar, Ph.D.	Clinical Pharmacology Reviewer

Division of Biometrics III

Ling Lan, Ph.D.	Biostatistics Reviewer
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Division of Biometrics VI

Meiyu Shen, Ph.D.	Biometrics Team Lead
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Office of Product Quality

Hitesh Shroff, Ph.D.	Chemistry Team Lead
Sandra Suarez, Ph.D.	Biopharmaceutics Team Lead
Meng Wang, Ph.D.	Biopharmaceutics Reviewer

SPONSOR ATTENDEES

Rozalyn Littler
Rameshwar Shukla, Ph.D.
Katy Morton

(b) (4)

Thomas Ottoboni, Ph.D.

Clynn Wilker, DVM, Ph.D., DACT
Matt Cravets, MA

Director, Regulatory Affairs
Director, Regulatory Affairs CMC
Regulatory Affairs Consultant
Executive Regulatory Affairs Consultant
Sr. Vice President, Pharmaceutical and
Translational Sciences
Vice President, Translational Sciences
Vice President, Biometrics

(b) (4)

Michael Lauw
Kimberly Manhard

Director, Clinical Operations
Executive Vice President, Drug Development

1.0 BACKGROUND

On October 14, 2016, Heron Therapeutics requested a meeting to discuss their pre-submission plans for their planned NDA for HTX-019 (aprepitant) injectable emulsion. Sponsor proposes to pursue the 505(b)(2) regulatory pathway relying on NDA 22023 Emend (fosaprepitant) I.V. as their proposed listed drug. HTX-019 is a lipid emulsion formulation of aprepitant, which sponsor indicates was designed to increase the low water solubility of aprepitant. The clinical studies sponsor plans to include in their planned 505(b)(2) NDA include two BE studies, Study 104 and 106.

Sponsor's proposed indication for HTX-019, which is planned to be available in two dosage strengths 130 mg and 100 mg is 1] prevention of acute and delayed nausea vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin, 2] prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

HTX-019 injectable emulsion 130 mg is proposed to be administered as a single dose regimen for HEC, and HTX-019 injectable emulsion 100 mg is proposed to be administered as a 3-day regimen for MEC (HTX-019 100 mg injection on day 1, and oral aprepitant 80 mg on days 2 and 3).

The October 14, 2016 meeting request was granted and the teleconference was scheduled for December 8, 2016. On October 21, 2016, sponsor submitted an additional separate Written Responses Only meeting request, which was also granted. The background packages for both meeting requests were received on November 8, 2016.

2.0 DISCUSSION

The format of these minutes provides for Heron's questions in regular typeface, followed by the Agency's December 6, 2016 responses in **bolded** print. The December 8, 2016 meeting discussion/post-meeting comments are presented in *italic and bolded* print.

Question 1:

Does the Agency agree that data from the 2 relative BA studies demonstrating bioequivalence of HTX-019 to EMEND for injection and the safety of HTX-019, in addition to the published literature supporting the safety of aprepitant at higher peak plasma levels than the approved doses, will support the safety and effectiveness of HTX-019 for the proposed indication?

FDA Response to Question 1:

We agree that the efficacy of HTX-019 infused over 30 minutes for single day treatment may be supported by the provided relative BA studies pending our review.

As for HTX-019 100 mg, we note that in your pilot relative BA study (n=12; Part 1 of Study 106), HTX-019 100 mg infused over 30 minutes resulted in 55% higher C_{max} and 32% higher AUC than those after IV Emend 115 mg infused over 15 minutes.

As part of your NDA, you should provide safety data to support the higher systemic exposure (C_{max} for 130 mg dose; C_{max} and AUC for 100 mg dose) associated with the use of your HTX-019 products (see response to Question 6).

We refer you to our previous response to Question 4 in the Written Responses issued on August 3, 2016,

“...you will still have to address the safety issues associated with the higher C_{max} of your proposed product. Generally, this requires a human safety study. Furthermore ... the safety concerns would be expected to be augmented if you pursue an even shorter infusion time.”

Theoretically, your proposal to support the higher C_{max} of HTX-019 130 mg and HTX-019 100 mg by using safety data from literature references could be acceptable. Whether the quality of the safety data from literature will be adequate to support the safety of the higher C_{max} associated with HTX-019 130 mg and HTX-019 100 mg will be a review issue.

Please confirm that it is not your intention to pursue a HEC indication for your 3 day regimen. If this is the case, please provide your rationale.

In addition, please note that the biowaiver for the lower strength can only be granted provided the following criteria are met:

- 1. The observed differences in C_{max} between 100 mg HTX-019 and the reference product (IV Emend 115 mg over 15 min) are not clinically relevant**
- 2. The low and high strengths formulations are proportionally similar in composition**
- 3. The low and high strengths have similar manufacturing process**
- 4. The in vitro release profiles are similar between low and high strengths (Refer to Question 8 for in vitro release profile recommendations).**

Discussion Summary

Sponsor clarified that their final product presentation will be one product presentation and that both doses will be drawn from one final product presentation. FDA indicated under this plan, a biowaiver will not be necessary for the lower dose. FDA also

indicated that if there are any medication error related concerns, that those comments will be provided during the NDA review.

Question 2:

For the prevention of acute and delayed nausea and vomiting in patients receiving HEC, does the Agency agree with using the February 2016 EMEND for injection PI to support the safety and efficacy of the 130 mg HTX-019 dosing regimen?

FDA Response to Question 2:

Given that your planned 505(b)(2) application will rely upon Emend for injection as the reference product, if approved, the PI for your proposed product would rely on the summary findings of efficacy and safety for the reference product. However, due to the higher Cmax of 130 mg HTX-019 infused over 30 minutes compared to 150 mg Emend for injection, based on the NDA safety review results, it may be necessary to adjust the information provided in Section 6 Adverse Reactions as well as other sections of the label. You should justify how drug-drug interaction potential (e.g., dexamethasone) of your product HTX-019 would be the same as the reference product EMEND IV despite its higher Cmax compared to reference product EMEND IV.

Discussion Summary:

We do not agree with your rationale for the extent of DDI based on equivalent AUC. It is our recommendation that DDI potential be assessed based on Cmax but not based on AUC. Given your HTX-019 resulted in 48% higher Cmax than that after fosaprepitant 150 mg infusion, we cannot assume that the extent of the DDI with CYP3A4 substrate will be the same. You should provide adequate justification for the dexamethasone dose. You may at least consider physiologically based Pharmacokinetic Analyses to justify the extent of drug-drug interaction with CYP3A4 substrate (e.g., dexamethasone) potential DDI. This will remain as a review issue.

Question 3:

For the prevention of (b) (4) nausea and vomiting in patients receiving MEC, does the Agency agree with using the EMEND for injection 115 mg data included in the August 2014 EMEND for injection PI to support the safety and efficacy of the 100 mg HTX-019 dosing regimen?

FDA Response to Question 3:

Given that your planned 505(b)(2) application will rely upon Emend for injection as the reference product, if approved, the PI for your proposed product would rely on the summary findings of efficacy and safety for the reference product. However, due to the higher Cmax of 100 mg HTX-019 infused over 30 minutes compared to 115 mg Emend for infusion, based on the NDA safety review results, it may be necessary to adjust the information provided in Section 6 Adverse Reactions as well as other sections of the label. You should justify how drug-drug interaction potential (e.g., dexamethasone) of your product HTX-019 would be the same as the reference product EMEND IV despite its higher Cmax compared to reference product EMEND IV.

Discussion Summary: *See discussion summary for Question 2*

Question 4:

Does the Agency agree that the proposed administration instructions will be adequate to inform healthcare providers how to prepare the 130 mg and the 100 mg doses from the single-dose vial?

FDA Response to Question 4:

The adequacy of the proposed preparation instructions and labeling considerations is a review issue and therefore, we may have recommendations when the NDA is submitted.

Additionally, we note the proposed labeling that indicates that the diluted drug product may be stored for up to 24 hours at room temperature. Please refer to our previous comments to the July 5, 2016 briefing package for Question 5 (i.e., Written Responses issued 7/19/16) for a description of the microbiological information needed to support a 24-hour holding time post-dilution.

Question 5:

Does the Agency prefer a written summary of the adverse reactions observed for HTX-019 and EMEND for injection from Study 104 and Study 106 Part B in Section 6.1 of the HTX-019 PI with or without an accompanying tabular presentation?

FDA Response to Question 5:

As part of your NDA, please provide a written and tabular summary of adverse reactions for HTX-019 and EMEND for injection from Study 104 and 106 for our review as part of your NDA.

For your proposed labeling, the Emend for injection PI should be used as the basis for the HTX-019 PI. As noted above, a decision about whether Section 6 Adverse Reactions or other parts of the label will need to be adjusted based on safety data related to the higher C_{max} of HTX-019 will be review issue.

Question 6:

Does the Agency agree with Heron's proposal to not perform an integrated safety analysis of the healthy volunteer data, to provide an analysis of safety data from Study 104 and Study 106 separately (side-by-side), and to provide an overall discussion and conclusion of the safety findings across studies of HTX-019 in Module 2.7.4 Summary of Clinical Safety?

FDA Response to Question 6:

Due to the differences in BE Studies 104 and 106 (different designs and infusion rates), we agree with your proposal to not provide an ISS and instead provide safety data from these studies side by side along with an overall discussion of safety in Module 2.7.4 Summary of Clinical Safety. In section 2.7.4, you should also provide safety data of your proposed

reference products and data to support the higher C_{max} associated with the use of your 100 mg and 130 mg HTX-019 products.

Question 7:

Does the Agency agree with Heron's proposal to provide an ISS that consists of links in Module 5 that refer to Module 2.7.4 Summary of Clinical Safety and CSRs and CRFs in Module 5.3?

FDA Response to Question 7:

Your proposal appears reasonable. See our response to Question 6 above.

Question 8:

Does the Agency agree that the information indicating that aprepitant measured in the bioequivalence studies of HTX-019 130 mg was released from the emulsion addresses the Agency's comment and that no additional analyses are needed for the NDA?

FDA Response to Question 8:

No, you have not directly demonstrated that the measured aprepitant from your proposed product HTX-019 in the relative BA study was free aprepitant that was already released from the oil globules. The literature references that you have provided also do not directly support this conclusion either. Therefore, you should provide further justification and supporting evidence for how bioavailability assessed based on total drug can support the comparable efficacy between two products. At a minimum, you should characterize the ex-vivo release rate of aprepitant from the HTX-019 emulsion in human plasma to support your claim that aprepitant is rapidly released from the emulsion.

We have the following recommendations in terms of in vitro release testing method as the drug product development progresses and that will help to support your claim on rapid drug release:

- **Develop an appropriate in vitro drug release method for the proposed formulation and include it as a QC test for batch release and stability testing.**
- **Provide an in vitro release method development report in a future IND amendment or in the NDA submission, including a detailed description of the in vitro drug release method being proposed for the evaluation of your drug product and the development parameters (selection of the equipment/apparatus, in vitro release media, agitation, pH, sink condition, biorelevance, etc.) used to select the proposed in vitro release method as the optimal method for your product. In addition, describe any discriminating ability of the proposed in vitro release method with respect to the most relevant critical material attributes and critical process parameters (i.e., $\pm 10\text{-}20\%$ change to the specification-ranges of these variables). The testing conditions used for each test should be clearly specified.**
- **Since the dosage form of your drug product may be a (b) (4) provide the information to justify that the drug measured in the in vitro release test is the released free drug in lieu of encapsulated drug. If you use dialysis method, please**

also provide the particle size distribution & particle size specification of your final drug product. The release profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend the use of at least twelve samples per sampling time point.

- Provide in vitro drug release data and profiles for the method development studies in addition to the narrative summaries. The FDA recommends use of the complete in vitro release profile data (i.e., 10, 15, 20, 30, 45, 60 min, etc.) from the pivotal clinical batches for setting the in vitro release acceptance criterion. The in vitro release profile should encompass the timeframe over which at least 85% of the drug is released or where a plateau is reached, if incomplete drug release occurs. The in vitro drug release acceptance criterion should be based on average in vitro drug release data ($n = 12$). The selection of the specification time point should be where $Q = \frac{(b)}{(4)} \%$ in vitro drug release occurs, assuming the drug release from the emulsion follows immediate release characteristics. Include a detailed discussion of the justification of the proposed in vitro drug release acceptance criterion in the appropriate section of the eCTD.
- Note that you have the option to request the FDA's assessment of the acceptability of the in vitro drug release method prior to NDA submission. Should you decide to choose this option, submit the updated in vitro drug release method development report as an amendment to this IND, stating in the cover letter that the FDA feedback is being requested.

Discussion Summary:

Sponsor presented their responding comments (see attached slides). At this time, FDA cannot agree. The additional information will be reviewed and if necessary comments will be provided as post meeting comments. FDA indicated an in vitro release testing method will need to be developed and provided for quality control purpose.

Post-meeting comments:

We acknowledge your PK modeling approach to support the comparable unbound (released from oil droplets) aprepitant between HTX-019 and fosaprepitant I.V. At this point we have no comments. The adequacy of your modeling approach will be reviewed during the NDA review and will be considered as the totality of information, including but not limited to, the in-vitro release testing results.

With regard to the in vitro release method requirement, we consider this product formulation an emulsion, and not a true solution. Therefore, an in vitro release method has to be developed for drug product quality control purposes, i.e., drug performance and drug quality tests. The use of the in vitro release methodology is mainly for assessing the in vitro release kinetics of aprepitant over time from the proposed drug product (performance) and for assessing any changes in composition/formulation, manufacturing site, the process, etc. of your drug product (quality). We clarify that the purpose of the in vitro release method is mainly for quality control purposes as described above and not necessarily for determination of the product release characterization (i.e., immediate release vs. extended release).

The in vitro release method would facilitate quality comparisons of drug product batches manufactured at different times. We strongly recommend you to develop and validate this in vitro release method, especially if there will be proposed changes in composition/formulation, manufacturing site, the process, etc. of your drug product (quality).

Ideally, this method should be biopredictive (e.g., a method that is representative of the in vivo release profile) and serve as a quality control tool for release and during stability testing. Note that the release rate characteristics of a drug product supporting its designation (e.g., immediate vs. modified release) are mainly based on in vivo data including concentration-time profiles.

Question 9:

Does the Agency agree that Heron's proposed approach to address extractables and leachables in the container closures is sufficient for the NDA filing?

FDA Response to Question 9:

Your proposed approach for extractables and leachables in the container closure system appears sufficient for the NDA filing.

Question 10:

Does the Agency agree with Heron's proposed format and content of the NDA?

FDA Response to Question 10:

From a technical standpoint (not content related) yes, the proposed format for the planned NDA is acceptable. However, please see additional comments below.

- 1.6.2 and 1.6.3 (Correspondence regarding meetings) – a single pdf file of all meeting documents can be provided (instead of separate pdf files for each meeting document) with proper bookmarks, table of contents and hyperlinks
 - Providing m2.1 (TOC), is not necessary in the eCTD structure. Instead, it will be helpful to reviewers, if a linked reviewer's aid is provided, that briefly describes where information can be found throughout the application.
 - Providing a single 3.2.S section and using leaf titles of documents to differentiate between manufacturers, is acceptable and preferred

Additional Clinical Pharmacology Comments:

- For all of the PK/PD studies that you plan to submit in the NDA submission, please provide datasets containing individual plasma concentrations and PD data as well as datasets for individual PK and PD parameters along with its corresponding define files. For the datasets containing PK and PD parameters, please provide the files in a readily analyzable format with each PK parameter in a distinct column. In

addition, the PK parameter dataset should also include subject ID, treatment, period, and sequence in different columns.

Discussion Summary:

Sponsor indicated they will prepare the PK datasets in the format requested. FDA requested the dataset be submitted with the NDA submission under each clinical study report.

Post-meeting comments:

The Agency began to require SDTM/ADaM format data for those studies that start after 12/16/2016. Therefore, it is acceptable that you submit the legacy data in the requested format since your studies started before 12/16/2016. However, Trial Summary (TS) will be required for the submission after 12/16/2016 even if you plan to submit the legacy data.

Please put the raw CRF data into datasets/tabulations/legacy and put analysis datasets into datasets\analysis\legacy folder.

Please refer to the folder structure on page 27 of the study data technical conformance guide:

<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>

3.0 ADDITIONAL COMMENTS

Additional Microbiology Comment:

For more information on the information to submit to the NDA please refer to the following Guidance document(s):

Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf>)

Sterile Drug Products Produced by Aseptic Processing- Current Good Manufacturing Practice

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf>)

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an

assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such

pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a “bridge” to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 ATTACHMENTS AND HANDOUTS

Sponsor provided the below attached handout for the December 8, 2016 meeting.

22 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H CHUNG
12/19/2016