CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209296Orig1s000

OTHER REVIEW(S)

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	**209296**
PMR/PMC Set (####-#)	**3289-1**
Product Name:	**Cinvanti (aprepitant) injectable emulsion**
Applicant Name:	**Heron Therapeutics, Inc.**
ODE/Division:	**ODE III/ DGIEP**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

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.

2. PMR/PMC Schedule Milestones[2, 3]

Draft Protocol Submission:	MM /YYYY
Final Protocol Submission:	07/2020
Study/Trial Completion:	11/2026
Interim /Other:	MM /YYYY
Final Report Submission:	05/2027

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

This is a PREA PMR study to evaluate the PK, safety, and tolerability in pediatric patients 0 months to 17 years of a single dose of Cinvanti (aprepitant) injectable emulsion, as part of a 3-day regimen, as compared with the systemic exposure on Day 1 after a 3-day oral regimen of aprepitant, sequentially performed by age group from adolescents to neonates to ensure safe progression to younger ages.

A population PK modeling approach will be used to evaluate Cmax, AUC, and C24hr in pediatric patients, based on modeling of serial PK data in adults.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☒ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

postapproval and why the issue does not need to be addressed *prior to* approval.]

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]*****.** ***Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either "Yes" or "No" and provide the appropriate responses.]

☐ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **<u>For all PMRs and PMCs</u>: What type of study or clinical trial is needed to achieve the goal described in Q1 *<u>or</u>* Q4.a above?**
*[Select ONE OPTION only under *<u>either</u>* "Type of Study" *<u>or</u>* "Type of clinical Trial"]*

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☒ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

- ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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
11/08/2017

ANIL K RAJPAL
11/08/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Pediatric Labeling Review

From:	Amy M. Taylor, MD, MHS Medical Officer Pediatric and Maternal Health Staff
Through:	John J. Alexander, MD, MPH Deputy Director Division of Pediatric and Maternal Health
NDA Number:	209-296
Sponsor:	Heron Therapeutics, Inc.
Drug:	Cinvanti™ (aprepitant) injectable emulsion
Dosage Form and Route of Administration:	Injectable emulsion, for intravenous infusion

Proposed Indications:

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin
- Prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)

Division Consult Request: The Division of Gastroenterology and Inborn Errors Products (DGIEP) requests DPMH's assistance with the review of this application and its labeling (PI).

Background

The sponsor submitted a 505(b)(2) application for Cinvanti™ (aprepitant) injectable emulsion relying on listed drug NDA 22-023 Emend®(fosaprepitant) for Injection. The

proposed product is a lipid emulsion formulation of aprepitant, which the sponsor indicates was designed to increase the low water solubility of aprepitant which is currently only available in oral dosage form.

Reference Listed Drug

Emend® (fosaprepitant) for Injection was approved for marketing on January 25, 2008 with indications for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy including high-dose cisplatin (HEC CINV) and prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC CINV). Emend® for Injection is designed to be given in combination with other antiemetic agents. The original dosing regimen was a 3-day dosing regimen. On November 12, 2010 a single-dose regimen was approved for HEC CINV. On February 1, 2016, a single-dose regimen was approved for MEC CINV. There are no approved pediatric indications. (b) (4)

.

Emend® for Injection has the following post-marketing requirements under the Pediatric Research Equity Act:

> A PK/PD study to characterize aprepitant PK parameters following administration of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist and dexamethasone, in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation. (b) (4)

A Written Request (WR) was originally issued on February 2, 2009. The WR has been amended (b) (4)

Agreed Initial Pediatric Study Plan (iPSP) for Cinvanti™

On December 23, 2016, the FDA and the sponsor came to an agreement on the iPSP.

In the originally submitted iPSP, the sponsor planned (b) (4)

(b) (4)

he sponsor did not propose to conduct pediatric clinical effectiveness and safety studies, but rather proposed to rely on findings of safety and efficacy of Emend® for oral use.

DPMH participated in the review of the iPSP and provided comments to DGIEP. The sponsor was told that (b) (4)

he age range should include adolescents because additional PK and safety information in the 12 to17 years population would be needed to support dosing.

Ultimately, after negotiation between FDA and the sponsor, the agreed iPSP consists of a planned deferral in the 0 months to 17 years age group. The sponsor plans to conduct a study to evaluate pharmacokinetics, safety and tolerability of a single dose of aprepitant injectable emulsion as part of a 3-day regimen and to utilize modeling and simulation to support the single dose (1-day) regimen in pediatric patients undergoing treatment with single day emetogenic chemotherapy. (b) (4)

The timeline for the pediatric development plan is as follows:

Final Study Protocol	July 2020
Study Completion:	November 2026
Final Clinical Study Report	May 2027

Reviewer's comment: The timeline is delayed in order to provide time for the expected Emend® for Injection pediatric studies to be submitted. (b) (4)

Sponsor proposed pediatric labeling with suggested edits (strikethroughs represent deletions and underlining represents additions)

Reviewer comment: The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

8. USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of CINVANTI have (b) (4) not been established in pediatric patients.

Recommendations

The edit noted above for subsection 8.4 should be incorporated.

Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations (see approval letter).

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

/s/

AMY M TAYLOR
10/03/2017

JOHN J ALEXANDER
10/03/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 28, 2017
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Error Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, BSN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	CINVANTI (aprepitant) injectable emulsion
Dosage Form and Route:	for intravenous use
Application Type/Number:	NDA (b) (4)
Applicant:	Heron Therapeutics

1 INTRODUCTION

On January 11, 2017, Heron Therapeutics submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 209296 for CINVANTI (aprepitant) injectable emulsion, for intravenous use. The Reference Listed Drug is EMEND (fosaprepitant dimeglumine) for injection, for intravenous NDA 022023. The proposed indication for CINVANTI (aprepitant) (b) (4), for intravenous use is, in combination with other antiemetic agents in adults, for the prevention of:

- acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including highdose cisplatin.
- (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on January 27, 2017, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for CINVANTI (aprepitant) injectable emulsion, for intravenous use.

2 MATERIAL REVIEWED

- Draft CINVANTI (aprepitant) injectable emulsion, for intravenous use PPI received on January 11, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 20, 2017.
- Draft CINVANTI (aprepitant) injectable emulsion, for intravenous use Prescribing Information (PI) received on January 11, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 20, 2017.
- Approved EMEND (fosaprepitant dimeglumine) for injection, for intravenous use comparator labeling dated August 9, 2017.

3 REVIEW METHODS

In 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

3 Page(s) of Draft Labeling have 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/

TWANDA D SCALES
09/28/2017

MEETA N PATEL
09/28/2017

MARCIA B WILLIAMS
09/28/2017

LASHAWN M GRIFFITHS
09/28/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 27, 2017

To: Mary Chung, Pharm.D., Senior Regulatory Project Manager, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for CINVANTI (aprepitant) injectable emulsion, for intravenous use

NDA: 209296

In response to DGIEP consult request dated January 30, 2017, OPDP has reviewed the proposed product labeling (PI), and patient package insert (PPI) for the original NDA submission for Cinvanti.

OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DGIEP on September 20, 2017. We have no comments on the proposed PI.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

24 Page(s) of Draft Labeling have 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/

MEETA N PATEL
09/28/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 9/18/2017 **Date consulted:** 1/27/17

From: Catherine Roca, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: CINVANTI (Aprepitant injection emulsion)

NDA: 209296

Applicant: Heron Therapeutics

Subject: Pregnancy and Lactation Labeling

Indication: 1) Prevention of acute and delayed nausea and 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)

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 209296
- DPMH review of EMEND (fosaprepitant dimeglumine injection), NDA 22023/S006, Christos Mastroyannis, M.D., January 6, 2015. DARRTS ID #3878366

- DPMH review of EMEND (aprepitant) capsules and powder, NDA 21549/S025 and NDA 207865, Carrie Ceresa, Pharm. D., MPH, July 2, 2015. DARRTS ID #3787085
- (b) (4)

Consult Question: "DGIEP requests DPMH Pediatric and Maternal Health team's assistance with the review of this application and its label (PI)."

INTRODUCTION

The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) on January 27, 2017 regarding the applicant's labeling proposal, more specifically the proposed pregnancy and lactation labeling rule (PLLR) language (Sections 8.1-8.3).

REGULATORY HISTORY

On January 11, 2017, Heron Therapeutics, submitted a 505(b)(2) new drug application for CINVANTI (aprepitant injection emulsion). The applicant's submission relies on information from EMEND (fosaprepitant), NDA 22023, which was originally approved on January 25, 2008 for the treatment of acute and delayed nausea and vomiting associated with initial and repeat courses of both HEC and MEC. The active ingredient of the applicant's aprepitant 130mg is equivalent to the reference listed drug (RLD) EMEND (fosaprepitant) 150mg. (Fosaprepitant is the prodrug of aprepitant.) The inactive ingredients include (b) (4) (2.6g), soybean oil (1.7g), ethanol (0.5g), sucrose (1g), sodium oleate (0.1g) and water for injection (12g).

BACKGROUND

Drug Characteristics[1]

Aprepitant is a substance P/neurokinin (NK_1) receptor antagonist. Aprepitant augments the antiemetic activity of the 5HT3-receptor antagonist ondansetron and the corticosteroid dexamethasone.

- The molecular weight is 534.43 Daltons.
- The terminal half-life is approximately 9-13 hours.
- It is greater than 95% protein bound.
- It crosses the blood brain barrier in humans.
- Serious adverse reactions include hypersensitivity reactions and drug-drug interactions with warfarin, hormonal contraceptives and drugs utilizing the CYP3A4 metabolic pathway.

Weight Gain and Pregnancy[2]

Excessive nausea and vomiting during chemotherapy can cause malnutrition and insufficient weight gain in pregnancy, should a patient experiencing those illnesses become pregnant. Insufficient weight gain during pregnancy has been associated with adverse maternal and fetal outcomes. Insufficient weight gain during pregnancy is defined as weight gain that is less than the recommended range of total weight based on the pre-pregnancy weight category and

[1] CINVANTI proposed package insert
[2] CDC Reproductive Health, Weight Gain During Pregnancy, accessed 12/30/2016 https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-weight-gain.htm

can result in fetal growth restriction, and having a low birth weight infant. See table 1 below for the Institute of Medicine's weight gain recommendations for pregnancy.[3]

Table 1. Institute of Medicine Weight Gain Recommendations for Pregnancy

Prepregnancy Weight Category	Body Mass Index*	Recommended Range of Total Weight (lb)	Recommended Rates of Weight Gain† in the Second and Third Trimesters (lb) (Mean Range [lb/wk])
Underweight	Less than 18.5	28–40	1 (1–1.3)
Normal Weight	18.5–24.9	25–35	1 (0.8–1)
Overweight	25–29.9	15–25	0.6 (0.5–0.7)
Obese (includes all classes)	30 and greater	11–20	0.5 (0.4–0.6)

*Body mass index is calculated as weight in kilograms divided by height in meters squared or as weight in pounds multiplied by 703 divided by height in inches.

†Calculations assume a 1.1–4.4 lb weight gain in the first trimester.

Modified from Institute of Medicine (US). Weight gain during pregnancy: reexamining the guidelines. Washington, DC. National Academies Press; 2009. ©2009 National Academy of Sciences.

Current State of the Labeling[4]

The most recent labeling for the RLD, EMEND, is in PLLR format. There is no contraindication for either pregnancy or lactation.

- Section 8.1, Pregnancy, presents no human data, but reports that animal reproduction studies show no adverse developmental effects in rats and rabbits.
- Section 8.2, Lactation, has no human data, but notes that aprepitant is present in rat milk.
- Section 8.3, Females and Males of Reproductive Potential, states "Upon administration of EMEND, the efficacy of hormonal contraceptives may be reduced. Advise females of reproductive potential using hormonal contraceptives to use and effective alternative or back-up non-hormonal contraceptive (such as condoms and spermicides) during treatment with EMEND and for 1 month following the last dose.

Pregnancy and Lactation Labeling

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[5] also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and

[3] Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines. May, 2009. https://www.nationalacademies.org/hmd/~/media/Files/Report%20Files/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines/Report%20Brief%20-%20Weight%20Gain%20During%20Pregnancy.pdf

[4] Approved EMEND labeling, Drugs@FDA.gov

[5] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[6] format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW
PREGNANCY

Nonclinical Experience
In animal reproduction studies, no adverse developmental effects were observed in rats or rabbits exposed during the period of organogenesis to systemic drug levels (AUC) approximately equivalent to the exposure at the recommended human dose (RHD) of 150mg. For additional information, the reader is referred to the nonclinical review by Emmanuel Akinshola, Ph.D.

Applicant's Review of Literature
The applicant did not provide a review of the literature.

DPMH Review of Literature
Recent DPMH reviews of the literature for EMEND (fosaprepitant dimeglumine injection) NDA 22023[7], and EMEND (aprepitant) capsules and powder for suspension, NDA 21549 (b) (4) (b) (4) have found no information about the use of these drugs in pregnant women or on fetal/neonatal outcomes. An additional search of the literature by DPMH for this review was performed with PubMed, Embase, Reprotox, and Micromedex[9] using the search term "aprepitant" and the following terms, "pregnancy," "pregnant women," "pregnancy and birth defects," "fetal malformations," "stillbirth," and "miscarriage." No studies or case reports were found in the published literature.

Micromedex[9] states, "Fetal risk cannot be ruled out."

Alcohol and Pregnancy
The aprepitant injection emulsion contains 0.5 gm ethanol as one of the excipients (see Regulatory History above), which is 3.6% the amount of ethanol contained in standard alcoholic drink (14 grams).[10] While this is a comparatively small amount of ethanol, a safe threshold of alcohol exposure in pregnancy has not been determined. Maternal alcohol use is the leading known cause of developmental and cognitive disabilities, and is a preventable cause of birth defects.[11] Children exposed to alcohol *in utero* are at risk for growth deficiencies, facial deformities, central nervous system impairment, behavioral disorders, and impaired

[6] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).
[7] DPMH review by Christos Mastroyannis, Medical Officer, 1/6/2015 DARRTS ID #3878366
[8] DPMH review by Carrie Ceresa, Clinical Analyst, 7/2/2015, DARRTS ID #3787085
[9] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 4/10/2017
[10] NIAAA website: https://www.niaaa nih.gov/alcohol-health/overview-alcohol-consumption/what-standard-drink, accessed 8/25/2017
[11] Fetal alcohol exposure, NIAAA https://pubs niaaa.nih.gov/publications/fasdfactsheet/fasd.pdf

intellectual development. Consuming alcohol during pregnancy also increases the risk of miscarriage, low birth weight, and stillbirth. Because a safe threshold level of alcohol exposure in pregnancy is not known, professional organizations such as the American College of Obstetricians and Gynecologists[12] (ACOG), and public health agencies like the Centers for Disease Control[13] (CDC) recommend that pregnant women abstain from consuming alcohol during pregnancy. The Surgeon General[14] also published an advisory in 2005 that stated that pregnant women should abstain from consuming alcohol during pregnancy.

Summary

There are no data to inform a drug-associated risk of aprepitant use during pregnancy. Animal studies in two species have not demonstrated any adverse developmental effects.

CINVANTI includes ethanol as one of its inactive ingredients. Therefore, the following statement will be included under Clinical Considerations:

> CINVANTI contains alcohol. Published studies have demonstrated that alcohol is associated with fetal harm including central nervous system abnormalities, behavioral disorders and impaired intellectual development. There is no safe level of alcohol exposure in pregnancy, therefore, avoid use of CINVANTI in pregnant women.

LACTATION

Nonclinical Experience

Aprepitant was observed in the milk of lactating rats administered 1000mg/kg twice daily. At this dose, the mean concentration of aprepitant in the milk was 90% the mean maternal plasma concentration. For additional information, the reader is referred to the nonclinical review by Emmanuel Akinshola, Ph.D.

Applicant's Review of Literature

The applicant did not provide a review of the literature.

DPMH Review of Literature

DPMH conducted a search of *Medications in Mother's Milk,* the Drugs and Lactation Database (LactMed),[15] Micromedex,[9] and of the published literature in PubMed and Embase using the search terms "aprepitant" and the terms, "lactation," and "breast-feeding." No articles on aprepitant were found in the literature search, and aprepitant is not referenced in LactMed.

In *Medications and Mother's Milk*[16], Thomas Hale, a breastfeeding expert, rates aprepitant as "No Data- Probably Compatible." He states, "Side effect profiles appear minimal. Levels in

[12] http://www.acog.org/About_ACOG/News_Room/News_Releases/2008/Alcohol_and
[13] http://www.cdc.gov/ncbddd/fasd/alcohol-use.html
[14] http://www.surgeongeneral.gov/news/2005/02/sg02222005 html
[15] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[16] Hale, Thomas (2016). Medications and Mother's Milk. Amarillo, Texas. Hale Publishing, pg. 73.

milk will likely be minimal due to moderately large molecular weight. Currently there are no data available on the transfer of aprepitant into human milk although it will likely be minimal."

Micromedex[9] states, "Infant risk cannot be ruled out."

Summary

Aprepitant is present in rat milk. No lactation studies have been conducted in humans to determine if the drug is present in human milk or if the drug has effects on a breastfed infant, or the effects on milk production. DPMH recommends the following language:

> There are no data on the presence of aprepitant in human milk, the effects on the breastfed infant, or the effects on milk production. Aprepitant is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CINVANTI and any potential adverse effects on the breastfed infant from CINVANTI from the underlying maternal condition.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Oral aprepitant did not affect the fertility of male or female rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the RHS of 150mg and exposure in female rats approximately equivalent to the human exposure). For additional information, the reader is referred to the nonclinical review by Emmanuel Akinshola, Ph.D.

Applicant's Review of Literature

The applicant did not provide a review of the literature.

DPMH Review of Literature

DPMH conducted a review of Micromedex, Embase, and PubMed using the term "aprepitant" with the following search terms, "fertility," "contraception," "hormonal contraceptives," and "infertility." A search of the literature did not yield studies on the effects of aprepitant on human fertility.

The RLD, EMEND (fosaprepitant) states in its current labeling that when oral aprepitant was administered as a three day regimen with ondansetron and dexamethasone, and coadministered with an oral contraceptive containing ethinyl estradiol and norethindrone, the trough concentrations of both ethinyl estradiol and norethindrone were reduced by as much as 64% for three weeks post treatment.[4]

Summary

No clear adverse effects of aprepitant on human fertility were found in the published literature. Data from the RLD indicate an interaction of aprepitant with hormonal contraceptives, potentially reducing the efficacy of the contraceptive. DPMH recommends that section 8.3 be included in labeling, with a recommendation that effective alternative or back-up non-hormonal contraceptives be used during treatment with CINVANTI and for 1 month following administration of CINVANTI.

CONCLUSIONS

The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of CINVANTI labeling were structured to be consistent with the PLLR, as follows:

- **Warnings and Precautions, Section 5.4**
  - Based on the potential for aprepitant to reduce the efficacy of hormonal contraception, a subsection describing this potential as well as mitigation measures must be placed in the Warnings and Precautions section of labeling as required by regulation (21 CFR 201.57(c)(9)(i)(A)(4)).
- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of labeling was formatted in the PLLR format to include the following headings: "Risk Summary," "Clinical Considerations," and "Data."
- **Lactation, Section 8.2**
  - The "Lactation" subsection of labeling was formatted in the PLLR format to include the following heading: "Risk Summary."
- **Females and Males of Reproductive Potential, Section 8.3**
  - The "Females and Males of Reproductive Potential" subsection of labeling was formatted in the PLLR format to include the following heading: "Contraception."
- **Patient Counseling Information, Section 17**
  The "Patient Counseling Information" section of labeling was updated to correspond with changes made to sections 8.1 and 8.3 of labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 5.4, 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------WARNINGS AND PRECAUTIONS----------

Hormonal Contraceptives: Efficacy of contraceptives may be reduced during administration of and for 28 days following administration of aprepitant. Use effective alternative or back-up methods of non-hormonal contraception (5.4, 7.1, 8.3).

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: May cause fetal harm (8.1).

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

5.4 Risk of Reduced Efficacy of Hormonal Contraceptives

Upon coadministration with CINVANTI, the efficacy of hormonal contraceptives may be reduced during administration of and for 28 days following the last dose of CINVANTI *[see Clinical Pharmacology (12.3)]*. Advise patients to use effective alternative or back-up methods of non-hormonal contraception during treatment with CINVANTI and for 1 month following administration of CINVANTI or oral aprepitant, whichever is administered last *[see Drug Interactions (7.1), Use in Specific Populations (8.3)]*.

7 DRUG INTERACTIONS

7.1 Effect of Aprepitant on the Pharmacokinetics of Other Drugs

Hormonal Contraceptives	
Clinical Impact	Decreased estrogen and progestin exposure during administration of and for 28 days after administration of the last dose of aprepitant *[see Warnings and Precautions (5.4), Use in Specific Populations (8.3), Clinical Pharmacology (12.3)]*.
Intervention	Effective alternative or back-up methods of contraception (such as condoms or spermicides) should be used during treatment with CINVANTI and for 1 month following administration of CINVANTI or oral aprepitant, whichever is administered last.
Examples	Birth control pills, skin patches, implants, and certain IUDs

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on CINVANTI use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Avoid use of CINVANTI in pregnant women due to the alcohol content *(see Clinical Considerations)*. In animal reproduction studies, no adverse developmental effects were observed in rats or rabbits exposed during the period of organogenesis to systemic drug concentrations (area under the plasma-concentration time curve [AUC]) of aprepitant approximately equivalent to the exposure at the recommended human dose (RHD) of CINVANTI 130 mg *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

CINVANTI contains alcohol. Published studies have demonstrated that alcohol is associated with fetal harm including central nervous system abnormalities, behavioral disorders and impaired intellectual development. There is no safe level of alcohol exposure in pregnancy, therefore, avoid use of CINVANTI in pregnant women.

Data

Animal Data

In embryo-fetal development studies in rats and rabbits, aprepitant was administered during the period of organogenesis at oral doses up to 1000 mg/kg twice daily (rats) and up to the maximum tolerated dose of 25 mg/kg/day (rabbits). No embryofetal lethality or malformations were observed at any dose levels in either species. The exposures (AUC) in pregnant rats at 1000 mg/kg twice daily and in pregnant rabbits at 125 mg/kg/day were approximately

equivalent to the exposure at the RHD of CIVANTI 130 mg. Aprepitant crosses the placenta in rats and rabbits.

8.2 Lactation

Risk Summary

There are no data on the presence of aprepitant in human milk, the effects on the breastfed infant, or the effects on milk production. Aprepitant is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CINVANTI and any potential adverse effects on the breastfed infant from CINVANTI or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Upon administration of CINVANTI, the efficacy of hormonal contraceptives may be reduced. Advise females of reproductive potential using hormonal contraceptives to use an effective alternative or back-up non-hormonal contraceptives (such as condoms or spermicides) during treatment with CINVANTI and for 1 month following the last dose of CINVANTI or oral aprepitant, whichever is administered last *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

17 PATIENT COUNSELING INFORMATION

Drug Interactions

Hormonal Contraceptives: Advise patients that administration of CINVANTI may reduce the efficacy of hormonal contraceptives. Instruct patients to use effective alternative or back-up methods of non-hormonal contraception (such as condoms or spermicides) during treatment with CINVANTI and for 1 month following administration of CINVANTI or oral aprepitant, whichever is administered last *[see Warnings and Precautions (5.4), Use in Specific Populations (8.3)]*.

Pregnancy

Advise pregnant women of the potential risk to a fetus and to avoid use of CINVANTI during pregnancy *[see Use in Specific Populations (8.1)]*.

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

/s/

CATHERINE A ROCA
09/18/2017

MIRIAM C DINATALE
09/18/2017

LYNNE P YAO
09/20/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 19, 2017
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	NDA 209296
Product Name and Strength:	Cinvanti (aprepitant) Emulsion for Injection, 130 mg/18 mL
Applicant/Sponsor Name:	Heron Therapeutics, Inc.
Submission Date:	September 13, 2017
OSE RCM #:	2017-135-1
DMEPA Safety Evaluator:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMO

DGIEP requested that we review the revised carton labeling and container label for Cinvanti (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton labeling and container label for Cinvanti is acceptable from a medication error perspective. However, we have recommendations to improve consistency of the labeling throughout (See Section 3). Additionally, we are requesting the applicant submit the proposed container label for the patient assistance program for our review.

3 RECOMMENDATIONS FOR HERON THERAPEUTICS

We recommend the following be implemented prior to approval of this NDA:

[a] Barlow, M. Label and Labeling Review for Cinvanti (NDA 209296). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 26. RCM No.: 2017-135.

A. **All Carton labeling**
    a. 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**
    a. Please submit the proposed container label for the Patient Assistance Program for the Agency to review.

2 Page(s) of Draft Labeling have 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/

MATTHEW J BARLOW
09/19/2017

SARAH K VEE
09/20/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209296 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Established/Proper Name: aprepitant Dosage Form: injectable emulsion Strengths: Route(s) of Administration: intravenous		
Applicant: Heron Therapeutics, Inc. Agent for Applicant (if applicable): Not applicable (NA)		
Date of Application: January 12, 2017 Date of Receipt: January 12, 2017 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: November 12, 2017	Action Goal Date (if different):	
Filing Date: March 13, 2017	Date of Filing Meeting: February 22, 2017	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): prevention of 1] acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin, 2] (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 125926 aprepitant inj.	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.***	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☒	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		

• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☒	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
002	Emend (fosaprepitant dimeglumine) I.V.	D-155	February 1, 2019

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency	☐	☐		Not applicable

and, where applicable, content uniformity, disintegration times, and/or dissolution rates.				
Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☐	☒		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included.* ***Forms** include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required***[3]	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829 htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837 htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☐	☐ ☐	☐ ☒	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**	☐	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):**	☐	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐			

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 22, 2017

BACKGROUND:
Heron Therapeutics submitted a new 505(b)(2) NDA 209296 aprepitant inj. emulsion relying on listed drug NDA 22023 Emend (fosaprepitant) I.V. The proposed product HTX-019 (aprepitant injectable emulsion for intravenous use) is a lipid emulsion formulation of aprepitant, which sponsor indicates was designed to increase the low water solubility of aprepitant (which is currently only available in oral dosage forms). The applicant's clinical program in support of this NDA includes two relative BA studies- study 104 and 106. In these two open-label, randomized, crossover, bioequivalence studies, a total of 200 subjects were dosed with 130 mg of HTX-019 and 150 mg of fosaprepitant for injection. An agreed iPSP was issued on December 23, 2016 under the referenced IND 125926 aprepitant.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mary Chung	Y
	CPMS/TL:	Brian Strongin	
Cross-Discipline Team Leader (CDTL)			
Division Director/Deputy	Donna Griebel		Y
Office Director/Deputy			N/A
Clinical	Reviewer:	Aisha Johnson	Y
	TL:	Anil Rajpal	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Insook Kim	Y
	TL:	Christine (Yuen-Yi) Hon	Y
• Genomics	Reviewer:		

• Pharmacometrics	Reviewer:	Jee Eun Lee	Y
Biostatistics	Reviewer:		
	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Emmanuel (Babatunde) Akinshola	Y
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Hitesh Shroff	Y
	RBPM:	Rabiya Laiq	Y
• Drug Substance	Reviewer:	Caroline Strasinger	Y
• Drug Product	Reviewer:	Ben (Benjamin) Stevens	N
• Process	Reviewer:	Peter Krommenhoek	N
• Microbiology	Reviewer:	Helen Ngai	N
• Facility	Reviewer:	Allison Aldridge	N
• Biopharmaceutics	Reviewer:	Sandra Suarez	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:	Catherine Roca/ DPMH Maternal	Y
	TL:	Miriam Dinatale/ DPMH Maternal	Y
Other attendees	Nicholas Miles (RPM)/OSE		Y
	Joette Meyer (Associate Director for Labeling)/DGIEP		Y
	Maria Walsh (ADRA)/ODE III		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues:	☐ Not Applicable
o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	The applicant submitted two BA/BE studies (study 104 and 106) which compared applicant's proposed 130 mg of HTX-019 with 150 mg of fosaprepitant for injection (listed drug).
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: The application did not raise significant safety or efficacy issues.
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☒ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Donna Griebel **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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
03/08/2017

BRIAN K STRONGIN
03/08/2017