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APPLICATION NUMBER:

209296Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	November 8, 2017
From	Lisa Soule, M.D., Acting Associate Director, Division of Gastroenterology and Inborn Errors Products
Subject	Division Director Summary Review
NDA/BLA #	NDA 209-296
Applicant Name	Heron Therapeutics, Inc.
Date of Submission	January 12, 2017
PDUFA Goal Date	November 12, 2017
Proprietary Name / Established (USAN) Name	Cinvanti Aprepitant injectable emulsion
Dosage Forms / Strength	Emulsion for intravenous use available in single-dose glass vial, 130 mg/18 mL (7.2 mg/mL)
Proposed Indication(s)	CINVANTI (b) (4) in combination with other antiemetic agents, is indicated in adults for the prevention of: • acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin • nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) Limitations of Us: CINVANTI has not been studied for the treatment of established nausea and vomiting
Action/Recommended Action:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Cross-Discipline Team Leader	Anil Rajpal, M.D., M.P.H.
Medical Officer Review	Aisha Johnson, M.D., M.P.H., M.B.A
Pharmacology Toxicology Review	Babatunde Emmanuel Akinshola, Ph.D./Sushanta Chakder, Ph.D.
CMC Review/OBP Review	Hitesh Shroff, Ph.D. (application technical lead), Friedrich Burnett, Ph.D. (drug substance), Caroline Strasinger, Ph.D. (drug product, labeling, & environmental analysis), Peter Krommenhoek, Ph.D. (process), Helen Ngai, Ph.D. (microbiology), Sandra Suarez, Ph.D. (biopharmaceutics), Allison Aldridge (manufacturing facility), Oumou Barry (regulatory business process manager)
Clinical Pharmacology Review	Xinyuan Zhang, Ph.D., Insook Kim, Ph.D.
Office of Prescription Drug Promotion	Meeta Patel, Pharm.D., Kathleen Klemm
Office of Study Integrity and	Angel Johnson (Division of New Drug Bioequivalence

Surveillance	Evaluation)
OSE/DMEPA	Matthew Barlow, R.N., B.S.N./Sarah Vee, Pharm.D.
Other: Division of Pediatric and Maternal Health	Amy Taylor, M.D., M.H.S./John Alexander, M.D., M.P.H. (pediatrics) Catherine Roca, M.D., M.S./Miriam Dinatale, D.O./Lynne Yao, M.D. (maternal health)
Other: Division of Medical Policy Programs, Patient Labeling Team	Twanda Scales, RN, BSN, MSN/Ed./Marcia Williams Ph.D./LaShawn Griffiths, MSHS-PH, BSN, RN

OND=Office of New Drugs

OPDP=Office of Prescription Drug Promotion

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

OSI=Office of Scientific Investigations

CDTL=Cross-Discipline Team Leader

1. Introduction

The Applicant submitted an NDA under Section 505(b)(2) of the Food, Drug, and Cosmetic Act for aprepitant injectable emulsion (Cinvanti) for the prevention of chemotherapy-induced nausea and vomiting (CINV) associated with highly and moderately emetogenic chemotherapy (HEC and MEC, respectively). The application relies on the listed drug Emend (fosaprepitant) for injection, approved in 2008 under NDA 22-023. Fosaprepitant is the prodrug of aprepitant, which is a selective agonist of human Substance P/neurokinin 1 (NK₁) receptors. Unlike Cinvanti, Emend contains polysorbate 80 (b) (4). The oil-in-water emulsion formulation of Cinvanti is intended to overcome the insolubility of aprepitant (b) (4), which has been associated with hypersensitivity reactions.

Emend is approved for prevention of:

- acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy [HEC] including high-dose cisplatin
- delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy [MEC]

Emend and Cinvanti are intended to be given intravenously (IV), and in combination with other antiemetic agents (i.e., dexamethasone and a 5-HT₃ antagonist).

The current application is based on demonstration of bioequivalence to the listed drug, Emend for injection, to permit reliance on the Agency's findings of safety and efficacy for this formulation of Emend. While the original approval of Emend for injection was for a 3-day dosing regimen for both HEC CINV and MEC CINV, an efficacy supplement submitted in 2010 (S-004) provided for a single-dose regimen for HEC CINV in addition to the already-labeled 3-day dosing regimen. In 2016, S-006 provided for a single-dose regimen for MEC CINV. The 3-day dosing regimen was removed from labeling for both HEC CINV and MEC CINV (for reasons not relating to safety or efficacy) in S-006. The product is currently approved only for the single-dose regimen (150 mg IV infusion approximately 30" prior to chemotherapy).

The Applicant is proposing the following regimens, to be administered over 30 minutes:

- single dose (130 mg IV infusion) for HEC
- a 3-day dosing regimen (single 100 mg IV infusion on Day 1, followed by 80 mg aprepitant orally for two additional days) for MEC

Therefore, the Applicant sought to rely upon the discontinued labeling for Emend for infusion with respect to the 3-day dosing regimen for MEC CINV. Regulatory considerations with respect to this reliance are discussed in Section 10.

Emend is also marketed as aprepitant in capsule (NDA 21-549) and oral suspension (NDA 207-865) formulations; however, the current 505(b)(2) application does not rely upon these products. Emend capsules are indicated for patients 12 years and older; Emend oral suspension is indicated for patients over the age of 6 months and for patients who are unable to swallow capsules. There is no approved pediatric indication for Emend for injection.

The review of this application was conducted as a Standard review.

2. Background

CINV has been observed to occur both acutely after chemotherapy administration (i.e., within 0-24 hours) and as a delayed reaction (between 24-120 hours after chemotherapy).

Aprepitant has been shown in animal models to inhibit CINV through actions in the central nervous system; animal and human studies have shown aprepitant to cross the blood-brain barrier and to occupy brain NK₁ receptors. Dr. Johnson's review includes a comprehensive listing of currently approved drugs for the prevention of CINV.

Cinvanti was developed under IND 125,926. The Division held a PreIND meeting with the Applicant in May 2015 to discuss the planned development program for a 505(b)(2) approach to a marketing application. The Division made recommendations about the chemistry, manufacturing, and controls (CMC) components of the application, and advised the Applicant to justify the safety of excipients, and to conduct an *in vitro* hemolysis study. The Division also provided advice about the indication that would be supported by the proposed bridging plan, and stated that if systemic exposure of the proposed product varied from that of the reference product in the BA study(ies), safety and/or efficacy of the proposed product would have to be addressed in the NDA.

Multiple Type C Written Response Only (WRO) communications were provided in 2016 to clarify nonclinical, CMC and clinical requirements under a 505(b)(2) approach. The Division advised in August 2016 that therapeutic equivalents must be pharmaceutical equivalents, which must contain the same active ingredient; aprepitant and fosaprepitant are considered different active ingredients. Further, the Division stated that safety of the higher exposure (C_{max}) observed for the 130 mg dose of the proposed drug vs. the 150 mg dose of Emend must be justified. The Division did not agree that the data from Study 104 using a 30'' infusion rate would support labeled infusion time (b) (4)'. Finally, the Division stated that Study 104 would not support both the studied 130 mg dose and a 100 mg dose, noting that a biowaiver request would need to be submitted, including justification (b) (4)

Another Type C WRO was provided in October 2016 for further advice on the clinical program. The Division found the Applicant's proposal to support safety of higher plasma levels of aprepitant 130 mg compared to the listed drug using published literature to be reasonable. Further, a biowaiver would not be required to support the lower dose (100 mg) prepared from the same drug product (a 20 mL vial) as that for the higher dose (130 mg); i.e., if a single product presentation were proposed.

A pre-NDA teleconference was held in December 2016 to discuss the intended indications the Applicant sought, and the data to be provided in support of the marketing application. While the Division was in general agreement that current labeling for Emend for injection would support the safety and efficacy of the proposed product, it noted that the higher exposure of the two doses of the proposed product compared to the relevant reference product doses might necessitate modification of information in Section 6, and of drug interaction information (e.g., with dexamethasone). The Division recommended that drug interaction potential be assessed based on C_{max}, not on AUC, and encouraged the Applicant to consider using physiologically-based PK analyses to justify the extent of drug interaction with CYP3A4 substrates. In addition, a Type C WRO was provided in December 2016, along with the teleconference; the WRO addressed more technical aspects of the NDA submission.

The Division conveyed its agreement to the Applicant's initial Pediatric Study Plan (iPSP) on Dec. 23, 2016 (see Section 9).

3. CMC/Device

I concur with the OPQ recommendation for approval. The following conclusions were made by the OPQ review team:

- The Applicant provided Letters of Authorization to reference Drug Master Files (DMFs) for both manufacturers of the active pharmaceutical ingredient; these DMFs have been reviewed in 2017, and found adequate.
- The Applicant has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.
- An expiry period of 24 months is granted; the product should be stored at refrigerated conditions (2-8°C). Once diluted, the drug solution is stable at ambient room temperature for 6 hours in 0.9% sodium chloride injection, or 12 hours in 5% dextrose injection.
- The microbiology-related aspects of manufacturing, sterilization, (b) (4) and relevant attributes of drug product specifications, including endotoxins, sterility, and container-closure integrity, were reviewed and found acceptable.
- The drug product's formulation, *in vitro* drug release characteristics, and comparison of PK characteristics with approved immediate release (IR) products support the claim that this is an IR product. The *in vitro* drug release method was deemed acceptable.
- The claim for Categorical Exclusion for the Environmental Assessment was granted.
- The Office of Process and Facilities made a final overall "Approval" recommendation for the facilities involved in this application.
- The CMC sections of the revised labeling were found acceptable.

The formulation concentration is 7.2 mg/mL, provided in 20 mL glass vials. The same vial is used to deliver both doses; for the 130 mg dose, 18 mL are withdrawn and mixed with 130 mL of normal saline or 5% dextrose; for the 100 mg dose, 14 mL are withdrawn and mixed with 100 mL of normal saline or 5% dextrose. The emulsifier is egg lecithin (b) (4); there are no novel excipients.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

The Applicant relied upon a 505(b)(2) approach to support nonclinical safety of Cinvanti, and also submitted PK studies in rats, a repeat dose toxicology study in rats, a local tolerance study in rabbits, and an *in vitro* hemolysis study using rat, dog, and human blood. Results of these studies are discussed in Dr. Akinshola's review, and did not present any approvability concerns.

Labeling of Sections 8.1, 8.2, and 13 was found to be acceptable.

5. Clinical Pharmacology

I concur with the clinical pharmacology review team's conclusion that the application is acceptable provided agreement on labeling is reached (see Section 11).

The Applicant conducted two relative bioavailability (BA) studies in healthy volunteers to support the bridge between the 130 mg dose of the proposed product and the 150 mg dose of Emend for injection for this 505(b)(2) application:

- Study HTX-019 C2015-104 (hereafter referred to as Study 104), which evaluated the systemic exposure of a 130 mg IV infusion of Cinvanti vs. a 150 mg IV infusion of Emend, both over 30"
- Study HTX-019-106 (hereafter referred to as Study 106), which evaluated the systemic exposure of a 30" IV infusion of Cinvanti 100 mg vs. a 15" infusion of 115 mg of Emend (Part A) and the systemic exposure of a 30" IV infusion of Cinvanti 130 mg vs. a 20" infusion of 150 mg of Emend (Part B)

The 130 mg dose of Cinvanti is equivalent to 150 mg of Emend for injection in terms of the molar mass of the active ingredient, aprepitant. The infusion times evaluated for Cinvanti differ from those labeled for Emend for infusion (Cinvanti 130 mg - 30" vs. Emend 100 mg - 20-30"; Cinvanti 100 mg - 30" vs. Emend 115 mg - 15").

Study 104 and Study 106 (Part B) provided data to support the bioequivalence of Cinvanti 130 mg to 150 mg Emend for infusion, to be used in a single dose regimen for HEC CINV. Study 106 (Part A) characterized the C_{max} of the two drug products. The results of the studies are shown in Table 1.

Table 1 Bioequivalence Results for Proposed Product Compared to Emend

Test	Reference	Test/Reference Point Estimate (90% CI)		
		AUC _{0-last}	AUC _{0-∞}	Cmax
Study 104 (n=97)				
Cinvanti 130 mg 30 min IV infusion	Emend 150 mg 30 min IV infusion	99.0% (96.7%, 101.4%)	98.3% (95.6%, 101.1%)	147.9% (142.1%, 153.9%)
Study 106 Part B (n=96)				
Cinvanti 130 mg 30 min IV infusion	Emend 150 mg 20 min IV infusion	96.7% (94.0%, 99.5%)	96.1% (93.3%, 98.9%)	127.7% (122.2%, 133.4%)
Study 106 Part A Cohorts 4 and 5 (n=12 per cohort)				
Cinvanti 100 mg 30 min IV infusion	Emend 115 mg 15 min IV infusion	132.0% (111.1%, 156.9%)	132.0% (108.3%, 160.9%)	155.3% (129.9%, 185.7%)

Source: Table 1, CDTL review by Anil Rajpal, M.D., dated October 12, 2017

The statistical criteria applied to demonstration of bioequivalence (BE) were met in Studies 104 and 106, Part B for AUC_{0-last} and AUC_{0-∞}, but C_{max} was higher by 28-48% for the 130 mg Cinvanti vs. the 150 mg Emend for injection. In Study 106, Part A, Cinvanti 100 mg had higher AUC_{0-last} (32%), AUC_{0-∞} (32%), and C_{max} (55%) compared to Emend for injection 115 mg.

Because systemic exposure of the two Cinvanti doses was equal to or greater than that of the comparable doses of Emend for injection, the efficacy of both doses of Cinvanti is supported. The Clinical Pharmacology reviewer, Dr. Zhang, noted that the observed C_{max} after administration of the 130 mg dose of Cinvanti is covered by the systemic exposure studied in the Emend thorough QT study, which did not identify a QT prolongation signal; thus, there is

no concern for QT prolongation at the 130 mg dose. Further evidence of the safety of the higher peak plasma concentration associated with the 130 mg dose of Cinvanti is discussed in Section 7. Dr. Zhang noted that safety of the 100 mg dose of Cinvanti was bracketed by the safety of the 130 mg dose.

Aprepitant is a weak-to-moderate inhibitor and an inducer of CYP3A4. Dr. Zhang noted that the higher C_{max} after administration of Cinvanti compared to Emend for injection would not be expected to alter the dosage reduction recommended for CYP3A4 substrates because the higher C_{max} is transient, and the two products had a comparable concentration-time profile beginning 15” after the infusion was complete.

6. Clinical/Statistical-Efficacy

This NDA did not include any efficacy studies, as it relies upon the Agency’s findings of safety and efficacy for Emend, based upon demonstration of bioequivalence to that listed drug.

7. Safety

There were no safety findings of concern in the two BA studies conducted in healthy adults, as discussed in Dr. Johnson’s review. The two studies included a total of 270 healthy subjects exposed to Cinvanti and Emend for infusion, the majority in a cross-over manner. Of these, 217 received the 130 mg dose of Cinvanti and 12 received the 100 mg dose. There were no deaths or serious adverse events. Four subjects withdrew from the studies prior to completing both treatment periods due to an adverse event (AE), three while receiving Emend. Common AEs across both products included headache, vessel puncture site pain, fatigue and lethargy, and were of similarly low frequency for both products.

Hypersensitivity is labeled in the Warnings and Precautions section of the Emend labeling, and was considered an AE of interest. Eight AEs of dyspnea were reported in the BA trials, some with associated AEs that suggest a hypersensitivity reaction, such as tachycardia, nausea, flushing, hyperhidrosis, dizziness and abdominal pain. Of these, eight occurred following Emend infusion, and two following Cinvanti, one of which was associated with respiratory tract congestion and was reported five days after the infusion.

Dr. Johnson evaluated the safety implications of the higher C_{max} observed for the doses of Cinvanti relative to the comparable doses of Emend for injection. She based her conclusions on data from Studies 104 and 106, and from review of published literature. She examined the data from the BA trials looking at AEs occurring in the first 60” of infusion, the period during which the higher plasma concentration of aprepitant associated with Cinvanti 130 mg compared to Emend for infusion 150 mg was observed. In both Studies 104 and 106, the incidence of AEs in the first 60” was notably higher following Emend for infusion (15-20%) vs. Cinvanti (1-5%). Several publications were submitted by the Applicant that reported on reassuring AE profiles associated with maximum aprepitant plasma concentrations that exceeded the C_{max} reported for Cinvanti 130 mg in the BA studies. Dr. Johnson concluded that the higher C_{max} for Cinvanti 130 mg is not expected to be associated with new safety concerns.

8. Advisory Committee Meeting

The product was not a new molecular entity, and relied upon a 505(b)(2) approach referencing an approved drug. Therefore, advisory committee consideration was not warranted.

9. Pediatrics

The Applicant submitted the agreed initial Pediatric Study Plan (iPSP) on Nov. 23, 2016, stating that it planned to rely on the Agency's finding of safety and effectiveness for Emend for injection (NDA 22-023) for adult indications under a 505(b)(2) approach, and that the Emend Applicant has previously conducted pediatric efficacy studies for the active ingredient for both the capsule and oral suspension formulations. Emend labeling specifies use of capsules for patients aged 12 years and older, and use of the oral suspension for patients aged 6 months to 12 years. In addition, the current Applicant proposed to conduct a PK, safety, and tolerability study in pediatric patients aged 0 months to 17 years, performed sequentially from adolescents to neonates. Dose selection for patients aged 12 to 17 years will be based on identifying a dose of Cinvanti that matches the PK (C_{max} and AUC) of the approved pediatric dose of Emend capsule, and for patients aged 6 months to 12 years, by matching the PK of the approved pediatric dose of Emend oral suspension, using a population PK modeling approach. Effectiveness will be extrapolated from the pediatric information available in labeling for these two Emend products with pediatric indications. Because exclusivity still applies to these Emend data, the Cinvanti pediatric study will not be conducted until the exclusivity has expired. The Applicant requested deferral of the pediatric study because the NDA for adult use was ready for submission, and the pediatric study was not yet complete.

The Applicant does not intend to develop a pediatric formulation, as it believes that the formulation proposed in this NDA is appropriate for pediatric patients of all ages (aside from those with known egg allergies).

The Division agreed with the iPSP on Dec. 23, 2016.

The application was discussed at the Pediatric Review Committee (PeRC) on September 27, 2017. PeRC agreed to the plan for a deferral of the pediatric study, and to the proposed timeline of submission of the study report. The pediatric study in patients aged 0 months to 17 years will be completed as a post-marketing requirement; submission of the final study report has been deferred until May 2027 (see Section 12).

10. Other Relevant Regulatory Issues

Dr. Johnson's review includes the financial disclosure assessment.

The Office of Study Integrity and Surveillance (OSIS) recommended further scrutiny of the data from Study 104, without an on-site inspection. The study site (Spaulding Clinical Research, LLC) had been inspected recently (b) (4), and observations of study misconduct (b) (4)

(b) (4) OSIS noted that the dates of conduct of Study 104 (b) (4) and therefore suggested that the review team consider these findings in evaluating the acceptability of the data from Study 104.

Dr. Zhang of Clinical Pharmacology concluded that the findings in this previous inspection were unlikely to have an impact on the PK study results. Dr. Rajpal carefully reviewed the deficiencies identified (b) (4)

He concluded that the data from Study 104 appear acceptable in support of safety of the product.

OSIS recommended accepting data without an on-site inspection for the analytical site (b) (4) based on the inspectional outcome and recommendation to the review division for the previous inspection, which was classified as VAI.

Regarding the Applicant's reliance upon the FDA's findings of safety and effectiveness for NDA 22-023, two issues arose regarding the regulatory acceptability of the reliance:

- Because the 115 mg Emend vial is no longer marketed, the study investigators drew up 115 mg from the marketed 150 mg Emend vial for use in Study 106.
- The Applicant's bridge relied upon the approval of the discontinued 115 mg Emend for injection product, which had a 3-day IV/oral/oral dosing regimen approved for the indication of "prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy." However, the currently approved indication for Emend for injection includes "prevention of *delayed* nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)" [italics added].

These issues were discussed with the Offices of Regulatory Affairs and Chief Counsel on July 18, 2017. The 115 mg dose of Emend was not withdrawn for reasons of safety or effectiveness.¹ It was determined that the use of 115 mg of Emend drawn from the 150 mg vial for the BE study was not an issue of concern from a regulatory perspective provided the bridging were scientifically justifiable. Further, it was determined that reliance on the labeling for the discontinued Emend for injection 3-day dosing regimen for MEC was acceptable.

There are no other unresolved relevant regulatory issues.

11. Labeling

DMEPA conditionally approved the proprietary name Cinvanti.

Labeling generally follows that for Emend for injection (NDA 22-023), which had a recent labeling revision approved relating to anaphylactic shock (S-016). This language was incorporated into the Cinvanti labeling. Dr. Rajpal's review outlines certain areas of Cinvanti labeling that differ from that of Emend for injection; these were not considered approvability issues.

Major issues addressed during labeling discussions with the Applicant included the inclusion of anaphylaxis language in the Warnings and Precautions section. The Applicant argued that

¹ <https://www.federalregister.gov/documents/2014/02/18/2014-03458/determination-that-ganite-gallium-nitrate-injectable-and-five-other-drug-products-were-not-withdrawn>

these serious reactions were attributable (b) (4) in Emend. (b) (4)
the Applicant proposed that the language be clarified (b) (4)

he Division agreed to the inclusion of adverse reactions that occurred in >1% of subjects treated with Cinvanti in the BA trials (headache and fatigue) without providing data from the Emend arms. The maternal health reviewer from DPMH reviewed the labeling and made recommendations with respect to the Pregnancy and Lactation Labeling Rule (PLLR).

Carton and container labeling was found acceptable by DMEPA and OPQ. Final agreement with the Applicant on labeling was reached on October 19, 2017, and recommendations by the primary and consulting review disciplines, including DPMH, DMEPA, DMPP and OPDP, have been incorporated into the labeling.

12. Decision/Action/Risk Benefit Assessment

• Regulatory Action

I agree with the recommendation of the CDTL, Anil Rajpal, M.D., M.P.H., and the other review disciplines that Cinvanti injectable emulsion be approved for the agreed-upon indications relating to acute and delayed CINV due to HEC and CINV due to MEC.

• Risk Benefit Assessment

The data submitted in this 505(b)(2) NDA do not change the benefit/risk assessment of aprepitant/fosaprepitant in general, and do not raise any additional risks specific to the injectable emulsion formulation. While the BA studies showed somewhat higher exposure for Cinvanti compared to the relevant doses of Emend, there are data showing the safety of plasma levels of aprepitant that are higher than those obtained with the 130 mg Cinvanti dose, and safety of the 100 mg Cinvanti dose is supported by the safety of the higher dose. The benefit/risk analysis remains favorable for the agreed-upon indications.

• Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None are needed beyond labeling.

• Recommendation for other Postmarketing Requirements and Commitments

The Applicant has agreed to a post-marketing requirement to conduct a pediatric study to evaluate pharmacokinetics, safety, and tolerability of a single dose of Cinvanti as part of a 3-day regimen in pediatric patients ages 0-17 years. The Applicant will utilize modeling and simulation to support the single dose (1-day) regimen in pediatric patients ages 0-17 years who are undergoing treatment with single-day emetogenic chemotherapy. The agreed-upon milestones are:

- Final Protocol Submission: 7/2020
- Study/Trial Completion: 11/2026
- Final Report Submission: 5/2027

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

/s/

LISA M SOULE
11/08/2017