

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**209296Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

|                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>From</b>                                        | Anil Rajpal, MD, MPH, Clinical Team Leader<br>Division of Gastroenterology and Inborn Errors Products                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Subject</b>                                     | Cross-Discipline Team Leader Review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>NDA/ BLA #</b>                                  | NDA 209296                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Applicant</b>                                   | Heron Therapeutics, Inc. (Heron)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Date of Submission</b>                          | January 12, 2017                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>PDUFA Goal Date</b>                             | November 12, 2017                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Proprietary Name / Established (USAN) names</b> | aprepitant injectable emulsion / Cinvanti                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Dosage forms / Strength</b>                     | Emulsion for intravenous use available in single-dose glass vial, 130 mg/18 mL (7.2 mg/mL)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Proposed Indication*</b>                        | CINVANTI (b) (4) in combination with other antiemetic agents, is indicated in adults for the prevention of: <ul style="list-style-type: none"> <li>acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin.</li> <li>(b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).</li> </ul> Limitations of Use<br>CINVANTI has not been studied for the treatment of established nausea and vomiting. |
| <b>Recommended Action:</b>                         | Approval                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

\*The original text proposed by the Applicant is shown here.

(b) (4)

Pending agreement with the Applicant on labeling, all disciplines recommend approval of Cinvanti (aprepitant injectable emulsion) in adults for the prevention of: (i) acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin; and (ii) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC). I am in agreement with this recommendation.

This summary review reflects the CDTL considerations of the summary conclusions from all review disciplines. The overall conclusions do not differ from those of the primary clinical reviewer.

This summary review is based on the following:

- Office of Pharmaceutical Quality Reviews 1 and 2 by Hitesh Shroff, 10/10/17
- Pediatric Review (Division of Pediatric and Maternal Health) by Amy Taylor, 10/3/17
- Clinical Pharmacology Review by Xinyuan Zhang, 10/2/17
- Clinical Review by Aisha Peterson Johnson, 10/2/17
- Patient Labeling Review (Office of Prescription Drug Promotion Review by Meeta Patel / Division of Medical Policy Programs Review by Twanda Scales), 9/28/17
- Nonclinical Review by Babatunde Akhinshola, 9/28/17

- Office of Prescription Drug Promotion Review by Meeta Patel, 9/28/17
- Maternal Health Review (Division of Pediatric and Maternal Health) by Catherine Roca, 9/20/17
- Labeling Reviews (Division of Medication Error Prevention and Analysis) by Matthew Barlow, 9/20/17 and 7/26/17
- Office of Study Integrity and Surveillance, Division of New Drug Bioequivalence Evaluation, Bioequivalence Establishment Inspection Report Review by Angel Johnson, 8/21/17 (Spaulding Clinical Research), and 7/14/17 (QPS, LLC)
- Proprietary Name Review (Division of Medication Error Prevention and Analysis) by Matthew Barlow, 2/8/17

This is a 505(b)(2) application referencing Emend for Injection (NDA 22023).

Emend for Injection contains fosaprepitant, a prodrug of aprepitant; accordingly, its antiemetic effects are attributable to aprepitant. The proposed drug Cinvanti is an emulsion of aprepitant for intravenous use. Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK1) receptors. It should be noted that Emend for Injection contains polysorbate 80 (b) (4) whereas Cinvanti does not contain this agent.

The current Emend for Injection (NDA 22023) dosing recommendations are for **only**:

- **a single dose regimen** (single 150 mg IV infusion) [**HEC** and **MEC**]

In the past (see sNDA 22023/11;<sup>2</sup> 8/12/14), Emend for Injection had dosing recommendations for **either**:

- **a single dose regimen** (single 150 mg IV infusion) [**HEC** only]
- **a three-day dosing regimen** (single 115 mg IV infusion followed by 80 mg PO for two additional days) [**HEC** and **MEC**]

The three-day dosing regimen was not discontinued for reasons of safety and efficacy.

The Applicant proposes to rely on the discontinued Emend for Injection label described above. This was confirmed to be acceptable with the Office of Regulatory Policy (in a meeting that occurred with DGIEP on July 18, 2017).

Specifically, the Applicant proposes the following:

- **a single dose regimen** (single 130 mg IV infusion) [**HEC** only]
- **a three-day dosing regimen** (single 100 mg IV infusion followed by 80 mg PO for two additional days) [**MEC** only]

---

<sup>1</sup> OPQ Review

<sup>2</sup> <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022023> (accessed 10/5/17)

Some differences between the proposed Cinvanti label and the referenced Emend label are presented below as background; however, none of these items were identified as approvability issues by the review team.

- A recommendation for a specific aprepitant PO product on Days 2 and 3 is not proposed for the three-day dosing regimen of Cinvanti, but there is a recommendation for Emend capsules on Days 2 and 3 in the corresponding Emend three-day dosing regimen.
- Only an indication in MEC is proposed for the Cinvanti three-day dosing regimen, but there are indications in both HEC and MEC for the corresponding Emend three-day dosing regimen.
- One dosage strength is proposed for Cinvanti (130 mg in a single use vial) but there are two recommended doses (130 mg and 100 mg); thus, it is necessary that the preparation instructions state that only a portion of the vial should be used for preparing the low dose (100 mg). In contrast, Emend had two dosage strengths (150 mg in a single use vial and 115 mg in a single use vial), thus allowing the preparation instructions to state that the entire vial corresponding to the appropriate dose (150 mg or 115 mg) should be used.
- The proposed infusion duration of **Cinvanti** is “**over 30 minutes**” for both the high dose (single dose regimen) and the low dose (first day of three day dosing regimen). In contrast, the infusion duration of **Emend** in the referenced label is “**over 20-30 minutes**” for the high dose (single dose regimen) and “**over 15 minutes**” for the low dose (first day of three day dosing regimen).

Two relative BA studies, Study HTX-019 C2015-104 (“Study 104”) and Study HTX-019-106 (“Study 106”; Part A and Part B), were submitted in the current application.

- Study 104: open-label single dose 2-way crossover study in healthy subjects (n=100):
  - **Cinvanti** 130 mg 30 min IV infusion vs **Emend** 150 mg 30 min IV infusion
- Study 106 Part A: randomized PK study of 5 parallel cohorts (total n=70):
  - **Cinvanti** 130 mg 30 min IV infusion (Cohort 1)
  - **Emend** 150 mg 30 min IV infusion (Cohort 2)
  - **Emend** 150 mg 20 min IV infusion (Cohort 3)
  - **Cinvanti** 100 mg 30 min IV infusion (Cohort 4)
  - **Emend** 115 mg 15 min IV infusion (Cohort 5)
- Study 106 Part B: open-label single dose 2-way crossover; healthy subjects (n=100):
  - **Cinvanti** 130 mg 30 min IV infusion vs **Emend** 150 mg 20 min IV infusion

Pertinent results are summarized below.

**Table 1. Results - Relative BA Studies (Studies 104, 106 Part B, and 106 Part A Cohorts 4 and 5)<sup>3</sup>**

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

In Studies 104 and 106 Part B, the BE criteria for AUC<sub>0-last</sub> and AUC<sub>0-∞</sub> were met (130 mg Cinvanti IV vs. 150 mg Emend IV), but the C<sub>max</sub> was 28%-48% higher for 130 mg Cinvanti IV than for 150 mg EMEND IV (see table above). Thus, the Cinvanti 130 mg dose is expected to be at least as efficacious as the Emend for infusion 150 mg dose.

In order to address potential safety concerns due to the higher C<sub>max</sub>, the Clinical Reviewer conducted a review of safety from the studies submitted (270 healthy subjects), and conducted a review of literature submitted by the Applicant to support the safety of higher plasma levels of aprepitant. The Clinical Reviewer concluded based on these data that 130 mg Cinvanti IV is not expected to be associated with any new safety concerns when compared with 150 mg Emend IV.

In Study 106 Part A Cohorts 4 and 5, AUC<sub>0-last</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub> were 32%, 32%, and 55% higher, respectively for Cinvanti 100 mg IV than for Emend 115 mg IV (see table above). Thus, the Cinvanti 100 mg dose (of the three-day dosing regimen) is expected to be at least as efficacious as the Emend for infusion 115 mg dose (of the three-day dosing regimen).

A nearly dose-proportional increase in exposure was observed from 100 mg to 130 mg Cinvanti IV (see table below). The Clinical Pharmacology Reviewer concluded that the safety of the Cinvanti 100 mg dose is supported by the safety of the Cinvanti 130 mg dose.

**Table 2. C<sub>max</sub> and AUC<sub>0-last</sub> for Cinvanti 100 mg IV and 130 mg IV<sup>4</sup>**

| Dose                                         | Mean C <sub>max</sub> [ng/mL] | Mean AUC <sub>0-last</sub> [h*ng/mL] |
|----------------------------------------------|-------------------------------|--------------------------------------|
| Cinvanti 100 mg IV over 30 mins*             | 4,290                         | 27,826                               |
| Cinvanti 130 mg IV over 30 mins <sup>#</sup> | 5,813                         | 39,499                               |
| Cinvanti 130 mg IV over 30 mins <sup>†</sup> | 6,265                         | 43,729                               |

\*Study 106 Part A; <sup>#</sup>Study 106 Part B; <sup>†</sup>Study 104

The Clinical Pharmacology Reviewer found the submission acceptable provided agreement with the Applicant is reached on labeling.

<sup>3</sup> Source: Tables 2 and 3 (Page 6) of Clinical Pharmacology Review

<sup>4</sup> Source: Table 5 (Page 13) of Clinical Pharmacology Review

(b) (4)

[REDACTED] recommended that the clinical data for Study 104 be further scrutinized without an on-site inspection because Spaulding Clinical Research, LLC., the site of Study 104 (b) (4)

[REDACTED]

[REDACTED]

(b) (4)

The Clinical Pharmacology Reviewer concluded that it is unlikely that the PK study results would have been affected by the findings (b) (4)

[REDACTED]

(b) (4)

[REDACTED]

Based on the above, I believe the observations (if these were to occur in Study 104) would not be significant, and the data generated by Study 104 appear acceptable in support of the evaluation of safety. Each of the categories of observations (from the previously inspected study) is discussed below (as these would apply to Study 104):

- i. The eligibility criteria of Study 104 are aimed at enrolling healthy subjects. Even if some subjects with initial laboratory test results that are outside of acceptable protocol ranges were re-tested with laboratory test results that made them eligible for entry, it seems unlikely that subjects with medical conditions severe enough to interfere with the identification of adverse events would be enrolled because: (1) laboratory abnormalities truly indicating a medically significant condition would not be expected to resolve after a short period of time; and (2) there are numerous other eligibility criteria aimed at enrollment of healthy subjects (such as age 18-55 years of age, body mass index of 18 to 35 kg/m<sup>2</sup>, “good health” as determined by a physician via medical history and physical examination, exclusion of patients with a history of various medical conditions, and exclusion of patients based on ECG results).
- ii. The protocol violation of failure to report a clinically significant (b) (4) appears to be only a technical violation as data reconciliation several weeks later had identified this oversight. If a similar oversight were to occur in Study 104, it appears that it would also be identified during data reconciliation. Also, the safety review of Study 104 does not suggest under-reporting of AE's; for example, total AE's for Cinvanti were higher in Study 104 than in Study 106 Part B (21% vs. 13%).<sup>6</sup>

The safety profile was generally comparable to the known safety profile described in the product label for Emend for Infusion.

The most common adverse reactions in Study 104 (Cinvanti vs. Emend) were headache (5% vs. 8%), vessel puncture site pain (5% vs. 0), and fatigue (2% vs. 0); the most common adverse reactions in Study 106 Part B (Cinvanti vs. Emend) were lethargy (2% vs. 0) and fatigue (2% vs. 3%).<sup>7</sup>

Overall adverse reactions leading to discontinuation in Study 104 were 0 (Cinvanti) vs 2% (Emend) (2 subjects: “dyspnea, hot flush, nausea” and “abdominal pain, dizziness, dyspnea”). Overall adverse reactions leading to discontinuation in Study 106 Part B were

<sup>5</sup><https://www.fda.gov/downloads/aboutfda/transparency/publicdisclosure/glossaryofacronymsandabbreviations/ucm212061.pdf> (accessed 10/10/17)

<sup>6</sup> Source: Clinical Review Table 16 (page 43)

<sup>7</sup> Source: Clinical Review Table 16 (page 43)

1% (Cinvanti) (1 subject: “dyspnea and hyperhidrosis”) vs. 2% (Emend) (2 subjects: “peripheral nerve injury” and “dyspnea and tachycardia”).<sup>8</sup>

No deaths or serious AE’s were reported in Studies 104 or 106.<sup>9</sup>

The Cinvanti safety evaluation did not identify any new or unexpected safety signals or serious reactions attributable to treatment.

A focus of the review was the assessment of hypersensitivity reactions (a safety concern with Emend for Infusion). The Applicant implicated (b) (4) as the cause of hypersensitivity reactions, and asserted that Cinvanti has a safety advantage (b) (4).

The Clinical Reviewer identified 8 cases of hypersensitivity reactions across the two studies; all the cases had dyspnea in temporal association with the infusion, and most of the cases had one or more associated symptoms (including tachycardia, nausea, flushing, hyperhidrosis, dizziness, and abdominal pain). In Study 104, these reactions were 1% (Cinvanti) (1 subject: “dyspnea, respiratory tract congestion, and chest pain”) vs. 3% (Emend) (3 subjects: “dyspnea, hot flush, nausea”, “dyspnea, abdominal pain, dizziness”, and “dyspnea”).<sup>11</sup> In study 106 Part B, these reactions were 1% (Cinvanti) (1 subject: “dyspnea, hyperhidrosis”) vs. 3% (Emend) (3 subjects: “dyspnea, tachycardia”, “dyspnea, abdominal pain, paresthesia, visual impairment”, and “dyspnea, cough”).<sup>12</sup>

The OPQ Reviews concluded/recommended the following:

- The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The claim for the Categorical Exclusion for the Environmental Assessment is granted. The Office of Process and Facilities (OPF) has made a final overall “Approval” recommendation for the facilities involved in this application as of this review.
- The NDA is recommended for approval from a quality perspective.

No nonclinical approvability issue was identified. Nonclinical sections of the labeling were adopted from the Emend label; however, changes to the Pregnancy (8.1), Lactation (8.2), and Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1) subsections were recommended to comply with the PLLR (see specific language in the Nonclinical Review).

The Maternal Health Review recommended revisions to the Pregnancy (8.1), Lactation (8.2), and Females and Males of Reproductive Potential (8.3) subsections of Cinvanti

<sup>8</sup> Source: ISS Table 5.3.5.3.2-2 (page 5)

<sup>9</sup> Source: Clinical Review Sections 7.3.1 and 7.3.2 (Page 32)

<sup>10</sup> Clinical Review page 38

<sup>11</sup> Clinical Review Table 11 (page 37)

<sup>12</sup> Clinical Review Table 11 (page 37)

labeling to be consistent with the PLLR (see specific language in the Maternal Health Review).

DMEPA concluded that the proprietary name of “Cinvanti” was acceptable (see the Proprietary Name Review). DMEPA recommended a number of changes to the carton and container labels prior to approval of the current NDA (see DMEPA Labeling Reviews).

Based on the totality of the data submitted, the benefit-risk profile for Cinvanti is favorable. Cinvanti (130 mg dose) is expected to be at least as efficacious as Emend for infusion (150 mg dose) as the BE criteria for  $AUC_{0-last}$  and  $AUC_{0-\infty}$  were met and the  $C_{max}$  was 28%-48% higher (Cinvanti 130 mg IV vs. Emend 150 mg IV). The higher  $C_{max}$  (Cinvanti 130 mg IV vs. Emend 150 mg IV) is not expected to represent greater risk of this product as a review of the studies submitted identified no new safety concerns and a review of the literature supported the safety of higher plasma levels of aprepitant. Cinvanti (100 mg dose on Day 1 of the three-day dosing regimen) is expected to be at least as efficacious as Emend for infusion (115 mg dose on Day 1 of the three-day dosing regimen) as  $AUC_{0-last}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  were 32%, 32%, and 55% higher, respectively (Cinvanti 100 mg IV vs. Emend 115 mg IV); safety of the Cinvanti 100 mg dose is supported by the safety of the Cinvanti 130 mg dose. (b) (4)

(b) (4) Cinvanti does not confer a safety advantage over the reference drug Emend for Infusion (b) (4)

(b) (4) a review of the studies submitted did not definitively demonstrate such a safety advantage. Dosing errors are a possible risk of this product as it has only a single dosage strength (130 mg in a single use vial) but two recommended doses (130 mg and 100 mg); however, this risk is mitigated through the professional labeling (see preparation instructions table in Section 2.2 of the label).

A REMS is not necessary for Cinvanti to ensure the benefits outweigh the risks.

A pediatric study is recommended as a postmarketing requirement (PMR) (see Clinical and Pediatric Reviews). The PREA PMR language below is recommended. It should be noted that the timeline is delayed in order to provide time for the expected Emend for Injection pediatric studies to be submitted (see Pediatric Review).

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

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

Final Protocol Submission: 07/2020  
Study/Trial Completion: 11/2026  
Final Report Submission: 05/2027

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

/s/  
-----

ANIL K RAJPAL  
10/12/2017