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APPLICATION NUMBER:

209296Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Review

NDA Number	209296
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Submission Date	January 12, 2017
Submission Type	Original Submission / New Dosage Form, 505(b)(2)
Brand Name	Cinvanti TM
Generic Name	Aprepitant (HTX-019)
Dosage Form and Strength	Injection, Emulsion
Route of Administration	Intravenous (IV)
Proposed Indication	CINVANTI (b) (4) is indicated in adults, in combination with other antiemetic agents, 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. • (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).
Applicant	Heron Therapeutics, Inc. (Heron)
Associated IND	125926
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1. EXECUTIVE SUMMARY

Heron Therapeutics, Inc. (the applicant) is seeking approval of aprepitant (b) (4) (also known as HTX-019, proposed brand name, Cinvanti™) for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV).

EMEND for injection (the listed drug) is approved, in combination with other antiemetic agents, 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, delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) at 150 mg single dose.

The applicant proposed to rely on the Agency's previous finding of efficacy and safety for EMEND for injection (fosaprepitant dimeglumine, NDA 022023). To establish a bridge between the proposed product at 130 mg and EMEND for injection at 150 mg, the applicant conducted two relative bioavailability (BA) studies (HTX-019 C2015-104, and HTX-019-106) to compare the systemic exposure to aprepitant, the active moiety of fosaprepitant, after administration of 130 mg HTX-019 infused over 30 minutes and 150 mg EMEND for injection infused over 20 minutes or 30 minutes. The 130 mg aprepitant dose for the proposed HTX-019 was equivalent to 150 mg fosaprepitant in aprepitant molar mass. In the relative BA studies, 130 mg HTX-019 showed comparable systemic exposure (AUC) and 28% - 48% higher Cmax¹ to aprepitant than 150 mg EMEND for injection. As such, the efficacy of the proposed product is supported by higher Cmax and comparable AUC. The safety of the higher Cmax was supported by the two relative BA studies in healthy subjects (See the clinical review for more details).

In addition, the applicant proposed 100 mg HTX-019 as a substitute of day 1 oral dose in a 3-day oral aprepitant regimen. EMEND (oral aprepitant) 3-day oral regimen was approved in 2003 with 125 mg on day 1 and 80 mg on days 2 to 3. EMEND for injection at 115 mg infused over 15 minutes was approved to substitute day 1 oral dose in 2008. In 2014, the three day oral aprepitant regimen was withdrawn from the market not for reasons of safety or effectiveness, and subsequently 115 mg EMEND for injection was removed from the current EMEND for injection label². Because the 100 mg HTX-019 was to be prepared from the same vial for the proposed 130 mg dose, a biowaiver request was not considered relevant to link the different dosage strengths³. In support of the 100 mg HTX-019, the applicant submitted PK data for 100 mg HTX-019 and 115 mg fosaprepitant (a parallel relative BA study with 12 subjects in each arm as Part A of Study HTX-019-106). In a relative BA study with a parallel design, the systemic exposure, AUC and Cmax to aprepitant was 32% and 55% higher for 100 mg HTX-019 infused over 30 minutes than 115 mg fosaprepitant infused over 15 minutes. Of note, due to the

¹ The 28% higher Cmax was obtained based on study 106 (part B) where EMEND for injection 150 mg was infused over 20 minutes. The 48% higher Cmax was obtained based on study 104 where EMEND for injection 150 mg was infused over 30 minutes. Per EMEND for injection label, EMEND for injection is administered via infusion over 20 to 30 minutes.

² Federal Register Notice on 02/18/2014 indicated that EMEND (fosaprepitant dimeglumine) Powder; Intravenous, EQ 115 mg Base/Vial was not withdrawn from sale for reasons of safety or effectiveness.

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

³ [Application 209296 - 1.6.3 Correspondence Regarding Meetings](#)

discontinuation of 115 mg ENEND for injection, the applicant prepared 115 mg fosaprepitant from 150 mg EMEND for injection vial in the relative BA study. The bioavailability of 115 mg fosaprepitant after intravenous infusion is self-evident and the preparation of 115 mg fosaprepitant from 150 mg EMEND for injection was acceptable for the purpose of a relative BA study. In consultation with ORP (Office of Regulatory Policy) and OCC (Office of the Chief Counsel), the ‘compounding’ is not an issue for bridging from a regulatory perspective if the bridging is scientifically justifiable. The safety of the higher systemic exposure for 100 mg HTX-019 is supported by the higher dose of 130 mg.

No other clinical trials were conducted in support of safety and efficacy of HTX-019.

1.1 Recommendations

The Office of Clinical Pharmacology has found the submission acceptable from a clinical pharmacology standpoint provided that a mutual agreement on labeling is reached between the FDA and the applicant.

In response to an inspection request, the Office of Study Integrity and Surveillance (OSIS) recommended that “the clinical data for Study HTX-019 C2015-104 be further scrutinized without an on-site inspection”⁴ based on the previous inspection findings including protocol violations and failing to report a clinically significant adverse event for the same clinical site but a different program. Refer to the memorandum by Office of Study Integrity and Surveillance dated 8/16/17. It is unlikely that the PK study results would have been affected by such findings.

1.2 Post-Marketing Requirements and Commitments

There is no Post-Marketing Requirement (PMR) or Post-Marketing Commitment (PMC).

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK1) receptors⁵. Pharmacokinetic parameters following intravenous infusion over 30 minutes of a single 100 mg or 130 mg dose of HTX-019 to healthy subjects are summarized in [Table 1](#).

Aprepitant is eliminated primarily by metabolism with major contribution from CYP3A4, and minor from CYP1A2 and CYP2C19. Aprepitant is not renally excreted. The apparent terminal half-life ranged approximately 9 to 13 hours⁶. In an in vitro protein binding study conducted by the applicant, aprepitant from HTX-019 is highly bound to plasma protein (plasma unbound fraction, fup ~ 0.3%).

⁴ Bioequivalence Establishment Inspection Report Review dated 8/21/2017:
<http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af80455c44>

⁵ NDA 022023 EMEND for injection label approved on 05/31/2017:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022023s015lbl.pdf

⁶ NDA 022023 EMEND for injection label approved on 05/31/2017:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022023s015lbl.pdf

Table 1: Summary of key plasma PK parameters of aprepitant after IV administration of HTX-019 and EMEND for injection (Study 104 and Study 106)⁷

Study	Treatment	Infusion Duration (min)	N	Mean (%CV)		
				AUC _{0-t} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	C _{max} (ng/mL)
104	HTX-019 130 mg	30	97	43729 (32.7)	45460 (36.8)	6265 (26.2)
	EMEND for injection 150 mg	30	97	44130 (32.0)	46163 (36.6)	4303 (32.3)
106, Part A	HTX-019 100 mg	30	12	27826 (23.5)	28978 (27.5)	4290 (28.0)
	HTX-019 130 mg	30	21	39499 (52.1)	39057 (30.4)	5813 (26.3)
	EMEND for injection 115 mg	15	12	21141 (31.3)	22300 (40.8)	2704 (19.7)
	EMEND for injection 150 mg	20	12	44710 (14.1)	48026 (19.3)	4949 (14.1)
	EMEND for injection 150 mg	30	12	45657 (35.4)	49353 (42.0)	5108 (33.5)
106, Part B	HTX-019 130 mg	30	96	43937 (28.8)	46311 (32.5)	6056 (25.1)
	EMEND for injection 150 mg	20	97	45811 (35.1)	48287 (41.5)	4846 (32.3)

Source: Module 2.7.2 Summary of Clinical Pharmacology Studies

Relative bioavailability between HTX-019 and EMEND for injection

The main clinical pharmacology review question is whether adequate bridge has been established between HTX-019 and EMEND for injection to support the reliance of the efficacy and safety for both the high (130 mg) and low (100 mg) strengths. The 130 mg aprepitant dose for the proposed HTX-019 was equivalent to 150 mg fosaprepitant in aprepitant molar mass. In the relative BA studies with crossover design, 130 mg HTX-019 showed comparable systemic exposure (AUC) but 28% - 48% higher C_{max} ([Table 2](#)) to aprepitant than 150 mg EMEND for injection. The lower C_{max} observed in EMEND for injection was due to the conversion from fosaprepitant to aprepitant. As such, the efficacy of the proposed product is supported by higher C_{max} and comparable AUC. The safety of the higher C_{max} was supported by the two relative BA studies in healthy subjects (See the clinical review for more details).

In a parallel relative BA study, the systemic exposure (AUC) and C_{max} to aprepitant was 32% and 55% higher, respectively, for 100 mg HTX-019 infused over 30 minutes compared to 115 mg fosaprepitant infused over 15 minutes ([Table 3](#)). Combined with the safety supported by the higher dose (130 mg), the efficacy and safety of the proposed 100 mg HTX-019 is bridged to those of 115 mg EMEND for injection.

⁷ [EDR Module 2.7.2 Summary of Clinical Pharmacology Studies](#)

Table 2: Summary of statistical analysis for aprepitant comparing single dose administration of 130 mg HTX-019 and 150 mg EMEND for injection⁸

Study	PK parameters	Point Estimate (T/R)×100	Lower Bound of 90% CI	Upper Bound of 90% CI
Study 104 ^a (N = 97)	AUC _{0-t} (ng*hr/mL)	99.05	96.75	101.41
	AUC _{0-inf} (ng*hr/mL)	98.29	95.59	101.06
	C _{12hr} (ng/mL)	97.14	94.28	100.09
	C _{max} (ng/mL) ^c	147.86	142.06	153.89
Study 106, part B ^b (N = 96)	AUC _{0-t} (ng*hr/mL)	96.73	94.02	99.53
	AUC _{0-inf} (ng*hr/mL)	96.09	93.35	98.92
	C _{12hr} (ng/mL)	98.95	96.08	101.90
	C _{max} (ng/mL) ^c	127.68	122.22	133.39

Source: Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods*

* The reviewer repeated the analysis and reached the same conclusions although the results were numerically different from the applicant's analysis.

^a Study 104: Test = HTX-019 130 mg 30-minute IV infusion; Reference = EMEND for injection 150 mg 30-minute IV infusion

^b Study 106, part B: Test = HTX-019 130 mg 30-minute IV infusion; Reference = EMEND for injection 150 mg 20-minute IV infusion

^c C_{max} analysis was conducted by the reviewer.

Table 3: Summary of analysis for aprepitant after administration of 100 mg HTX-019 and 115 mg fosaprepitant*

Study	PK parameters	Point Estimate (T/R) *100	Lower Bound of 90% CI	Upper Bound of 90% CI
106, Part A, cohort 4 and 5 (N=12)	AUC _{0-t} (ng*hr/mL)	132.00	111.06	156.90
	AUC _{0-inf} (ng*hr/mL)	132.00	108.26	160.93
	C _{max} (ng/mL) ^c	155.32	129.92	185.68

* This is a pilot parallel relative BA study with small number of subjects. The analysis was conducted by the reviewer. The applicant conducted point estimate comparison in the Response to Information Request submitted on May 15, 2017⁹ and similar results were obtained (Also see [Section 4.3.3](#))

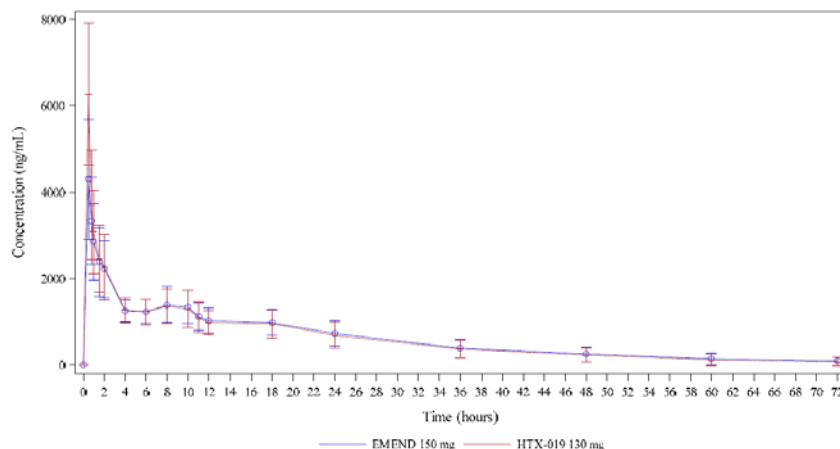
Study 106, Part A: Test = Cohort 4 HTX-019 100 mg 30-minute IV infusion; Reference = Cohort 5 fosaprepitant 115 mg 15-minute IV infusion

The measured plasma concentrations represent total concentrations of aprepitant and do not differentiate aprepitant in oil globules and aprepitant released from oil globules. Nevertheless, the comparable PK profiles of aprepitant after intravenous infusion of HTX-019 (aprepitant injectable emulsion) to those after intravenous infusion of EMEND for injection (fosaprepitant dimeglumine powder for intravenous infusion) provided supportive evidence that the emulsion formulation did not significantly affect the PK of aprepitant and indirectly supported the release and availability of aprepitant from the oil globules into plasma following administration of the proposed emulsion to a comparable degree as the listed drug product. The high degree (greater than 99%) of protein binding and the similar unbound fraction after incubating aprepitant in emulsion and aprepitant, the API in plasma further supported that aprepitant was released from the oil globules.

⁸ [EDR Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods](#)

⁹ Response to Information Request submitted on May 15, 2017: [Application 209296 - Sequence 0014 - 0014 \(14\) 05/15/2017 ORIG-1 /Clinical/Response To Information Request](#)

Figure 1: Mean $\pm$ SD Plasma Aprepitant Concentration (ng/mL)-Time Profile, Linear Scale (PK Population)



Source: HTX-019 C2015-104 study report Figure 11-2

Safety of higher C_{max}

Per the label of EMEND for injection, in a randomized, double-blind, positive-controlled, thorough QTc study, a single 200-mg dose of fosaprepitant (approximately 1.3 times the recommended dose) had no effect on the QTc interval.

Based on cross-study comparisons, the mean C_{max} after a single 200 mg dose of fosaprepitant were comparable to that achieved with HTX-019 130 mg dose based on mean C_{max} values from study 104, and study 106, respectively (mean ratio: 1.01 and 1.08, respectively). The mean C_{max} after a single 200 mg dose of fosaprepitant were 1.47-fold higher than that achieved with HTX-019 100 mg dose ([Table 5](#)). As such, the proposed labeling addresses the potential effects on the QT interval at the proposed doses. Refer to the review of safety profile of HTX-019 to the clinical review.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed infusion time for HTX-019 is over 30 minutes while the approved infusion duration for EMEND for injection is over 20-30 minutes (150 mg) or over 15 minutes (115 mg). Longer infusion time generally decreases C_{max} while does not have much impact on exposure, and therefore, has an impact on test-to-reference geometric mean ratio of C_{max}. The C_{max} aprepitant after infusion of 130 mg HTX-109 over 30 minutes was 28% higher and 48% higher than those after EMEND for injection was infused over 20 minutes or over 30 minutes, respectively.

The proposed dose and the infusion duration of 30 minutes is supported by the comparable AUC to 150 mg EMEND for injection and safety information from the relative BA studies with about 200 healthy subjects.

The applicant proposes the infusion duration of 30 minutes for 100 mg HTX-109 while the approved infusion duration for 115 mg EMEND for injection was 15 minutes. In the relative bioavailability study, the Cmax of aprepitant after 100 mg HTX-109 was higher than that of 115 mg fosaprepitant infused over 15 minutes despite a longer infusion duration for 100 mg HTX-109. As such, the longer infusion duration is not expected to adversely affect the efficacy and supported for the efficacy.

Agent	Day 1	Day 2	Day 3	Day 4
Single Dose Regimen for Prevention of Nausea and Vomiting Associated with HEC: CINVANTI 130 mg				
CINVANTI	130 mg IV over 30 min approximately 30 min prior to chemotherapy	None	None	None
Oral Aprepitant	None	None	None	None
Dexamethasone	12 mg orally	8 mg orally	8 mg orally twice daily	8 mg orally twice daily
5-HT3 antagonist	See selected 5-HT3 antagonist PI for recommended dosage	None	None	None
3-Day Dose Regimen for Prevention of Nausea and Vomiting Associated with MEC: CINVANTI 100 mg				
CINVANTI injectable emulsion	100 mg IV over 30 min approximately 30 min prior to chemotherapy	None	None	
Oral Aprepitant	None	80 mg orally	80 mg orally	
Dexamethasone	12 mg orally	None	None	
5-HT3 antagonist	See selected 5-HT3 antagonist PI for recommended dosage	None	None	

2.2.2 Therapeutic individualization

Not applicable.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The labeling is largely relied on the label of EMEND for injection. PK information for the proposed product at 130 mg is based on Study 106. The labeling of PK information for 100 mg dose was not proposed in the initial label. We have following major recommendations on the label.

1. Include the PK data for aprepitant after single dose administration of 100 mg HTX-109 in the label.
2. Revise the protein binding data (greater than (b) (4) 99%) based on the applicant's data rather than the data from the current labeling of EMEND for injection.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

HTX-019 (aprepitant) injectable is developed as an emulsion formulation for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV). Aprepitant was originally approved in 2003 (EMEND, NDA 021549) as oral capsules (40mg, 80mg, and 125mg). Aprepitant is practically insoluble in water and therefore developing injectable solution is challenging. In 2008, a soluble prodrug of aprepitant, fosaprepitant dimeglumine, was approved as powder for injection (EMEND for injection, 115 mg/vial, NDA 022023). Fosaprepitant is converted to aprepitant upon IV administration. A higher strength (150 mg/vial) of fosaprepitant was approved in 2010. Later on, the lower strength (115 mg/vial) was withdrawn not for safety or efficacy reasons. In 2016, aprepitant oral suspension was approved under brand name EMEND (NDA 207865, 125 mg/kit). The applicant is seeking approval for both the high dose (130 mg aprepitant corresponding to 150 mg fosaprepitant) and low dose (100 mg aprepitant corresponding to 115 mg fosaprepitant) regimens by referencing EMEND for injection.

HTX-019 is a sterile oil-in-water emulsion for IV injection contained in a single-dose clear glass vial. Each vial of HTX-019 contains 130 mg aprepitant in 18 ml total volume. The dose of 100 mg aprepitant is achieved by withdrawing 14 mL from the same single-dose vial¹⁰. The drug product is an oil-in-water emulsion containing, on a weight-to-weight basis, (b) (4) aprepitant, (b) (4) soybean oil, (b) (4) ethanol, (b) (4) sucrose, (b) (4) water for injection¹¹. The emulsion has a target mean particle size of (b) (4) at release.

In the current application, two relative BA studies (Study 104, and Study 106) were submitted to support the reliance of safety and efficacy of HTX-019 (test) infused over 30 minutes on EMEND for injection (reference). EMEND for injection 150 mg was infused over 30 minutes in study 104 and over 20 minutes in study 106.

It should be noted that for both HTX-019 and EMEND for injection, the lower strengths were prepared from higher strengths in both studies, while the original lower strength of EMEND for injection was available in a single vial. In consultation with ORP (Office of Regulatory Policy) and OCC (Office of the Chief Counsel), the ‘compounding’ is not an issue for bridging from a regulatory perspective if the bridging is scientifically justifiable.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Pharmacokinetic properties after IV administration of HTX-019 are summarized in [Table 1](#). Pharmacological and general PK properties of aprepitant can be found in approved label for EMEND^{12,13,14}.

¹⁰ [EDR Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods](#)

¹¹ [EDR Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods](#)

¹² [EMEND \(aprepitant capsules, NDA 021549\) label approved in 2017](#)

¹³ [EMEND \(fosaprepitant\) for injection \(NDA 022023\) label approved in 2017](#)

¹⁴ [EMEND \(aprepitant\) for oral suspension \(NDA 207865\) label approved in 2015](#)

High strength (130 mg HTX-019 vs. 150 mg EMEND for injection)

Two relative BA studies showed that AUC_{0-72h} and AUC_{0-inf} of aprepitant met 80%-125% BE criteria comparing 130 mg HTX-019 infused over 30 minutes and 150 mg EMEND for injection infused over 30 minutes or 20 minutes. About 28%-48% higher C_{max} of aprepitant was observed for HTX-019 compared to EMEND for injection. BE results are summarized in [Table 2](#).

Nevertheless, equivalence was demonstrated for aprepitant concentrations at each time point after 45 minutes of administration based on 90% confidence intervals (CIs) within (80%, 125%) (See [Section 4.3.2](#)). Considering that higher exposure and C_{max} generally provide better effect, the efficacy of high dose (130 mg HTX-019) is established.

Low strength (100 mg HTX-019 vs. 115 mg EMEND for injection)

The Part A of study 106 was conducted as a pilot study with the parallel study design and the limited number of subjects (N=12) and supported the proposed infusion duration of 30 minutes for 100 mg, which differed from the infusion duration for 115 mg EMEND for the efficacy. A parallel study comparing 100 mg HTX-019 infusion over 30 minutes and 115 mg fosaprepitant infusion over 15 minutes showed 32% and 55% higher in AUC and C_{max} , respectively. A dose-proportional increase in aprepitant AUC was observed with a dose increase from 100 mg to 130 mg HTX-019. A greater than dose-proportional increase in aprepitant exposure was previously noted. According to the clinical pharmacology review for EMEND for injection¹⁵ ‘a single-dose PK study (P012L1) of fosaprepitant demonstrated that a 30% increase in dose (from 115 mg to 150 mg) corresponded to an increase in $AUC_{0-\infty}$ and C_{max} of approximately 50% and 47%, respectively, following a 15-minute infusion. This may in part explain the higher systemic exposure to aprepitant after 100 mg HTX-019 than after 115 mg EMEND. PK comparison is summarized in [Table 3](#).

The potential consequences of observed higher C_{max} and resolution are summarized in [Table 4](#). In summary, the results of relative BA studies support the efficacy of HTX-019 130 mg and 100 mg.

Table 4: Summary of issues and recommendation caused by higher C_{max} of the test product

Issues	Recommendation
Efficacy	In general, higher C_{max} and AUC lead to better efficacy if not equivalent. Therefore, HTX-019 has established efficacy via the bridging studies.
Safety concern	Refer to the Clinical Review for safety assessment.
DDI potential via CYP3A4	The increased C_{max} does not lead to labeling change regarding drug-drug interaction potential (see Section 3.3.4 for detailed analysis).
QT prolongation	The increased C_{max} is covered by a previously conducted QT prolongation study (see Section 3.3.5 for detailed analysis). Therefore, there is no additional QT prolongation study recommended.

¹⁵ NDA 022023 clinical pharmacology review dated 07/22/2010:
<http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af801e5a94>

Effect of intrinsic factors on PK

According to the label of EMEND for injection, the PK differences caused by age (geriatric population), sex, and ethnicity are not considered clinically meaningful. The PK differences in severe renal impairment and end-stage renal disease (ESRD) requiring hemodialysis patients are not considered clinically meaningful. The differences in mild (Child-Pugh score 5-6) and moderate (Child-Pugh score 7-9) hepatic impairment are not considered clinically meaningful. The PK change within body mass index (BMI) range of 18 kg/m² to 36 kg/m² is not considered clinically meaningful.

Effect of extrinsic factors on PK

Aprepitant is a substrate, inhibitor, and inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9 but unlikely to interact with P-gp substrates. There is no new drug-drug interaction (DDI) study submitted in this application. The DDI potential of HTX-019 is similar to that of EMEND for injection (see [Section 3.3.4](#) and [Section 4.2](#) for detailed analysis).

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

Yes. The applicant relies on the FDA's findings of effectiveness for the previously approved product, EMEND for injection. The bridging data are from two relative BA studies: Study 104 and Study 106. In the relative BA studies, 130 mg HTX-019 infused over 30 minutes showed comparable systemic exposure (AUC) and 28% - 48% higher C_{max} to aprepitant than 150 mg EMEND for injection infused over 20-30 minutes. In a relative BA study with a parallel design, AUC and C_{max} to aprepitant was 32% and 55% higher for 100 mg HTX-019 infused over 30 minutes than 115 mg fosaprepitant infused over 15 minutes (See [Section 3.2](#)). Therefore, the submitted data support the evidence of effectiveness.

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimens are the same as approved for EMEND for injection. The proposed infusion time was different from that of EMEND for injection.

- 130 mg HTX-019 over 30 minutes vs. 150 mg EMEND for injection over 20-30 minutes
- 100 mg HTX-019 over 30 minutes vs. 115 mg EMEND for injection over 15 minutes

The proposed general dosing regimens for HTX-019 are appropriate as the reliance on the previous finding of safety and efficacy for EMEND for injection was supported by relative BA studies.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Not applicable.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

The proposed labeling for the drug-drug interaction is appropriate for HTX-019. Food-drug interaction is not applicable as proposed product, HTX-019, is an injectable emulsion.

Drug – drug interaction (DDI)

Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. The focus of this review is to assess whether the observed increase in aprepitant C_{max} after administration of HTX-019 emulsion may alter the effect of aprepitant on the PK of other drugs.

The about 50% increase in aprepitant C_{max} after administration of HTX-019 compared to EMEND for injection is not expected to change the currently recommended dosage reduction for CYP3A4 substrates, dexamethasone and methylprednisolone because higher C_{max} of aprepitant is a transient effect. The AUC to aprepitant was comparable with superimposable concentration-time profile from 15 minutes after completion of infusion. Therefore, the proposed dose reduction by approximately 50% for dexamethasone based on the about 2-fold increase in dexamethasone AUC by 150 mg fosaprepitant is applicable to 130 mg HTX-019.

3.3.5 Is there a QT prolongation concern?

Per the label of EMEND for injection, a single 200-mg dose of fosaprepitant had no effect on the QT_c interval based on a thorough QT_c study. The original QT prolongation study (study No. P016L1) for EMEND for injection was a three-arm study: 200 mg EMEND IV over 15 minutes, a single oral dose of 400-mg moxifloxacin (positive control), and placebo. There was no QT signal for EMEND for injection 200 mg infused over 15 minutes.¹⁶

Based on the cross study comparison of mean PK parameters, the observed mean C_{max} after administration of the proposed high dose (130 mg) of HTX-019 is covered by the systemic exposure studied in the previous tQT study. The mean C_{max} for aprepitant after 150 mg fosaprepitant administration tended to be higher in the trial in this submission than in the EMEND label but was in similar range to the C_{max} in the label.

Doses and mean PK parameters comparison (cross study comparison) are shown in [Table 5](#). The mean values of C_{max} and AUC were obtained from the study report¹⁷. In the label, the applicant proposed “Maximum aprepitant concentrations after a single 200 mg dose of fosaprepitant were a 1.04- and 1.5-fold higher than that achieved with CINVANTI 130 mg and 100 mg dose, respectively”. In module 2.7.4 Summary of Clinical Safety (page 23), the applicant cited “The maximum aprepitant concentration after fosaprepitant 200 mg administration was 6300 ng/mL”. Although there is a numeric difference in the mean C_{max} values, the reported 6300 ng/mL was within the 90% CI plasma C_{max} of aprepitant following a 200-mg fosaprepitant administered over 15 minutes (5510, 6620) ng/mL¹⁷. Using the mean value of 6300 ng/mL, the C_{max} of

¹⁶ EMEND for injection (NDA 22023) Clinical Pharmacology Review dated 07/22/2010:
<http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af801e5a94>

¹⁷ NDA022023 [Application 022023 - 5.3.4.1 \[\[Study ID\]\] - \[\[Study Title\]\] - p016l1 - Reference P016L1 - MRL Clinical Study Report: A Double-Blind, Double-Dummy, Randomized, Placebo-Controlled, 3-Period, Single-Dose, Crossover Study to Assess the Effect of MK-0517 on QTc Interval in Healthy Subjects \(Protocol 016\)](#)

aprepitant after a single 200 mg dose of fosaprepitant were about 1.01-1.08, and 1.5-fold of that achieved with HTX-019 130 mg and 100 mg dose, respectively ([Table 5](#)). Therefore, the proposed labeling language is appropriate.

Table 5: Summary of PK parameters from various studies

Dosing Regimen	study #	Dose (EQ aprepitant, mg)	Mean Cmax (ng/mL)	Mean AUCt (h*ng/mL)	Dose ratio	Cmax ratio	AUCt ratio	Cmax ratio based on 6300 ng/mL
200 mg EMEND IV over 15 min	P016L1	174	6070	59700	1.00	1.00	1.00	1.00
150mg EMEND IV over 20 min, observed Cp	EMEND label ¹⁸	130	4.2 (± 1.2) µg/mL	37.4(±14.8) µg*hr/mL	0.86	0.69	0.63	0.67
130 mg HTX-019 over 30 min, observed Cp	104	130	6265	43729	0.75	1.03	0.73	0.99
130 mg HTX-019 over 30 min, observed Cp	106	130	5813	39499	0.75	0.96	0.66	0.92
100 mg HTX-019 over 30 min, observed Cp	106	100	4290	27826	0.57	0.71	0.47	0.68
150mg EMEND IV over 20 min, observed Cp	106	130	4949	44710	0.75	0.82	0.75	0.79
150mg EMEND IV over 30 min, observed Cp	104	130	4303	44130	0.75	0.71	0.74	0.68
150mg EMEND IV over 30 min, observed Cp	106	130	5108	45657	0.75	0.84	0.76	0.81

¹⁸ EMEND for injection (NDA 22023) label approved on 5/31/2017:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022023s015lbl.pdf

4. APPENDICES

4.1 Bioanalytical Method Report

The applicant submitted the bioanalytical method validation reports ((b) (4) 431-1503 and Amendment 1)¹⁹ and the bioanalytical study reports for study 104²⁰ and study 106²¹. Total aprepitant in human plasma was quantified by the adequately validated bioanalytical assay method using an LC-MS/MS method. The summary of assay validation is shown in [Table 6](#).

Table 6: Summary of bioanalytical validation

Report Title	Validation of a Method for the Determination of Fosaprepitant and Aprepitant in Human Plasma by LC-MS/MS
Study Number	(b) (4) 431-1503
Analyte Name	Aprepitant
Internal Standard (IS)	Aprepitant-d ₄
Analytical Method Type	LC-MS/MS
Extraction Method	Protein Precipitation
Sample Volume	100 µL
QC Concentrations	10, 30, 300, 2000, and 4000 ng/mL
Standard Curve Concentrations	10, 20, 50, 150, 500, 1500, 4500, and 5000 ng/mL
Lower Limit Of Quantitation	10 ng/mL
Upper Limit Of Quantitation	5000 ng/mL
Mean Recovery of Analyte (%)	105.2
Mean Recovery of Internal Standard (%)	NA ^a
LLOQ QC Intraday Precision Range (%CV)	3.9 to 5.6
LLOQ QC Intraday Accuracy Range (%RE)	-18.9 to 1.0
Analytical QC Intraday Precision Range (%CV)	0.9 to 2.7
Analytical QC Intraday Accuracy Range (%RE)	-10.3 to -0.3
LLOQ QC Interday Precision (%CV)	10.7
LLOQ QC Interday Accuracy (%RE)	-6.6
Analytical QC Interday Precision Range (%CV)	1.8 to 5.3
Analytical QC Interday Accuracy Range (%RE)	-5.3 to -3.5
Stock Solution Stability in Methanol	69 Days -20°C ^b 6 Hours at Ambient Temperature ^b
Processed Sample Stability	193 Hours at 4°C
Benchtop Stability in Plasma	6 Hours at Ambient Temperature
Freeze/Thaw Stability in Plasma	5 Cycles at -20°C and -70°C
Benchtop Stability in Whole Blood	2 Hours at Ambient Temperature
Long-term Storage Stability in Plasma	85 Days at -20°C and -70°C
Dilution Integrity	10000 ng/mL diluted 20-fold
Selectivity	≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS
2% Hemolyzed Plasma Test	No impact on assay performance
Lipemic Plasma Test	No impact on assay performance

^a Not applicable since a stable isotope labeled internal standard was used. The results are expected to be similar to those of the unlabeled analyte.

^b Refer to (b) (4) report 431-1404 Amendment 1

Source: bioanalytical report (b) (4) 431-1503 Amendment 1

¹⁹ Module 5.3.1.4: Validation of a method for the determination of fosaprepitant and aprepitant in human plasma by LC-MS/MS: [Application 209296 - Sequence 0001 - Bioanalytical Report \(b\) \(4\) 431-1503](#)
[Application 209296 - Sequence 0001 - Bioanalytical Report \(b\) \(4\) 431-1503 Amendment 1](#)

²⁰ Module 5.3.1.2: Bioanalytical report for study 104: [Application 209296 - Sequence 0004 - Compliance and-or Drug Concentration Data](#)

²¹ [Application 209296 - Sequence 0001 - Bioanalytical Reports](#)

Reviewer's comments: Total aprepitant plasma concentrations were measured using the above-validated method. The validation method results are within the acceptable range. All study samples (study 104 and study 106) were analyzed within the established long-term stability of 85 days at -70°C. For study 104, 238/3549 (=6.7%) samples were selected for incurred sample reanalysis for aprepitant, and 100% met the acceptance criteria. For study 106 part A, 140/1512 (=9.3%) samples were selected for incurred sample reanalysis for aprepitant, and 100% met the acceptance criteria. For study 106 part B, 235/3611 (=6.5%) samples were selected for incurred sample reanalysis for aprepitant, and 98.7% met the acceptance criteria.

The Office of Study Integrity and Surveillance (OSIS) recommended accepting the bioanalytical data without an on-site inspection²².

It was noted that in the study 106 report, the study duration was indicated from September 18 2016 to October 26 2016 while in the bioanalytical report for study 106, 1674 samples were received and analyzed between September 9 2016 and September 19 2016. Further investigation indicated that those samples were from part A study, which was conducted prior to September 18 2016.

4.2 Drug-Drug Interaction Assessment

[Table 7](#) shows assessments on the proposed effects of aprepitant on PK of other drugs.

Table 7: Effects of Aprepitant on the Pharmacokinetics of Other Drugs

CYP3A4 Substrates		Data	Reviewer's assessment
Pimozide			
Clinical Impact	Increased pimozide exposure	significantly increased plasma concentrations of pimozide, potentially resulting in prolongation of the QT interval	Increased Cmax will not affect labeling language due to contraindication statement.
Intervention	Aprepitant is contraindicated		
Benzodiazepines			
Clinical Impact	Increased exposure to midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) may increase the risk of adverse reactions	Fosaprepitant 150 mg administered as a single IV dose on Day 1 increased the AUCt of midazolam by approximately 1.8-fold on Day 1 and had no effect on Day 4 when midazolam was coadministered as a single oral dose of 2 mg on Days 1 and 4 ²³ .	Proposed labeling is appropriate while clinical monitoring is recommended.
Intervention	Monitor for benzodiazepine-related adverse reactions.		
Dexamethasone (CYP3A4 substrate)			
Clinical Impact	Increased dexamethasone exposure	Concomitant administration of oral aprepitant regimen (125mg on day 1 /80mg on days 2-5) increased dexamethasone AUC by about 2-fold. Higher dose regimen of oral aprepitant (375 mg on day 1/250 mg	See comments under Section 3.3.4
Intervention	Reduce the dose of oral dexamethasone by approximately 50%		

²² Memo from the Division of New Drug Bioequivalence Evaluation (DNDBE), Office of Study Integrity and Surveillance to the Division of Gastroenterology and Inborn Errors Products (DGIEP) dated 7/14/2017

<http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af8044af96>.

²³ EMEND for injection (NDA 022023) label approved on 08/09/2017:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022023s0161b1.pdf

		on days 2-5) resulted in increase in dexamethasone AUC 2.5 and 4 times on Days 1 and Day 5, respectively. ²⁴	
Methylprednisolone (CYP3A4 substrate)			
Clinical Impact	Increased methylprednisolone exposure	Oral aprepitant increases the AUC of orally methylprednisolone by 2.5 fold. Based on the difference observed with oral versus intravenous administration of methylprednisolone, aprepitant appears to have greater inhibitory effect when the CYP3A4 substrate is administered orally than when it is administered intravenously. ²⁴	
Intervention	Reduce the dose of oral methylprednisolone by approximately 50% on Days 1 and 2 for patients receiving HEC and on Day 1 for patients receiving MEC. Reduce the dose of intravenous methylprednisolone by 25% on Days 1 and 2 for patients receiving HEC and on Day 1 for patients receiving MEC.		
Chemotherapeutic Agents that are Metabolized by CYP3A4			
Clinical Impact	Increased exposure of the chemotherapeutic agent may increase the risk of adverse reactions	Due to the small number of patients in clinical studies who received the CYP3A4 substrates vinblastine, vincristine, or ifosfamide, particular caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4 that were not studied. In clinical studies, EMEND was administered with the following chemotherapeutic agents metabolized primarily or in part by CYP3A4: etoposide, vinorelbine, docetaxel, and paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions. ²⁴	See comments under Section 3.3.4
Intervention	<u>Vinblastine, vincristine, or ifosfamide or other chemotherapeutic agents</u> • Monitor for chemotherapeutic-related adverse reactions. <u>Etoposide, vinorelbine, paclitaxel, and docetaxel</u> • No dosage adjustment needed.		
Hormonal Contraceptives			
Clinical Impact	Decreased hormonal exposure during administration of and for 28 days after administration of the last dose of aprepitant	The reported maximum decrease was 64% in ethinyl estradiol trough concentration, and 60% in norethindrone trough concentration ^{24,25} .	The label recommends alternative or back-up methods of contraception. Therefore, the concern on the change in aprepitant Cmax after administration of HTX-019 compared with EMEND for injection is minimized.
Intervention	Effective alternative or back-up methods of contraception (such as condoms and spermicides) should be used during treatment with aprepitant and for 1 month following administration of aprepitant.		
Examples	birth control pills, skin patches, implants, and certain IUDs		

²⁴ EMEND (NDA021549) Clinical Pharmacology review dated 03/13/2003:

<http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af80191f2f>

²⁵ EMEND (NDA 022023) for injection clinical pharmacology review dated 01/25/2008:

<http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af801636ee>

CYP2C9 Substrates			
Warfarin			
Clinical Impact	Decreased warfarin exposure and prolongation of prothrombin time (INR)	A single 125 mg oral dose of aprepitant on day 1 and 80 mg/day on days 2 and 3 did not affect the plasma AUC of R(+) or S(-) warfarin on day 3 after aprepitant administration. There was a 34% decrease in S(-) warfarin (a CYP2C9 substrate) trough concentration accompanied by a 14% decrease in the prothrombin time (reported as International Normalized Ratio or INR) 5 days after completion of dosing with oral aprepitant.	DDI with warfarin was not re-assessed in EMEND for injection application although higher Cmax of aprepitant was observed after administration of EMEND for injection compared to oral aprepitant. The proposed label is appropriate with INR monitoring.
Intervention	In patients on chronic warfarin therapy, monitor the prothrombin time (INR) in the 2-week period, particularly at 7 to 10 days, following administration of aprepitant with each chemotherapy cycle.		
Other			
5-HT3 Antagonists			
Clinical Impact	No change in the exposure of the 5-HT3 antagonist	Aprepitant has little or no affinity for serotonin (5-HT3), dopamine, and corticosteroid receptors ²⁶ . Higher dose regimen of aprepitant (375 mg on day 1/250 mg on days 2-5) did not affect ondansetron. ²⁴	It is unlikely that the change in aprepitant Cmax will affect the interaction potential with 5-HT3 antagonist since aprepitant has little or no affinity for 5-HT3 and no change in the exposure of the 5-HT3 antagonist based on previous findings.
Intervention	No dosage adjustment needed		
Examples	ondansetron, granisetron, dolasetron		

Source: proposed labeling

4.3 Review of Individual Studies

4.3.1 In Vitro Protein Binding: Heron Study Number: 33-70²⁷

Objective: To determine the binding of HTX-019 and aprepitant (API) in human plasma using rapid equilibrium dialysis (RED) device after incubating in human plasma for 8 hours at 37°C. The mean and standard deviation of aprepitant percent unbound in human plasma using HTX-019 and aprepitant at 1, 3, and 10 µM are summarized in [Table 8](#).

Table 8: Summary of the mean and standard deviation of aprepitant in vitro protein binding

Nominal Conc. (µM)	Percent Unbound (Mean ± SD) ^a	
	HTX-019	Aprepitant (API)
1	0.30 ± 0.03	0.30 ± 0.03
3	0.29 ± 0.02	0.34 ± 0.02
10	0.31 ± 0.02	0.33 ± 0.02
Overall	0.30 ± 0.02	0.32 ± 0.03

^a Mean and SD represent N=3

Source: In vitro protein binding in human plasma study report page 8.

²⁶ EMEND label approved on 5/31/2017:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021549s027,207865s001lbl.pdf

²⁷ In vitro protein binding in human plasma: [Application 209296 - 5.3.2.1 Plasma Protein Binding Study Reports \[Study ID - Study Title\]](#)

Reviewer's comments: The protein binding was consistent in tested concentrations up to 10µM corresponding to 534.4 - 5344.3 ng/mL. The highest mean C_{max} after administration of 130 mg HTX-019 over 30 minutes was 6265 ng/mL ([Table 1](#)). Although the highest tested concentration is slightly lower than the highest observed mean C_{max}, considering that the protein binding percentage (greater than 99%) is already high, the similar protein binding is expected at C_{max}. Aprepitant in the test formulation showed similar protein binding percentage as the active pharmaceutical ingredient (API). The high degree (greater than 99%) of protein binding and the similar unbound fraction between the emulsion and the API further supported that aprepitant was released from the oil globules.

Of note the current labeling for EMEND for injection states that the protein binding is > 95%.

4.3.2 Relative BA study: HTX-019 C2015-104²⁸

Title: An Open-Label, Randomized, Two-Way Crossover Evaluation of the Bioequivalence of HTX-019 and EMEND® IV Administered as a Single Intravenous Dose in **Healthy Subjects**

Objectives:

Primary Objective: determine the bioequivalence of a single 130 mg IV dose of aprepitant emulsion (HTX-019) with commercially available EMEND for injection (fosaprepitant) 150 mg dose in healthy adult subjects.

Secondary Objective: assess the safety and tolerability of IV aprepitant emulsion (HTX-019) and EMEND for injection in healthy adult subjects.

Study design: Single dose, 2 treatment periods, cross-over, 7-day washout between periods

Treatment groups and number of subjects:

- HTX-019 130 mg (N = 97), 30-minute infusion
- EMEND for injection 150 mg (N = 97), 30-minute infusion

PK blood sampling: pre-dose, and at 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 11, 12, 18, 24, 36, 48, 60, and 72 hours after the start of the infusion in each treatment period. 7-day washout period

Results:

Refer to [Figure 1](#) for the mean PK profiles.

²⁸ Study report and listings: [Application 209296 - 5.3.1.2 \[\[Study ID\]\] - \[\[Study Title\]\] - HTX-019-104 - HTX-019-C2015-104 - An Open-Label, Randomized, Two-Way Crossover Evaluation of the Bioequivalence of HTX-019 and Emend IV Administered as a Single Intravenous Dose in Healthy Subjects](#)

Table 9: Summary of BE analysis for aprepitant comparing single dose of HTX-019 130 mg over 30-minute intravenous infusion and EMEND for injection 150 mg over 30-minute infusion .

Table 11-6 Summary of Bioequivalence Analyses for Aprepitant Adding Group Effect (Period 1 and Period 2) (PK Population)

PK Parameter (Units)	Point Estimate (Test/Reference) * 100	90% Confidence Interval	
		Low	High
AUC _{0-t} (ng*h/mL)	99.05	96.747	101.406
AUC _{0-inf} (ng*h/mL)	98.29	95.594	101.057
C _{12hr} (ng/mL)	97.14	94.282	100.088

Abbreviations: h/hr, hour; PK, pharmacokinetic.

Source: [Table 14.2.6.](#)

Source data: HTX-019 C2015-104 study report Table 11-6, and Table 11-7

Reviewer's analysis: The reviewer repeated the BE analysis using RStudio (Version 0.99). PK parameters (C_{max} , AUC_{0-t}, and AUC_{0-inf}) were calculated for each subject. Subjects 1024 was excluded due to protocol violation and did not provide PK data in both periods. Subject 1068, and 1098 were discontinued due to adverse events and did not provide PK in both periods. AUC_{0-inf} was calculated using R package ("PK") based on the last four plasma concentrations. The reviewer's analysis was summarized in [Table 10](#).

Table 10: BE analysis for study 104 by the reviewer.

PK metrics	Point Estimate (T/R) *100	Lower Bound of 90% CI	Upper Bound of 90% CI
C _{max} (ng/mL)	147.86	142.06	153.89
AUC _{0-t} (ng*h/mL)	99.02	96.71	101.38
AUC _{0-inf} (ng*h/mL)	99.25	96.03	102.58
C _{0.5h} (ng/mL)	148.16	142.28	154.28
C _{0.75h} (ng/mL)	110.14	106.57	113.82
C _{1h} (ng/mL)	107.70	104.51	110.99
C _{1.5h} (ng/mL)	103.31	100.11	106.62
C _{2h} (ng/mL)	101.19	98.15	104.32
C _{4h} (ng/mL)	101.12	99.40	102.88
C _{6h} (ng/mL)	99.26	97.39	101.17
C _{8h} (ng/mL)	97.34	94.84	99.91
C _{10h} (ng/mL)	96.75	94.15	99.42
C _{11h} (ng/mL)	99.29	94.31	104.54
C _{12h} (ng/mL)	97.06	94.19	100.02
C _{18h} (ng/mL)	95.78	92.36	99.33
C _{24h} (ng/mL)	95.83	92.13	99.69
C _{36h} (ng/mL)	93.31	88.46	98.43
C _{48h} (ng/mL)	91.25	85.72	97.14

Reviewer's comments: This is the pivotal study that the applicant used as the 'bridge' to support

the approval of HTX-019 referencing EMEND for injection. The study design was a straightforward two-way crossover BE study. PK parameters of aprepitant were the primary endpoints for comparison. Two formulations for comparison were HTX-019 (aprepitant emulsion, 130 mg, test) and EMEND for injection (fosaprepitant dimeglumine, a prodrug of aprepitant, e.q. 150 mg base, reference). The 130 mg aprepitant dose for the proposed HTX-019 was equivalent to 150 mg fosaprepitant in aprepitant molar mass

Per the applicant's analysis, the least square (LS) mean ratio was 148.16% (90% CI: 142.276, 154.279) for C_{max} . The LS mean ratio was 110.14% (90% CI: 106.57%, 113.82%) for the 45-minute (0.75-hr) time point. From 0.75 to 72 hours, geometric LS mean ratios ranged from 88.59% to 110.14%. All 90% CIs during these collection time points were within typical bioequivalent standards of 80% to 125% with a minimum of 81.25% and a maximum of 113.82%.

The reviewer reached the same conclusion as the applicant based on average BE analysis comparing HTX-019 130 mg over 30 min infusion and EMEND for injection 150 mg over 30 min infusion.

- 90% CIs for aprepitant concentrations measured between 0.75 hr (45 min) and 72 hr were within [80.00%, 125.00%] limits.
- 90% CIs for aprepitant AUC_t and AUC_{inf} were within [80.00%, 125.00%] limits.
- 90% CI for aprepitant C_{max} were outside of [80.00%, 125.00%] limits and higher after HTX-019 administration.

4.3.3 Relative BA study: HTX-019-106²⁹

Title: A phase 1 study of relative bioavailability of HTX-019 compared to EMEND for injection single doses in **healthy subjects**

Study design:

- Part A: Single dose, randomized information rate pilot study of parallel cohorts HTX-019 and EMEND for injection
- Part B: Single dose, open-label, randomized, 2-way crossover, BE, 14-day washout between periods

Treatment groups and number of subjects:

- Part A, 5 cohorts
 - Cohort 1 (N = 12) : 130 mg HTX-019, 30-minute infusion,
 - Cohort 2 (N = 21): 150 mg EMEND for injection, 30-minute infusion,
 - Cohort 3 (N = 12): 150 mg EMEND for injection, 20-minute infusion,
 - Cohort 4 (N = 12): 100 mg HTX-019, 30-minute infusion,
 - Cohort 5 (N = 12): 115 mg EMEND for injection, 15-minute infusion,
- Part B,

²⁹ Study report and listings: [Application 209296 - 5.3.1.2 \[\[Study ID\]\] - \[\[Study Title\]\] - HTX-019-106 - A Phase 1 Study of Relative Bioavailability of HTX-019 Compared to EMEND for Injection Single Doses in Healthy Subjects](#)

- o HTX-019 130 mg (N = 96), 30-minute infusion
- o EMEND for injection 150 mg (N = 97), 20-minute infusion

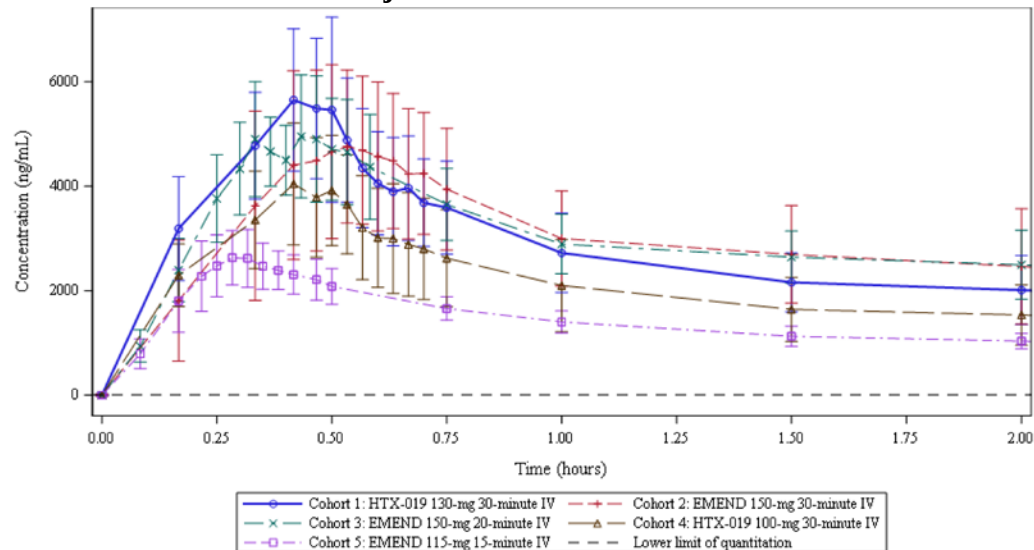
PK blood sampling:

The last sampling time point was at 72 hours for both part A and part B.

Results:

(1) PK assessment

Figure 2: Mean PK graphs for aprepitant after single dose IV administration of HTX-019 and EMEND for injection



Source: HTX-019-106 study report Figure 11-5

(2) BE Assessment

Table 11: Summary of BE analysis for aprepitant comparing HTX-019 130 mg infusion over 30 minutes and EMEND for injection 150 mg infusion over 20 minutes

Table 11-12: Summary of Bioequivalence Analyses for Aprepitant Adding Group Effect (PK Population)

PK Parameter (Units)	Point Estimate (Test/Reference) * 100	90% Confidence Interval	
		Low	High
AUC _{0-last} (ng*h/mL) ^a	96.73	94.017	99.531
AUC _{0-inf} (ng*h/mL) ^a	96.09	93.345	98.919
C _{12h} (ng/mL) ^a	98.95	96.082	101.899
C _{max} (ng/mL) ^b	130.73	124.719	137.022

Abbreviations: EMEND for injection, EMEND (fosaprepitant dimeglumine) for injection, for intravenous use; h, hour(s); HTX-019, HTX-019 (aprepitant) injectable emulsion, for intravenous use; PK, pharmacokinetic.

Test = HTX-019 130 mg 30-minute IV infusion; Reference = EMEND for injection 150 mg 20-minute IV infusion.

^a Primary bioequivalence analysis parameter.

^b Secondary bioequivalence analysis parameter.

Source: [Table 14.2.3](#).

Source: HTX-019-106 study report

- (3) Bridging for low strength (100 mg HTX-019 vs. 115 mg EMEND for injection)

Table 12: Key PK parameter ratios of aprepitant after single dose IV infusion of HTX-019 100 mg over 30 minutes and fosaprepitant 115 mg over 15 minutes (Part A of study 106)

Treatment	Infusion Duration (min)	N	Mean (%CV)			
			AUC _{0-t} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	C _{max} (ng/mL)	C _{12hr} (ng/mL)
HTX-019 100 mg	30	12	27826 (23.5)	28978 (27.5)	4290 (28.0)	665.2 (24.5)
EMEND for injection 115 mg	15	12	21141 (31.3)	22300 (40.8)	2704 (19.7)	627.5 (24.9)
PK Ratio HTX-019/EMEND	--	--	1.32	1.30	1.59	1.06

Abbreviations: AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the time of the last measurable plasma concentration; AUC_{0-inf}, area under the plasma concentration-time curve from time 0 extrapolated to infinity; C_{12hr}, plasma concentration at 12 hours; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; EMEND for injection, EMEND (fosaprepitant dimeglumine) for injection, for intravenous use; HTX-019, HTX-019 (aprepitant) injectable emulsion, for intravenous use; min, minute(s); N, number of subjects; PK, pharmacokinetic.

Source: Section 5.3.1.2, Study 106 CSR, Section 14, [Table 14.2.2.1](#).

Source: Table 3 in Response to Information Request submitted on May 15, 2017³⁰

Reviewer's comments: The applicant's analysis is similar to the reviewer's analysis shown in [Table 3](#).

4.4 Population PK Analysis: Heron Study Number: 33-72³¹

Reviewer's comments: The exploratory population PK modeling was conducted to estimate the free aprepitant (i.e. release from oil globule) following administration of HTX-019. The analysis was considered exploratory and not reviewed thoroughly.

³⁰ Response to Information Request submitted on May 15, 2017: [Application 209296 - Sequence 0014 - 0014 \(14\) 05/15/2017 ORIG-1 /Clinical/Response To Information Request](#)

³¹ Pharmacokinetic modeling study report: [Application 209296 - 5.3.3.5 \[\[Study ID\]\] - \[\[Study Title\]\] - 33-72 - Pharmacokinetic Modeling Report, Pharmacokinetic Analyses of HTX-019 \(Aprepitant\)](#)

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/s/

XINYUAN ZHANG
10/02/2017

INSOOK KIM
10/02/2017