

CINVANTI- aprepitant injection, emulsion

Heron Therapeutics, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CINVANTI® safely and effectively. See full prescribing information for CINVANTI.

CINVANTI® (aprepitant) injectable emulsion, for intravenous use

Initial U.S. Approval: 2003

----- RECENT MAJOR CHANGES -----

Indications and Usage (1)	10/2019
Dosage and Administration (2.1, 2.2)	02/2019, 10/2019
Warnings and Precautions (5.2)	02/2019

----- INDICATIONS AND USAGE -----

CINVANTI is a substance P/neurokinin-1 (NK₁) receptor antagonist, 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 as a single-dose regimen. (1)
- delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) as a single-dose regimen. (1)
- nausea and vomiting associated with initial and repeat courses of MEC as a 3-day regimen. (1)

Limitations of Use:

CINVANTI has not been studied for treatment of established nausea and vomiting. (1)

----- DOSAGE AND ADMINISTRATION -----

Recommended Dosage (2.1):

- Administer CINVANTI intravenously as an injection over 2 minutes or an infusion over 30 minutes; complete the injection or infusion approximately 30 minutes prior to chemotherapy.
- HEC and MEC (Single-Dose Regimen): The recommended dosage in adults is 130 mg on Day 1.
- MEC (3-Day Regimen): The recommended dosage in adults is 100 mg on Day 1. Aprepitant capsules (80 mg) are given orally on Days 2 and 3.
- CINVANTI is part of a regimen that includes a corticosteroid and a 5-HT₃ antagonist.

Preparation:

- See the full prescribing information for instructions. (2.2)

----- DOSAGE FORMS AND STRENGTHS -----

Injectable emulsion: 130 mg aprepitant in single-dose vial (3)

----- CONTRAINDICATIONS -----

- Known hypersensitivity to any component of this drug. (4, 5.2)
- Concurrent use with pimozide. (4)

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

- CYP3A4 Interactions: Aprepitant is a substrate, weak-to-moderate (dose-dependent) inhibitor and an inducer of CYP3A4; see Full Prescribing Information for recommendations regarding contraindications, risk of adverse reactions, and dosage adjustment of CINVANTI and concomitant drugs. (4, 5.1, 7.1, 7.2)
- Hypersensitivity Reactions (including anaphylaxis): May occur during or soon after administration. If symptoms occur, discontinue CINVANTI and do not reinitiate it. (4, 5.2)
- Warfarin (a CYP2C9 substrate): Risk of decreased INR of prothrombin time; monitor INR in 2–week period, particularly at 7 to 10 days, following initiation of CINVANTI. (5.3, 7.1)
- Hormonal Contraceptives: Efficacy of contraceptives may be reduced during and for 28 days following administration of aprepitant. Use effective alternative or back-up methods of non-hormonal contraception. (5.4, 7.1, 8.3)

----- ADVERSE REACTIONS -----

- Most common adverse reactions are:
- Single-dose fosaprepitant with MEC (≥2%): fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral neuropathy,

- leukopenia, dyspepsia, urinary tract infection, pain in extremity. (6.1)
- 3-day oral aprepitant with MEC ($\geq 1\%$ and greater than standard therapy): fatigue and eructation. (6.1)
 - Single-dose fosaprepitant with HEC: generally similar to 3-day oral aprepitant. In addition, infusion site reactions (3%) occurred. (6.1)
 - Single-dose CINVANTI ($\geq 2\%$): headache and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Heron Therapeutics, Inc. at 1-844-437-6611 and www.CINVANTI.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----- **DRUG INTERACTIONS** -----

See full prescribing information for a list of clinically significant drug interactions. (4, 5.1, 5.3, 5.4, 7.1, 7.2)

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

Pregnancy: May cause fetal harm. (8.1)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling.

Revised: 10/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CINVANTI, 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 as a single-dose regimen.
- delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) as a single-dose regimen.
- nausea and vomiting associated with initial and repeat courses of MEC as a 3-day regimen.

Limitations of Use

- CINVANTI has not been studied for the treatment of established nausea and vomiting.

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Nausea and Vomiting Associated with HEC and MEC

The recommended dosages in adults of CINVANTI, dexamethasone, and a 5-HT₃ antagonist for the prevention of nausea and vomiting associated with administration of HEC or MEC are shown in Table 1, Table 2 and Table 3 respectively. Administer CINVANTI intravenously either by injection over a two (2) minute period or by infusion over a thirty (30) minute period on Day 1, completing the injection or infusion approximately 30 minutes prior to chemotherapy.

Table 1. Recommended Dosage of CINVANTI for the Prevention of Nausea and Vomiting Associated with HEC (Single-Dose Regimen)

Agent	Day 1	Day 2	Day 3	Day 4
CINVANTI	130 mg intravenously	None	None	None
Dexamethasone*	12 mg orally	8 mg orally	8 mg orally twice daily	8 mg orally twice daily
5-HT ₃ antagonist	See selected 5-HT ₃ antagonist prescribing information for recommended dosage	None	None	None

* Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. Also administer dexamethasone in the evenings on Days 3 and 4. A 50% dosage reduction of dexamethasone on Days 1 and 2 is recommended to account for a drug interaction with aprepitant [see *Clinical Pharmacology* (12.3)].

Table 2. Recommended Dosage of CINVANTI for the Prevention of Nausea and Vomiting Associated with MEC (Single-Dose Regimen)

Agent	Day 1
CINVANTI	130 mg intravenously
Dexamethasone*	12 mg orally
5-HT ₃ antagonist	See selected 5-HT ₃ antagonist prescribing information for recommended dosage

* Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1. A 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with aprepitant [see *Clinical Pharmacology* (12.3)].

Table 3. Recommended Dosage of CINVANTI for the Prevention of Nausea and Vomiting Associated with MEC (3-Day Regimen with Oral Aprepitant on Days 2 and 3)

Agent	Day 1	Day 2	Day 3
CINVANTI	100 mg intravenously	None	None
Oral Aprepitant	None	80 mg orally	80 mg orally
Dexamethasone*	12 mg orally	None	None
5-HT ₃ antagonist	See selected 5-HT ₃ antagonist prescribing information for recommended dosage	None	None

* Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1. A 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with aprepitant [see *Clinical Pharmacology* (12.3)].

2.2 Preparation of CINVANTI for Administration

Intravenous Injection over a period of 2 minutes

For intravenous injection over a period of 2 minutes, administer 130 mg of CINVANTI as part of a HEC or MEC regimen or 100 mg as part of a MEC regimen as a single dose on Day 1.

Aseptically withdraw **18 mL for the 130 mg dose** or **14 mL for the 100 mg dose** from the vial. Do not dilute.

The infusion line should be flushed with normal saline before and after administration of CINVANTI.

Intravenous Infusion over a period of 30 minutes

Table 4 includes preparation instructions for CINVANTI for HEC or MEC as a 130 mg single-dose regimen, and for MEC as a 100 mg single-dose followed by 2 days of oral aprepitant as a 3-day regimen. Differences in preparation for each dose are displayed as bolded text.

Table 4. Preparation Instructions for CINVANTI Intravenous Infusion

Step 1	Aseptically withdraw 18 mL for the 130 mg dose or 14 mL for the 100 mg dose from the vial and transfer it into an infusion bag* filled with 100 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose for Injection, USP.
Step 2	Gently invert the bag 4 to 5 times. Avoid shaking.
Step 3	Before administration, inspect the bag for particulate matter and discoloration. Discard the bag if particulate and/or discoloration are observed.

Note: The differences in preparation for each recommended dosage of CINVANTI are displayed in bolded text (see Table 1 for HEC Regimen and Table 2 for MEC Regimen).

* Use only Non-DEHP tubing, non-PVC infusion bags

Caution: Do not mix CINVANTI with solutions for which physical and chemical compatibility have not been established.

In-Use Storage Conditions for CINVANTI in Acceptable Intravenous Diluents

Diluted CINVANTI solution is stable at ambient room temperature for up to 6 hours in 0.9% Sodium Chloride Injection, USP or 12 hours in 5% Dextrose Injection, USP or up to 72 hours if stored under refrigeration in 0.9% Sodium Chloride Injection, USP or in 5% Dextrose Injection, USP.

2.3 Compatibilities

CINVANTI is compatible with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.

2.4 Incompatibilities

CINVANTI is incompatible with any solutions containing divalent cations (e.g. calcium, magnesium), including Lactated Ringer's Solution and Hartmann's Solution.

3 DOSAGE FORMS AND STRENGTHS

Injectable emulsion: 130 mg/18 mL (7.2 mg/mL) aprepitant as an opaque, off-white to amber emulsion, in single-dose vial

4 CONTRAINDICATIONS

CINVANTI is contraindicated in patients:

- who are hypersensitive to any component of the product [*see Description (11)*]. Hypersensitivity reactions including anaphylaxis have been reported [*see Warnings and Precautions (5.2), Adverse Reactions (6.2)*].
- taking pimoziide. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of pimoziide, which is a CYP3A4 substrate, potentially causing serious or life-threatening reactions, such as QT prolongation, a known adverse reaction of pimoziide [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Clinically Significant CYP3A4 Drug Interactions

Aprepitant is a substrate, weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4.

- Use of CINVANTI with other drugs that are CYP3A4 substrates may result in increased plasma concentration of the concomitant drug.
 - Use of pimoziide with CINVANTI is contraindicated due to the risk of significantly increased plasma concentrations of pimoziide, potentially resulting in prolongation of the QT interval, a known adverse reaction of pimoziide [*see Contraindications (4)*].
- Use of CINVANTI with strong or moderate CYP3A4 inhibitors (e.g., ketoconazole, diltiazem) may increase plasma concentrations of aprepitant and result in an increased risk of adverse reactions related to CINVANTI.
- Use of CINVANTI with strong CYP3A4 inducers (e.g., rifampin) may result in a reduction in aprepitant plasma concentrations and decreased efficacy of CINVANTI.

See Table 8 and Table 9 for a listing of potentially significant drug interactions [*see Drug Interactions (7.1, 7.2)*].

5.2 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis during or soon after administration of CINVANTI have occurred. Symptoms including dyspnea, eye swelling, flushing, pruritus and wheezing have been reported [see *Adverse Reactions (6.2)*].

Monitor patients during and after administration. If hypersensitivity reactions occur, discontinue CINVANTI and administer appropriate medical therapy. Do not reinitiate CINVANTI in patients who experience these symptoms with previous use.

5.3 Decrease in INR with Concomitant Warfarin

Coadministration of CINVANTI with warfarin, a CYP2C9 substrate, may result in a clinically significant decrease in the International Normalized Ratio (INR) of prothrombin time [see *Clinical Pharmacology (12.3)*]. Monitor the INR in patients on chronic warfarin therapy in the 2-week period, particularly at 7 to 10 days, following initiation of CINVANTI with each chemotherapy cycle [see *Drug Interactions (7.1)*].

5.4 Risk of Reduced Efficacy of Hormonal Contraceptives

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

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions [see *Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of CINVANTI was evaluated as a single-dose in healthy subjects and established from adequate and well-controlled studies of intravenous fosaprepitant and/or oral aprepitant [see *Clinical Studies (14)*]. Adverse reactions observed in these adequate and well-controlled studies are described below.

Safety of CINVANTI

A total of 200 healthy subjects received a single 130 mg dose of CINVANTI as a 30-minute infusion. Adverse reactions reported in at least 2% of subjects were headache (3%) and fatigue (2%). The safety profile of CINVANTI in 50 healthy subjects who received a single 2-minute injection was similar to that seen with a 30-minute infusion.

Single-Dose Intravenous Fosaprepitant -- HEC

In an active-controlled clinical study in patients receiving HEC, safety was evaluated for 1143 patients receiving a single intravenous dose of fosaprepitant, a prodrug of aprepitant, compared to 1169 patients receiving a 3-day regimen of oral aprepitant [see *Clinical Studies (14.1)*]. When administered intravenously, fosaprepitant is converted to aprepitant within 30 minutes. The safety profile was generally similar to that seen in prior HEC studies with a 3-day regimen of oral aprepitant. However, infusion-site reactions occurred at a higher incidence in patients in the intravenous fosaprepitant group (3%) compared to those in the oral aprepitant group (0.5%). The reported infusion-site reactions

included: infusion-site erythema, infusion-site pruritus, infusion-site pain, infusion-site induration and infusion-site thrombophlebitis.

Adverse reactions associated with oral aprepitant may also be expected to occur with CINVANTI. See the full prescribing information for oral aprepitant for complete safety information.

Single-Dose Intravenous Fosaprepitant -- MEC

In an active-controlled clinical trial in patients receiving MEC, safety was evaluated in 504 patients receiving a single dose of intravenous fosaprepitant in combination with ondansetron and dexamethasone (intravenous fosaprepitant regimen) compared to 497 patients receiving ondansetron and dexamethasone alone (standard therapy). The most common adverse reactions are listed in Table 5.

Table 5. Most Common Adverse Reactions in Patients Receiving MEC*

	Intravenous fosaprepitant, ondansetron, and dexamethasone[†] (N=504)	Ondansetron and dexamethasone[‡] (N=497)
Fatigue	15%	13%
Diarrhea	13%	11%
Neutropenia	8%	7%
Asthenia	4%	3%
Anemia	3%	2%
Peripheral Neuropathy	3%	2%
Leukopenia	2%	1%
Dyspepsia	2%	1%
Urinary Tract Infection	2%	1%
Pain In Extremity	2%	1%

* Reported in $\geq 2\%$ of patients treated with the intravenous fosaprepitant regimen and at a greater incidence than standard therapy.

[†] Intravenous fosaprepitant regimen

[‡] Standard therapy

Infusion-site reactions were reported in 2.2% of patients treated with the intravenous fosaprepitant regimen compared to 0.6% of patients treated with standard therapy. The infusion-site reactions included: infusion-site pain (1.2%, 0.4%), injection-site irritation (0.2%, 0.0%), vessel puncture-site pain (0.2%, 0.0%), and 8 infusion-site thrombophlebitis (0.6%, 0.0%), reported in the intravenous fosaprepitant regimen compared to standard therapy, respectively.

3-Day Oral Aprepitant -- MEC

In 2 active-controlled clinical trials in patients receiving MEC, 868 patients were treated with a 3-day oral aprepitant regimen during Cycle 1 of chemotherapy and 686 of these patients continued into extensions for up to 4 cycles of chemotherapy. In both studies, oral aprepitant was given in combination with ondansetron and dexamethasone (oral aprepitant regimen) and was compared to ondansetron and dexamethasone alone (standard therapy) [see *Clinical Studies (14.2)*].

In the combined analysis of Cycle 1 data for these 2 studies, adverse reactions were reported in approximately 14% of patients treated with the aprepitant regimen compared with approximately 15% of patients treated with standard therapy. Treatment was discontinued due to adverse reactions in 0.7% of patients treated with the aprepitant regimen compared with 0.2% of patients treated with standard therapy.

The most common adverse reactions reported in patients treated with the oral aprepitant regimen with an

incidence of at least 1% and greater than standard therapy are listed in Table 6.

Table 6. Adverse Reactions ($\geq 1\%$) in Patients Receiving MEC with a Greater Incidence in the Oral 3-Day Aprepitant Regimen Relative to Standard Therapy

	Oral Aprepitant Regimen (N = 868)	Standard Therapy (N = 846)
Fatigue	1.4	0.9
Eructation	1.0	0.1

A listing of adverse reactions reported in less than 1% in patients treated with the oral aprepitant regimen that occurred at an incidence greater than in patients treated with standard therapy are presented in the *Less Common Adverse Reactions* subsection below.

Less Common Adverse Reactions

Adverse reactions reported in studies in patients treated with the 3-day oral aprepitant regimen with an incidence $< 1\%$ and greater than standard therapy are listed in Table 7.

Table 7. Adverse Reactions (incidence $< 1\%$) in Patients Observed in Studies with a Greater Incidence in the Oral Aprepitant Regimen Relative to Standard Therapy

<i>Infection and infestations</i>	candidiasis, staphylococcal infection
<i>Blood and the lymphatic system disorders</i>	anemia, febrile neutropenia
<i>Metabolism and nutrition disorders</i>	weight gain, polydipsia
<i>Psychiatric disorders</i>	disorientation, euphoria, anxiety
<i>Nervous system disorders</i>	dizziness, dream abnormality, cognitive disorder, lethargy, somnolence
<i>Eye disorders</i>	conjunctivitis
<i>Ear and labyrinth disorders</i>	tinnitus
<i>Cardiac disorders</i>	bradycardia, cardiovascular disorder, palpitations
<i>Vascular disorders</i>	hot flush, flushing
<i>Respiratory, thoracic and mediastinal disorders</i>	pharyngitis, sneezing, cough, postnasal drip, throat irritation
<i>Gastrointestinal disorders</i>	nausea, acid reflux, dysgeusia, epigastric discomfort, obstipation, gastroesophageal reflux disease, perforating duodenal ulcer, vomiting, abdominal pain, dry mouth, abdominal distension, feces hard, neutropenic colitis, flatulence, stomatitis
<i>Skin and subcutaneous tissue disorders</i>	rash, acne, photosensitivity, hyperhidrosis, oily skin, pruritus, skin lesion
<i>Musculoskeletal and connective tissue disorders</i>	muscle cramp, myalgia, muscular weakness
<i>Renal and urinary disorders</i>	polyuria, dysuria, pollakiuria
<i>General disorders and administration site condition</i>	edema, chest discomfort, malaise, thirst, chills, gait disturbance
<i>Investigations</i>	alkaline phosphatase increased, hyperglycemia, microscopic hematuria, hyponatremia, weight decreased, neutrophil count decreased

In another chemotherapy-induced nausea and vomiting study, Stevens-Johnson syndrome was reported as a serious adverse reaction in a patient receiving aprepitant with cancer chemotherapy.

The adverse experience profiles in the Multiple-Cycle extensions of HEC and MEC studies for up to 6 cycles of chemotherapy were similar to that observed in Cycle 1.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of intravenous fosaprepitant and/or intravenous or oral aprepitant. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: pruritus, rash, urticaria, Stevens-Johnson syndrome/toxic epidermal necrolysis [see *Warnings and Precautions (5.2)*].

Immune system disorders: hypersensitivity reactions including anaphylaxis and anaphylactic shock [see *Contraindications (4), Warnings and Precautions (5.2)*].

Nervous system disorders: ifosfamide-induced neurotoxicity reported after aprepitant and ifosfamide coadministration.

7 DRUG INTERACTIONS

7.1 Effect of Aprepitant on the Pharmacokinetics of Other Drugs

Aprepitant is a substrate, weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9 [see *Clinical Pharmacology (12.3)*].

Some substrates of CYP3A4 are contraindicated with CINVANTI [see *Contraindications (4)*]. Dosage adjustment of some CYP3A4 and CYP2C9 substrates may be warranted, as shown in Table 8.

Table 8. Effects of Aprepitant on the Pharmacokinetics of Other Drugs

CYP3A4 Substrates	
Pimozide	
<i>Clinical Impact</i>	Increased pimozide exposure.
<i>Intervention</i>	CINVANTI is contraindicated [see <i>Contraindications (4)</i>].
Benzodiazepines	
<i>Clinical Impact</i>	Increased exposure to midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) may increase the risk of adverse reactions [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention</i>	Monitor for benzodiazepine-related adverse reactions.
Dexamethasone	
<i>Clinical Impact</i>	Increased dexamethasone exposure [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention</i>	Reduce the dose of oral dexamethasone by approximately 50% [see <i>Dosage and Administration (2.1)</i>].
Methylprednisolone	
<i>Clinical Impact</i>	Increased methylprednisolone exposure [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention</i>	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	
<i>Clinical Impact</i>	Increased exposure of the chemotherapeutic agent may increase the risk of adverse reactions [see <i>Clinical Pharmacology (12.3)</i>].
	Vinblastine, vincristine, or ifosfamide or other chemotherapeutic agents

<i>Intervention</i>	<ul style="list-style-type: none"> • Monitor for chemotherapeutic-related adverse reactions.
	<u>Etoposide, vinorelbine, paclitaxel, and docetaxel</u>
	<ul style="list-style-type: none"> • No dosage adjustment needed.

Hormonal Contraceptives

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

CYP2C9 Substrates

Warfarin

<i>Clinical Impact</i>	Decreased warfarin exposure and decreased prothrombin time (INR) [see <i>Warnings and Precautions (5.3)</i> , <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention</i>	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 CINVANTI with each chemotherapy cycle.

Other Antiemetic Agents

5-HT₃ Antagonists

<i>Clinical Impact</i>	No change in the exposure of the 5-HT ₃ antagonist [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention</i>	No dosage adjustment needed.
<i>Examples</i>	ondansetron, granisetron, dolasetron

7.2 Effect of Other Drugs on the Pharmacokinetics of Aprepitant

Aprepitant is a CYP3A4 substrate [see *Clinical Pharmacology (12.3)*]. Co-administration of CINVANTI with drugs that are inhibitors or inducers of CYP3A4 may result in increased or decreased plasma concentrations of aprepitant, respectively, as shown in Table 9.

Table 9. Effects of Other Drugs on Pharmacokinetics of Aprepitant

Moderate to Strong CYP3A4 Inhibitors

<i>Clinical Impact</i>	Significantly increased exposure of aprepitant may increase the risk of adverse reactions associated with CINVANTI [see <i>Adverse Reactions (6.1)</i> and <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention</i>	Avoid concomitant use of CINVANTI.
<i>Examples</i>	<u>Moderate inhibitor:</u> diltiazem <u>Strong inhibitors:</u> ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir

Strong CYP3A4 Inducers

<i>Clinical Impact</i>	Substantially decreased exposure of aprepitant in patients chronically taking a strong CYP3A4 inducer may decrease the efficacy of CINVANTI [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention</i>	Avoid concomitant use of CINVANTI.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Clinical Considerations

Fetal/Neonatal adverse reactions

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

Data

Animal Data

In embryofetal development studies in rats and rabbits, aprepitant was administered during the period of organogenesis at oral doses up to 1000 mg/kg twice daily (rats) and up to the maximum tolerated dose of 25 mg/kg/day (rabbits). No embryofetal lethality or malformations were observed at any dose level in either species. The exposures (AUC) in pregnant rats at 1000 mg/kg twice daily and in pregnant rabbits at 125 mg/kg/day were approximately equivalent to the exposure at the RHD of CINVANTI 130 mg. Aprepitant crosses the placenta in rats and rabbits.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

Upon administration of CINVANTI, the efficacy of hormonal contraceptives may be reduced. Advise females of reproductive potential using hormonal contraceptives to use an effective alternative or back-up non-hormonal contraceptive (such as condoms or spermicides) during treatment with CINVANTI and for 1 month following the last dose of CINVANTI or oral aprepitant, whichever is administered last [*see Warnings and Precautions (5.4), Drug Interactions (7.1), Clinical Pharmacology (12.3)*].

8.4 Pediatric Use

The safety and effectiveness of CINVANTI have not been established in pediatric patients.

8.5 Geriatric Use

Of the 1649 adult cancer patients treated with intravenous fosaprepitant in HEC and MEC clinical studies, 27% were aged 65 and over, while 5% were aged 75 and over. Other reported clinical experience with fosaprepitant and/or oral aprepitant has not identified differences in responses between elderly and younger patients. In general, use caution when dosing elderly patients as they have a greater frequency of decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy [see *Clinical Pharmacology (12.3)*].

8.6 Hepatic Impairment

The pharmacokinetics of aprepitant in patients with mild and moderate hepatic impairment were similar to those of healthy subjects with normal hepatic function. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 9). There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score greater than 9). Therefore, additional monitoring for adverse reactions in these patients may be warranted when CINVANTI is administered [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

There is no specific information on the treatment of overdosage with aprepitant.

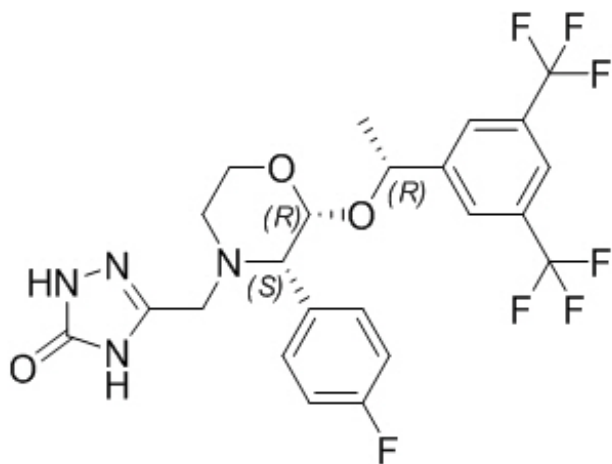
In the event of overdose, CINVANTI should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of CINVANTI, drug-induced emesis may not be effective in cases of CINVANTI overdosage.

Aprepitant is not removed by hemodialysis.

11 DESCRIPTION

CINVANTI injectable emulsion contains the active ingredient, aprepitant. Aprepitant is a substance P/neurokinin 1 (NK₁) receptor antagonist, an antiemetic agent, chemically described as 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one.

Its empirical formula is C₂₃H₂₁F₇N₄O₃, and its structural formula is:



Aprepitant is a white to off-white crystalline solid, with a molecular weight of 534.43. It is practically insoluble in water. Aprepitant is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile.

CINVANTI (aprepitant) injectable emulsion is a sterile, opaque, off-white to amber liquid in a single-dose vial for intravenous use. Each vial contains 130 mg aprepitant in 18 mL of emulsion. The emulsion also contains the following inactive ingredients: egg lecithin (2.6 g), ethanol (0.5 g), sodium oleate (0.1 g), soybean oil (1.7 g), sucrose (1 g), and water for injection (12 g).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK₁) receptors. Aprepitant has little or no affinity for serotonin (5-HT₃), dopamine, and corticosteroid receptors. Aprepitant has been shown in animal models to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Animal and human Positron Emission Tomography (PET) studies with aprepitant have shown that it crosses the blood brain barrier and occupies brain NK₁ receptors. Animal and human studies show that aprepitant augments the antiemetic activity of the 5-HT₃-receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a randomized, double-blind, positive-controlled, thorough QTc study, a single 200 mg intravenous dose of fosaprepitant, a prodrug of aprepitant, had no effect on the QTc interval. In a cross-study comparison, maximum aprepitant concentrations (C_{max}) after a single 200 mg dose of fosaprepitant were 1.04- and 1.5-fold higher than that achieved with CINVANTI 130 mg dose and 100 mg dose given as a 30-minute infusion, respectively.

12.3 Pharmacokinetics

Pharmacokinetic parameters following administration of a single intravenous 130 mg dose of CINVANTI administered as a 2-minute injection or 100 mg or 130 mg dose of CINVANTI administered as a 30-minute infusion to healthy subjects are summarized in Table 10.

Table 10. Aprepitant Pharmacokinetic Parameters (Mean (± Standard Deviation)) After Single Dose Intravenous Administration of CINVANTI

	CINVANTI 130 mg 2-minute intravenous injection	CINVANTI 130 mg 30-minute intravenous infusion	CINVANTI 100 mg 30-minute intravenous infusion
AUC _{0-72hr} (mcg•hr/mL)	45.6 (± 15.5)	43.9 (± 12.7)	27.8 (± 6.5)
C _{max} (mcg/mL)	13.9 (±3.8)	6.1 (± 1.5)	4.3 (± 1.2)

Distribution

Aprepitant is greater than 99% bound to plasma proteins. The mean apparent volume of distribution at steady state (Vd_{ss}) was approximately 70 L in humans.

Aprepitant crosses the blood brain barrier in humans [see *Clinical Pharmacology (12.1)*].

Elimination

Metabolism

Aprepitant undergoes extensive metabolism. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism is largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6, CYP2C9, or CYP2E1 was detected.

In healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300 mg dose of [¹⁴C]-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma.

Excretion

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. The apparent terminal half-life ranged from approximately 9 to 13 hours.

Specific Populations

Geriatric Patients

Following oral administration of a single 125 mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 through 5, the AUC_{0-24hr} of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (65 years and older) relative to younger adults. The C_{max} was 10% higher on Day 1 and 24% higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful [see *Use in Specific Populations (8.5)*].

Male and Female Patients

Following oral administration of a single dose of aprepitant ranging from 40 mg to 375 mg, the AUC_{0-24hr} and C_{max} are 14% and 22% higher in females as compared with males. The half-life of aprepitant is 25% lower in females as compared with males and T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful.

Racial or Ethnic Groups

Following oral administration of a single dose of aprepitant, ranging from 40 mg to 375 mg, the AUC_{0-24hr} and C_{max} are approximately 27% and 19% higher in Hispanics as compared with Caucasians. The AUC_{0-24hr} and C_{max} were 74% and 47% higher in Asians as compared to Caucasians. There was no difference in AUC_{0-24hr} or C_{max} between Caucasians and Blacks. These differences are not considered clinically meaningful.

Patients with Renal Impairment

A single 240 mg oral dose of aprepitant was administered to patients with severe renal impairment (creatinine clearance less than 30 mL/min/1.73 m² as measured by 24-hour urinary creatinine clearance) and to patients with end stage renal disease (ESRD) requiring hemodialysis.

In patients with severe renal impairment, the AUC_{0-∞} of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects (creatinine clearance greater than 80 mL/min estimated by Cockcroft-Gault method). In patients with ESRD undergoing hemodialysis, the AUC_{0-∞} of total aprepitant decreased by 42% and C_{max} decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal impairment compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

Patients with Hepatic Impairment

Following administration of a single 125 mg oral dose of aprepitant on Day 1 and 80 mg once daily on Days 2 and 3 to patients with mild hepatic impairment (Child-Pugh score 5 to 6), the AUC_{0-24hr} of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the AUC₀₋

t_{24hr} of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, as compared with healthy subjects given the same regimen. These differences in AUC_{0-24hr} are not considered clinically meaningful. There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score greater than 9) [see *Use in Specific Populations (8.6)*].

Body Mass Index (BMI)

For every 5 kg/m² increase in BMI AUC_{0-24hr} and C_{max} of aprepitant decrease by 9% and 10%. BMI of subjects in the analysis ranged from 18 kg/m² to 36 kg/m². This change is not considered clinically meaningful.

Drug Interactions Studies

Aprepitant is a substrate, and a weak-to-moderate (dose-dependent) inhibitor of CYP3A4. Aprepitant is also an inducer of CYP3A4, and CYP2C9. Aprepitant is unlikely to interact with drugs that are substrates for the P- glycoprotein transporter.

Effects of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs

CYP3A4 Substrates:

Midazolam: Fosaprepitant 150 mg (corresponding to CINVANTI 130 mg) administered as a single intravenous dose on Day 1 increased the $AUC_{0-\infty}$ 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.

Corticosteroids:

Dexamethasone: Fosaprepitant administered as a single 150 mg (corresponding to CINVANTI 130 mg) intravenous dose on Day 1 increased the AUC_{0-24hr} of dexamethasone, administered as a single 8 mg oral dose on Days 1, 2, and Day 3, by approximately 2-fold on Days 1 and 2 [see *Dosage and Administration (2.1)*, *Drug Interactions (7.1)*].

Methylprednisolone: When oral aprepitant as a 3-day regimen (125 mg/80 mg/80 mg) was administered with intravenous methylprednisolone 125 mg on Day 1 and oral methylprednisolone 40 mg on Days 2 and 3, the AUC of methylprednisolone was increased by 1.34-fold on Day 1 and by 2.5-fold on Day 3 [see *Drug Interactions (7.1)*].

Chemotherapeutic agents:

Docetaxel: In a pharmacokinetic study, oral aprepitant administered as a 3-day regimen (125 mg/80 mg/80 mg) did not influence the pharmacokinetics of docetaxel [see *Drug Interactions (7.1)*].

Vinorelbine: In a pharmacokinetic study, oral aprepitant administered as a 3-day regimen (125 mg/80 mg/80 mg) did not influence the pharmacokinetics of vinorelbine to a clinically significant degree [see *Drug Interactions (7.1)*].

CYP2C9 substrates (Warfarin, Tolbutamide):

Warfarin: A single 125 mg dose of oral aprepitant was administered on Day 1 and 80 mg/day on Days 2 and 3 to subjects who were stabilized on chronic warfarin therapy. Although there was no effect of oral aprepitant on the plasma AUC of R(+) or S(-) warfarin determined on Day 3, there was a 34% decrease in S(-) warfarin 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 [see *Drug Interactions (7.1)*].

Tolbutamide: Oral aprepitant, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide by 23% on Day 4, 28% on Day 8, and 15% on Day 15, when a single dose of tolbutamide 500 mg was administered prior to the administration of the 3-day

regimen of oral aprepitant and on Days 4, 8, and 15. This effect was not considered clinically important.

Other Drugs:

Oral contraceptives: When oral aprepitant was administered as a 3-day regimen (125 mg/80 mg/80 mg) with ondansetron and dexamethasone, and coadministered with an oral contraceptive containing ethinyl estradiol and norethindrone, the trough concentrations of both ethinyl estradiol and norethindrone were reduced by as much as 64% for 3 weeks post-treatment [see *Drug Interactions (7.1)*].

P-glycoprotein substrates: Aprepitant is unlikely to interact with drugs that are substrates for the P-glycoprotein transporter, as demonstrated by the lack of interaction of oral aprepitant with digoxin in a clinical drug interaction study.

5-HT₃ antagonists: In clinical drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Effect of Other Drugs on the Pharmacokinetics of Fosaprepitant/Aprepitant

Rifampin: When a single 375 mg dose of oral aprepitant was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampin, a strong CYP3A4 inducer, the AUC of aprepitant decreased approximately 11-fold and the mean terminal half-life decreased approximately 3-fold [see *Drug Interactions (7.2)*].

Ketoconazole: When a single 125 mg dose of oral aprepitant was administered on Day 5 of a 10-day regimen of 400 mg/day of ketoconazole, a strong CYP3A4 inhibitor, the AUC of aprepitant increased approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold [see *Drug Interactions (7.2)*].

Diltiazem: In a study in 10 patients with mild to moderate hypertension, administration of 100 mg of fosaprepitant as an intravenous infusion with 120 mg of diltiazem, a moderate CYP3A4 inhibitor administered three times daily, resulted in a 1.5-fold increase in the aprepitant AUC and a 1.4-fold increase in the diltiazem AUC.

When fosaprepitant was administered with diltiazem, the mean maximum decrease in diastolic blood pressure was significantly greater than that observed with diltiazem alone [24.3 ± 10.2 mm Hg with fosaprepitant versus 15.6 ± 4.1 mm Hg without fosaprepitant]. The mean maximum decrease in systolic blood pressure was also greater after co-administration of diltiazem with fosaprepitant than administration of diltiazem alone [29.5 ± 7.9 mm Hg with fosaprepitant versus 23.8 ± 4.8 mm Hg without fosaprepitant]. Co-administration of fosaprepitant and diltiazem; however, did not result in any additional clinically significant changes in heart rate or PR interval, beyond those changes observed with diltiazem alone [see *Drug Interactions (7.2)*].

Paroxetine: Coadministration of once daily doses of oral aprepitant 170 mg, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and C_{max} by approximately 20% of both aprepitant and paroxetine. This effect was not considered clinically important.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Sprague-Dawley rats and in CD-1 mice for 2 years. In the rat carcinogenicity studies, animals were treated with oral doses ranging from 0.05 to 1000 mg/kg twice daily. The highest dose produced systemic exposures to aprepitant approximately equivalent to (female

rats) or less than (male rats) the human exposure at the CINVANTI RHD of 130 mg. Treatment with aprepitant at doses of 5 to 1000 mg/kg twice daily caused an increase in the incidences of thyroid follicular cell adenomas and carcinomas in male rats. In female rats, it produced hepatocellular adenomas at 5 to 1000 mg/kg twice daily and hepatocellular carcinomas and thyroid follicular cell adenomas at 125 to 1000 mg/kg twice daily. In the mouse carcinogenicity studies, the animals were treated with oral doses ranging from 2.5 to 2000 mg/kg/day. The highest dose produced a systemic exposure approximately 2 times the human exposure at the RHD of CINVANTI 130 mg. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice.

Mutagenesis

Aprepitant was not genotoxic in the Ames test, the human lymphoblastoid cell (TK6) mutagenesis test, the rat hepatocyte DNA strand break test, the Chinese hamster ovary (CHO) cell chromosome aberration test and the mouse micronucleus test.

Impairment of Fertility

Oral aprepitant did not affect the fertility or general reproductive performance of male or female rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the RHD of CINVANTI 130 mg and exposure in female rats approximately equivalent to the human exposure).

14 CLINICAL STUDIES

The safety and efficacy of CINVANTI have been established based on adequate and well-controlled adult studies of a single-dose of intravenous fosaprepitant, a prodrug of aprepitant, and a 3-day regimen of oral aprepitant in chemotherapy-induced nausea and vomiting associated with HEC and MEC, respectively. Below is a description of the results of these adequate and well-controlled studies of fosaprepitant/aprepitant in these conditions.

14.1 Prevention of Nausea and Vomiting Associated with HEC

In a randomized, parallel, double-blind, active-controlled study, 150 mg fosaprepitant as a single intravenous infusion (N = 1147) was compared to a 3-day oral aprepitant regimen (N = 1175) in patients receiving a HEC regimen that included cisplatin (≥ 70 mg/m²). All patients in both groups received dexamethasone and ondansetron (see Table 11). Patient demographics were similar between the two treatment groups. Of the total 2322 patients, 63% were men, 56% White, 26% Asian, 3% American Indian/Alaska Native, 2% Black, 13% Multi-Racial, and 33% Hispanic/Latino ethnicity. Patient ages ranged from 19 to 86 years of age, with a mean age of 56 years. Other concomitant chemotherapy agents commonly administered were fluorouracil (17%), gemcitabine (16%), paclitaxel (15%), and etoposide (12%).

Table 11. Treatment Regimens in HEC Trial*

	Day 1	Day 2	Day 3	Day 4
Intravenous Fosaprepitant Regimen				
Fosaprepitant	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy	None	None	None
Oral dexamethasone [†]	12 mg	8 mg	8 mg twice daily	8 mg twice daily
Ondansetron	Ondansetron [‡]	None	None	None
Oral Aprepitant Regimen				
Aprepitant capsules	125 mg	80 mg	80 mg	None
Oral dexamethasone [§]	12 mg	8 mg	8 mg	8 mg

Ondansetron	Ondansetron [‡]	None	None	None
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- * Fosaprepitant placebo, aprepitant placebo and dexamethasone placebo (in the evenings on Days 3 and 4) were used to maintain blinding.
- † Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. Dexamethasone was also administered in the evenings on Days 3 and 4. The 12 mg dose of dexamethasone on Day 1 and the 8 mg once daily dose on Day 2 reflects a dosage adjustment to account for a drug interaction with the fosaprepitant regimen [see *Clinical Pharmacology (12.3)*].
- ‡ Ondansetron 32 mg intravenous was used in the clinical trial. Although this dose was used in the clinical trial, this is no longer the currently recommended dose. Refer to the ondansetron prescribing information for the current recommended dose.
- § Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The 12 mg dose of dexamethasone on Day 1 and the 8 mg once daily dose on Days 2 through 4 reflects a dosage adjustment to account for a drug interaction with the oral aprepitant regimen [see *Clinical Pharmacology (12.3)*].

The efficacy of a single-dose of intravenous fosaprepitant was evaluated based on the primary and secondary endpoints listed in Table 12 and was shown to be non-inferior to that of the 3-day oral aprepitant regimen with regard to complete response in each of the evaluated phases. The pre-specified non-inferiority margin for complete response in the overall phase was 7%. The pre-specified non-inferiority margin for complete response in the delayed phase was 7.3%. The pre-specified non-inferiority margin for no vomiting in the overall phase was 8.2%.

Table 12. Percent of Patients Receiving HEC Responding by Treatment Group and Phase — Cycle 1

ENDPOINTS	Intravenous Fosaprepitant Regimen (N = 1106)* %	Oral aprepitant Regimen (N = 1134)* %	Difference [†] (95% CI)
PRIMARY ENDPOINT			
Complete Response [‡]			
Overall [§]	71.9	72.3	-0.4 (-4.1, 3.3)
SECONDARY ENDPOINTS			
Complete Response [‡]			
Delayed phase [¶]	74.3	74.2	0.1 (-3.5, 3.7)
No Vomiting			
Overall [§]	72.9	74.6	-1.7 (-5.3, 2.0)

* N: Number of patients included in the primary analysis of complete response.

† Difference and Confidence interval (CI) were calculated using the method proposed by Miettinen and Nurminen and adjusted for gender.

‡ Complete Response = no vomiting and no use of rescue therapy.

§ Overall = 0 to 120 hours post-initiation of cisplatin chemotherapy.

¶ Delayed phase = 25 to 120 hours post-initiation of cisplatin chemotherapy.

14.2 Prevention of Nausea and Vomiting Associated with MEC

Single-Dose Intravenous Fosaprepitant – MEC

In a randomized, parallel, double-blind, active comparator-controlled study, 150 mg fosaprepitant as a single intravenous infusion (N=502) in combination with ondansetron and dexamethasone (intravenous fosaprepitant regimen) was compared with ondansetron and dexamethasone alone (standard therapy) (N=498) (see Table 13) in patients receiving a MEC regimen. Patient demographics were similar

between the two treatment groups. Of the total 1,000 patients included in the efficacy analysis, 41% were men, 84% White, 4% Asian, 1% American Indian/Alaska Native, 2% Black, 10% Multi-Racial, and 19% Hispanic/Latino ethnicity. Patient ages ranged from 23 to 88 years of age, with a mean age of 60 years. The most commonly administered MEC chemotherapeutic agents were carboplatin (51%), oxaliplatin (24%), and cyclophosphamide (12%).

Table 13. Treatment Regimens in MEC Trial*

	Day 1	Day 2	Day 3
Intravenous Fosaprepitant Regimen			
Fosaprepitant	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy	None	None
Oral Dexamethasone [†]	12 mg	None	None
Oral Ondansetron [‡]	8 mg for 2 doses	None	None
Standard Therapy			
Oral Dexamethasone	20 mg	None	None
Oral Ondansetron [‡]	8 mg for 2 doses	8 mg twice daily	8 mg twice daily

* Fosaprepitant placebo and dexamethasone placebo (on Day 1) were used to maintain blinding.

[†] Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1. The 12 mg dose reflects a dosage adjustment to account for a drug interaction with the fosaprepitant regimen [see *Clinical Pharmacology* (12.3)].

[‡] The first ondansetron dose was administered 30 to 60 minutes prior to chemotherapy treatment on Day 1 and the second dose was administered 8 hours after first ondansetron dose.

The primary endpoint was complete response (defined as no vomiting and no rescue therapy) in the delayed phase (25 to 120 hours) of chemotherapy-induced nausea and vomiting. The results by treatment group are shown in Table 14.

Table 14. Percent of Patients Receiving MEC Responding by Treatment Group

ENDPOINTS	Intravenous Fosaprepitant Regimen (N = 502)* %	Standard Therapy Regimen (N = 498)* %	P-Value	Treatment Difference (95% CI)
PRIMARY ENDPOINT				
Complete Response [†]				
Delayed phase [‡]	78.9	68.5	<0.001	10.4 (5.1, 15.9)

* N: Number of patients included in the intention to treat population.

[†] Complete Response = no vomiting and no use of rescue therapy.

[‡] Delayed phase = 25 to 120 hours post-initiation of chemotherapy.

3-Day Oral Aprepitant -- MEC

In a multicenter, randomized, double-blind, parallel-group, clinical study in breast cancer patients, a 3-day oral aprepitant regimen was compared with a standard of care therapy in patients receiving a MEC regimen that included cyclophosphamide 750 to 1500 mg/m²; or cyclophosphamide 500 to 1500 mg/m² and doxorubicin (≤ 60 mg/m²) or epirubicin (≤ 100 mg/m²). Patients (N = 866) were randomized to either the aprepitant regimen (N = 438) or standard therapy (N = 428). The treatment regimens are defined in Table 15.

In this study, the most common chemotherapy combinations were cyclophosphamide plus doxorubicin (61%); and cyclophosphamide plus epirubicin and fluorouracil (22%).

Of the 438 patients who were randomized to receive the oral aprepitant regimen, 99.5% were women. Of these, approximately 80% were White, 8% Black, 8% Asian, 4% Hispanic, and < 1% Other. The aprepitant-treated patients in this clinical study ranged from 25 to 78 years of age, with a mean age of 53 years; 70 patients were 65 years or older, with 12 patients being over 74 years.

Table 15. Treatment Regimens in MEC Trial*

	Day 1	Day 2	Day 3
Oral Aprepitant Regimen			
Aprepitant	125 mg orally [†]	80 mg orally	80 mg orally
Dexamethasone	12 mg orally [‡]	None	None
Ondansetron	8 mg orally × 2 doses [§]	None	None
Standard Therapy			
Dexamethasone	20 mg orally	None	None
Ondansetron	8 mg orally × 2 doses	8 mg orally twice daily	8 mg orally twice daily

* Aprepitant placebo and dexamethasone placebo were used to maintain blinding.

[†] 1 hour prior to chemotherapy.

[‡] Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1.

[§] Ondansetron was administered 30 to 60 minutes prior to chemotherapy treatment on Day 1 and 8 hours after first ondansetron dose.

The antiemetic activity of oral aprepitant was evaluated based on the following endpoints in which emetic episodes included vomiting, retching, or dry heaves:

Primary endpoint:

- complete response (defined as no emetic episodes and no use of rescue therapy as recorded in patient diaries) in the overall phase (0 to 120 hours post-chemotherapy)

Other prespecified endpoints:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no nausea (maximum nausea visual analogue scale [VAS] score < 5 mm on a 0 to 100 mm scale)
- no significant nausea (maximum VAS score < 25 mm on a 0 to 100 mm scale)
- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum VAS score < 25 mm on a 0 to 100 mm scale)
- complete response during the acute and delayed phases.

A summary of the key results from this study is shown in Table 16.

Table 16. Percent of Patients Receiving MEC Responding by Treatment Group and Phase – Cycle 1

ENDPOINTS	Oral Aprepitant Regimen (N = 433)* %	Standard Therapy (N = 424)* %	p-Value
PRIMARY ENDPOINT[†]			
Complete Response	51	42	0.015
OTHER PRESPECIFIED ENDPOINTS[†]			
No Emesis	76	59	NS [‡]

No Nausea	33	33	NS
No Significant Nausea	61	56	NS
No Rescue Therapy	59	56	NS
Complete Protection	43	37	NS

* N: Number of patients included in the primary analysis of complete response.

† Overall: 0 to 120 hours post-chemotherapy treatment.

‡ NS when adjusted for prespecified multiple comparisons rule; unadjusted p-value < 0.001.

In this study, a statistically significantly ($p = 0.015$) higher proportion of patients receiving the oral aprepitant regimen in Cycle 1 had a complete response (primary endpoint) during the overall phase compared with patients receiving standard therapy. The difference between treatment groups was primarily driven by the "No Emesis Endpoint", a principal component of this composite primary endpoint. In addition, a higher proportion of patients receiving the oral aprepitant regimen in Cycle 1 had a complete response during the acute (0 to 24 hours) and delayed (25 to 120 hours) phases compared with patients receiving standard therapy; however, the treatment group differences failed to reach statistical significance, after multiplicity adjustments.

Additional Patient-Reported Outcomes: In this study, in patients receiving MEC, the impact of nausea and vomiting on patients' daily lives was assessed in Cycle 1 using the FLIE. A higher proportion of patients receiving the oral aprepitant regimen reported minimal or no impact on daily life (64% versus 56%). This difference between treatment groups was primarily driven by the "No Vomiting Domain" of this composite endpoint.

Multiple-Cycle Extension: Patients receiving MEC were permitted to continue into the Multiple-Cycle extension of the study for up to 3 additional cycles of chemotherapy. Antiemetic effect for patients receiving the aprepitant regimen is maintained during all cycles.

Oral Aprepitant Postmarketing Trial: In another multicenter, randomized, double-blind, parallel-group, clinical study in 848 cancer patients, the 3-day oral aprepitant regimen ($N = 430$) was compared with a standard of care therapy ($N = 418$) in patients receiving a MEC regimen that included any intravenous dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin; intravenous cyclophosphamide (less than 1500 mg/m^2); or intravenous cytarabine (greater than 1 g/m^2).

Of the 430 patients who were randomized to receive the oral aprepitant regimen, 76% were women and 24% were men. The distribution by race was 67% White, 6% Black or African American, 11% Asian, and 12% multiracial. Classified by ethnicity, 36% were Hispanic and 64% were non-Hispanic. The aprepitant-treated patients in this clinical study ranged from 22 to 85 years of age, with a mean age of 57 years; approximately 59% of the patients were 55 years or older with 32 patients being over 74 years. Patients receiving the aprepitant regimen were receiving chemotherapy for a variety of tumor types including 50% with breast cancer, 21% with gastrointestinal cancers including colorectal cancer, 13% with lung cancer and 6% with gynecological cancers.

The antiemetic activity of aprepitant was evaluated based on no vomiting (with or without rescue therapy) in the overall period (0 to 120 hours post-chemotherapy) and complete response (defined as no vomiting and no use of rescue therapy) in the overall period.

A summary of the key results from this study is shown in Table 17.

Table 17. Percent of Patients Receiving MEC Responding by Treatment Group for Study 2 – Cycle 1

ENDPOINTS	Oral Aprepitant Regimen (N = 430)*	Standard Therapy (N = 418)*	p-Value
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	%	%	
No Vomiting Overall	76	62	< 0.0001
Complete Response Overall	69	56	0.0003

* N = Number of patients who received chemotherapy treatment, study drug, and had at least one post-treatment efficacy evaluation.

In this study, a statistically significantly higher proportion of patients receiving the oral aprepitant regimen (76%) in Cycle 1 had no vomiting during the overall phase compared with patients receiving standard therapy (62%). In addition, a higher proportion of patients receiving the aprepitant regimen (69%) in Cycle 1 had a complete response in the overall phase (0 to 120 hours) compared with patients receiving standard therapy (56%). In the acute phase (0 to 24 hours following initiation of chemotherapy), a higher proportion of patients receiving aprepitant compared to patients receiving standard therapy were observed to have no vomiting (92% and 84%, respectively) and complete response (89% and 80%, respectively). In the delayed phase (25 to 120 hours following initiation of chemotherapy), a higher proportion of patients receiving aprepitant compared to patients receiving standard therapy were observed to have no vomiting (78% and 67%, respectively) and complete response (71% and 61%, respectively).

In a subgroup analysis by tumor type, a numerically higher proportion of patients receiving aprepitant were observed to have no vomiting and complete response compared to patients receiving standard therapy. For gender, the difference in complete response rates between the aprepitant and standard regimen groups was 14% in females (64.5% and 50.3%, respectively) and 4% in males (82.2% and 78.2%, respectively) during the overall phase. A similar difference for gender was observed for the no vomiting endpoint.

16 HOW SUPPLIED/STORAGE AND HANDLING

CINVANTI injectable emulsion is supplied as an opaque, off-white to amber emulsion in a single-dose glass vial containing 130 mg/18 mL aprepitant:

NDC 47426-201-01	1 single-dose vial per carton
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Storage

CINVANTI injectable emulsion vials must be refrigerated, store at 2°C-8°C (36°F-46°F). CINVANTI injectable emulsion vials can remain at room temperature up to 60 days.

Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity

Advise patients that hypersensitivity reactions, including anaphylaxis, have been reported [*see Warnings and Precautions (5.2)*]. Advise patients to stop taking CINVANTI and seek immediate medical attention if they experience signs or symptoms of a hypersensitivity reaction, such as hives, rash and itching, skin peeling or sores, or difficulty in breathing or swallowing, or dizziness, rapid or weak heartbeat or feeling faint.

Drug Interactions

Advise patients to discuss all medications they are taking, including other prescription, non-prescription medication or herbal products [*see Contraindications (4), Warnings and Precautions (5.1)*].

Warfarin: Instruct patients on chronic warfarin therapy to follow instructions from their healthcare provider regarding blood draws to monitor their INR during the 2-week period, particularly at 7 to 10 days, following initiation of CINVANTI with each chemotherapy cycle [see *Warnings and Precautions (5.3)*].

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

Pregnancy

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

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PATIENT INFORMATION
CINVANTI (sin van' tee)
(aprepitant)
injectable emulsion, for intravenous use

What is CINVANTI?

CINVANTI is a prescription medicine used with other medicines that treat nausea and vomiting in adults to prevent nausea and vomiting caused by certain anti-cancer (chemotherapy) medicines.

- CINVANTI is not used to treat nausea and vomiting that you already have.
- It is not known if CINVANTI is safe and effective in children.

Do not receive CINVANTI if you:

- are allergic to aprepitant, or any of the ingredients in CINVANTI. See the end of this leaflet for a complete list of the ingredients in CINVANTI.
- are taking pimozide (ORAP).

Before receiving CINVANTI, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems.
- are pregnant or plan to become pregnant. CINVANTI may harm your unborn baby.
 - Women who use birth control medicines containing hormones to prevent pregnancy (birth control pills, skin patches, implants, and certain IUDs) should also use a backup method of birth control that does not contain hormones, such as condoms and spermicides, during treatment with CINVANTI and for 1 month after receiving the last dose of CINVANTI.
- are breastfeeding or plan to breastfeed. It is not known if CINVANTI passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive CINVANTI.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

CINVANTI may affect the way other medicines work, and other medicines may affect the way CINVANTI works, causing serious side effects.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How will I receive CINVANTI?

- CINVANTI is given on Day 1. It will be given to you by intravenous (IV) injection or infusion in your vein about 30 minutes before you start your chemotherapy treatment.
 - If you take the blood thinner medicine warfarin sodium (COUMADIN, JANTOVEN), your healthcare provider may do blood tests after you receive CINVANTI to check your blood clotting.
-

What are the possible side effects of CINVANTI?

CINVANTI may cause serious side effects, including:

- **Serious allergic reactions.** Serious allergic reactions can happen during your CINVANTI infusion. Tell your healthcare provider or nurse right away if you get any of these symptoms during or soon after your infusion:
 - trouble breathing or swallowing, shortness of breath or wheezing
 - swelling of your eyes, face, tongue, or throat
 - flushing or redness of your face or skin
 - hives, rash, itching
 - dizziness, a rapid or weak heartbeat, or you feel faint

The most common side effects of CINVANTI include:

- tiredness
- diarrhea
- low white blood cell and red blood cell counts
- weakness
- feeling weak or numb in your arms and legs
- headache
- indigestion
- urinary tract infection
- belching or burping
- pain in your arms and legs

Infusion-site side effects with CINVANTI may include: pain, hardening, redness or itching at the site of infusion. Swelling (inflammation) of a vein caused by a blood clot can also happen at the infusion site. Tell your healthcare provider if you get any infusion-site side effects.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of CINVANTI. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of CINVANTI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about CINVANTI that is written for health professionals.

What are the ingredients in CINVANTI?

Active ingredient: aprepitant

Inactive ingredients: egg lecithin, ethanol, sodium oleate, soybean oil, sucrose, and water for injection.

Manufactured for: Heron Therapeutics, Inc., San Diego, CA, 92121, USA

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For more information about CINVANTI call 1-844-437-6611 or go to www.CINVANTI.com.

This Patient Information has been approved by the U.S. Food and Drug Administration

Approved: October 2019

PRINCIPAL DISPLAY PANEL - 130 mg/18 mL Vial Carton

NDC 47426-201-01

Rx Only

CINVANTI®
(aprepitant)
injectable emulsion

130 mg/18 mL
(7.2 mg/mL)

For Intravenous Use Only

Must be refrigerated. Store at
2°C-8°C (36°F-46°F). Do Not Freeze.

1 Sterile Single-Dose Vial
Discard Unused Portion

HERON
THERAPEUTICS

NDC 47426-201-01

Rx Only

CINVANTI®

(aprepitant)
injectable emulsion

130 mg/18 mL (7.2 mg/mL)

For Intravenous Use Only

**Must be refrigerated. Store at
2°C-8°C (36°F-46°F). Do Not Freeze.**

**1 Sterile Single-Dose Vial
Discard Unused Portion**



PRINCIPAL DISPLAY PANEL - 130 mg/18 mL Vial Carton - Not For Sale

NDC 47426-201-01

Rx Only

CINVANTI®

(aprepitant)
injectable emulsion

130 mg/18 mL
(7.2 mg/mL)

For Intravenous Use Only

Must be refrigerated. Store at
2°C-8°C (36°F-46°F). Do Not Freeze.

1 Sterile Single-Dose Vial
Discard Unused Portion

Not For Sale

HERON
THERAPEUTICS

NDC 47426-201-01

Rx Only

CINVANTI[®]

(aprepitant)
injectable emulsion

130 mg/18 mL (7.2 mg/mL)

For Intravenous Use Only

**Must be refrigerated. Store at
2°C-8°C (36°F-46°F). Do Not Freeze.**

**1 Sterile Single-Dose Vial
Discard Unused Portion**

Not For Sale



CINVANTI

aprepitant injection, emulsion

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:47426-201
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
APREPITANT (UNII: 1NF15YR6UY) (APREPITANT - UNII:1NF15YR6UY)	APREPITANT	130 mg in 18 mL

Inactive Ingredients

Ingredient Name	Strength
EGG PHOSPHOLIPIDS (UNII: 1Z74184RGV)	2.6 g in 18 mL
ALCOHOL (UNII: 3K9958V90M)	0.5 g in 18 mL
SODIUM OLEATE (UNII: 399SL044HN)	0.1 g in 18 mL
SOYBEAN OIL (UNII: 241ATL177A)	1.7 g in 18 mL
SUCROSE (UNII: C15IH8M554)	1 g in 18 mL
WATER (UNII: 059QF0KO0R)	12 g in 18 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:47426-201-01	1 in 1 CARTON	01/03/2018	
1		18 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA209296	01/03/2018	

Labeler - Heron Therapeutics, Inc. (102099843)**Registrant** - Heron Therapeutics, Inc. (102099843)**Establishment**

Name	Address	ID/FEI	Business Operations
Alcami Corporation		832394733	manufacture(47426-201)

Establishment

Name	Address	ID/FEI	Business Operations
Sharp Corporation		143696495	label(47426-201)

Establishment

Name	Address	ID/FEI	Business Operations
OSO BioPharmaceuticals Manufacturing, LLC		078268825	manufacture(47426-201)