

HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do **not** include all the information needed to use FOSAPREPITANT FOR INJECTION safely and effectively. See full prescribing information for FOSAPREPITANT FOR INJECTION.

FOSAPREPITANT for injection, for intravenous use Initial U.S. Approval: 2008

RECENT MAJOR CHANGES	
Warnings and Precautions (5.2)	08/2017
Warnings and Precautions (5.3)	03/2018

INDICATIONS AND USAGE

Fosaprepitant for injection is a substance P/neurokinin-1 (NK₁) receptor antagonist, indicated in adults, in combination with other antiemetic agents, for the prevention of (1):

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

Limitations of Use (1)

- Fosaprepitant for injection has not been studied for treatment of established nausea and vomiting.

DOSAGE AND ADMINISTRATION

- Recommended Dosage (2.1)**
- Adults: 150 mg on Day 1.
- Administer Fosaprepitant for injection on Day 1 as an intravenous infusion over 20 to 30 minutes (adults), completing the infusion approximately 30 minutes prior to chemotherapy.
- See Full Prescribing Information for dosages of concomitant antiemetic(s). (2.1)

DOSAGE FORMS AND STRENGTHS

Fosaprepitant for injection: 150 mg fosaprepitant, lyophilized powder in single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

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

DOSAGE AND ADMINISTRATION

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CONTRAINDICATIONS

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- Concurrent use with pimozide. (4)

INDICATIONS AND USAGE
1. Prevention of Nausea and Vomiting Associated with HEC and MEC in Adult Patients
2. Preparation of Fosaprepitant for Injection

DOSAGE AND ADMINISTRATION

- Prevention of Nausea and Vomiting Associated with HEC and MEC in Adult Patients
- Preparation of Fosaprepitant for Injection

DOSAGE FORMS AND STRENGTHS

Fosaprepitant for injection: 150 mg fosaprepitant, lyophilized powder in single-dose vial for reconstitution. (3)

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

Limitations of Use (1)

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

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WARNINGS AND PRECAUTIONS

- CYP3A4 Interactions:** Fosaprepitant is a weak inhibitor of CYP3A4, and aprepitant, the active moiety, is a substrate, inhibitor, and inducer of CYP3A4; see Full Prescribing Information for recommendations regarding contraindications, risk of adverse reactions, and dosage adjustment of Fosaprepitant for injection and concomitant drugs. (4, 5.1, 7.1, 7.2)
- Hypersensitivity Reactions (including anaphylaxis and anaphylactic shock):** May occur during or soon after infusion. If symptoms occur, discontinue the drug. Do not reintitiate Fosaprepitant for injection if symptoms occur with previous use. (4, 5.2)
- Infusion Site Reactions (including thrombophlebitis, necrosis, and vasculitis):** Majority of reactions reported in patients receiving vesicant chemotherapy. Avoid infusion into small veins. Discontinue infusion and administer treatment if a severe reaction develops. (5.3)
- 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 Fosaprepitant for injection. (5.4, 7.1)
- Hormonal Contraceptives:** Efficacy of contraceptives may be reduced during and for 28 days following administration of Fosaprepitant for injection . Use effective alternative or back-up methods of contraception. (5.5, 7.1, 8.3)

ADVERSE REACTIONS

- Most common adverse reactions in adults (≥2%) are: fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral neuropathy, leukopenia, dyspepsia, urinary tract infection, pain in extremity. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 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, 5.4, 5.5, 7.1, 7.2)

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

Pediatric use information is approved for Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.'s Emend (fosaprepitant) for injection. However, due to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

ADVERSE REACTIONS

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USE IN SPECIFIC POPULATIONS

- Pregnancy
- Lactation
- Females and Males of Reproductive Potential
- Pediatric Use
- Geriatric Use
- Patients with Hepatic Impairment

OVERDOSAGE

DESCRIPTION

CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics

NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility

CLINICAL STUDIES

- Prevention of Nausea and Vomiting Associated with HEC in Adults
- Prevention of Nausea and Vomiting Associated with MEC in Adults

HOW SUPPLIED/STORAGE AND HANDLING

PATIENT COUNSELING INFORMATION

- Sections or subsections omitted from the full prescribing information are not listed.

Emend (fosaprepitant) for injection. However, due to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

DOSAGE AND ADMINISTRATION

- Prevention of Nausea and Vomiting Associated with HEC and MEC in Adult Patients

The recommended dosage of fosaprepitant for injection, dexamethasone, and a 5-HT₃ antagonist for the prevention of nausea and vomiting associated with administration of HEC or MEC in adults is shown in Table 1 or Table 2, respectively. Administer fosaprepitant for injection as an intravenous infusion on Day 1 over 20 to 30 minutes, completing the infusion approximately 30 minutes prior to chemotherapy.

Table 1 Recommended Adult Dosing for the Prevention of Nausea and Vomiting Associated with HEC				
	Day 1	Day 2	Day 3	Day 4
Fosaprepitant for injection	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy	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 the 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 fosaprepitant for injection [see *Clinical Pharmacology* (12.3)].

Table 2 Recommended Adult Dosing for the Prevention of Nausea and Vomiting Associated with MEC

Day 1	
Fosaprepitant for injection	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy
Dexamethasone*	12 mg orally
5-HT ₃ antagonist	See selected 5-HT ₃ antagonist prescribing information for the 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 fosaprepitant for injection [see *Clinical Pharmacology* (12.3)].

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Preparation of Fosaprepitant for Injection

Table 5 Preparation Instructions for Fosaprepitant for Injection (150 mg)	
Step 1	Aseptically inject 5 mL 0.9% Sodium Chloride Injection, USP into the vial. Assume that 0.9% Sodium Chloride Injection, USP is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and letting 0.9% Sodium Chloride Injection, USP into the vial.
Step 2	Aseptically prepare an infusion bag filled with 145 mL of 0.9% Sodium Chloride Injection, USP.
Step 3	Aseptically withdraw the entire volume from the vial and transfer it into the infusion bag containing 145 mL of 0.9% Sodium Chloride Injection, USP to yield a total volume of 150 mL and a final concentration of 1 mg/mL.
Step 4	Gently invert the bag 2 to 3 times.
Step 5	Adults <p>The entire volume of the prepared infusion bag (150 mL) should be administered.</p>
Step 6	Before administration, inspect the bag for particulate matter and discoloration. Discard the bag if particulate and/or discoloration are observed.

Caution: Do not mix or reconstitute fosaprepitant for injection with solutions for which physical and chemical compatibility have not been established. Fosaprepitant for injection is incompatible with any solutions containing divalent cations (e.g., Ca²⁺, Mg²⁺), including Lactated Ringer's Solution and Hartmann's Solution.

Storage

The reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25°C (77°F)].

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DOSAGE FORMS AND STRENGTHS

Fosaprepitant for injection: 150 mg fosaprepitant, white to off-white lyophilized powder in single-dose glass vial for reconstitution.

CONTRAINDICATIONS

Fosaprepitant for injection is contraindicated in patients:

- who are hypersensitive to any component of the product. Hypersensitivity reactions including anaphy-

lactic reactions, flushing, erythema, and dyspnea have been reported [see *Warnings and Precautions* (5.2), *Adverse Reactions* (6.2)].

- taking pimozide. Inhibition of CYP3A4 by aprepitant, the active moiety, could result in elevated plasma concentrations of this drug, which is a CYP3A4 substrate, potentially causing serious or life-threatening reactions, such as QT prolongation, a known adverse reaction of pimozide [see *Warnings and Precautions* (5.1)].

WARNINGS AND PRECAUTIONS

Clinically Significant CYP3A4 Drug Interactions

5.1 Fosaprepitant, a prodrug of aprepitant, is a weak inhibitor of CYP3A4, and aprepitant is a substrate, inhibitor, and inducer of CYP3A4.

- Use of fosaprepitant for injection with other drugs that are CYP3A4 substrates, may result in increased plasma concentration of the concomitant drug.
 - Use of pimozide with fosaprepitant for injection is contraindicated due to the risk of significantly increased plasma concentrations of pimozide, potentially resulting in prolongation of the QT interval, a known adverse reaction of pimozide [see *Contraindications* (4)].
- Use of fosaprepitant for injection 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 fosaprepitant for injection.
- Use of fosaprepitant for injection with strong CYP3A4 inducers (e.g., rifampin) may result in a reduction in aprepitant plasma concentrations and decreased efficacy of fosaprepitant for injection.

See Table 7 and Table 8 for a listing of potentially significant drug interactions [see *Drug Interactions* (7.1, 7.2)].

5.2 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock, during or soon after infusion of fosaprepitant have occurred. Symptoms including flushing, erythema, dyspnea, hypotension and syncope have been reported [see *Adverse Reactions* (6.2)].

Monitor patients during and after infusion. If hypersensitivity reactions occur, discontinue the infusion and administer appropriate medical therapy. Do not reintitiate fosaprepitant for injection in patients who experience these symptoms with previous use [see *Contraindications* (4)].

5.3 Infusion Site Reactions

Infusion site reactions (ISRs) have been reported with the use of fosaprepitant for injection [see *Adverse Reactions* (6.1)]. The majority of severe ISRs, including thrombophlebitis and vasculitis, were reported with concomitant vesicant (anthracycline-based) chemotherapy administration, particularly when associated with extravasation. Necrosis was also reported in some patients with concomitant vesicant chemotherapy. Most ISRs occurred with the first, second or third exposure to single doses of fosaprepitant for injection and in some cases, reactions persisted for two weeks or longer. Treatment of severe ISRs consisted of medical, and in some cases surgical, intervention.

Avoid infusion of fosaprepitant for injection into small veins or through a butterfly catheter. If a severe ISR develops during infusion, discontinue the infusion and administer appropriate medical treatment.

5.4 Decrease in INR with Concomitant Warfarin

Coadministration of fosaprepitant for injection 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 fosaprepitant for injection with each chemotherapy cycle [see *Drug Interactions* (7.1)].

5.5 Risk of Reduced Efficacy of Hormonal Contraceptives

Upon coadministration with fosaprepitant for injection, the efficacy of hormonal contraceptives may be reduced during administration of and for 28 days following the last dose of fosaprepitant for injection [see *Clinical Pharmacology* (12.3)]. Advise patients to use effective alternative or back-up methods of contraception during treatment with fosaprepitant for injection and for 1 month following administration of fosaprepitant for injection [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)]
- Infusion Site Reactions [see *Warnings and Precautions* (5.3)]

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 overall safety of fosaprepitant for injection was evaluated in approximately 1600 adult patients.

Adverse Reactions in Adults for the Prevention of Nausea and Vomiting Associated with MEC

In an active-controlled clinical trial in patients receiving MEC, safety was evaluated in 504 patients receiving a single dose of fosaprepitant for injection in combination with ondansetron and dexamethasone (fosaprepitant for injection regimen) compared to 497 patients receiving ondansetron and dexmethasone alone (standard therapy). The most common adverse reactions are listed in Table 6.

Table 6 Most Common Adverse Reactions in Patients Receiving MEC*

	Fosaprepitant for injection, 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 ≥2% of patients treated with the fosaprepitant for injection regimen and at a greater incidence than standard therapy.

[†] Fosaprepitant for injection regimen

[‡] Standard therapy

Infusion-site reactions were reported in 2.2% of patients treated with the fosaprepitant for injection 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 infusion-site thrombophlebitis (0.6%, 0.0%), reported in the fosaprepitant for injection regimen compared to standard therapy, respectively.

Adverse Reactions in Adults for the Prevention of Nausea and Vomiting Associated with HEC.

In an active-controlled clinical study in patients receiving HEC, safety was evaluated for 1,143 patients receiving a single dose of fosaprepitant for injection compared to 1,169 patients receiving the 3-day regimen of oral aprepitant [see *Clinical Studies* (14.1)]. The safety profile was generally similar to that seen in the MEC study with fosaprepitant and prior HEC studies with aprepitant. However, infusion-site reactions occurred at a higher incidence in patients in the fosaprepitant group (3.0%) compared to those in the aprepitant group (0.5%). The following additional infusion-site reactions occurred in the HEC study and were not reported in the MEC study described above: infusion-site erythema (0.5%, 0.1%), infusion-site pruritus (0.3%, 0.0%), and infusion-site induration (0.2%, 0.1%), reported in the fosaprepitant group compared to the aprepitant group, respectively.

Because fosaprepitant is converted to aprepitant, those adverse reactions associated with aprepitant might also be expected to occur with fosaprepitant for injection. See the full prescribing information for aprepitant capsules for complete safety information regarding studies performed with oral aprepitant.

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6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of fosaprepitant for injection. 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 fosaprepitant for injection and ifosfamide coadministration.

7 DRUG INTERACTIONS

7.1 Effect of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs

When administered intravenously, fosaprepitant, a prodrug of aprepitant, is converted to aprepitant within 30 minutes. Therefore, drug interactions following administration of fosaprepitant for injection are likely to occur with drugs that interact with oral aprepitant.

Fosaprepitant, given as a single 150-mg dose, is a weak inhibitor of CYP3A4, and the weak inhibition of CYP3A4 continues for 2 days after single dose administration. Single dose fosaprepitant does not induce CYP3A4. Aprepitant is a substrate, an 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 fosaprepitant for injection [see *Contraindications* (4)]. Dosage adjustment of some CYP3A4 and CYP2C9 substrates may be warranted, as shown in Table 7.

Table 7 Effects of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs

CYP3A4 Substrates	
<i>Pimozide</i>	
<i>Clinical Impact</i>	Increased pimozide exposure.
<i>Intervention</i>	Fosaprepitant for injection is contraindicated [see <i>Contraindications</i> (4)].
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</i> (12.3)].
<i>Intervention</i>	Monitor for benzodiazepine-related adverse reactions.
Dexamethasone	
<i>Clinical Impact</i>	Increased dexamethasone exposure [see <i>Clinical Pharmacology</i> (12.3)].
<i>Intervention</i>	Reduce the dose of oral dexamethasone by approximately 50% [see <i>Dosage and Administration</i> (2.1)].
Methylprednisolone	
<i>Clinical Impact</i>	Increased methylprednisolone exposure [see <i>Clinical Pharmacology</i> (12.3)].
<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</i> (12.3)].
<i>Intervention</i>	Vinblastine, vincristine, or ifosfamide or other chemotherapeutic agents: <ul style="list-style-type: none">Monitor for chemotherapeutic-related adverse reactions. <p>Etoposide, vinorelbine, paclitaxel, and docetaxel <ul style="list-style-type: none">No dosage adjustment needed.</p>
Hormonal Contraceptives	
<i>Clinical Impact</i>	Decreased hormonal exposure during administration of and for 28 days after administration of the last dose of fosaprepitant for injection [see <i>Warnings and Precautions</i> (5.5), <i>Use in Specific Populations</i> (8.3), and <i>Clinical Pharmacology</i> (12.3)].
<i>Intervention</i>	Effective alternative or back-up methods of contraception (such as condoms and spermicides) should be used during treatment with fosaprepitant for injection and for 1 month following administration of fosaprepitant for injection.
<i>Examples</i>	birth control pills, skin patches, implants, and certain IUDs
CYP2C9 Substrates	
Warfarin	
<i>Clinical Impact</i>	Decreased warfarin exposure and prolongation of prothrombin time (INR) [see <i>Warnings and Precautions</i> (5.4), <i>Clinical Pharmacology</i> (12.3)].
<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 fosaprepitant for injection with each chemotherapy cycle.
Other	
5-HT ₃ Antagonists	
<i>Clinical Impact</i>	No change in the exposure of the 5-HT ₃ antagonist [see <i>Clinical Pharmacology</i> (12.3)].
<i>Intervention</i>	No dosage adjustment needed.
<i>Examples</i>	ondansetron, granisetron, dolasetron

7.2 Effect of Other Drugs on the Pharmacokinetics of Fosaprepitant/Aprepitant

Aprepitant is a CYP3A4 substrate [see *Clinical Pharmacology* (12.3)]. Co-administration of fosaprepitant for injection with drugs that are inhibitors or inducers of CYP3A4 may result in increased or decreased plasma concentrations of aprepitant, respectively, as shown in Table 8.

Table 8 Effects of Other Drugs on Pharmacokinetics of Fosaprepitant/Aprepitant

Moderate to Strong CYP3A4 Inhibitors	
<i>Clinical Impact</i>	Significantly increased exposure of aprepitant may increase the risk of adverse reactions associated with fosaprepitant for injection [see <i>Adverse Reactions</i> (6.1), <i>Clinical Pharmacology</i> (12.3)].
<i>Intervention</i>	Avoid concomitant use of fosaprepitant for injection.
Examples	
	Moderate inhibitor: diltiazem
	Strong inhibitors: ketoconazole, itraconazole, nefazodone, troleanandomycin, clarithromycin, rifampin, neflavinir
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 fosaprepitant for injection [see <i>Clinical Pharmacology</i> (12.3)].
<i>Intervention</i>	Avoid concomitant use of fosaprepitant for injection.
<i>Examples</i>	rifampin, carbamazepine, phenytoin

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Risk Summary

There are insufficient data on use of fosaprepitant for injection in pregnant women to inform a drug associated risk. In animal reproduction studies, no adverse developmental effects were observed in rats or rabbits exposed during the period of organogenesis to systemic drug levels (AUC) approximately equivalent to the exposure at the recommended human dose (RHD) of 150 mg [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown

maximum feasible dose of 1000 mg/kg twice daily from the early postnatal period (Postnatal Day 10 (equivalent to a newborn human) through Postnatal Day 58 (approximately equivalent to a 15 year old human)). Slight changes in the onset of sexual maturation were observed in female and male rats; however, there were no effects on mating, fertility, embryonic-fetal survival, or histomorphology of the reproductive organs. There were no effects in neurobehavioral tests of sensory function, motor function, and learning and memory.

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8.5 Geriatric Use

Of the 1649 adult cancer patients treated with intravenous fosaprepitant for injection 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 for injection 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 Patients with 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 fosaprepitant for injection is administered *[see Clinical Pharmacology (12.3)].*

10 OVERDOSAGE

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

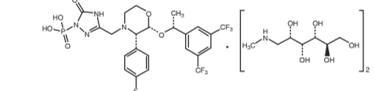
In the event of overdose, fosaprepitant for injection should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of fosaprepitant for injection, drug-induced emesis may not be effective in cases of fosaprepitant for injection overdosage.

Aprepitant is not removed by hemodialysis.

11 DESCRIPTION

Fosaprepitant for injection is a sterile, lyophilized formulation containing fosaprepitant dimeglumine, a prodrug of aprepitant (100 mg), and the NK1 receptor antagonist, an antiemetic agent, chemically described as 1-Deoxy-1-(methylamino)-D-glucitol[3-[[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]phosphonate (2:1 (salt)).

Its empirical formula is C₂₃H₂₂F₇N₄O₆ • 2(C₈H₁₇NO₅) and its structural formula is:



Fosaprepitant dimeglumine is a white to off-white amorphous powder with a molecular weight of 1004.83. It is freely soluble in water.

Each vial of fosaprepitant for injection for administration as an intravenous infusion contains 150 mg of fosaprepitant (equivalent to 245.3 mg of fosaprepitant dimeglumine) and the following inactive ingredients: edetate disodium (5.4 mg), polysorbate 80 (75 mg), lactose anhydrous (375 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fosaprepitant is a prodrug of aprepitant and accordingly, its antiemetic effects are attributable to aprepitant.

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, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CINV). 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 have shown 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 **Cardiac Electrophysiology**
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.

12.3 Pharmacokinetics

Aprepitant after Fosaprepitant Administration

Following administration of a single intravenous 150-mg dose of fosaprepitant, a prodrug of aprepitant administered as a 20-minute infusion to healthy subjects, the mean AUC_{0-24h} of aprepitant was 37.4 (± 14.8) mcg•hr/mL and the mean maximal aprepitant concentration (C_{max}) was 4.2 (± 1.2) mcg/mL. Plasma concentrations of fosaprepitant are below the limits of quantification (10 ng/mL) within 30 minutes of the completion of infusion.

Distribution

Aprepitant is greater than 95% bound to plasma proteins. The mean apparent volume of distribution at steady state (V_{dss}) was approximately 70 L in humans.

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

Elimination

Metabolism

Fosaprepitant is converted to aprepitant in *in vitro* incubations with human liver preparations and in S9 preparations from multiple other human tissues including kidney, lung and ileum. Thus, it appears that the conversion of fosaprepitant to aprepitant can occur in multiple extrahaptic tissues in addition to the liver.

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*
Following administration of a single intravenous 100-mg dose of [¹⁴C]-fosaprepitant to healthy subjects, 57% of the radioactivity was recovered in urine and 45% in feces.

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. The apparent terminal half-life ranged from approximately 8 to 13 hours.

Specific Populations

Age: Geriatric Population

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_{0-24h} 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)].*

Sex

Following oral administration of a single dose of aprepitant, ranging from 40 mg to 375 mg, the AUC_{0-24h} and C_{max} are 9% and 17% higher in females as compared with males. The half-life of aprepitant is approximately 25% lower in females as compared with males and T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful.

Race/Ethnicity

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

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.

Hepatic Impairment

Fosaprepitant is metabolized in various extrahepatic tissues; therefore hepatic impairment is not expected to alter the conversion of fosaprepitant to aprepitant.

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_{0-24h} 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 AUC_{0-24h} 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_{0-24h} 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)

Fosaprepitant, given as a single 150-mg dose, is a weak inhibitor of CYP3A4, with no evidence of inhibition or induction of CYP3A4 observed on Day 4. The weak inhibition of CYP3A4 continues for 2 days after single dose administration of fosaprepitant. Aprepitant is a substrate, an inhibitor, and an inducer of CYP3A4. Apreitant is also an inducer of CYP2C9.

Pediatric use information is approved for Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. s Emend (fosaprepitant) for injection. However, due to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

Drug Interactions Studies

Fosaprepitant, given as a single 150-mg dose, is a weak inhibitor of CYP3A4, with no evidence of inhibition or induction of CYP3A4 observed on Day 4. The weak inhibition of CYP3A4 continues for 2 days after single dose administration of fosaprepitant. Aprepitant is a substrate, an inhibitor, and an inducer of CYP3A4. Apreitant is also an inducer of CYP2C9.

Fosaprepitant or 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 administered as a single intravenous dose on Day 1 increased the AUC_{0-∞} 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 *[see Drug Interactions (7.1)].*

Corticosteroids:

Dexamethasone: Fosaprepitant administered as a single 150 mg intravenous dose on Day 1 increased the AUC_{0-24h} of dexamethasone, administered as a single 8-mg oral dose on Days 1, 2, and 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.

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.

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)].*

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

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: Co-administration 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

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 1,000 mg/kg twice daily. The highest dose produced systemic exposures to aprepitant approximately equivalent to (female rats) or less than (male rats) the adult human exposure at the RHD of 150 mg. Treatment with aprepitant at doses of 5 to 1,000 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 1,000 mg/kg twice daily and hepatocellular carcinomas and thyroid follicular cell adenomas at 125 to 1,000 mg/kg twice daily. In the mouse carcinogenicity studies, the animals were treated with oral doses ranging from 2.5 to 2,000 mg/kg/day. The highest dose produced a systemic exposure approximately 2 times the adult human exposure at the RHD of 150 mg. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice. Carcinogenicity studies were not conducted with fosaprepitant.

Mutagenesis

Aprepitant and fosaprepitant were 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

Fosaprepitant, when administered intravenously, is rapidly converted to aprepitant. In the fertility studies conducted with fosaprepitant and aprepitant, the highest systemic exposures to aprepitant were obtained following oral administration of aprepitant. 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 1,000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the recommended adult human dose of 150 mg and exposure in female rats approximately equivalent to the adult human exposure).

14 CLINICAL STUDIES

14.1 Prevention of Nausea and Vomiting Associated with HEC in Adults

In a randomized, parallel, double-blind, active-controlled study, fosaprepitant for injection 150 mg as a single intravenous infusion (N=1,147) was compared to a 3-day oral aprepitant regimen (N=1,179) 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 2,322 patients, 63% were men, 56% White, 26% Asian, 3% American Indian/Alaska Native, 2% Black, 13% Multi-Racial, and 3% 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%).

	Day 1	Day 2	Day 3	Day 4
Fosaprepitant/Aprepitant Regimen				
Fosaprepitant for injection	150 mg intravenously over 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

* Fosaprepitant for injection placebo, aprepitant capsules 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. The 12 mg dose reflects a dosage adjustment to account for a drug interaction with the fosaprepitant for injection regimen *[see Clinical Pharmacology (12.3)].*

[‡] Ondansetron 32 mg intravenous was used in the clinical trials of fosaprepitant/aprepitant. Although this dose was used in clinical trials, 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 Day 2 reflects a dosage adjustment to account for a drug interaction with the oral aprepitant regimen *[see Clinical Pharmacology (12.3)].*

The efficacy of fosaprepitant for injection 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 Adult Patients Receiving HEC Responding by Treatment Group and Phase – Cycle 1

ENDPOINTS	Fosaprepitant for Injection Regimen (N = 1,106)*	Oral Aprepitant Regimen (N = 1,134)*	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 Mettinen 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 in Adults

In a randomized, parallel, double-blind, active comparator-controlled study, fosaprepitant for injection 150 mg as a single intravenous infusion (N=502) in combination with ondansetron and dexamethasone (fosaprepitant for injection 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%).

	Day 1	Day 2	Day 3
Fosaprepitant for injection Regimen			
Fosaprepitant for injection	150 mg intravenously over 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 for injection 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 for injection 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 Adult Patients Receiving MEC Responding by Treatment Group

ENDPOINTS	Fosaprepitant for Injection Regimen (N = 892)*	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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Fosaprepitant for injection is a