HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FOSAPREPITANT DIMEGLUMINE FOR INJECTION safely and effectively. See full prescribing information for FOSAPREPITANT DIMEGLUMINE FOR INJECTION.

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

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

Dosage and Administration (2.1, 2.2) 01/2016

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

Fosaprepitant dimeglumine for injection is a substance P/neurokinin-1 (NK_1) 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.

Limitations of Use (1)

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

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

Dosage (2.1)

- Recommended dosage in adults is 150 mg on Day 1 as an intravenous infusion over 20 to 30 minutes approximately 30 minutes prior to chemotherapy.
- See Full Prescribing Information for recommended dosages of concomitant dexamethasone and a 5-HT_3 antagonist for HEC.

Preparation (2.2)

- Reconstitute with 5 mL of 0.9% sodium chloride.
- Add to infusion bag containing 145 mL 0.9% sodium chloride for a final concentration of 1 mg/mL.

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

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

----------CONTRAINDICATIONS----------

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

----------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 and concomitant drugs. (4, 5.1, 7.1, 7.2)
- Hypersensitivity Reactions: These may occur during infusion; if symptoms occur, discontinue the drug. Do not reinitiate the infusion if symptoms occur with first-time use. (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 fosaprepitant. (5.3, 7.1)
- Hormonal Contraceptives: Efficacy of contraceptives may be reduced during and for 28 days following administration of fosaprepitant. Use effective alternative or back-up methods of contraception. (5.4, 7.1, 8.3)

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

Most common adverse reactions (≥ 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, 5.2, 5.3, 5.4, 7.1, 7.2)

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

Revised: 5/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fosaprepitant dimeglumine for injection, 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.

Limitations of Use

- Fosaprepitant dimeglumine for injection 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

The recommended dosage of fosaprepitant dimeglumine for injection, dexamethasone, and a 5-HT_3 antagonist in adults for the prevention of nausea and vomiting associated with administration of HEC is shown in Table 1. Administer fosaprepitant dimeglumine for injection as an intravenous infusion on Day 1 over 20 to 30 minutes approximately 30 minutes prior to chemotherapy.

Table 1. Recommended Dosing for the Prevention of Nausea and Vomiting Associated with HEC

	Day 1	Day 2	Day 3	Day 4
Fosaprepitant dimeglumine 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 dimeglumine for injection *[see Clinical Pharmacology (12.3)]*.

2.2 Preparation of Fosaprepitant Dimeglumine for Injection

Table 3. Preparation Instructions for Fosaprepitant Dimeglumine for Injection

Step 1	Aseptically inject 5 mL 0.9% Sodium Chloride Injection, USP into the vial. Assure 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 jetting 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	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 dimeglumine for injection with solutions for which physical and chemical compatibility have not been established. Fosaprepitant dimeglumine for injection is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), 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)].

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

Fosaprepitant is contraindicated in patients:

- who are hypersensitive to any component of the product. Hypersensitivity reactions including anaphylactic reactions, flushing, erythema, and dyspnea have been reported *[see 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)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Clinically Significant CYP3A4 Drug Interactions

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

- Use of fosaprepitant with other drugs that are CYP3A4 substrates, may result in increased plasma concentration of the concomitant drug.
  - Use of pimozide with fosaprepitant 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 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.
- Use of fosaprepitant with strong CYP3A4 inducers (e.g., rifampin) may result in a reduction in aprepitant plasma concentrations and decreased efficacy of fosaprepitant.

See Table 5 and Table 6 for a listing of potentially significant drug interactions *[see Drug Interactions (7.1, 7.2)]*.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions during infusion of fosaprepitant including flushing, erythema, dyspnea, and anaphylaxis have been reported. If symptoms occur, discontinue the infusion and administer appropriate medical therapy. Do not reinitiate the infusion in patients who experience these symptoms during first-time use.

5.3 Decrease in INR with Concomitant Warfarin

Co-administration of fosaprepitant 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 with each chemotherapy cycle *[see Drug Interactions (7.1)]*.

5.4 Risk of Reduced Efficacy of Hormonal Contraceptives

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

6 ADVERSE REACTIONS

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.

Adverse Reactions 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 dimeglumine 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%) compared to those in the aprepitant group (0.5%). The following additional infusion-site reactions occurred in 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%), and infusion-site induration (0.2%, 0.1%), reported in the fosaprepitant group compared to the aprepitant group, respectively.

Since fosaprepitant is converted to aprepitant, those adverse reactions associated with aprepitant might also be expected to occur with fosaprepitant dimeglumine for injection.

See the full prescribing information for aprepitant capsules for complete safety information regarding studies performed with oral aprepitant.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of fosaprepitant/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.

Immune system disorders: hypersensitivity reactions including anaphylactic reactions *[see Contraindications (4)]*.

Nervous system disorders: ifosfamide-induced neurotoxicity reported after fosaprepitant and ifosfamide co-administration.

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 dimeglumine 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 *[see Contraindications (4)]*. Dosage adjustment of some CYP3A4 and CYP2C9 substrates may be warranted, as shown in Table 5.

Table 5. Effects of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs

CYP3A4 Substrates	
Pimozide	
Clinical Impact	Increased pimozide exposure.
Intervention	Fosaprepitant is contraindicated *[see Contraindications (4)]*.
Benzodiazepines	
Clinical Impact	Increased exposure to midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) may increase the risk of adverse reactions *[see Clinical Pharmacology (12.3)]*.
Intervention	Monitor for benzodiazepine-related adverse reactions.
Dexamethasone	
Clinical Impact	Increased dexamethasone exposure *[see Clinical Pharmacology (12.3)]*.
Intervention	Reduce the dose of oral dexamethasone by approximately 50% *[see Dosage and Administration (2.1)]*.
Methylprednisolone	
Clinical Impact	Increased methylprednisolone exposure *[see Clinical Pharmacology (12.3)]*.
Intervention	Reduce the dose of oral methylprednisolone by approximately 50% on Days 1 and 2 for patients receiving HEC. Reduce the dose of intravenous methylprednisolone by 25% on Days 1 and 2 for patients receiving HEC.
Chemotherapeutic agents that are metabolized by CYP3A4	
Clinical Impact	Increased exposure of the chemotherapeutic agent may increase the risk of adverse reactions *[see Clinical Pharmacology (12.3)]*.
Intervention	Vinblastine, vincristine, or ifosfamide or other chemotherapeutic agents • Monitor for chemotherapeutic-related adverse reactions. Etoposide, vinorelbine, paclitaxel, and docetaxel • No dosage adjustment needed.
Hormonal Contraceptives	
Clinical Impact	Decreased hormonal exposure during administration of and for 28 days after administration of the last dose of fosaprepitant *[see Warnings and Precautions (5.4), Use in Specific Populations (8.3), and Clinical Pharmacology (12.3)]*.
Intervention	Effective alternative or back-up methods of contraception (such as condoms and spermicides) should be used during treatment with fosaprepitant and for 1 month following administration of fosaprepitant.
Examples	birth control pills, skin patches, implants, and certain IUDs
CYP2C9 Substrates	
Warfarin	
Clinical Impact	Decreased warfarin exposure and prolongation of prothrombin time (INR) *[see Warnings and Precautions (5.3), Clinical Pharmacology (12.3)]*.
Intervention	In patients on chronic warfarin therapy, monitor the prothrombin time (INR) in the 2-week period, particularly at 7 to 10 days, following administration of fosaprepitant with each chemotherapy cycle.
Other	
5-HT_3 Antagonists	
Clinical Impact	No change in the exposure of the 5-HT_3 antagonist *[see Clinical Pharmacology (12.3)]*.
Intervention	No dosage adjustment needed.
Examples	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 with drugs that are inhibitors or inducers of CYP3A4 may result in increased or decreased plasma concentrations of aprepitant, respectively, as shown in Table 6.

Table 6. Effects of Other Drugs on Pharmacokinetics of Fosaprepitant/Aprepitant

Moderate to Strong CYP3A4 Inhibitors	
Clinical Impact	Significantly increased exposure of aprepitant may increase the risk of adverse reactions associated with fosaprepitant *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.
Intervention	Avoid concomitant use of fosaprepitant.
Examples	Moderate inhibitor: diltiazem Strong inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir
Strong CYP3A4 Inducers	
Clinical Impact	Substantially decreased exposure of aprepitant in patients chronically taking a strong CYP3A4 inducer may decrease the efficacy of fosaprepitant *[see Clinical Pharmacology (12.3)]*.
Intervention	Avoid concomitant use of fosaprepitant.
Examples	rifampin, carbamazepine, phenytoin

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data on use of fosaprepitant 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. 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.

Data

Animal Data

In embryofetal development studies in rats and rabbits, aprepitant was administered during the period of organogenesis at oral doses up to 1,000 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 1,000 mg/kg twice daily and in pregnant rabbits at 125 mg/kg/day were approximately equivalent to the exposure at the RHD of 150 mg. Aprepitant crosses the placenta in rats and rabbits.

8.2 Lactation

Risk Summary

Lactation studies have not been conducted to assess 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 fosaprepitant and any potential adverse effects on the breastfed infant from fosaprepitant or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Upon administration of fosaprepitant, 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 and spermicides) during treatment with fosaprepitant and for 1 month following the last dose *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

8.4 Pediatric Use

The safety and effectiveness of fosaprepitant dimeglumine for injection have not been established in pediatric patients.

8.5 Geriatric Use

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 is administered *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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

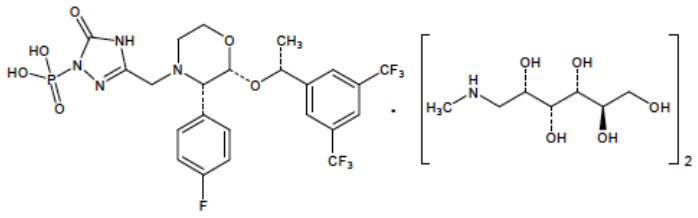
In the event of overdose, fosaprepitant should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, drug-induced emesis may not be effective in cases of fosaprepitant overdosage.

Aprepitant is not removed by hemodialysis.

11 DESCRIPTION

Fosaprepitant dimeglumine for injection is a sterile, lyophilized prodrug of aprepitant, a substance P/neurokinin-1 (NK_1) 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 structural formula is:



$C_{23}H_{22}F_7N_4O_6P \cdot 2(C_7H_{17}NO_5)$ **M.W. 1004.83**

Fosaprepitant dimeglumine is a white to off-white amorphous powder. It is freely soluble in water.

Each vial of fosaprepitant dimeglumine for injection for administration as an intravenous infusion contains 245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg of fosaprepitant free acid and the following inactive ingredients: edetate disodium (18.8 mg), polysorbate 80 (75 mg), lactose anhydrous (375 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment). Fosaprepitant dimeglumine hereafter will be referred to as fosaprepitant.

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 (NK_1) receptors. Aprepitant has little or no affinity for serotonin (5-HT_3), 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 NK_1 receptors. Animal and human studies show that aprepitant augments the antiemetic activity of the 5-HT_3-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 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 $AUC_{0-\infty}$ 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 (Vd_{ss}) 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 extrahepatic 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 [^{14}C]-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 [^{14}C]-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 9 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 $AUC_{0\text{-}24hr}$ 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)]*.

Sex

Following oral administration of a single dose of aprepitant, ranging from 40 mg to 375 mg, the $AUC_{0\text{-}24hr}$ 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.

Race/Ethnicity

Following oral administration of a single dose of aprepitant, ranging from 40 mg to 375 mg, the $AUC_{0\text{-}24hr}$ and C_{max} are approximately 42% and 29% higher in Hispanics as compared with Caucasians. The $AUC_{0\text{-}24hr}$ and C_{max} were 62% and 41% higher in Asians as compared to Caucasians. There was no difference in $AUC_{0\text{-}24hr}$ 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 m^2 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 $AUC_{0-\infty}$ 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 $AUC_{0-\infty}$ 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_{0-24hr} 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 AUC_{0-24hr} 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/m^2 increase in BMI, AUC_{0-24hr} and C_{max} of aprepitant decrease by 11%. BMI of subjects in the analysis ranged from 18 kg/m^2 to 36 kg/m^2. This change is not considered clinically meaningful.

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. Aprepitant 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 $AUC_{0-\infty}$ of midazolam by approximately 1.8-fold on Day 1 and had no effect on Day 4 when midazolam was co-administered as a single oral dose of 2 mg on Days 1 and 4.

Corticosteroids

Dexamethasone: Fosaprepitant administered as a single 150 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 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 co-administered 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-HT_3 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

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 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 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 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 RHD of 150 mg and exposure in female rats approximately equivalent to the human exposure).

14 CLINICAL STUDIES

14.1 Prevention of Nausea and Vomiting Associated with HEC

In a randomized, parallel, double-blind, active-controlled study, fosaprepitant dimeglumine for injection 150 mg as a single intravenous infusion (N=1,147) was compared to a 3-day oral aprepitant regimen (N=1,175) in patients receiving a HEC regimen that included cisplatin ($\geq$ 70 mg/m^2). All patients in both groups received dexamethasone and ondansetron (see Table 7). 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 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 7. Treatment Regimens in HEC Trial*

	Day 1	Day 2	Day 3	Day 4
Fosaprepitant/Aprepitant Regimen				
Fosaprepitant dimeglumine for injection	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

* Fosaprepitant dimeglumine 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 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 dimeglumine 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 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 fosaprepitant dimeglumine for injection was evaluated based on the primary and secondary endpoints listed in Table 8 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 8. Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase – Cycle 1

ENDPOINTS	Fosaprepitant Dimeglumine 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)

* 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Fosaprepitant dimeglumine for injection is a white to off-white lyophilized powder, supplied as follows:

Product No.	NDC No.	Strength	Size
972010	63323-972-10	150 mg per vial	Single dose vial, packaged individually.

Storage

Fosaprepitant dimeglumine for injection vials must be refrigerated; store at 2° to 8°C (36° to 46°F).

For intravenous use only after reconstitution and dilution. The reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25°C (77°F)].

The container closure is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Infusion Site Reactions

Advise patients that hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving fosaprepitant. Advise patients to stop fosaprepitant 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. Advise patients who develop an infusion site reaction such as erythema, edema, pain, or thrombophlebitis on how to care for the local reaction and when to seek further evaluation.

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 fosaprepitant with each chemotherapy cycle *[see Warnings and Precautions (5.3)]*.

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

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Issued: May 2016

PATIENT INFORMATION

Fosaprepitant Dimeglumine

(FOS a PREP i tant dye MEG loo meen)

for Injection

Read this Patient Information before you start receiving fosaprepitant dimeglumine for injection and each time you are scheduled to receive fosaprepitant dimeglumine for injection. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is fosaprepitant dimeglumine for injection?

Fosaprepitant dimeglumine for injection 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.

- Fosaprepitant dimeglumine for injection is not used to treat nausea and vomiting that you already have.
- It is not known if fosaprepitant dimeglumine for injection is safe and effective in children.

Who should not receive fosaprepitant dimeglumine for injection?

Do not receive fosaprepitant dimeglumine for injection if you:

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

What should I tell my healthcare provider before receiving fosaprepitant dimeglumine for injection?

Before receiving fosaprepitant dimeglumine for injection, tell your healthcare provider if you:

- have liver problems
- are pregnant or plan to become pregnant. It is not known if fosaprepitant dimeglumine for injection can 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 fosaprepitant dimeglumine for injection and for 1 month after receiving fosaprepitant dimeglumine for injection.
- are breastfeeding or plan to breastfeed. It is not known if fosaprepitant dimeglumine for injection passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive fosaprepitant dimeglumine for injection.

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

Fosaprepitant dimeglumine for injection may affect the way other medicines work, and other medicines may affect the way fosaprepitant dimeglumine for injection 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 fosaprepitant dimeglumine for injection?

Fosaprepitant dimeglumine for injection is given on Day 1. It will be given to you by intravenous (IV) 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 fosaprepitant dimeglumine for injection to check your blood clotting.

What are the possible side effects of fosaprepitant dimeglumine for injection?

Fosaprepitant dimeglumine for injection may cause serious side effects, including:

- **Serious allergic reactions.** Allergic reactions can happen with fosaprepitant dimeglumine for injection and may be serious. Tell your doctor or nurse right away if you have hives, rash, itching, flushing or redness of your face or skin, or trouble breathing or swallowing during or soon after you receive fosaprepitant dimeglumine for injection, as you may need emergency medical care.
- Severe skin reactions which may include rash, skin peeling, or sores may occur.

The most common side effects of fosaprepitant dimeglumine for injection include:

- tiredness
- diarrhea
- low white blood cell and red blood cell counts
- weakness
- feeling weak or numb in your arms and legs
- painful, difficult, or changes in your digestion (dyspepsia)
- urinary tract infection
- pain in your arms and legs

Infusion-site side effects with fosaprepitant dimeglumine for injection 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 fosaprepitant dimeglumine for injection. For more information ask your healthcare provider or pharmacist.

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 fosaprepitant dimeglumine for injection

If you would like more information about fosaprepitant dimeglumine for injection, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about fosaprepitant dimeglumine for injection that is written for health professionals. For more information about fosaprepitant dimeglumine for injection, call 1-800-551-7176 or go to www.fresenius-kabi.us.

What are the ingredients in fosaprepitant dimeglumine for injection?

Active ingredient: fosaprepitant dimeglumine

Inactive ingredients: edetate disodium, polysorbate 80, lactose anhydrous, sodium hydroxide and/or hydrochloric acid (for pH adjustment)

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

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451448

Issued: May 2016