

# Fosaprepitant for Injection

Rx only



## 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

**INDICATIONS AND USAGE**  
Fosaprepitant for Injection is a substance P/neurokinin-1 (NK<sub>1</sub>) 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.

**DOSE AND ADMINISTRATION**  
**Dosage (2.1)**

- The recommended dosage in adults is 150 mg on Day 1 as an intravenous infusion over 20 to 30 minutes completing the infusion approximately 30 minutes prior to chemotherapy.
- See Full Prescribing Information for dosages of concomitant antiemetic(s) of Fosaprepitant for Injection.

**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.

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## FULL PRESCRIBING INFORMATION

**1 INDICATIONS AND USAGE**  
Fosaprepitant 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.
- delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

**Limitations of Use**

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

## 2 DOSE AND ADMINISTRATION

### 2.1 Recommended Dosage

The recommended dosage of Fosaprepitant for Injection, dexamethasone, and a 5-HT<sub>3</sub> 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 Dosage 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	none	none	none
Dexamethasone*	12 mg orally	8 mg orally	8 mg orally twice daily	8 mg orally twice daily
5-HT <sub>3</sub> antagonist	See selected 5-HT <sub>3</sub> 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 Dosage for the Prevention of Nausea and Vomiting Associated with MEC**

	Day 1
Fosaprepitant for Injection	150 mg intravenously over 20 to 30 minutes
Dexamethasone*	12 mg orally
5-HT <sub>3</sub> antagonist	See selected 5-HT <sub>3</sub> 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)].

### 2.2 Preparation Instructions

**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. 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 jettling 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 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., calcium, magnesium), including Lactated Ringer's Solution and Hartmann's Solution.

## Storage

The reconstituted final drug solution is stable for 24 hours at ambient room temperature (4° or below 25°C (77°F)).

## 3 DOSE FORMS AND STRENGTHS

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

## 4 CONTRAINDICATIONS

Fosaprepitant for Injection 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 Warnings and Precautions (5.2), Adverse Reactions (6.2)].
- taking pimoizide. 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 pimoizide [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 for Injection with other drugs that are CYP3A4 substrates, may result in increased plasma concentration of the concomitant drug.
  - Use of pimoizide with Fosaprepitant for Injection is contraindicated due to the risk of significantly increased plasma concentrations of pimoizide, potentially resulting in prolongation of the QT interval, a known adverse reaction of pimoizide [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 reinitiate 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 therapy.

### 5.4 Decrease in INR with Concomitant Warfarin

Concomitant administration 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 concomitant administration 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 safety of Fosaprepitant for Injection has been established from adequate and well-controlled studies of another intravenous fosaprepitant product in chemotherapy induced nausea and vomiting [see Clinical Studies (14)]. Adverse reactions reported in these studies are described below.

**Adverse Reactions 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 adult patients receiving a single intravenous dose of fosaprepitant compared to 1169 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.

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of another intravenous formulation of fosaprepitant. 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 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.

-----**DOSE 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 pimoizide. (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 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 reinitiate 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 (≥2%) are: fatigue, diarrhea, dyspepsia, asthenia, anemia, peripheral neuropathy, leukopenia, dyspepsia, urinary tract infection, pain in extremity. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals USA, Inc. at 1-888-838-2872 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.**

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

**Table 7**  
**Effects of Fosaprepitant/Aprepitant on the Pharmacokinetics of CYP3A4 Substrates**

Clinical Impact	Increased pimoizide exposure
Intervention	Fosaprepitant for Injection is contraindicated [see Contraindications (4)].
<b>Benzodiazepines</b>	
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.
<b>Dexamethasone</b>	
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)].
<b>Methylprednisolone</b>	
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 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.
<b>Chemotherapeutic agents that are metabolized by CYP3A4</b>	
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 <ul style="list-style-type: none"> <li>• Monitor for chemotherapeutic-related adverse reactions.</li> <li>• Etoposide, vinorelbine, paclitaxel, and docetaxel                             <ul style="list-style-type: none"> <li>• No dosage adjustment needed.</li> </ul> </li> </ul>
<b>Hormonal Contraceptives</b>	
Clinical Impact	Decreased hormonal exposure during administration of and for 28 days after administration of the last dose of Fosaprepitant for Injection [see Warnings and Precautions (5.5), Use in Specific Populations (8.3), Clinical Pharmacology (12.3)].
Intervention	Effective alternative or back-up methods of contraception (such as condoms or spermicides) should be used during treatment with Fosaprepitant for Injection and for 1 month following administration of Fosaprepitant for Injection.
Examples	birth control pills, skin patches, implants, and certain IUDs

### CYP2C9 Substrates

#### Warfarin

Clinical Impact Decreased warfarin exposure and decreased prothrombin time (INR) [see Warnings and Precautions (5.4), 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 for Injection with each chemotherapy cycle.

### Other

#### 5-HT<sub>3</sub> Antagonists

Clinical Impact No change in the exposure of the 5-HT<sub>3</sub> 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)]. Coadministration 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**

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

There is no available data on use of fosaprepitant in pregnant women to inform a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, no adverse developmental effects were observed in rats or rabbits exposed during the period of organogenesis to systemic exposures (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. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

#### 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/day (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 25 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

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

### 8.3 Females and Males of Reproductive Potential

#### Contraception

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

#### 8.4 Pediatric Use

This Fosaprepitant for Injection product is not approved for use in pediatric patients.

This Fosaprepitant for Injection product contains 18.8 mg of edetate disodium (EDTA) per vial [see Description (11)]. Edetate disodium is a chelator of metal ions, including calcium. Other fosaprepitant for injection products may contain less edetate disodium.

#### 8.5 Geriatric Use

**Specific Populations**

**Geriatric Patients**

Following oral administration of a single 125-mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 through 5, the AUC<sub>0-24hr</sub> 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<sub>max</sub> was 10% higher on Day 1 and 24% higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful [see Use in Specific Populations (8.5)].

**Male and Female Patients**

Following oral administration of a single dose of aprepitant, ranging from 40 mg to 375 mg, the AUC<sub>0-24hr</sub> and C<sub>max</sub> 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<sub>max</sub> occurs at approximately the same time. These differences are not considered clinically meaningful.

**Racial or Ethnic Groups**

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

**Patients with Renal Impairment**

A single 240-mg oral dose of aprepitant was administered to patients with severe renal impairment (creatinine clearance less than 30 mL/min/1.73 m<sup>2</sup> 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<sub>0-∞</sub> of total aprepitant (unbound and protein bound) decreased by 21% and C<sub>max</sub> 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<sub>0-∞</sub> of total aprepitant decreased by 42% and C<sub>max</sub> decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal impairment compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

**Patients with Hepatic Impairment**

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<sub>0-24hr</sub> 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<sub>0-24hr</sub> 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<sub>0-24hr</sub> 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<sup>2</sup> increase in BMI, AUC<sub>0-24hr</sub> and C<sub>max</sub> of aprepitant decrease by 9% and 10%. BMI of subjects in the analysis ranged from 18 kg/m<sup>2</sup> to 36 kg/m<sup>2</sup>. 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<sub>0-∞</sub> 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<sub>0-24hr</sub> 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.

**CYP2C9 Substrates (Warfarin, Tolbutamide):**

**Warfarin:** A single 125-mg dose of oral aprepitant was administered on Day 1 and 80 mg/day on Days 2 and 3 to subjects who were stabilized on chronic warfarin therapy. Although there was no effect of oral aprepitant on the plasma AUC of R(+) or S(-) warfarin determined on Day 3, there was a 34% decrease in S(-) warfarin trough concentration accompanied by a 14% decrease in the prothrombin time (reported as International Normalized Ratio or INR) 5 days after completion of dosing with oral aprepitant [see Drug Interactions (7.1)].

**Tolbutamide:** Oral aprepitant, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide by 23% on Day 4, 28% on Day 8, and 15% on Day 15, when a single dose of tolbutamide 500 mg was administered prior to the administration of the 3-day regimen of oral aprepitant and on Days 4, 8, and 15. This effect was not considered clinically important.

**Other Drugs**

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

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

**5-HT<sub>2</sub> 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]. Coadministration of fosaprepitant and diltiazem; however, did not result in any additional clinically significant changes in heart rate or PR interval, beyond those changes observed with diltiazem alone [see Drug Interactions (7.2)].

**Paroxetine:** Coadministration of once daily doses of oral aprepitant 170 mg, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and C<sub>max</sub> 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 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**

The safety and efficacy of Fosaprepitant for Injection have been established based on adequate and well-controlled adult studies of another intravenous fosaprepitant product in chemotherapy induced nausea and vomiting. Below is a display of the results of these adequate and well-controlled studies of fosaprepitant in these conditions.

**14.1 Prevention of Nausea and Vomiting Associated with HEC in Adults**

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

**Table 11 Treatment Regimens in Adult HEC Trial\***

	Day 1	Day 2	Day 3	Day 4
Intravenous Fosaprepitant Regimen				
Fosaprepitant	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy	none	none	none
Oral dexamethasone†	12 mg	8 mg	8 mg twice daily	8 mg twice daily
Ondansetron	Ondansetron‡	none	none	none
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 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 regimen [see Clinical Pharmacology (12.3)].

‡Ondansetron 32 mg intravenously was used in the clinical trials of fosaprepitant. 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 capsules regimen [see Clinical Pharmacology (12.3)].

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

**Table 12 Percent of Adult Patients Receiving HEC Responding by Treatment Group and Phase - Cycle 1**

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

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

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

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

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

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

**14.2 Prevention of Nausea and Vomiting Associated with MEC in Adults**

In a randomized, parallel, double-blind, active comparator-controlled study, fosaprepitant 150 mg as a single intravenous infusion (N=502) in combination with ondansetron and dexamethasone (intravenous fosaprepitant regimen) was compared with ondansetron and dexamethasone alone (standard therapy) (N=498) (see Table 13) in patients receiving a MEC regimen. Patient demographics were similar between the two treatment groups. Of the total 1,000 patients included in the efficacy analysis, 41% were men, 84% White, 4% Asian, 1% American Indian/Alaska Native, 2% Black, 10% Multi-Racial, and 19% Hispanic/Latino ethnicity. Patient ages ranged from 23 to 88 years of age, with a mean age of 60 years. The most commonly administered MEC chemotherapeutic agents were carboplatin (51%), oxaliplatin (24%), and cyclophosphamide (12%).

**Table 13 Treatment Regimens in Adult MEC Trial\***

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

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

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

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

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

**Table 14 Percent of Adult Patients Receiving MEC Responding by Treatment Group**

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

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

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

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

**16 HOW SUPPLIED/STORAGE AND HANDLING**

One single-dose glass vial containing 150 mg fosaprepitant as a sterile, white to off-white lyophilized powder for reconstitution. Supplied as follows:

NDC 0591-4385-79 1 vial per carton.

Storage Store at 2° to 8°C (36° to 46°F).

For storage of reconstituted drug solution see Dosage and Administration 2.2.

**17 PATIENT COUNSELING INFORMATION**

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

**Hypersensitivity**

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

**Infusion Site Reactions**

Advise patients to seek medical attention if they experience new or worsening signs or symptoms of an infusion site reaction, such as erythema, edema, pain, necrosis, vasculitis, or thrombophlebitis at or near the infusion site [see Warnings and Precautions (5.3)].

**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 for Injection with each chemotherapy cycle [see Warnings and Precautions (5.4)].

**Hormonal Contraceptives:** Advise patients that administration of Fosaprepitant for Injection may reduce the efficacy of hormonal contraceptives. Instruct patients to use effective alternative or back-up methods of contraception (such as condoms or spermicides) during treatment with Fosaprepitant for Injection and for 1 month following administration of Fosaprepitant for Injection [see Warnings and Precautions (5.5), Use in Specific Populations (8.3)].

Manufactured in Romania By:

**Sindan Pharma SRL**

11 Ion Mihalache Blvd.

Bucharest 1, Romania 011171

Or

Manufactured in Italy By:

**Actavis Italy Spa A Socio Unico**

Nerviano, Italy, 20014

Manufactured For:

**Teva Pharmaceuticals USA, Inc.**

North Wales, PA 19454

**Patient Information FOSAPREPITANT for injection (FOS a PRE pi tant) for intravenous use**

**What is Fosaprepitant for Injection?**

Fosaprepitant 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 for Injection is not used to treat nausea and vomiting that you already have.

• It is not known if Fosaprepitant for Injection is safe and effective in children.

**Do not receive Fosaprepitant for Injection if you:**

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

**Before receiving Fosaprepitant for Injection, tell your healthcare provider about all your medical conditions including, if you:**

- have liver problems.
- are pregnant or plan to become pregnant. It is not known if Fosaprepitant 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 or spermicides, during treatment with Fosaprepitant for Injection and for 1 month after receiving the last dose of Fosaprepitant for Injection.
- are breastfeeding or plan to breastfeed. It is not known if Fosaprepitant for Injection passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive Fosaprepitant for Injection.

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

Fosaprepitant for Injection may affect the way other medicines work, and other medicines may affect the way Fosaprepitant 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 for Injection?**

Fosaprepitant for Injection will be given on Day 1 of chemotherapy treatment. It will be given to you by intravenous (IV) infusion in your vein about 50 to 60 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 for Injection to check your blood clotting.

**What are the possible side effects of Fosaprepitant for Injection?**

**Fosaprepitant for Injection may cause serious side effects, including:**

- **Serious allergic reactions.** Allergic reactions can happen with Fosaprepitant for Injection and may be serious. Tell your healthcare provider or nurse right away if you have hives, rash, itching, flushing or redness of your face or skin, trouble breathing or swallowing, dizziness, a rapid or weak heartbeat, or you feel faint during or soon after you receive Fosaprepitant for Injection, as you may need emergency medical care.
- **Severe skin reactions,** which may include rash, skin peeling, or sores, may occur. Get medical care right away if you have signs of a severe skin reaction.
- **Infusion site reactions (ISR)** at or near the infusion site have happened with Fosaprepitant for Injection.

Most severe ISR have happened with a certain type of chemotherapy medicine that can burn or blister your skin (vesicant) with side effects, including pain, swelling and redness. Death of skin tissue (necrosis) has happened in some people getting this type of chemotherapy medicine. Most ISR can happen with the first, second,