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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

FOCINVEZ (fosaprepitant injection) for intravenous use

Initial U.S. Approval: 2008

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

FOCINVEZ is a substance P/neurokinin-1 (NK_1) receptor antagonist, indicated in adults and pediatric patients 6 months of age and older, 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)

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

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

Recommended Adult Dosage (2.1)

- FOCINVEZ 150 mg on Day 1 as an intravenous infusion over 20 to 30 minutes;
- Complete the infusion approximately 30 minutes prior to chemotherapy.

Recommended Dosage for Pediatric Patients (6 months to 17 years) Weighing at Least 6 kg (2.2)

- See full prescribing information for pediatric dosage regimens by age.
- *Single dose chemotherapy regimens:* single dose of FOCINVEZ on Day 1.
- *Single or multi-day chemotherapy regimens:* 3-day regimen of FOCINVEZ on Day 1 and aprepitant capsules or aprepitant for oral suspension on Days 2 and 3.
- Administer FOCINVEZ through a central venous catheter on Day 1 as an intravenous infusion over 30 minutes (12 years to 17 years) or 60 minutes (6 months to less than 12 years).
- Complete the infusion approximately 30 minutes prior to chemotherapy.

Concomitant Antiemetics

- See full prescribing information for additional information. (2.1, 2.2)

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

Injection: 150 mg/50 mL (3 mg/mL) of fosaprepitant, in a single-dose vial. (3)

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

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

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

- CYP3A4 Interactions: 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 FOCINVEZ 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 FOCINVEZ 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 FOCINVEZ. (5.4, 7.1)
- Hormonal Contraceptives: Efficacy of contraceptives may be reduced during treatment and for 1 month following administration of the last dose of either fosaprepitant or oral aprepitant. Use effective alternative or back-up methods of contraception. (5.5, 7.1, 8.3)

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

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

REACTIONS, contact Steriscience at 1-888-278-1784 or FDA at 1-800-FDA-1088 orwww.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.

Additional pediatric use information is approved for Merck Sharp & Dohme LLC's EMEND (fosaprepitant) for injection. However, due to Merck Sharp & Dohme LLC's marketing exclusivity rights, this drug product is not labeled with that information.

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FULL PRESCRIBING INFORMATION: DETAILS

1 INDICATIONS AND USAGE

FOCINVEZ, in combination with other antiemetic agents, is indicated in adults and pediatric patients 6 months of age and older 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

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for the Prevention of Nausea and Vomiting Associated with HEC and MEC in Adult Patients

The recommended dosage of FOCINVEZ, dexamethasone, and a 5-HT_3 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 FOCINVEZ as an intravenous infusion on Day 1 over 20 to 30 minutes, completing the infusion approximately 30 minutes prior to chemotherapy.

Table 1

Recommended Adult Dosage for the Prevention of Nausea and Vomiting Associated with HEC

	Day 1	Day 2	Day 3	Day 4
FOCINVEZ[a]	150 mg intravenously over 20 to 30 minutes	none	none	none
Dexamethasone[b]	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

[a] The concentration of FOCINVEZ is 3 mg/mL.

[b] 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 FOCINVEZ *[see Clinical Pharmacology (12.3)]*.

Table 2

Recommended Adult Dosage for the Prevention of Nausea and Vomiting Associated with MEC

	Day 1
FOCINVEZ[a]	150 mg intravenously over 20 to 30 minutes
Dexamethasone[b]	12 mg orally
5-HT_3 antagonist	See selected 5-HT_3 antagonist prescribing information for the recommended dosage

[a] The concentration of FOCINVEZ is 3 mg/mL.

[b] 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 FOCINVEZ *[see Clinical Pharmacology (12.3)]*.

2.2 Recommended Dosage for the Prevention of Nausea and Vomiting Associated with HEC and MEC in Pediatric Patients

The recommended pediatric dosage regimens of FOCINVEZ, to be administered with a 5-HT_3 antagonist, with or without a corticosteroid, for the prevention of nausea and vomiting associated with administration of single or multi-day chemotherapy regimens of HEC or MEC, are shown in Tables 3 and 4. Single-day chemotherapy regimens include those regimens in which HEC or MEC is administered for a single day only. Multi-day chemotherapy regimens include chemotherapy regimens in which HEC or MEC is administered for 2 or more days.

FOCINVEZ Dosage Regimens for Use with Single-Day Chemotherapy Regimens

For pediatric patients weighing at least 6 kg receiving single-day HEC or MEC, FOCINVEZ may be administered as:

- a single dose regimen of FOCINVEZ infused through a central venous catheter on Day 1, as shown in Table 3; or
- as a 3-day fosaprepitant/aprepitant regimen consisting of FOCINVEZ as an intravenous infusion through a central venous catheter on Day 1 and aprepitant capsules or aprepitant for oral suspension on Days 2 and 3, as shown in Table 4.

Administer FOCINVEZ on Day 1 over 30 minutes (12 years to 17 years) or 60 minutes (6 months to less than 12 years), completing the infusion approximately 30 minutes prior to chemotherapy.

Table 3

FOCINVEZ Single Dose Regimen for the Prevention of Nausea and Vomiting Associated with Single-Day Regimens of HEC or MEC in Pediatric Patients 6 Months[a] to 17 Years

Drug	Age	Regimen
FOCINVEZ[b]	12 Years to 17 Years	150 mg intravenously over 30 minutes
	2 Years to less than 12 Years	4 mg/kg (maximum dose 150 mg) intravenously over 60 minutes
	6 Months to less than 2 Years	5 mg/kg (maximum dose 150 mg) intravenously over 60 minutes
Dexamethasone[c]	6 Months to 17 Years	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 and 2.
5-HT_3 antagonist	6 Months to 17 Years	See selected 5-HT_3 antagonist prescribing information for the recommended dosage

[a] Dosing in pediatric patients less than 6 kg is not recommended

[b] The concentration of FOCINVEZ is 3 mg/mL.

[c] Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1

FOCINVEZ Dosage Regimen for Use with Multi-Day Chemotherapy Regimens

For pediatric patients weighing at least 6 kg receiving multi-day regimens of HEC or MEC, administer FOCINVEZ as an intravenous infusion through a central venous catheter on Day 1 and aprepitant capsules or aprepitant for oral suspension on Days 2 and 3, as shown in Table 4.

Administer FOCINVEZ over 30 minutes (12 years to 17 years) or 60 minutes (6 months to less than 12 years), completing the infusion approximately 30 minutes prior to chemotherapy.

Table 4. 3-Day Fosaprepitant/Aprepitant Dosage Regimen for Prevention of Nausea and Vomiting Associated with Single or Multi-day Regimens of HEC or MEC in Pediatric Patients 6 Months[a] to 17 Years

Age Group	Drug	Day 1	Day 2	Day 3
12 Years to 17 Years	FOCINVEZ[b]	115 mg intravenously over 30 minutes	-	-
	Aprepitant capsules[c]	-	80 mg orally	80 mg orally
6 Months to Less than 12 Years	FOCINVEZ	3 mg/kg (maximum dose 115 mg) intravenously over 60 minutes	-	-
	Aprepitant for oral suspension[d]	-	2 mg/kg orally (maximum 80 mg)	2 mg/kg orally (maximum 80 mg)
6 Months to 17 Years	Dexamethasone[e]	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 through 4		
6 Months to 17 Years	5-HT_3 antagonist	See selected 5-HT_3 antagonist prescribing information for the recommended dosage		

[a] Dosing in pediatric patients less than 6 kg is not recommended

[b] The concentration of FOCINVEZ is 3 mg/mL.

[c] For patients 12 years to 17 years who cannot swallow oral capsules, aprepitant for oral suspension can be used instead.

[d] For patients less than 12 years of age who weigh at least 40 kg and who are able to swallow oral capsules, aprepitant capsules can be used on Days 2 and 3.

[e] Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1.

Additional pediatric use information is approved for Merck Sharp & Dohme LLC's EMEND (fosaprepitant) for injection. However, due to Merck Sharp & Dohme LLC's marketing exclusivity rights, this drug product is not labeled with that information.

2.3 Preparation of FOCINVEZ

FOCINVEZ is **ready-to-use** for intravenous infusion. The concentration of FOCINVEZ is **3 mg/mL.**

Determine the volume to be administered from the injection vial directly based on the recommended dose *[see Dosage and Administration (2.1, 2.2)]*.

Adults

The entire volume of the vial (50 mL) should be administered.

Pediatrics

In patients 12 years and older, the volume to be administered is calculated as follows:

- Volume to administer (mL) = the recommended dose (mg) / **3 (mg/mL)** *

In patients 6 months to less than 12 years, the volume to be administered is calculated as follows:

- Volume to administer (mL) = the recommended dose (mg/kg) x weight (kg) / **3 (mg/mL)** *

Note: Do not exceed the maximum dose [see Dosage and Administration (2.2)]

- In pediatric patients, the entire volume in vial may **NOT** be required. Discard the unused portion.
- * The recommended dose of FOCINVEZ is based on the patient's age and weight. The concentration of FOCINVEZ is **3 mg/mL.**
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is cloudy, contains precipitates, or if the red flip top cap is not intact.
- Vial may be inverted for use with a medical infusion set. The vial hanger can be separated from the vial label and hanged from an IV pole.
- Allow FOCINVEZ to come to room temperature before use if the injection is **NOT** stored at room temperature.
- *Caution:* Do not mix FOCINVEZ with solutions for which physical and chemical compatibility have not been established. FOCINVEZ is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), including Lactated Ringer's Solution and Hartmann's Solution.

FOCINVEZ is compatible with 0.9% Sodium Chloride Injection.

3 DOSAGE FORMS AND STRENGTHS

Injection: 150 mg/50 mL (3 mg/mL) of fosaprepitant, a clear and colorless solution, in a single-dose vial.

4 CONTRAINDICATIONS

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

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 FOCINVEZ 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 intravenous fosaprepitant *[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 intravenous fosaprepitant 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 FOCINVEZ into small veins or through a butterfly catheter. If a severe ISR develops during infusion, discontinue the infusion and administer appropriate medical treatment.

5.4 Decrease in INR with Concomitant Warfarin

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

5.5 Risk of Reduced Efficacy of Hormonal Contraceptives

Upon coadministration 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 FOCINVEZ and for 1 month following administration of the last dose of fosaprepitant or oral aprepitant *[see Drug Interactions (7.1) and 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 FOCINVEZ has been established from adequate and well-controlled studies of another intravenous formulation of fosaprepitant *[see Clinical Studies (14)]*. Below is a display of the adverse reactions of fosaprepitant in these studies.

The overall safety of intravenous fosaprepitant was evaluated in approximately 1800 adult and pediatric patients.

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

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

Table 6

Most Common Adverse Reactions in Patients Receiving MEC[a]

	Intravenous fosaprepitant, ondansetron, and dexamethasone[b] (N=504)	Ondansetron and dexamethasone[c] (N=497)
fatigue	15%	13%
diarrhea	13%	11%
neutropenia	8%	7%
asthenia	4%	3%
anemia	3%	2%
peripheral neuropathy	3%	2%
leukopenia	2%	1%
dyspepsia	2%	1%
urinary tract infection	2%	1%
pain in extremity	2%	1%

[a] Reported in ≥2% of patients treated with the intravenous fosaprepitant regimen and at a greater incidence than standard therapy (ondansetron and dexamethasone alone).

[b] Intravenous fosaprepitant regimen

[c] Standard therapy

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

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

In an active-controlled clinical study in patients receiving HEC, safety was evaluated for 1143 patients receiving a single dose of intravenous 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.

Adverse Reactions in Pediatric Patients 6 Months to 17 Years of Age for the Prevention of Nausea and Vomiting Associated with HEC or MEC

Single-Dose Intravenous Fosaprepitant Regimen

The safety of a single dose of intravenous fosaprepitant in pediatric patients (6 months to 17 years) was evaluated in two active-controlled and a single-arm clinical study in patients who received either HEC or MEC. Patients also received ondansetron with or without dexamethasone. The adverse reaction profile was similar to adults. The safety analysis included 69 pediatric patients who received the recommended dose. An additional 70 patients received a single, higher-than-recommended dose. The most common adverse reactions that occurred in >15% of patients who received the recommended dose were anemia, neutropenia, thrombocytopenia, and febrile neutropenia.

3-Day Intravenous Fosaprepitant/Oral Aprepitant/Oral Aprepitant Regimen

In pediatric patients (12 to 17 years), the safety of the 3-day intravenous fosaprepitant/oral aprepitant/oral aprepitant regimen was evaluated in a single-arm clinical study including 12 patients who received a regimen of either HEC or MEC. In pediatric patients 6 months to 12 years of age, the safety of the 3-day regimen was not directly evaluated. The safety of a single-dose of intravenous fosaprepitant (3 mg/kg) administered on day 1 of the 3-day regimen was evaluated in one active-controlled and one single-arm study including 48 patients who received a regimen of either HEC or MEC.

In these clinical studies, pediatric patients also received ondansetron with or without dexamethasone. The adverse reaction profile was similar to adults and pediatric patients receiving a single dose of intravenous fosaprepitant.

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

Additional pediatric use information is approved for Merck Sharp & Dohme LLC's EMEND (fosaprepitant) for injection. However, due to Merck Sharp & Dohme LLC's marketing exclusivity rights, this drug product is not labeled with that information.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use 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 FOCINVEZ 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 FOCINVEZ *[see Contraindications (4)]*. Dosage adjustment of some CYP3A4 and CYP2C9 substrates may be warranted, as shown in Table 7.

Table 7

Effects of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs

CYP3A4 Substrates	
Pimozide	
Clinical Impact	Increased pimozide exposure
Intervention	FOCINVEZ 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 and on Day 1 for patients receiving MEC. Reduce the dose of intravenous methylprednisolone by 25% on Days 1 and 2 for patients receiving HEC and on Day 1 for patients receiving MEC.
Chemotherapeutic agents that are metabolized by CYP3A4	
Clinical Impact	Increased exposure of the chemotherapeutic agent may increase the risk of adverse reactions *[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 (5.5), 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 FOCINVEZ and for 1 month following administration of the last dose of fosaprepitant or oral aprepitant
Examples	birth control pills, transdermal systems, implants, and certain intrauterine systems
CYP2C9 Substrates	
Warfarin	
Clinical Impact	Decreased warfarin exposure and decreased prothrombin time (INR) *[see Warnings and Precautions (5.4) and 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 FOCINVEZ 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 FOCINVEZ with drugs that are inhibitors or inducers of CYP3A4 may result in increased or decreased plasma concentrations of aprepitant, respectively, as shown in Table 8.

Table 8

Effects of Other Drugs on Pharmacokinetics of Fosaprepitant/Aprepitant

Moderate to Strong CYP3A4 Inhibitors	
Clinical Impact	Significantly increased exposure of aprepitant may increase the risk of adverse reactions associated with FOCINVEZ *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.
Intervention	Avoid concomitant use of FOCINVEZ
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 FOCINVEZ *[see Clinical Pharmacology (12.3)]*.
Intervention	Avoid concomitant use of FOCINVEZ
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 identify a drug associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. 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 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 1000 mg/kg twice daily (rats) and up to the maximum tolerated dose of 25 mg/kg/day (rabbits). No embryofetal lethality or malformations were observed at any dose level in either species. The exposures (AUC) in pregnant rats at 1000 mg/kg twice daily and in pregnant rabbits at 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. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FOCINVEZ and any potential adverse effects on the breastfed infant from FOCINVEZ or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Upon administration of FOCINVEZ, 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 FOCINVEZ and for 1 month following the last dose of fosaprepitant or oral aprepitant *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

8.4 Pediatric Use

The safety and effectiveness of a single dose regimen of FOCINVEZ and a 3-day intravenous fosaprepitant/oral aprepitant/oral

Patient Information
FOCINVEZ (FOR sin vez)
(fosaprepitant injection)
for intravenous use

Read this Patient Information before you start receiving FOCINVEZ and each time you are scheduled to receive FOCINVEZ. 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 FOCINVEZ?

FOCINVEZ is a prescription medicine used with other medicines that treat nausea and vomiting in patients 6 months of age and older to prevent nausea and vomiting caused by certain anti-cancer (chemotherapy) medicines.

- FOCINVEZ is not used to treat nausea and vomiting that you already have.
- It is not known if FOCINVEZ is safe and effective in children less than 6 months of age.

Who should not receive FOCINVEZ?

Do not receive FOCINVEZ if you:

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

What should I tell my healthcare provider before receiving FOCINVEZ?

Before receiving FOCINVEZ, tell your healthcare provider if you:

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

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

FOCINVEZ may affect the way other medicines work, and other medicines may affect the way FOCINVEZ 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 FOCINVEZ?

Adults 18 years of age and older:

FOCINVEZ 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.

Children 6 months to 17 years of age:

FOCINVEZ will be given to your child by intravenous (IV) infusion into a large vein through a type of IV line called a central venous catheter, about 1 hour to 1 ½ hours before the start of their chemotherapy treatment.

Depending on the chemotherapy treatment, there are 2 ways that FOCINVEZ may be given:

1. FOCINVEZ is given on Day 1 only (single day of chemotherapy).
2. FOCINVEZ is given on Day 1 (single or multiple days of chemotherapy).

- Your child may also receive capsules of aprepitant or an oral suspension of aprepitant on Days 2 and 3. If your child will receive either of these, see the Patient Information for aprepitant capsules or aprepitant for oral suspension for further information.

If you take the blood thinner medicine warfarin sodium (COUMADIN, JANTOVEN), your healthcare provider may do blood tests after you receive FOCINVEZ to check your blood clotting.

What are the possible side effects of FOCINVEZ?

FOCINVEZ may cause serious side effects, including:

- **Serious allergic reactions.** Allergic reactions can happen with FOCINVEZ 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, trouble breathing or swallowing, dizziness, a rapid or weak heartbeat, or you feel faint during or soon after you receive FOCINVEZ, as you may need emergency medical care.
  - Severe skin reactions, which may include rash, skin peeling, or sores, may occur.
- **Infusion site reactions (ISR) at or near the infusion site have happened with FOCINVEZ.** Most severe ISR have happened with a certain type of chemotherapy medicine that can burn or blister your skin (vesicant) with side eff

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, or third dose and some can last up to 2 weeks or longer. Tell your healthcare provider right away if you get any infusion site side effects.

In adults, the most common side effects of FOCINVEZ 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

In children 6 months to 17 years of age, the most common side effects of FOCINVEZ include:

- low red blood cell count
- low white blood cell count
- low blood platelet count
- low white blood cell count with a fever

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 FOCINVEZ. 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 FOCINVEZ.

If you would like more information about FOCINVEZ, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about FOCINVEZ that is written for health professionals. For more information about FOCINVEZ call 1-877-835-5472.

What are the ingredients in FOCINVEZ?

Active ingredient: fosaprepitant

Inactive ingredients: betadex sulfobutyl ether sodium, edetate disodium, sodium hydroxide (for pH adjustment) and water for injection

Additional pediatric use information is approved for Merck Sharp & Dohme LLC's EMEND (fosaprepitant) for injection. However, due to Merck Sharp & Dohme LLC's marketing exclusivity rights, this drug product is not labeled with that information.

Manufactured by:
Steriscience Specialties Private Limited
Sterile Product Division, Opp IIM, Bilekahalli, Bannerghatta Road, Bengaluru, India 560076

Distributed by:
Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

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aprepitant regimen have been established in pediatric patients 6 months to 17 years for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC and MEC.

Use of FOCINVEZ in this age group is supported by evidence from adequate and well-controlled studies of intravenous fosaprepitant in adults, with additional safety, efficacy and pharmacokinetic data in pediatric patients 6 months to 17 years. Efficacy and safety were also supported by data from an adequate and well controlled study of a 3-day oral aprepitant regimen in pediatric patients 6 months to 17 years. See the full prescribing information for aprepitant capsules for complete clinical information regarding studies performed with oral aprepitant. Adverse reactions were similar to those reported in adult patients. *[See Dosage and Administration (2.2), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)].*

The safety and effectiveness of FOCINVEZ for the prevention of nausea and vomiting associated with HEC or MEC have not been established in patients less than 6 months of age.

Juvenile Animal Toxicity Data

In juvenile dogs treated with fosaprepitant, changes in reproductive organs were observed. In juvenile rats treated with aprepitant, slight changes in sexual maturation were observed without an effect on reproduction. No effects on neurobehavior, sensory and motor function, or learning and memory were observed in rats.

In a toxicity study in juvenile dogs treated with fosaprepitant from postnatal day 14 (equivalent to a newborn human) to day 42 (approximately equivalent to a 2 year old human), decreased testicular weight and Leydig cell size were seen in the males at 6 mg/kg/day and increased uterine weight, hypertrophy of the uterus and cervix, and edema of vaginal tissues were seen in females from 4 mg/kg/day. A study was also conducted in young rats to evaluate the effects of aprepitant on growth and on neurobehavioral and sexual development. Rats were treated at oral doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male and female rats lower than the exposure at the recommended pediatric human dose) from the early postnatal period (Postnatal Day 10 (equivalent to a newborn human) through Postnatal Day 58 (approximately equivalent to a 15 year old human)). Slight changes in the onset of sexual maturation were observed in female and male rats; however, there were no effects on mating, fertility, embryonic-fetal survival, or histomorphology of the reproductive organs. There were no effects in neurobehavioral tests of sensory function, motor function, and learning and memory.

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8.5 Geriatric Use

Of the 1649 adult cancer patients treated with intravenous fosaprepitant in HEC and MEC clinical studies, 27% were aged 65 and over, while 5% were aged 75 and over. Other reported clinical experience with fosaprepitant has not identified differences in responses between elderly and younger adult patients. No clinically meaningful differences in the pharmacokinetics of oral aprepitant were observed in healthy adult subjects 65 years of age and over compared to younger adult subjects *[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 FOCINVEZ is administered *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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

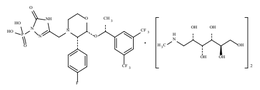
In the event of overdose, FOCINVEZ should be discontinued and general supportive treatment and monitoring should be provided.

Aprepitant is not removed by hemodialysis.

11 DESCRIPTION

FOCINVEZ (fosaprepitant injection) is a sterile, ready-to-use, clear and colorless solution formulation containing fosaprepitant dimeglumine, a 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-[3,5bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1*H*-1,2,4triazol-1-yl]phosphonate (2:1) (salt).

Its empirical formula is $C_{37}H_{36}F_7N_4O_8P \cdot 2(C_6H_{15}NO_5)$ and its structural formula is:



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

Each 50 mL vial of FOCINVEZ for administration as an intravenous infusion contains 150 mg of fosaprepitant (equivalent to 245.3 mg of fosaprepitant dimeglumine) and the following inactive ingredients: Betadex sulfobutyl ether sodium (8 g), edetate disodium (5.4 mg), sodium hydroxide (for pH adjustment) in water for injection.

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 ($5\text{-}HT_3$), 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 have shown that aprepitant augments the antiemetic activity of the $5\text{-}HT_3$ 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 mg/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

Geriatric Patients

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

Pediatric Patients

Single-Dose Intravenous Fosaprepitant Regimen: Simulated systemic exposures of aprepitant in patients 2 years to less than 12 years and observed systemic exposures in patients 6 months to less than 2 years and 12 to 17 years are shown in Table 9, including AUC_{0-24hr}, peak plasma concentration (C_{max}) on Day 1 and concentrations at the end of Day 1 (C_{24}), Day 2 (C_{48}) and Day 3 (C_{72}).

Table 9

Systemic Exposures of Aprepitant for Single-Dose Intravenous Fosaprepitant Regimen in Pediatric Patients

Population	Single-Dose of Intravenous Fosaprepitant Regimen	Geometric Mean				
		AUC_{0-24hr} (mcg*hr/mL)	C_{max} (mcg/mL)	C_{24} (mcg/mL)	C_{48} (mcg/mL)	C_{72} (mcg/mL)
12 Years to 17 Years	150 mg	29.4	3.4	0.7	ND[1]	ND[2]
6 Years to less than 12 Years	4 mg/kg	35.2	3.6	0.7	0.2	0.05
2 Years to less than 6 Years		28.2	3.1	0.4	0.1	0.02
6 Months to less than 2 Years	5 mg/kg	32.7	3.3	0.4	NE[3]	ND[2]

[1] ND = Not Determined. Pharmacokinetic samples were not collected to support the parameter value of interest.
[2] NE = Not Estimated. The geometric mean could not be estimated due to values being below the limitation of quantification.

3-Day intravenous fosaprepitant/Oral aprepitant/Oral aprepitant Regimen: Simulated aprepitant systemic exposures in patients 6 months to less than 12 years and observed systemic exposures in patients 12 to 17 years are shown in Table 10, including AUC_{0-24hr}, peak plasma concentration (C_{max}) on Day 1 and concentrations at the end of Day 1 (C_{24}), Day 2 (C_{48}) and Day 3 (C_{72}).

Table 10

Systemic Exposures of Aprepitant for 3-Day Intravenous/Oral/Oral Regimen in Pediatric Patients

Population	3-Day Dose of fosaprepitant/ aprepitant (IV/Oral/Oral*)	Geometric Mean				
		AUC_{0-24hr} (mcg*hr/mL)	C_{max} (mcg/mL)	C_{24} (mcg/mL)	C_{48} (mcg/mL)	C_{72} (mcg/mL)
12 Years to 17 Years	115/80/80 mg	18.0	3.0	0.4	0.2	NE[1]
6 Years to less than 12 Years	3/2/2 mg/kg	25.7	2.7	0.5	0.3	0.3
2 Years to less than 6 Years		20.2	2.3	0.3	0.2	0.2
6 Months to less than 2 Years		16.6	1.9	0.2	0.1	0.1

[1] Intravenous fosaprepitant on Day 1, oral aprepitant on Day 2, and oral aprepitant on Day 3
[2] NE = Not Estimated. The geometric mean could not be estimated due to values being below the limitation of quantification.

Plasma concentrations of fosaprepitant are negligible within 15 – 30 minutes after the completion of the infusion in pediatric patients.

Male and Female Patients

Following oral administration of a single dose of aprepitant, ranging from 40 mg to 375 mg, the AUC_{0-24hr} and C_{max} are 9% and 17% higher in females as compared with males. The half-life of aprepitant is approximately 25% lower in females as compared with males and T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful. A population pharmacokinetic analysis of aprepitant in pediatric patients (6 months to 17 years) suggests that sex has no clinically meaningful effect on the pharmacokinetics of aprepitant.

Racial and Ethnic Groups

Following oral administration of a single dose of aprepitant, ranging from 40 mg to 375 mg, the AUC_{0-24hr} and C_{max} are approximately 27% and 19% higher in Hispanics as compared with Caucasians. The AUC_{0-24hr} and C_{max} were 74% and 47% higher in Asians as compared to Caucasians. There was no difference in AUC_{0-24hr} or C_{max} between Caucasians and Blacks.

These differences are not considered clinically meaningful. A population pharmacokinetic analysis of aprepitant in pediatric patients (6 months to 17 years) suggests that race has no clinically meaningful effect on the pharmacokinetics of aprepitant.

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^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.

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_{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 9% and 10%. 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 Interaction 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 coadministered as a single oral dose of 2 mg on Days 1 and 4 *[see Drug Interactions (7.1)]*.

Corticosteroids:

Dexamethasone: Fosaprepitant administered as a single 150 mg intravenous dose on Day 1 increased the AUC_{0-24hr} 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) and 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 (125mg/80-mg/80-mg) did not influence the pharmacokinetics of docetaxel.

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

CYP2C9 substrates (warfarin, tolbutamide):

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

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

Other Drugs

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

$5\text{-}HT_3$ 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: Coadministration of once daily doses of oral aprepitant 170 mg, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and C_{max} by approximately 20% of both aprepitant and paroxetine. This effect was not considered clinically important.

Additional pediatric use information is approved for Merck Sharp & Dohme LLC's EMEND (fosaprepitant) for injection. However, due to Merck Sharp & Dohme LLC's marketing exclusivity rights, this drug product is not labeled with that information.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Sprague-Dawley rats and in CD-1 mice for 2 years. In the rat carcinogenicity studies, animals were treated with oral doses ranging from 0.05 to 1000 mg/kg twice daily. The highest dose produced systemic exposures to aprepitant approximately equivalent to female rats) or less than (male rats) the adult human exposure at the RHD of 150 mg. Treatment with aprepitant at doses of 5 to 1000 mg/kg twice daily caused an increase in the incidences of thyroid follicular cell adenomas and carcinomas in male rats. In female rats, it produced hepatocellular adenomas at 5 to 1000 mg/kg twice daily and hepatocellular carcinomas and thyroid follicular cell adenomas at 125 to 1000 mg/kg twice daily. In the mouse carcinogenicity studies, the animals were treated with oral doses ranging from 2.5 to 2000 mg/kg/day. The highest dose produced a systemic exposure approximately 2 times the 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 1000 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 FOCINVEZ have been established based on adequate and well-controlled adult studies of another intravenous formulation of fosaprepitant for the prevention and of chemotherapy induced nausea and vomiting. Below is a description of the results of these adequate and well-controlled studies of fosaprepitant.

14.1 Prevention of Nausea and Vomiting Associated with HEC in Adults

In a randomized, parallel, double-blind, active-controlled study, fosaprepitant 150 mg as a single intravenous infusion (N=1147) was compared to a 3-day oral aprepitant regimen (N=1175) in patients receiving a HEC regimen that included cisplatin (≥70 mg/m^2). 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[1]

	Day 1	Day 2	Day 3	Day 4
Fosaprepitant Regimen				
intravenous fosaprepitant	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy	none	none	none
Oral dexamethasone[2]	12 mg	8 mg	8 mg twice daily	8 mg twice daily
Ondansetron	Ondansetron[3]	none	none	none

[1] Intravenous fosaprepitant placebo, aprepitant capsules placebo and dexamethasone placebo (in the evenings on Days 3 and 4) were used to maintain blinding.
[2] 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 intravenous fosaprepitant regimen *[see Clinical Pharmacology (12.3)]*.
[3] Ondansetron 32 mg intravenous was used in the clinical trials of intravenous 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.
[4] 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 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 prespecified non-inferiority margin for complete response in the overall phase was 7%. The prespecified non-inferiority margin for complete response in the delayed phase was 7.3%. The prespecified 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)[a] %	Oral aprepitant Regimen (N = 1134)[a] %	Difference[b] (95% CI)
PRIMARY ENDPOINT			
Complete Response[c]			
Overall[d]	71.9	72.3	-0.4 (-4.1, 3.3)
SECONDARY ENDPOINTS			
Complete Response[c]			
Delayed phase[e]	74.3	74.2	0.1 (-3.5, 3.7)
No Vomiting			
Overall[d]	72.9	74.6	-1.7 (-5.3, 2.0)

[a] N: Number of patients included in the primary analysis of complete response.
[b] Difference and Confidence interval (CI) were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.
[c] Complete Response = no vomiting and no use of rescue therapy.
[d] Overall = 0 to 120 hours post-initiation of cisplatin chemotherapy.
[e] 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, intravenous 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[a]

	Day 1	Day 2	Day 3
Intravenous fosaprepitant Regimen			
Intravenous fosaprepitant	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy	none	none
Oral Dexamethasone[b]	12 mg	none	none
Oral Ondansetron[c]	8 mg for 2 doses	none	none
Standard Therapy			
Oral Dexamethasone	20 mg	none	none
Oral Ondansetron[c]	8 mg for 2 doses	8 mg twice daily	8 mg twice daily

[a] Intravenous fosaprepitant placebo and dexamethasone placebo (on Day 1) were used to maintain blinding.
[b] 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 intravenous fosaprepitant regimen *[see Clinical Pharmacology (12.3)]*.
[c] 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)[a] %	Standard Therapy Regimen (N = 498)[a] %	P-Value	Treatment Difference (95% CI)
PRIMARY ENDPOINT				
Complete Response[b]				
Delayed phase[c]	78.9	68.5	<0.001	10.4 (5.1, 15.9)

[a] N: Number of patients included in the intention to treat population.
[b] Complete Response = no vomiting and no use of rescue therapy.
[c] Delayed phase = 25 to 120 hours post-initiation of chemotherapy.

16 HOW SUPPLIED/STORAGE AND HANDLING

FOCINVEZ (fosaprepitant injection) contains 150 mg/50 mL (3 mg/mL) of fosaprepitant as a clear and colorless ready-to-use injection solution in a single-dose vial. Supplied as follows:

NDC 70121-2631-1 1 vial per carton.

Storage

- Refrigerate FOCINVEZ at 2°C to 8°C (36°F to 46°F).
- FOCINVEZ vials, when kept in original carton, can remain at room temperature 20°C to 25°C (68°F to 77°F) for up to 90 days.

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, nonprescription medication or herbal products *[see Contraindications (4) and 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 FOCINVEZ with each chemotherapy cycle *[see Warnings and Precautions (5.4)]*.

Hormonal Contraceptives: Advise patients that administration of FOCINVEZ 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 FOCINVEZ and for 1 month following administration of the last dose of fosaprepitant or oral aprepitant *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.3)]*.

Manufactured by:
Steriscience Specialties Private Limited
Sterile Product Division, Opp IIM, Bilekahalli, Bannerghatta Road, Bengaluru, India 560076

Distributed by:
Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

Rev. 02/2024

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1200007825

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Literature Open dimensions : 440 x 400 mm
Paper GSM : 40 GSM Bible Paper

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steriscience Corporate, Bangalore, India	ARTWORK DETAIL LABEL INFORMATION			
Product	Fosaprepitant injection 150 mg/50 mL (3 mg/mL)			
Buyer/Country	Amneal/US	Component	Literature	
Dimension	440 x 400 mm Folding Dimension: 37 x 50 mm		Pack	NA
New Item Code	1200007825	Old Item code	NA	
Color Shades	Black		No of colours	1
Change Control No.	NA		Artwork Version	1.0 (February 2024)
Design/Style	Front & Back Printing. To be supplied in folded size of 37x50 mm with Brand name facing front after final folding.			
Substrate	40 GSM Paper			
Special Instruction	Printing Clarity to be clear and sharp.			
Autocartonator Requirements	NA			
Prepared By:	Reviewed By:	Approved By:	Approved By:	Authorized By:
PDC	Mkt/BD	RA	FD/PDN	QA
		Robert Dieso Digitally signed by Robert Dieso Date: 2024.03.04 10:03:51 -05'00'		
FOR ARTWORK REVISION PURPOSE				
To be filled by SCM	Effective Date:	NA	Sign & Date	NA

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