Fosaprepitant Dimeglumine for injection 150 mg/vial

Aprintant IV

To be sold by retail on the prescription of an Oncologist Only

PRESCRIBING INFORMATION

1. GENERIC NAME

Fosaprepitant Dimeglumine for injection 150 mg/vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains
Fosaprepitant Dimeglumine 245.3 mg Equivalent to
Fosaprepitant ..... 150 mg

3. DOSAGE FORM AND STRENGTH

Fosaprepitant Dimeglumine is available as injection 150 mg/vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Fosaprepitant is indicated for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic (HEC) cisplatin-based cancer chemotherapy in adults.
Fosaprepitant is also indicated for the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic (MEC) cancer chemotherapy in adults.

4.2 Posology and Method of Administration

Prevention of Nausea and Vomiting Associated with HEC and MEC in Adult Patients
The recommended dose is 150 mg administered as an infusion over 20-30 minutes on Day 1, initiated approximately 30 minutes prior to chemotherapy. Fosaprepitant should be administered in conjunction with a corticosteroid and a 5-HT3 antagonist as specified in the tables below.
The following regimens are recommended for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy.

Table 1: Recommended dosing for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy regimen in adults

	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-HT3 antagonist	See selected 5-HT3 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.

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

	Day 1
Fosaprepitant Dimeglumine for injection	150 mg intravenously over 20 to 30 minutes
Dexamethasone*	12 mg orally
5-HT3 antagonist	See selected 5-HT3 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.

Preparation of Fosaprepitant dimeglumine for injection

Table 3: Preparation Instructions for Fosaprepitant dimeglumine 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 jetting 0.9% Sodium Chloride Injection, USP into the vial.
Step 2	Aseptically prepare an infusion bag filled with 145 mL of 0.9% Sodium Chloride Injection, USP.
Step 3	Aseptically withdraw the entire volume from the vial and transfer it into the infusion bag containing 145 mL of 0.9% Sodium Chloride Injection, USP to yield a total volume of 150 mL and a final concentration of 1 mg/mL.
Step 4	Gently invert the bag 2 to 3 times.
Step 5	Determine the volume to be administered from this prepared infusion bag, based on the recommended dose. Adults The entire volume of the prepared infusion bag (150 mL) should be administered.
Step 6	If necessary, for volumes less than 150 mL, the calculated volume can be transferred to an appropriate size bag or syringe prior to administration by infusion.
Step 7	Before administration, inspect the bag for particulate matter and discoloration. Discard the bag if particulate and/or discoloration are observed.

The recommended dose of Fosaprepitant Dimeglumine for injection is based on the patient's age and weight.
Caution: Do not mix or reconstitute Fosaprepitant Dimeglumine for injection with solutions for which physical and chemical compatibility have not been established. Fosaprepitant Dimeglumine for injection is incompatible with any solutions containing divalent cations (e.g., Ca2+, Mg2+), including Lactated Ringer's Solution and Hartmann's Solution.
Storage
The reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25ºC (77ºF)].

4.3 Contraindications

Fosaprepitant is contraindicated in patients:

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

4.4 Special Warnings and Precautions for Use Clinically Significant CYP3A4 Drug Interactions

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

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

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

Infusion Site Reactions

Infusion site reactions (ISRs) have been observed with the use of Fosaprepitant Dimeglumine for injection. The majority of severe ISRs, including thrombophlebitis and vasculitis, were observed with concomitant vesicant [anthracycline-based] chemotherapy administration, particularly when associated with extravasation. Necrosis was also observed in some patients with concomitant vesicant chemotherapy. Most ISRs occurred with the first, second or third exposure to single doses of Fosaprepitant Dimeglumine 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 Dimeglumine for injection into small veins or through a butterfly catheter. If a severe ISR develops during infusion, discontinue the infusion and administer appropriate medical treatment.

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. Monitor the INR in patients on chronic warfarin therapy in the 2-week period, particularly at 7 to 10 days, following initiation of Fosaprepitant with each chemotherapy cycle.

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. Advise patients to use effective alternative or back-up methods of contraception during treatment with Fosaprepitant and for 1 month following administration of Fosaprepitant.

Patients with moderate to severe hepatic impairment

There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment. Fosaprepitant should be used with caution in these patients.

4.5 Drug Interactions

Effect of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs

When administered intravenously, fosaprepitant, a prodrug of aprepitant, is converted to aprepitant within 30 minutes. Therefore, drug interactions following administration of Fosaprepitant Dimeglumine for injection are likely to occur with drugs that interact with oral aprepitant.
Fosaprepitant, given as a single 150-mg dose, is a weak inhibitor of CYP3A4, and the weak inhibition of CYP3A4 continues for 2 days after single dose administration. Single dose fosaprepitant does not induce CYP3A4. Aprepitant is a substrate, an inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. Some substrates of CYP3A4 are contraindicated with Fosaprepitant. Dosage adjustment of some CYP3A4 and CYP2C9 substrates may be warranted as shown in below table.

Table 4: Effects of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs

CYP3A4 Substrates	
Pimozide	
Clinical Impact	Increased pimozide exposure
Intervention	Fosaprepitant is contraindicated
Benzodiazepines	
Clinical Impact	Increased exposure to midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) may increase the risk of adverse reactions
Intervention	Monitor for benzodiazepine-related adverse reactions.
Dexamethasone	
Clinical Impact	Increased dexamethasone exposure [see Clinical Pharmacology
Intervention	Reduce the dose of oral dexamethasone by approximately 50%
Methylprednisolone	
Clinical Impact	Increased methylprednisolone exposure
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.
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.
Intervention	Effective alternative or back-up methods of contraception (such as condoms and spermicides) should be used during treatment with Fosaprepitant and for 1 month following administration of Fosaprepitant.
Examples	birth control pills, skin patches, implants, and certain IUDs
CYP2C9 Substrates	
Warfarin	Decreased warfarin exposure and decreased prothrombin time (INR)
Intervention	In patients on chronic warfarin therapy, monitor the prothrombin time (INR) in the 2-week period, particularly at 7 to 10 days, following administration of Fosaprepitant with each chemotherapy cycle.
Other	
5-HT3 Antagonists	
Clinical Impact	No change in the exposure of the 5-HT3 antagonist
Intervention	No dosage adjustment needed
Examples	ondansetron, granisetron, dolasetron

Effect of Other Drugs on the Pharmacokinetics of Fosaprepitant/Aprepitant

Aprepitant is a CYP3A4 substrate. Co-administration of Fosaprepitant with drugs that are inhibitors or inducers of CYP3A4 may result in increased or decreased plasma concentrations of aprepitant, respectively as shown in below table.

Table 5: Effects of Other Drugs on Pharmacokinetics of Fosaprepitant/Aprepitant

Moderate to Strong CYP3A4 Inhibitors	
Clinical Impact	Significantly increased exposure of aprepitant may increase the risk of adverse reactions associated with Fosaprepitant.
Intervention	Avoid concomitant use of Fosaprepitant
Examples	Moderate inhibitor: diltiazem Strong inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir
Strong CYP3A4 Inducers	
Clinical Impact	Substantially decreased exposure of aprepitant in patients chronically taking a strong CYP3A4 inducer may decrease the efficacy of Fosaprepitant
Intervention	Avoid concomitant use of Fosaprepitant
Examples	rifampin, carbamazepine, phenytoin

4.6 Use in Special Populations

Pregnancy

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

Lactation

Lactation studies have not been conducted to assess the presence of aprepitant in human milk, the effects on the breastfed infant, or the effects on milk production. Aprepitant is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fosaprepitant and any potential adverse effects on the breastfed infant from Fosaprepitant or from the underlying maternal condition.

Females and Males of Reproductive Potential

Contraception

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

Pediatric Use

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

Geriatric Use

In general, use caution when dosing elderly patients as they have a greater frequency of decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy.

Patients with Hepatic Impairment

No dosage adjustment is necessary for Aprepitant in patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 9). There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score greater than 9).
Therefore, additional monitoring for adverse reactions in these patients may be warranted when Fosaprepitant is administered.

4.7 Effects on Ability to Drive and Use Machines

Fosaprepitant may have minor influence on the ability to drive and use machines. Dizziness and fatigue may occur following administration of Fosaprepitant.

4.8 Undesirable Effects

The following clinically significant adverse reactions of Fosaprepitant:

- Hypersensitivity Reactions
- Infusion Site Reactions

Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 6: Tabulated list of adverse reactions

System organ class	Adverse reaction	Frequency
Infection and infestations	candidiasis, staphylococcal infection	rare
Blood and lymphatic system disorders	febrile neutropenia, anaemia	uncommon
Immune system disorders	hypersensitivity reactions including anaphylactic reactions	not known
Metabolism and nutrition disorders	decreased appetite	common
	polydipsia	rare
Psychiatric disorders	anxiety	uncommon
	disorientation, euphoric mood	rare
Nervous system disorders	headache	common
	dizziness, somnolence	uncommon
	cognitive disorder, lethargy, dysgeusia	rare
Eye disorders	conjunctivitis	rare
Ear and labyrinth disorders	tinnitus	rare
Cardiac disorders	palpitations	uncommon
	bradycardia, cardiovascular disorder	rare
Vascular disorders	hot flush/flushing	uncommon
Respiratory, thoracic and mediastinal disorders	hiccups	common
	oropharyngeal pain, sneezing, cough, postnasal drip, throat irritation	rare
Gastrointestinal disorders	constipation, dyspepsia	common
	eructation, nausea*, vomiting*, gastroesophageal reflux disease, abdominal pain, dry mouth, flatulence	uncommon
	duodenal ulcer perforation, stomatitis, abdominal distension, faeces hard, neutropenic colitis	rare
Skin and subcutaneous tissue disorders	rash, acne	uncommon
	photosensitivity reaction, hyperhidrosis, seborrhoea, skin lesion, rash pruritic, Stevens-Johnson syndrome/toxic epidermal necrolysis	rare
	pruritus, urticaria	not known
Musculoskeletal and connective tissue disorders	muscular weakness, muscle spasms	rare
Renal and urinary disorders	dysuria	uncommon
	pollakisuria	rare
General disorders and administration site conditions	fatigue	common
	asthenia, malaise	uncommon
	oedema, chest discomfort, gait disturbance	rare
Investigations	ALT increased	common
	AST increased, blood alkaline phosphatase increased	uncommon
	red blood cells urine positive, blood sodium decreased, weight decreased, neutrophil count decreased, glucose urine present, urine output increased	rare

*Nausea and vomiting were efficacy parameters in the first 5-days of post-chemotherapy treatment and were reported as adverse reactions only thereafter.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com >Contact us->Medical Enquiry/ to report a side effect. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on **1800 180 3024** or you can report to MSN Labs on **+91845830529/5/+917331134745**. By reporting side effects, you can help provide more information on the safety of this product.

4.9 Overdose

There is no specific information on the treatment of overdosage with fosaprepitant or aprepitant.
In the event of overdose, Fosaprepitant should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of Fosaprepitant, drug-induced emesis may not be effective in cases of Fosaprepitant overdosage.
Aprepitant is not removed by hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

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

5.2 Pharmacodynamic Properties

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.

5.3 Pharmacokinetic Properties

Aprepitant after Fosaprepitant Administration
Following administration of a single intravenous 150-mg dose of fosaprepitant, a prodrug of aprepitant administered as a 20-minute infusion to healthy subjects, the mean $AUC_{0-\infty}$ of aprepitant was 37.4 (± 14.8) mcg•hr/mL and the mean maximal aprepitant concentration (C_{max}) was 4.2 (± 1.2) mcg/mL. Plasma concentrations of fosaprepitant are below the limits of quantification (10 ng/mL) within 30 minutes of the completion of infusion.
Distribution
Aprepitant is greater than 95% bound to plasma proteins. The mean apparent volume of distribution at steady state (Vdss) was approximately 70 L in humans. Aprepitant crosses the blood brain barrier in humans.
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.
Excretion
Following administration of a single intravenous 100-mg dose of [^{14}C]-fosaprepitant, 57% of the radioactivity was recovered in urine and 45% in feces.
Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. The apparent terminal half-life ranged from approximately 9 to 13 hours.
Specific Populations
Age: Geriatric Population
Following oral administration of a single 125-mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 through 5, the AUC_{0-24hr} of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (65 years and older) relative to younger adults. The C_{max} was 10% higher on Day 1 and 24% higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful.
Sex
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.
Race/Ethnicity
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.
Renal Impairment
In patients with severe renal impairment, the $AUC_{0-\infty}$ of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects (creatinine clearance greater than 80 mL/min estimated by Cockcroft-Gault method). In patients with ESRD undergoing hemodialysis, the $AUC_{0-\infty}$ of total aprepitant decreased by 42% and C_{max} decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal impairment compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.
Hepatic Impairment
Fosaprepitant is metabolized in various extrahepatic tissues; therefore hepatic impairment is not expected to alter the conversion of fosaprepitant to aprepitant.
Following administration of a single 125-mg oral dose of aprepitant on Day 1 and 80 mg once daily on Days 2 and 3 to patients with mild hepatic impairment (Child-Pugh score 5 to 6), the AUC_{0-24hr} of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, given the same regimen. In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the AUC0-24hr of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, 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).
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 Interactions Studies
Fosaprepitant, given as a single 150-mg dose, is a weak inhibitor of CYP3A4, with no evidence of inhibition or induction of CYP3A4 observed on Day 4. The weak inhibition of CYP3A4 continues for 2 days after single dose administration of fosaprepitant. Aprepitant is a substrate, an inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.
Fosaprepitant or aprepitant is unlikely to interact with drugs that are substrates for the P glycoprotein transporter.
Effects of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs
CYP3A4 Substrates
Midazolam: Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the $AUC_{0-\infty}$ of midazolam by approximately 1.8-fold on Day 1 and had no effect on Day 4 when midazolam was coadministered as a single oral dose of 2 mg on Days 1 and 4.
Corticosteroids
Dexamethasone: Fosaprepitant administered as a single 150 mg intravenous dose on Day 1 increased the AUC0-24hr 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.
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.
Chemotherapeutic agents
Docetaxel: In a pharmacokinetic study, oral aprepitant administered as a 3-day regimen (125 mg/80-mg/80-mg) did not influence the pharmacokinetics of docetaxel.
Vinorelbine: In a pharmacokinetic study, oral aprepitant administered as a 3-day regimen (125 mg/80-mg/80-mg) did not influence the pharmacokinetics of vinorelbine to a clinically significant degree.
Oral contraceptives: When oral aprepitant was administered as a 3-day regimen (125-mg/80 mg/80-mg) with ondansetron and dexamethasone, and coadministered with an oral contraceptive containing ethinyl estradiol and norethindrone, the trough concentrations of both ethinyl estradiol and norethindrone were reduced by as much as 64% for 3 weeks post-treatment.
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.
Tolbutamide: Oral aprepitant, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide by 23% on Day 4, 28% on Day 8, and 15% on Day 15, when a single dose of tolbutamide 500 mg was administered prior to the administration of the 3-day regimen of oral aprepitant and on Days 4, 8, and 15. This effect was not considered clinically important.
Other Drugs
P-glycoprotein substrates: Aprepitant is unlikely to interact with drugs that are substrates for the P glycoprotein transporter, as demonstrated by the lack of interaction of oral aprepitant with digoxin in a clinical drug interaction study.
5-HT3 antagonists: In clinical drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).
Effect of Other Drugs on the Pharmacokinetics of Fosaprepitant/Aprepitant
Rifampin: When a single 375-mg dose of oral aprepitant was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampin, a strong CYP3A4 inducer, the AUC of aprepitant decreased approximately 11-fold and the mean terminal half-life decreased approximately 3-fold.
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.
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.
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.

6. NONCLINICAL PROPERTIES

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).

7. PHARMACEUTICAL PARTICULARS

7.1 Incompatibilities

None

7.2 Packing Information

10 mL USP type I clear tubular glass vial with 13 mm bromobutyl double slotted rubber stopper with 13 mm aluminum flip off seal.

7.3 Storage and Handling Instructions

Store at 2 to 8°C (36 to 46°F)
Keep out of reach of children.

8. PATIENT COUNSELLING 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.

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.

Drug Interactions

Advise patients to discuss all medications they are taking, including other prescription, non prescription medication or herbal products.

Warfarin: Instruct patients on chronic warfarin therapy to follow instructions from their healthcare provider regarding blood draws to monitor their INR during the 2-week period, particularly at 7 to 10 days, following initiation of Fosaprepitant with each chemotherapy cycle.

Hormonal Contraceptives: Advise patients that administration of Fosaprepitant may reduce the efficacy of hormonal contraceptives. Instruct patients to use effective alternative or back-up methods of contraception (such as condoms and spermicides) during treatment with Fosaprepitant and for 1 month following administration of Fosaprepitant.

9. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited,
Formulation Division, Unit-II,
Sy.no. 1277, 1319 to 1324,
Nandigama (Village & Mandal),
Rangareddy (District),
Telangana - 509 228, India.

10. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

5/MN/TS/2014/F/G, 26/08/2019

11. DATE OF REVISION

June-2021