PRESCRIBING INFORMATION
FOSEMRED (Fosaprepitant Powder for Solution for Infusion 150 mg/vial)

COMPOSITION

Each Lyophilized vial of FOSEMRED contains 245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg of fosaprepitant free acid

PRODUCT DESCRIPTION

White to off-white lyophilized cake or powder

Description of Reconstituted Solution: Clear, pale yellow colored solution, free from visible extraneous matter

Description of Diluted Solution: Colorless to slightly yellowish solution, free from visible extraneous matter.

Diluents Used: 0.9% Sodium Chloride Injection

CLINICAL PARTICULARS

Therapeutic indications

FOSEMRED, in combination with other antiemetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of:

- highly emetogenic cancer chemotherapy including high-dose cisplatin (see Dosage and administration).
- moderately emetogenic cancer chemotherapy (see Dosage and administration).

Dosage and Administration

FOSEMRED is administered on Day 1 as an infusion over 20 – 30 minutes initiated approximately 30 minutes prior to chemotherapy. FOSEMRED should be administered in conjunction with a corticosteroid and a 5-HT3 antagonist as specified in the tables below. The package insert for the co-administered 5-HT3 antagonist must be consulted prior to initiation of treatment with FOSEMRED.

Recommended dosing for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy:

	Day 1	**Day 2**	**Day 3**	**Day 4**
FOSEMRED	150 mg IV	none	none	none
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally bid	8 mg orally bid
5-HT_3 antagonist	See the package insert for the selected 5-HT_3 antagonist for the appropriate dosing information.	none	none	none

**Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. Dexamethasone should also be administered in the evenings on Days 3 and 4. The dose of dexamethasone accounts for drug interactions.

Recommended dosing for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy:

	Day 1
FOSEMRED	150 mg IV
Dexamethasone**	12 mg orally
5-HT3 antagonist	See the package insert for the selected 5-HT_3 antagonist for appropriate dosing information.

**Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone accounts for drug interactions.

Preparation of FOSEMRED 150 mg for intravenous administration:
1. Inject 5 ml sodium chloride 9 mg/ml (0.9 %) solution for injection into the vial. Assure that sodium chloride 9 mg/ml (0.9 %) solution for injection is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and jetting sodium chloride 9 mg/ml (0.9 %) solution for injection into the vial.

2. Prepare an infusion bag filled with 145 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection (for example, by removing 105 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection from a 250 ml sodium chloride 9 mg/ml (0.9 %) solution for injection infusion bag).

3. Withdraw the entire volume from the vial and transfer it into an infusion bag containing 145 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection to yield a total volume of 150 ml and final concentration of 1 mg/ml. Gently invert the bag 2-3 times.

4. Determine the volume to be administered from this prepared infusion bag, based on the recommended dose (see section Dosage and administration).

The reconstituted final drug solution is stable for 24 hours at ambient room temperature (at or below 25ºC).

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

FOSEMRED is incompatible with any solutions containing divalent cations (e.g., Ca2+, Mg2+), including Hartman's and Lactated Ringer's Solution. FOSEMRED must not be reconstituted or mixed with solutions for which physical and chemical compatibility have not been established.

General Information
See DRUG INTERACTIONS for additional information on the administration of FOSEMRED with corticosteroids.

Refer to the full prescribing information for coadministered antiemetic agents.

No dosage adjustment is necessary based on age, gender, race or Body Mass Index (BMI).

No dosage adjustment is necessary for patients with severe renal insufficiency (creatinine clearance <30 ml/min) or for patients with end stage renal disease undergoing hemodialysis.

No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency (Child-Pugh score 5 to 9). There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score >9).

Instructions for Use
Physicians should instruct their patients to read the patient package insert before starting therapy with FOSEMRED and to reread it each time the prescription is renewed.
Patients should follow the physician' s instructions for the FOSEMRED regimen. For the prevention of CINV, patients can be given a single dose of FOSEMRED 150 mg as an infusion over 20– 30 minutes, 30 minutes prior to chemotherapy on Day 1.

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 PRECAUTIONS).

FOSEMRED may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products.

Patients on chronic warfarin therapy should be instructed to have their clotting status closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of fosaprepitant with each chemotherapy cycle.

Concomitant administration of FOSEMRED may reduce the efficacy of hormonal contraceptives. Patients should be advised to use alternative or back-up methods of contraception during treatment with and for 1 month following administration of FOSEMRED

Incompatibilities
FOSEMRED is incompatible with any solutions containing divalent cations (e.g., Ca2+, Mg2+), including Hartman's and lactated Ringer's solutions.
FOSEMRED must be reconstituted and then diluted prior to administration.

Adults
The entire volume of the prepared infusion bag (150 ml) should be administered.

Children
In patients 12 years and older, the volume to be administered is calculated as follows:
• Volume to administer (ml) equals the recommended dose (mg)

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.
The appearance of the reconstituted solution is the same as the appearance of the diluent.

The reconstituted and diluted medicinal product should be inspected visually for particulate matter and discoloration before administration.

Discard any remaining solution and waste material. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
The medicinal product must not be reconstituted or mixed with solutions for which physical and chemical compatibility has not been established (see Incompatibilities)

Method of administration
FOSEMRED should be administered intravenously.

Contraindications

FOSEMRED is contraindicated in patients who are hypersensitive to FOSEMRED, aprepitant, polysorbate 80 or any other components of the product.

FOSEMRED should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions (see DRUG INTERACTIONS).

FOSEMRED is not recommended for the use below 12 years of age.

Precautions
Since fosaprepitant is rapidly converted to aprepitant (a weak to moderate inhibitor of CYP3A4), fosaprepitant should be used with caution in patients receiving concomitant orally administered medicinal products that are primarily metabolized through CYP3A4; some chemotherapy agents are metabolized by CYP3A4 (see DRUG INTERACTIONS). Weak inhibition of CYP3A4 by fosaprepitant 150 mg could result in elevated plasma concentrations of these concomitant medicinal products administered orally (see DRUG INTERACTIONS). Consequently, chemotherapeutic agents metabolized via CYP3A4 should be used with caution. Additionally, concomitant administration with irinotecan should be approached with particular caution as the combination may result in increased toxicity.

Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine.

Particular caution and careful monitoring are advised in patients receiving CYP3A4 substrates vinblastine, vincristine, or ifosfamide or other chemotherapy agents metabolized primarily by CYP3A4.

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

Coadministration of fosaprepitant with ergot alkaloid derivatives, which are CYP3A4 substrates, may result in elevated plasma concentrations of these medicinal products. Therefore, caution is advised due to the potential risk of ergot-related toxicity.

Concomitant administration of fosaprepitant with medicinal products that strongly induce CYP3A4 activity (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital) should be avoided as the combination results in reductions of the plasma concentrations of aprepitant. Concomitant administration of aprepitant with St. John's wort is not recommended.

Concomitant administration of fosaprepitant with medicinal products that inhibit CYP3A4 activity (e.g., ritonavir, ketoconazole, clarithromycin, telithromycin) should be approached cautiously as the combination results in increased plasma concentrations of aprepitant.

Immediate hypersensitivity reactions including flushing, erythema, dyspnea, and anaphylaxis/anaphylactic shock have occurred during or soon after infusion of fosaprepitant. These hypersensitivity reactions have generally responded to discontinuation of the infusion and administration of appropriate therapy. It is not recommended to reinitiate the infusion in patients who experience hypersensitivity reactions.

Infusion site reactions (ISRs) have been reported with the use of FOSEMRED (see SIDE EFFECTS). The

majority of severe ISRs, including thrombophlebitis and vasculitis, were reported with concomitant vesicant (e.g., anthracycline-based) chemotherapy administration, particularly when associated with extravasation. Necrosis was also reported in some patients with concomitant vesicant chemotherapy.

Coadministration of fosaprepitant with warfarin may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time. In patients on chronic warfarin therapy, the INR should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of fosaprepitant with each chemotherapy cycle (see DRUG INTERACTIONS).

The efficacy of hormonal contraceptives during and for 28 days after administration of fosaprepitant may be reduced. Alternative or back-up methods of contraception should be used during treatment with fosaprepitant and for 1 month following administration of fosaprepitant (see DRUG INTERACTIONS).

Chronic continuous use of FOSEMRED for injection for prevention of nausea and vomiting is not recommended because it has not been studied and because the drug interaction profile may change during chronic continuous use.

FOSEMRED should not be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion (see DOSAGE AND ADMINISTRATION). FOSEMRED should not be administered intramuscularly or subcutaneously. Mild injection site thrombosis has been observed at higher doses (see OVERDOSAGE). If signs or symptoms of local irritation occur, the injection or infusion should be terminated and restarted in another vein.

FOSEMRED is not recommended for the use below 12 years of age.

DRUG INTERACTIONS

When administered intravenously, fosaprepitant is rapidly converted to aprepitant. Therefore, drug interactions following administration of fosaprepitant are likely to occur with drugs that interact with oral aprepitant. The following information was derived from data of oral aprepitant and data of fosaprepitant coadministered with dexamethasone, midazolam or diltiazem.

Aprepitant is a substrate, a weak to moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

As a weak inhibitor of CYP3A4, the fosaprepitant 150 mg single dose can cause a transient increase in plasma concentrations of co-administered active substances that are metabolized through CYP3A4. The total exposure of CYP3A4 substrates may increase on Days 1 and 2 after coadministration with a single 150 mg fosaprepitant dose. Fosaprepitant must not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by fosaprepitant could result in elevated plasma concentrations of these active substances, potentially causing serious or life-threatening reactions. (See CONTRAINDICATIONS). Caution is advised during concomitant administration of fosaprepitant and active substances that are metabolized primarily through CYP3A4 and with a narrow therapeutic range, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine (see PRECAUTIONS).

<u>Effect of fosaprepitant/aprepitant on the pharmacokinetics of other agents</u>

Aprepitant, as a weak to moderate inhibitor of CYP3A4, and fosaprepitant, as a weak inhibitor of CYP3A4, can increase plasma concentrations of orally coadministered medicinal products that are metabolized through CYP3A4.

Fosaprepitant should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions (see CONTRAINDICATIONS).

Aprepitant has been shown to induce the metabolism of S(-) warfarin and tolbutamide, which are metabolized through CYP2C9. Coadministration of fosaprepitant with these drugs or other drugs that are known to be metabolized by CYP2C9, such as phenytoin, may result in lower plasma concentrations of these drugs.

Fosaprepitant 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.

5-HT3 antagonists: Aprepitant, when given as a regimen of 125 mg on Day 1 and 80 mg on Days 2 and 3, did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Corticosteroids:
Dexamethasone: Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the AUC0-24hr of dexamethasone, a CYP3A4 substrate on Days 1 and 2 when dexamethasone was coadministered as a single 8 mg oral dose on Days 1, 2, and 3. The oral dexamethasone dose on Days 1 and 2 should be reduced when coadministered with fosaprepitant 150 mg I.V. on Day 1 to achieve exposures of dexamethasone similar to those obtained when given without fosaprepitant 150 mg (see DOSAGE AND ADMINISTRATION).

Methylprednisolone: Oral aprepitant, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, increased the AUC of methylprednisolone, a CYP3A4 substrate on Day 1 and Day 3, when methylprednisolone was coadministered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3.

Chemotherapeutic agents: The oral aprepitant regimen was administered with the following chemotherapeutic agents metabolized primarily or in part by CYP3A4: etoposide, vinorelbine, docetaxel, ifosfamide, cyclophosphamide, irinotecan, and paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions. Caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4. Post marketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosfamide coadministration (see PRECAUTIONS).

Docetaxel: Oral aprepitant, (CINV regimen) did not influence the pharmacokinetics of docetaxel.

Vinorelbine: Oral aprepitant (CINV regimen) did not influence the pharmacokinetics of vinorelbine.

Warfarin: A single 125 mg dose of oral aprepitant was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy patient 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 decrease in S(-) warfarin (a CYP2C9 substrate) trough concentration accompanied by a decrease in the prothrombin time (reported as International Normalized Ratio or INR) 5 days after completion of dosing with oral aprepitant. In patients on chronic warfarin therapy, the prothrombin time (INR) should be closely monitored

in the 2-week period, particularly at 7 to 10 days, following initiation of fosaprepitant with each chemotherapy cycle.

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 (a CYP2C9 substrate) on Day 4, Day 8, and Day 15, when a single dose of tolbutamide 500 mg was administered orally prior to the administration of the 3-day regimen of oral aprepitant and on Days 4, 8, and 15.

Oral contraceptives: Aprepitant, when given once daily for 14 days as a 100-mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol, and decreased the AUC of norethindrone.

A single dose of an oral contraceptive containing ethinyl estradiol and norethindrone was administered on Days 1 through 21 with oral aprepitant, given as a regimen of 125 mg on Day 8 and 80 mg/day on Days 9 and 10 with ondansetron 32 mg IV on Day 8 and oral dexamethasone given as 12 mg on Day 8 and 8 mg/day on Days 9, 10, and 11. The AUC of ethinyl estradiol decreased on Day 10 and there was a decrease in ethinyl estradiol trough concentrations during Days 9 through 21. While there was no effect of oral aprepitant on the AUC of norethindrone on Day 10, there was a decrease in norethindrone trough concentrations during Days 9 through 21.

The efficacy of hormonal contraceptives during and for 28 days after administration of fosaprepitant may be reduced. Alternative or back-up methods of contraception should be used during treatment with fosaprepitant and for 1 month following administration of fosaprepitant.

Midazolam: Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the AUC0-∞ of midazolam 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. Fosaprepitant 150 mg I.V. is a weak CYP3A4 inhibitor as a single dose on Day 1 with no evidence of inhibition or induction of CYP3A4 observed on Day 4.

Effect of other agents on the pharmacokinetics of aprepitant

Aprepitant is a substrate for CYP3A4; therefore, coadministration of fosaprepitant with drugs that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of fosaprepitant with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir) should be approached cautiously. Because moderate CYP3A4 inhibitors (e.g., diltiazem) result in a increase in plasma concentrations of aprepitant, concomitant administration should also be approached with caution.

Aprepitant is a substrate for CYP3A4; therefore, coadministration of fosaprepitant with drugs that strongly induce CYP3A4 activity (e.g., rifampin, carbamazepine, phenytoin) may result in reduced plasma concentrations and decreased efficacy.

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 and the mean terminal half-life of aprepitant increased. Concomitant administration of fosaprepitant with strong CYP3A4 inhibitors should be approached cautiously.

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 and the mean

terminal half-life decreased. Coadministration of fosaprepitant with drugs that induce CYP3A4 activity may result in reduced plasma concentrations and decreased efficacy.

Additional interactions
Diltiazem: In patients with mild to moderate hypertension, infusion of 100 mg of fosaprepitant over 15 minutes with diltiazem 120 mg 3 times daily, resulted in an increase of aprepitant AUC and an increase in diltiazem AUC. The pharmacokinetic effects resulted in a small but clinically meaningful decrease in diastolic blood pressure (decrease of 16.8 mm Hg with fosaprepitant versus 10.5 mm Hg without fosaprepitant) and may result in a small but clinically meaningful decrease in systolic blood pressure (decrease of 24.4 mm Hg with fosaprepitant versus 18.8 mm Hg without fosaprepitant), but did not result in a clinically meaningful change in heart rate, or PR interval, beyond those changes induced by diltiazem alone.

Paroxetine: Coadministration of once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of the capsule formulation, with paroxetine 20 mg once daily, resulted in a decrease in AUC and Cmax of both aprepitant and paroxetine.

Fertility, pregnancy and lactation
Pregnancy
There are no adequate data in pregnant women. FOSEMRED should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and the fetus.

Breast-feeding
FOSEMRED when administered intravenously, is rapidly converted to aprepitant.

Aprepitant is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the possible adverse effects of aprepitant on nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

Undesirable effects
Since fosaprepitant is converted to aprepitant, those adverse experiences associated with aprepitant might also be expected to occur with FOSEMRED

Oral Aprepitant
Highly Emetogenic Chemotherapy (HEC)
The 3-day oral aprepitant regimen was given in combination with ondansetron and dexamethasone and was generally well tolerated. Most adverse experiences reported were described as mild to moderate in intensity.

In Cycle 1, drug-related clinical adverse experiences were reported in patients treated with the 3-day oral aprepitant regimen. Treatment was discontinued due to drug-related clinical adverse experiences in patients treated with the 3-day oral aprepitant regimen.

The most common drug-related adverse experiences reported in patients treated with the 3-day oral aprepitant regimen and greater than standard therapy were: hiccups, ALT increased, dyspepsia, constipation, headache, and decreased appetite.

The adverse experience profile was generally similar to that seen in the other HEC regimen with the 3-day oral aprepitant regimen.

Moderately Emetogenic Chemotherapy (MEC)
The 3-day oral aprepitant regimen was given in combination with ondansetron and dexamethasone and was generally well tolerated. Most adverse experiences reported were described as mild to moderate in intensity.

In the combined analysis of Cycle 1 data, drug-related adverse experiences were reported in patients treated with the 3-day oral aprepitant regimen. Treatment was discontinued due to drug-related adverse experiences in patients treated with the 3-day oral aprepitant regimen.

The most common drug-related adverse experience reported at a greater incidence in patients treated with the 3-day oral aprepitant regimen was fatigue.

Highly and Moderately Emetogenic Chemotherapy
The following drug-related adverse experiences were reported in patients treated with the 3-day oral aprepitant regimen and at a greater incidence than standard therapy: [Common, Uncommon, Rare]

Infection and infestations:
Rare: candidiasis, staphylococcal infection.

Blood and the lymphatic system disorders:
Uncommon: anemia, febrile neutropenia.

Metabolism and nutrition disorders:
Common: decreased appetite
Rare: polydipsia.

Psychiatric disorders:
Uncommon: anxiety
Rare: disorientation, euphoric mood.

Nervous system disorders:
Uncommon: dizziness, somnolence
Rare: cognitive disorder, lethargy, dysgeusia.

Eye disorders:
Rare: conjunctivitis.

Ear and labyrinth disorders:
Rare: tinnitus.

Cardiac disorders:
Uncommon: palpitations

Rare: bradycardia, cardiovascular disorder.

Vascular disorders:
Uncommon: hot flush.

Respiratory, thoracic and mediastinal disorders:
Common: hiccups
Rare: oropharyngeal pain, sneezing, cough, postnasal drip, throat irritation.

Gastrointestinal disorders:
Common: dyspepsia
Uncommon: eructation, nausea, gastroesophageal reflux disease, vomiting, abdominal pain, dry mouth, flatulence
Rare: feces hard, duodenal ulcer perforation, neutropenic colitis, stomatitis, abdominal distension.

Skin and subcutaneous tissue disorders:
Uncommon: rash, acne
Rare: photosensitivity reaction, hyperhidrosis, seborrhoea, skin lesion, rash pruritic.

Musculoskeletal and connective tissue disorders:
Rare: muscle spasms, muscular weakness.

Renal and urinary disorders:
Uncommon: dysuria
Rare: pollakiuria.

General disorders and administration site conditions:
Common: fatigue
Uncommon: asthenia, malaise
Rare: edema, chest discomfort, gait disturbance.

Investigations:
Common: ALT increased
Uncommon: AST increased, blood alkaline phosphatase increased
Rare: urine output increased, red blood cells urine positive, blood sodium decreased, weight decreased, glucose urine present, neutrophil count decreased.

The adverse experience profiles in the Multiple-Cycle extensions of HEC and MEC regimen for up to 6 cycles of chemotherapy were generally similar to those observed in Cycle 1.

Stevens-Johnson syndrome was reported as a serious adverse experience in a patient receiving aprepitant with cancer chemotherapy.

Fosaprepitant
Moderately Emetogenic Chemotherapy (MEC)
The following clinically important drug-related adverse experiences were reported in patients treated with the fosaprepitant regimen and at a greater incidence than in the control group. [Common, Uncommon]

Cardiac disorders:
Uncommon: palpitations.

Gastrointestinal disorders:
Common: constipation
Uncommon: abdominal distension, abdominal pain, abdominal pain upper, dyspepsia.

General disorders and administration site conditions:
Common: infusion site pain
Uncommon: asthenia.

Infections and infestations:
Uncommon: oral candidiasis.

Metabolism and nutrition disorders:
Uncommon: decreased appetite.

Respiratory, thoracic and mediastinal disorders:
Uncommon: cough, oropharyngeal pain, throat irritation.

Vascular disorders:
Uncommon: hot flush.

Highly Emetogenic Chemotherapy (HEC)
The safety profile was generally similar to that seen in the MEC regimen with fosaprepitant.

The following additional clinically important drug-related adverse experiences occurred with fosaprepitant 150 mg and have not been reported in earlier data with oral aprepitant, or in the MEC regimen with fosaprepitant. [Uncommon, Rare]

General disorders and administration site conditions:
Uncommon: infusion site erythema, infusion site pruritus
Rare: infusion site induration.

Investigations:
Uncommon: blood pressure increased.

Skin and subcutaneous tissue disorders:
Uncommon: erythema.

Vascular disorders:
Uncommon: flushing, thrombophlebitis (predominantly, infusion-site thrombophlebitis).

Other Data
Additional adverse reactions that were observed at a greater incidence than with the active comparator (ondansetron) included: ALT increased, abdominal pain upper, bowel sounds abnormal, dysarthria, dyspnea, hypoaesthesia, insomnia, miosis, nausea, sensory disturbance, stomach discomfort, visual acuity reduced, wheezing.

In addition, serious adverse experiences were reported in patients taking a higher dose of aprepitant: constipation, and sub-ileus.

Angioedema and urticaria was reported as a serious adverse event in a patient receiving aprepitant in a non-CINV/non-PONV data

Post-Marketing Experience:
The following adverse reactions have been identified during post-marketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to the drug.

Skin and subcutaneous tissue disorders:
pruritus, rash, urticaria, rarely Stevens-Johnson syndrome/toxic epidermal necrolysis

Immune system disorders:
hypersensitivity reactions including anaphylactic reactions/anaphylactic shock

Immediate hypersensitivity reactions have been observed during the infusion of fosaprepitant which may include the following: flushing, erythema, dyspnea (see PRECAUTIONS).

Overdose
No specific information is available on the treatment of overdosage. Single doses up to 200 mg of fosaprepitant IV and 600 mg of aprepitant were generally well tolerated in healthy subjects. Three out of 33 subjects receiving 200 mg of fosaprepitant experienced mild injection site thrombosis. Aprepitant was generally well tolerated when administered as 375 mg once daily for up to 42 days to patients in non-CINV studies. In 33 cancer patients, administration of a single 375 mg dose of aprepitant on Day 1 and 250 mg once daily on Days 2 to 5 was generally well tolerated.

Drowsiness and headache were reported in one patient who ingested 1440 mg of aprepitant.

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

Aprepitant cannot be removed by hemodialysis.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant, a substance P/neurokinin 1 (NK1) receptor antagonist. Plasma concentrations of fosaprepitant are below the limits of quantification (10 ng/ml) within 30 minutes of the completion of infusion.

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 at human substance P neurokinin 1 (NK1) receptors. Counter-screening assays showed that aprepitant was at least 3,000-fold selective for the NK1 receptor over other enzyme, transporter, ion channel and receptor sites including the dopamine and serotonin receptors that are targets for existing CINV therapy.

NK1-receptor antagonists have been shown pre-clinically to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Preclinical and human Positron Emission Tomography (PET) data with aprepitant have shown that it is brain penetrant and occupies brain NK1 receptors. Preclinical data show that aprepitant has a long duration of central activity, inhibits both the acute and delayed phases of cisplatin-induced emesis, and augments the antiemetic activity of the 5-HT3-receptor antagonist ondansetron and the corticosteroid dexamethasone against cisplatin-induced emesis.

Pharmacokinetic properties

Absorption

Following a single intravenous 150 mg dose of fosaprepitant administered as a 20-minute infusion to healthy volunteers the mean AUC0-∞ of aprepitant was 35.0 mcg·hr/ml and the mean maximal aprepitant concentration was 4.01 mcg/ml.

Distribution

Fosaprepitant is rapidly converted to aprepitant.

Aprepitant is greater than 95% bound to plasma proteins. The geometric mean apparent volume of distribution at steady state (Vdss) is approximately 66 L in humans.

Aprepitant crosses the placenta in rats, and crosses the blood brain barrier in rats and ferrets. PET data in humans indicate that aprepitant crosses the blood brain barrier (see Pharmacodynamic properties, Mechanism of Action).

Metabolism

Fosaprepitant was rapidly converted to aprepitant incubations with liver preparations from nonclinical species (rat and dog) and humans. Furthermore, fosaprepitant underwent rapid and nearly complete conversion to aprepitant 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. In humans, fosaprepitant administered intravenously was rapidly converted to aprepitant within 30 minutes following the end of infusion.

Aprepitant undergoes extensive metabolism. In healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300-mg dose of [14C]-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma. The metabolism of aprepitant occurs largely via oxidation at the morpholine ring and its side chains. Data using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19, and no metabolism by CYP2D6, CYP2C9, or CYP2E1.

All metabolites observed in urine, feces and plasma following an intravenous 100 mg [14C]- fosaprepitant dose were also observed following an oral dose of [14C]-aprepitant. Upon conversion of 245.3 mg of fosaprepitant dimeglumine (equivalent to 150 mg fosaprepitant free acid) to aprepitant, 23.9 mg of phosphoric acid and 95.3 mg of meglumine are liberated.

Elimination

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

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. Following administration of a single oral 300 mg dose of [14C]-aprepitant to healthy patients, 5% of the radioactivity was recovered in urine and 86% in feces.

The apparent terminal half-life of aprepitant ranged from approximately 9 to 13 hours.

Characteristics in Patients

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant.

Gender

Following oral administration of a single dose of aprepitant, the AUC0-24hr and Cmax for aprepitant are 9% and 17% higher, respectively, in females as compared with males. The half-life of aprepitant is approximately 25% lower in females as compared with males and its Tmax occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on gender.

Elderly

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 AUC0-24hr of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (≥ 65 years) relative to younger adults. The Cmax 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. No dosage adjustment is necessary in elderly patients.

Race

Following oral administration of a single dose of aprepitant, the AUC0-24hr is approximately 27% and 31% higher in Hispanics as compared with Caucasians and Blacks, respectively. The Cmax is 19% and 29% higher in Hispanics as compared with Caucasians and Blacks, respectively. Single dose administration of oral aprepitant in Asians resulted in a 74% and 47% increase in AUC0-24hr and Cmax, respectively, as compared to Caucasians. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on race.

Body Mass Index (BMI)

Body Mass Index (BMI) had no clinically meaningful effect on the pharmacokinetics of aprepitant.

Hepatic Insufficiency

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

Oral aprepitant was well tolerated in patients with mild to moderate hepatic insufficiency. Following administration of a single 125 mg dose of oral aprepitant on Day 1 and 80 mg once daily on Days 2 and 3 to patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), the AUC0-24hr of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, as compared with healthy patients given the same regimen. In patients with moderate hepatic insufficiency (Child- Pugh score 7 to 9), the AUC0-24hr of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, as compared with healthy patients given the same regimen. These differences in AUC0- 24hr are not considered clinically meaningful; therefore, no dosage adjustment is necessary in patients with mild to moderate hepatic insufficiency.

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9).

Renal Insufficiency
A single 240 mg dose of oral aprepitant was administered to patients with severe renal insufficiency (CrCl<30 ml/min) and to patients with end stage renal disease (ESRD) requiring hemodialysis.

In patients with severe renal insufficiency, the AUC0-∞ of total aprepitant (unbound and protein bound) decreased by 21% and Cmax decreased by 32%, relative to healthy patients. In patients with ESRD undergoing hemodialysis, the AUC0-∞ of total aprepitant decreased by 42% and Cmax 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 insufficiency compared with healthy patients. 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.

No dosage adjustment is necessary for patients with severe renal insufficiency or for patients with ESRD undergoing hemodialysis.

Pharmaceutical information
Shelf Life
Unopened vials: 24 months
The reconstituted final drug solution is stable for 24 hours at ambient room temperature (at or below 25°C).

Storage conditions
Unopened vials: Store in a refrigerator at 2-8°C
The reconstituted final drug solution is stable for 24 hours at ambient room temperature (at or below 25°C).

Nature and contents of container
10mL tubular clear USP Type-I glass lyo vial with 13mm neck finish with Grey colored double slotted elastromeric Bromobutyl rubber stopper, aluminium seal and red plastic disc.

Manufactured in India by:
DR. REDDY'S LABORATORIES LIMITED,
FTO-IX, Plot Nos Q1 to Q5, Phase- III,
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