

## Name of Medicine

### EMEND IV™

*fosaprepitant dimeglumine*

Intravenous

## Presentation

EMEND IV 115 mg is for intravenous use and comes in a 10 mL vial with a grey butyl stopper and aluminium seal with a light blue plastic flip off lid.

EMEND IV 150 mg is for intravenous use and comes in a 10 mL vial with a grey butyl stopper and aluminium seal with a dark grey plastic flip off lid.

Each 10 mL vial contains either 115 mg or 150 mg of fosaprepitant free acid as a white to off white lyophilised solid.

The reconstitution liquid is clear.

## Therapeutic Class

EMEND IV (fosaprepitant dimeglumine, MSD), is a prodrug of aprepitant, a substance P/neurokinin (NK<sub>1</sub>) receptor antagonist.

## Indications

EMEND IV, 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 (see Dosage and Administration)
- moderately emetogenic cancer chemotherapy (see Dosage and Administration).

## Dosage and Administration

EMEND IV for intravenous administration is a lyophilised prodrug of aprepitant (EMEND®) containing polysorbate 80 (PS80). EMEND IV is available as a 150 mg and 115 mg IV for infusion.

### EMEND IV 150 mg

EMEND IV 150 mg is administered on Day 1 only as an infusion **over 20 – 30 minutes** initiated approximately 30 minutes prior to chemotherapy. No capsules of EMEND are administered on Days 2 and 3. EMEND IV should be administered in conjunction with a corticosteroid and a 5-HT<sub>3</sub> antagonist as specified in the tables below. The recommended dosage of dexamethasone with EMEND IV 150 mg differs from the recommended dosage of dexamethasone with EMEND IV 115 mg on Days 3 and 4.

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

	Day 1	Day 2	Day 3	Day 4
EMEND IV	150 mg IV	none	none	none
Dexamethasone**	12 mg orally	8 mg orally	<b>8 mg orally bid</b>	<b>8 mg orally bid</b>
Ondansetron <sup>†</sup>	32 mg IV	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 medicine interactions.

† Ondansetron should be administered 30 minutes prior to chemotherapy treatment on Day 1.

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

	Day 1
EMEND IV	150 mg IV
Dexamethasone**	12 mg orally
Ondansetron <sup>†</sup>	32 mg IV

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

† Ondansetron 8-mg capsule should be administered 30 to 60 minutes prior to chemotherapy treatment and one 8-mg capsule should be administered 8 hours after the first dose on Day 1.

#### Preparation of EMEND IV for Injection 150 mg

1. Inject 5 mL saline into the vial. Assure that saline is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and jetting saline into the vial.
2. Prepare an infusion bag filled with 145 mL of saline.
3. Withdraw the entire volume from the vial and transfer it into an infusion bag containing 145 mL of saline to yield a total volume of 150 mL. Gently invert the bag 2-3 times.

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

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

#### **EMEND IV 115 mg**

EMEND IV 115 mg is administered on Day 1 only as an infusion **over 15 minutes** initiated approximately 30 minutes prior to chemotherapy. Capsules of EMEND 80 mg should be administered on Days 2 and 3. EMEND IV 115 mg should be administered in conjunction with a corticosteroid and a 5-HT<sub>3</sub> antagonist as specified in the tables below. The recommended dosage of dexamethasone with EMEND IV 115 mg differs from the recommended dosage of dexamethasone with EMEND IV 150 mg on Days 3 and 4.

Capsules of EMEND 125 mg may be substituted for EMEND IV 115 mg on Day 1.

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

	Day 1	Day 2	Day 3	Day 4
EMEND IV/EMEND	115 mg IV	80 mg orally	80 mg orally	none
Dexamethasone**	12 mg orally	8 mg orally	<b>8 mg orally</b>	<b>8 mg orally</b>
Ondansetron <sup>†</sup>	32 mg IV	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. The dose of dexamethasone accounts for medicine interactions.

† Ondansetron should be administered 30 minutes prior to chemotherapy treatment on Day 1.

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

	Day 1	Day 2	Day 3
EMEND IV/EMEND	115 IV	80 mg orally	80 mg orally
Dexamethasone**	12 mg orally	none	none
Ondansetron†	2 x 8 mg orally	none	none

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

† Ondansetron 8 mg capsule should be administered 30 to 60 minutes prior to chemotherapy treatment and one 8 mg capsule should be administered 8 hours after the first dose on Day 1.

#### Preparation of EMEND IV for Injection 115 mg

1. Inject 5 mL saline into the vial. Assure that saline is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and jetting saline into the vial.
2. Prepare an infusion bag filled with **110 mL** of saline.
3. Withdraw the entire volume from the vial and transfer it into an infusion bag containing 110 mL of saline to **yield a total volume of 115 mL**. Gently invert the bag 2-3 times.

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

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

EMEND IV is incompatible with any solutions containing divalent cations (e.g., Ca<sup>2+</sup>, Mg<sup>2+</sup>), including Hartman's and Lactated Ringer's Solution. EMEND IV must not be reconstituted or mixed with solutions for which physical and chemical compatibility have not been established.

#### **General Information**

See Interactions for additional information on the administration of EMEND IV with corticosteroids.

Refer to the full prescribing information for co-administered antiemetic agents.

No dosage adjustment is necessary for the elderly.

No dosage adjustment is necessary based on gender or race.

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 haemodialysis.

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).

## **Contraindications**

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

EMEND IV 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 medicines, potentially causing serious or life-threatening reactions (see Interactions).

## **Warnings and 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 metabolised through CYP3A4; some chemotherapy agents are metabolised by CYP3A4 (see Interactions). Moderate inhibition of CYP3A4 by aprepitant and weak inhibition of CYP3A4 by fosaprepitant 150 mg could result in elevated plasma concentrations of these concomitant medicinal products administered orally (see Interactions). The effect of oral aprepitant on the pharmacokinetics of orally administered CYP3A4 substrates is greater than the effect of oral aprepitant on the pharmacokinetics of intravenously administered CYP3A4 substrates (see Interactions).

Isolated reports of immediate hypersensitivity reactions including flushing, erythema, and dyspnoea have occurred during 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.

Co-administration of oral aprepitant with warfarin may result in a clinically significant decrease in International Normalised 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 Interactions).

The efficacy of hormonal contraceptives during and for 28 days after administration of fosaprepitant or oral aprepitant may be reduced. Alternative or back-up methods of contraception should be used during treatment with fosaprepitant or oral aprepitant and for one month following the last dose (see Interactions).

## **Pregnancy**

There are no adequate and well-controlled studies in pregnant women. EMEND IV should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and the foetus.

## **Nursing Mothers**

EMEND IV, when administered intravenously, is rapidly converted to aprepitant.

Aprepitant is excreted in the milk of lactating rats. It is not known whether this medicine is excreted in human milk. Because many medicines 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 medicine, taking into account the importance of the medicine to the mother.

## **Paediatric Use**

Safety and effectiveness of EMEND IV in paediatric patients have not been established.

## **Use In The Elderly**

In clinical studies, the efficacy and safety of aprepitant in the elderly ( $\geq 65$  years) were comparable to those seen in younger patients ( $< 65$  years). No dosage adjustment is necessary in elderly patients.

## **Animal Toxicology**

### Acute Toxicity

The approximate oral LD<sub>50</sub> of aprepitant was  $> 2000$  mg/kg in female mice and rats. The approximate LD<sub>50</sub> of fosaprepitant following intravenous administration was  $> 500$  mg/kg in female mice and  $> 200$  mg/kg in female rats.

### Chronic Toxicity

Fosaprepitant, when administered intravenously, is rapidly converted to aprepitant.

The toxicity potential of aprepitant was evaluated in a series of repeated-dose oral toxicity studies in rats and in dogs for up to 1 year.

In rats, oral administration of aprepitant for 6 months at doses up to the maximum feasible dose of 1000 mg/kg twice daily (approximately equivalent to [females] or lower than [males] the adult human dose based on systemic exposure following oral aprepitant 125 mg) produced increased hepatic weights that correlated with hepatocellular hypertrophy, increased thyroidal weights that correlated with thyroid follicular cell hypertrophy and/or hyperplasia, and pituitary cell vacuolation. These findings are a species-specific consequence of hepatic CYP enzyme induction in the rat, and are consistent with changes observed in rats with other structurally and pharmacologically dissimilar compounds that have been shown to induce hepatic CYP enzymes.

In dogs administered aprepitant orally for 9 months at doses  $\geq 5$  mg/kg twice daily (greater than or equal to 13 times the adult human dose based on systemic exposure following oral aprepitant 125 mg), toxicity was characterised by slight increases in serum alkaline phosphatase activity and decreases in the albumin/globulin ratio. Significantly decreased body weight gain, testicular degeneration, and prostatic atrophy were observed at doses  $\geq 25$  mg/kg twice daily (greater than or equal to 31 times the adult human dose based on systemic exposure following oral aprepitant 125 mg). A slight increase in hepatic weights with no histologic correlate was seen at 500 mg/kg twice daily (70 times the adult human dose based on systemic exposure following oral aprepitant 125 mg). No toxicity was observed in dogs administered 32 mg/kg/day (6 times the adult human dose based on systemic exposure following oral aprepitant 125 mg) for 1 year.

### Carcinogenesis

Carcinogenicity studies were conducted in mice and rats for 2 years with oral aprepitant. Mice developed hepatocellular adenomas and/or carcinomas at doses of 500 to 2000 mg/kg/day (females) and hepatocellular carcinomas at doses of 1000 and 2000 mg/kg/day (males). Systemic exposures at these doses in mice were approximately 2.5 to 3.6 times the exposure in humans at the recommended dose. Rats developed hepatocellular adenomas at doses of 5 to 1000 mg/kg twice daily (females) and 125 mg/kg twice daily (males), hepatocellular carcinomas at doses of 125 to 1000 mg/kg twice daily (females), thyroid follicular cell adenomas at doses of 125 to 1000 mg/kg twice daily (females and males), and thyroid follicular cell carcinomas at doses of 125 to 1000 mg/kg twice daily (males). Systemic exposures at these doses in rats were lower than or up to approximately 2 times the exposure in humans at the recommended dose. Liver and

thyroid tumours of these types are a species-specific consequence of hepatic CYP enzyme induction in rodents, and are consistent with changes observed in rodents with other structurally and pharmacologically dissimilar compounds that have been shown to induce hepatic CYP enzymes. Carcinogenicity studies were not conducted with fosaprepitant.

### Mutagenesis

Fosaprepitant and aprepitant were neither mutagenic nor genotoxic in assays conducted to detect mutagenicity, DNA strand breaks, and chromosomal aberrations. Aprepitant was negative in the *in vitro* microbial and TK6 human lymphoblastoid cell mutagenesis assays, the *in vitro* alkaline elution/rat hepatocyte DNA strand break test, the *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and the *in vivo* mouse micronucleus assay in bone marrow.

### Reproduction

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.

Aprepitant administered to female rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (approximately equivalent to the adult human dose based on systemic exposure following oral aprepitant 125 mg) had no effects on mating performance, fertility, or embryonic/foetal survival.

Administration of aprepitant to male rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (lower than the adult human dose based on systemic exposure following oral aprepitant 125 mg) produced no effects on mating performance, fertility, embryonic/foetal survival, sperm count and motility, testicular weights, or the microscopic appearance of the testes and epididymides.

### Development

Fosaprepitant, when administered intravenously, is rapidly converted to aprepitant. In the teratology studies conducted with fosaprepitant and aprepitant, the highest systemic exposures to aprepitant were obtained following oral administration of aprepitant.

In rats and rabbits administered oral doses of aprepitant up to 1000 mg/kg twice daily and 25 mg/kg/day, respectively (up to 1.5 times the systemic exposure at the adult human dose following oral aprepitant 125 mg), there was no evidence of developmental toxicity as assessed by embryonic/foetal survival, foetal body weight, and foetal external, visceral, and skeletal morphology. Placental transfer of aprepitant occurred in rats and rabbits at these doses. Concentrations of aprepitant in foetal plasma were approximately 27% and 56% of maternal plasma concentrations in rats and rabbits, respectively.

Significant concentrations of aprepitant were observed in the milk of lactating rats administered 1000 mg/kg twice daily. At this dose, the mean milk medicine concentration was 90% of the mean maternal plasma concentration.

### **Effects on the Ability to Drive and Use Machinery**

No studies of the effects of EMEND IV on the ability to drive and use of machines have been performed. However, certain adverse effects that have been reported with EMEND IV may affect some patients' ability to drive or operate machinery. Individual responses to EMEND IV may vary. (See Adverse Effects.)

## Adverse Effects

Since fosaprepitant is converted to aprepitant, those adverse experiences associated with aprepitant might also be expected to occur with EMEND IV.

The overall safety of fosaprepitant was evaluated in approximately 1100 individuals, and the overall safety of aprepitant was evaluated in approximately 6500 individuals.

## Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

### Oral Aprepitant

#### *Highly Emetogenic Chemotherapy (HEC)*

In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy, 544 patients were treated with aprepitant during Cycle 1 of chemotherapy and 413 of these patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. Oral aprepitant was given in combination with ondansetron and dexamethasone (aprepitant regimen) and was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.

In Cycle 1, medicine-related clinical adverse experiences were reported in approximately 17% of patients treated with the aprepitant regimen compared with approximately 13% of patients treated with standard therapy. Treatment was discontinued due to medicine-related clinical adverse experiences in 0.6% of patients treated with the aprepitant regimen compared with 0.4% of patients treated with standard therapy.

The most common medicine-related adverse experiences reported in patients treated with the aprepitant regimen and greater than standard therapy were: hiccups (4.6%), asthenia/fatigue (2.9%), ALT increased (2.8%), constipation (2.2%), headache (2.2%), and anorexia (2.0%).

In an additional active-controlled clinical study in 1169 patients receiving aprepitant and highly emetogenic chemotherapy, the adverse experience profile was generally similar to that seen in the other HEC studies with aprepitant.

#### *Moderately Emetogenic Chemotherapy (MEC)*

In 2 well-controlled clinical trials in patients receiving moderately emetogenic cancer chemotherapy, 868 patients were treated with aprepitant during Cycle 1 of chemotherapy and 686 of these patients continued into extensions for up to 4 cycles of chemotherapy. In both studies, oral aprepitant was given in combination with ondansetron and dexamethasone (aprepitant regimen) and was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.

In the combined analysis of Cycle 1 data for these 2 studies, medicine-related adverse experiences were reported in approximately 14% of patients treated with the aprepitant regimen compared with approximately 15% of patients treated with standard therapy. Treatment was discontinued due to medicine-related adverse experiences in 0.7% of patients treated with the aprepitant regimen compared with 0.2% of patients treated with standard therapy.

The most common medicine-related adverse experience reported at a greater incidence in patients treated with the aprepitant regimen than with standard therapy was fatigue (1.4%).

### *Highly and Moderately Emetogenic Chemotherapy*

The following medicine-related adverse experiences were observed in either HEC or MEC studies in patients treated with the aprepitant regimen and at a greater incidence than standard therapy:

*[Common ( $\geq 1/100$ ,  $< 1/10$ ) Uncommon ( $> 1/1000$ ,  $< 1/100$ )]*

Infection and infestations:

*Uncommon:* candidiasis, staphylococcal infection.

Blood and the lymphatic system disorders:

*Uncommon:* anaemia, febrile neutropenia.

Metabolism and nutrition disorders:

*Common:* anorexia

*Uncommon:* weight gain, polydipsia.

Psychiatric disorders:

*Uncommon:* disorientation, euphoria, anxiety.

Nervous system disorders:

*Common:* headache, dizziness

*Uncommon:* dream abnormality, cognitive disorder, lethargy, somnolence.

Eye disorders:

*Uncommon:* conjunctivitis.

Ear and labyrinth disorders:

*Uncommon:* tinnitus.

Cardiac disorders:

*Uncommon:* bradycardia, palpitations.

Vascular disorders:

*Uncommon:* hot flush.

Respiratory, thoracic and mediastinal disorders:

*Common:* hiccups

*Uncommon:* pharyngitis, sneezing, cough, post nasal drip, throat irritation.

Gastrointestinal disorders:

*Common:* constipation, diarrhoea, dyspepsia, eructation

*Uncommon:* nausea, acid reflux, dysgeusia, epigastric discomfort, obstipation, gastroesophageal reflux disease, perforating duodenal ulcer, vomiting, abdominal pain, dry mouth, enterocolitis, flatulence, stomatitis.

Skin and subcutaneous tissue disorders:

*Uncommon:* rash, acne, photosensitivity, hyperhidrosis, oily skin, pruritus, skin lesion.

Musculoskeletal and connective tissue disorders:

*Uncommon:* muscle cramp, myalgia.

Renal and urinary disorders:

*Uncommon:* polyuria, dysuria, pollakiuria.

General disorders and administration site conditions:

*Common:* asthenia/fatigue

*Uncommon:* oedema, flushing, sneezing, chest discomfort, malaise, thirst.

Investigations:

*Common:* ALT increased, AST increased

*Uncommon:* alkaline phosphatase increased, hyperglycaemia, microscopic haematuria, hyponatraemia, weight decreased.

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

In another chemotherapy induced nausea and vomiting (CINV) study, Stevens-Johnson syndrome was reported as a serious adverse experience in a patient receiving aprepitant with cancer chemotherapy.

### Fosaprepitant

In an active-controlled clinical study in patients receiving highly emetogenic chemotherapy, safety was evaluated for 1143 patients receiving the 1-day regimen of EMEND IV 150 mg compared to 1169 patients receiving the 3-day regimen of EMEND (aprepitant). The safety profile was generally similar to that seen in prior HEC studies with aprepitant.

The following additional clinically important medicine related adverse experiences occurred with fosaprepitant 150 mg and have not been reported in earlier clinical studies with oral aprepitant (3-day regimen) as described above.

*[Common ( $\geq 1/100$ ,  $< 1/10$ ) Uncommon ( $> 1/1000$ ,  $< 1/100$ )]*

General disorders and administration site conditions:

*Uncommon:* infusion site erythema, infusion site pruritus, infusion site induration, infusion site pain

Investigations:

*Uncommon:* blood pressure increased

Skin and subcutaneous tissue disorders:

*Uncommon:* erythema

Vascular disorders:

*Uncommon:* flushing, thrombophlebitis (predominantly, infusion-site thrombophlebitis)

Clinically significant laboratory analyses during the follow-up time period (Day 6 to 29) indicated a higher incidence of serum alanine aminotransferase  $>5X$  ULN in patients treated with the fosaprepitant regimen (1.8%) compared to patients treated with the aprepitant regimen (0.5%). Monitoring of liver function tests may be considered, especially in patients who have a known underlying hepatic condition.

### **Prevention of Postoperative Nausea and Vomiting (PONV)**

In well-controlled clinical studies in patients receiving general balanced anaesthesia, 564 patients were administered 40 mg aprepitant orally and 538 patients were administered 4 mg ondansetron IV. Aprepitant was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.

Medicine-related clinical adverse experiences were reported in approximately 4% of

patients treated with 40 mg aprepitant compared with approximately 6% of patients treated with 4 mg ondansetron IV.

The most common medicine-related adverse experience reported in patients treated with aprepitant and at a greater incidence than ondansetron was ALT increased (1.1%).

The following medicine-related adverse experiences were observed in patients treated with aprepitant and at a greater incidence than ondansetron:

*[Common (>1/100, <1/10) Uncommon (>1/1000, <1/100)]*

Psychiatric disorders:

*Uncommon:* insomnia.

Nervous system disorders:

*Uncommon:* dysarthria, hypoaesthesia, sensory disturbance.

Eye disorders:

*Uncommon:* miosis, visual acuity reduced.

Cardiac disorders:

*Uncommon:* bradycardia.

Respiratory, thoracic and mediastinal disorders:

*Uncommon:* dyspnoea, wheezing.

Gastrointestinal disorders:

*Uncommon:* abdominal pain upper, bowel sounds abnormal, dry mouth, nausea, stomach discomfort.

Investigations:

*Common:* ALT increased.

In addition, two serious adverse experiences were reported in postoperative nausea and vomiting (PONV) clinical studies in patients taking a higher dose of aprepitant: one case of constipation and one case of sub-ileus.

### Other Studies

Angioedema and urticaria were reported in a patient receiving aprepitant in a non-CINV/non-PONV study.

### **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 medicine.

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

*Immune system disorders:* hypersensitivity reactions including anaphylactic reactions

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

Warnings and Precautions).

## Interactions

Medicine interactions following administration of fosaprepitant are likely to occur with medicines that interact with oral aprepitant. The following information was derived from studies conducted with oral aprepitant and studies conducted with fosaprepitant co-administered 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.

EMEND IV 150 mg, given as a single dose, is a weak inhibitor of CYP3A4, and does not induce CYP3A4. It is anticipated that EMEND V 150 mg would cause less or no greater induction of CYP2C9 than that caused by the administration of oral aprepitant.

### Effect of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Agents

Aprepitant, as a weak to moderate inhibitor of CYP3A4, and EMEND IV 150 mg, as a weak inhibitor of CYP3A4, can increase plasma concentrations of orally co-administered medicinal products that are metabolised through CYP3A4.

Fosaprepitant should not be used concurrently with pimozone, terfenadine, astemizole, or cisapride. Dose-dependent inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these medicines, potentially causing serious or life-threatening reactions (see Contraindications).

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

Fosaprepitant or aprepitant are unlikely to interact with medicines that are substrates for the P-glycoprotein transporter, as demonstrated by the lack of interaction of oral aprepitant with digoxin in a clinical medicine interaction study.

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

In clinical medicine interaction studies, aprepitant 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 AUC<sub>0-24hr</sub> of dexamethasone, a CYP3A4 substrate, by approximately 2.0-fold on Days 1 and 2 when dexamethasone was co-administered 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 by approximately 50% when co-administered with fosaprepitant 150 mg IV on Day 1 to achieve exposures of dexamethasone similar to those obtained when given without fosaprepitant 150 mg.

Oral aprepitant, when given as a regimen of 125 mg with dexamethasone co-administered orally as 20 mg on Day 1, and oral aprepitant when given as 80 mg/day with dexamethasone co-administered orally as 8 mg on Days 2 through 5, increased the AUC of dexamethasone, a CYP3A4 substrate by 2.2-fold, on Days 1 and 5. The usual oral dexamethasone doses should be reduced by approximately 50% when co-administered with a regimen of fosaprepitant 115 mg followed by aprepitant to achieve exposures of

dexamethasone similar to those obtained when it is given without aprepitant. The daily dose of dexamethasone administered in clinical chemotherapy induced nausea and vomiting studies with oral aprepitant reflects an approximate 50% reduction of the dose of dexamethasone (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, by 1.3-fold on Day 1 and by 2.5-fold on Day 3, when methylprednisolone was co-administered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3. The usual IV methylprednisolone dose should be reduced by approximately 25%, and the usual oral methylprednisolone dose should be reduced by approximately 50% when co-administered with a regimen of fosaprepitant 115 mg followed by aprepitant to achieve exposures of methylprednisolone similar to those obtained when it is given without aprepitant.

### **Chemotherapeutic agents**

In clinical studies, the oral aprepitant regimen was administered with the following chemotherapeutic agents metabolised primarily or in part by CYP3A4: etoposide, vinorelbine, docetaxel, and paclitaxel. The doses of these agents were not adjusted to account for potential medicine interactions.

*Docetaxel:* In a separate pharmacokinetic study, oral aprepitant (CINV regimen) did not influence the pharmacokinetics of docetaxel.

*Vinorelbine:* In a separate pharmacokinetic study, 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 subjects who were stabilised on chronic warfarin therapy. Although there was no effect of oral aprepitant on the plasma AUC of R(+) or S(-) warfarin (a CYP2C9 substrate) 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 Normalised 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) by 23% on Day 4, 28% on Day 8, and 15% on 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 by 43%, and decreased the AUC of norethindrone by 8%.

In another study, 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. In the study, the AUC of ethinyl estradiol decreased by 19% on Day 10 and there

was as much as a 64% 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 as much as a 60% decrease in norethindrone trough concentrations during Days 9 through 21.

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

### **Midazolam**

Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the AUC<sub>0-∞</sub> of midazolam by approximately 1.8-fold on Day 1 and had no effect (1.0 fold) on Day 4 when midazolam was co-administered as a single oral dose of 2 mg on Days 1 and 4. Fosaprepitant 150 mg IV 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.

In addition, when fosaprepitant was administered as a dose of 100 mg over 15 minutes along with a single dose of midazolam 2 mg, the plasma AUC of midazolam was increased by 1.6-fold. This effect was not considered clinically important.

Oral aprepitant increased the AUC of midazolam, a sensitive CYP3A4 substrate, by 2.3-fold on Day 1 and 3.3-fold on Day 5, when a single oral dose of midazolam 2 mg was co-administered on Day 1 and Day 5 of a regimen of oral aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 through 5. The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) should be considered when co-administering these agents with fosaprepitant or aprepitant.

In another study with intravenous administration of midazolam, oral aprepitant was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, and midazolam 2 mg IV was given prior to the administration of the 3-day regimen of oral aprepitant and on Days 4, 8, and 15. Oral aprepitant increased the AUC of midazolam by 25% on Day 4 and decreased the AUC of midazolam by 19% on Day 8 relative to the dosing of oral aprepitant on Days 1 through 3. These effects were not considered clinically important. The AUC of midazolam on Day 15 was similar to that observed at baseline.

An additional study was completed with intravenous administration of midazolam and oral aprepitant. Intravenous midazolam 2 mg was given 1 hour after oral administration of a single dose of oral aprepitant 125 mg. The plasma AUC of midazolam was increased by 1.5-fold. This effect was not considered clinically important.

### **Effect of other agents on the pharmacokinetics of aprepitant**

Aprepitant is a substrate for CYP3A4; therefore, co-administration of fosaprepitant or aprepitant with medicines that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of fosaprepitant or aprepitant with strong CYP3A4 inhibitors (e.g., ketoconazole) should be approached cautiously; but concomitant administration of aprepitant with moderate CYP3A4 inhibitors (e.g., diltiazem) does not result in clinically meaningful changes in plasma concentrations of aprepitant.

Aprepitant is a substrate for CYP3A4; therefore, co-administration of fosaprepitant or aprepitant with medicines that strongly induce CYP3A4 activity (eg., rifampin) 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 approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold. Concomitant administration of fosaprepitant or aprepitant 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 approximately 11-fold and the mean terminal half-life decreased approximately 3-fold. Co-administration of fosaprepitant or aprepitant with medicines 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 fosaprepitant over 15 minutes with diltiazem 120 mg 3 times daily, resulted in a 1.5-fold increase of aprepitant AUC and a 1.4 fold 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.

In the same study, administration of aprepitant once daily, as a tablet formulation comparable to 230 mg of the capsule formulation, with diltiazem 120 mg 3 times daily for 5 days, resulted in a 2-fold increase of aprepitant AUC and a simultaneous 1.7-fold increase of diltiazem AUC. These pharmacokinetic effects did not result in clinically meaningful changes in ECG, heart rate, or blood pressure beyond those changes induced by diltiazem alone.

### Paroxetine

Co-administration 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 by approximately 25% and  $C_{max}$  by approximately 20% of both aprepitant and paroxetine.

## **Overdosage**

No specific information is available on the treatment of overdosage with EMEND IV. Single doses up to 200 mg of fosaprepitant 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, EMEND IV should be discontinued and general supportive

treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, medicine-induced emesis may not be effective.

Aprepitant cannot be removed by haemodialysis.

## **Actions**

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant, a substance P/neurokinin 1 (NK<sub>1</sub>) receptor antagonist. Plasma concentrations of fosaprepitant are below the limits of quantification (10 ng/mL) within 30 minutes of the completion of infusion.

Fosaprepitant is a prodrug of aprepitant and accordingly, its antiemetic effects are attributable to aprepitant.

Aprepitant has a unique mode of action; it is a selective high affinity antagonist at human substance P neurokinin 1 (NK<sub>1</sub>) receptors. Counter-screening assays showed that aprepitant was at least 3,000-fold selective for the NK<sub>1</sub> receptor over other enzyme, transporter, ion channel and receptor sites including the dopamine and serotonin receptors that are targets for existing CINV therapy.

NK<sub>1</sub>-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) studies with aprepitant have shown that it is brain penetrant and occupies brain NK<sub>1</sub> receptors. Preclinical studies 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-HT<sub>3</sub>-receptor antagonist ondansetron and the corticosteroid dexamethasone against cisplatin-induced emesis.

## **Pharmacodynamics - Cardiac Electrophysiology**

In a randomised, double-blind, positive controlled, thorough QTc study, a single 200 mg dose of fosaprepitant had no effect on the QTc interval.

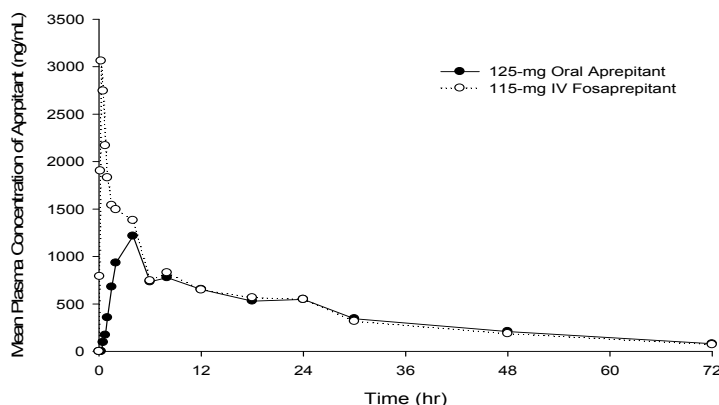
## **Pharmacokinetics**

### **Absorption**

Following a single intravenous 115 mg dose of fosaprepitant administered as a 15-minute infusion to healthy volunteers the mean AUC<sub>0-24hr</sub> of aprepitant was 19.8 mcg hr/mL and the mean maximal aprepitant concentration was 3.26 mcg/mL.

The AUC of aprepitant which is formed following administration of 115 mg of the IV prodrug fosaprepitant was equivalent to the AUC of 125 mg of orally administered aprepitant. Mean plasma concentrations following single doses are depicted in Figure 1.

Figure 1: Mean Plasma Concentration of Aprepitant Following 125 mg Oral Aprepitant and 115 mg IV Fosaprepitant



Following a single intravenous 150 mg dose of fosaprepitant administered as a 20-minute infusion to healthy volunteers the mean  $AUC_{0-\infty}$  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 ( $V_{d_{ss}}$ ) is approximately 66 L in humans.

Aprepitant crosses the placenta in rats, and crosses the blood brain barrier in rats and ferrets. PET studies in humans indicate that aprepitant crosses the blood brain barrier (see Actions).

### Metabolism

Fosaprepitant was rapidly converted to aprepitant in *in vitro* incubations with liver preparations from non-clinical 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 [ $^{14}C$ ]-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. The metabolism of aprepitant occurs largely via oxidation at the morpholine ring and its side chains. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolised primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19, and no metabolism by CYP2D6, CYP2C9, or CYP2E1.

All metabolites observed in urine, faeces and plasma following an intravenous 100 mg [ $^{14}C$ ]-fosaprepitant dose were also observed following an oral dose of [ $^{14}C$ ]-aprepitant. Upon conversion of 188 mg of fosaprepitant dimeglumine (equivalent to 115 mg fosaprepitant free acid) to aprepitant, 18.3 mg of phosphoric acid and 73 mg of meglumine are liberated. 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 [<sup>14</sup>C]-fosaprepitant to healthy subjects, 57% of the radioactivity was recovered in urine and 45% in faeces.

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

The apparent plasma clearance of aprepitant ranged from approximately 60 to 84 mL/min. The apparent terminal half-life 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 125 mg dose of aprepitant, the  $C_{max}$  for aprepitant is 16% higher in females as compared with males. The half-life of aprepitant is 25% lower in females as compared with males and its  $T_{max}$  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  $AUC_{0-24hr}$  of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly ( $\geq 65$  years) 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. No dosage adjustment is necessary in elderly patients.

### Paediatric

Fosaprepitant has not been evaluated in patients below 18 years of age.

### Race

Following oral administration of a single 125 mg dose of aprepitant, the  $AUC_{0-24hr}$  is approximately 25% and 29% higher in Hispanics as compared with Caucasians and Blacks, respectively. The  $C_{max}$  is 22% and 31% higher in Hispanics as compared with Caucasians and Blacks, respectively. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on race.

### Hepatic Insufficiency

Fosaprepitant is metabolised 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  $AUC_{0-24hr}$  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 insufficiency (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; 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 ( $\text{CrCl} < 30 \text{ mL/min}$ ) and to patients with end stage renal disease (ESRD) requiring haemodialysis.

In patients with severe renal insufficiency, the  $\text{AUC}_{0-\infty}$  of total aprepitant (unbound and protein bound) decreased by 21% and  $\text{C}_{\text{max}}$  decreased by 32%, relative to healthy subjects. In patients with ESRD undergoing haemodialysis, the  $\text{AUC}_{0-\infty}$  of total aprepitant decreased by 42% and  $\text{C}_{\text{max}}$  decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound medicine was not significantly affected in patients with renal insufficiency compared with healthy subjects. Haemodialysis 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 haemodialysis.

## Pharmaceutical Precautions

Vials: Store at 2-8°C (36-46°F).

## Medicine Classification

Prescription Medicine

## Package Quantities

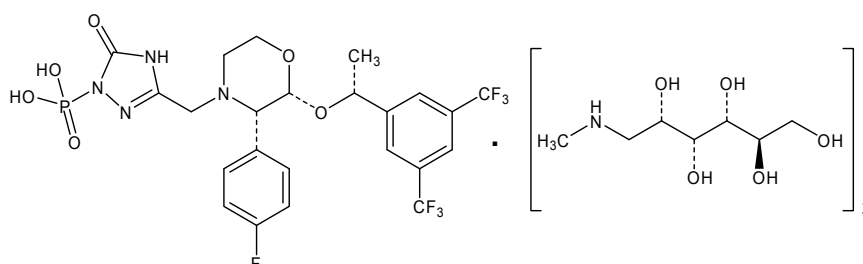
10 mL single dose vial containing either 115 mg or 150 mg fosaprepitant as the free acid.

## Further Information

### Chemistry

Fosaprepitant dimeglumine is a prodrug of aprepitant and is chemically described as 1-Deoxy-1-(methylamino)-D-glucitol [3-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]phosphonate (2:1) (salt).

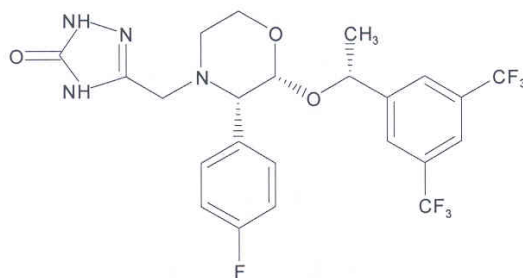
Its empirical formula is  $\text{C}_{23}\text{H}_{22}\text{F}_7\text{N}_4\text{O}_6\text{P} \cdot 2(\text{C}_7\text{H}_{17}\text{NO}_5)$  and its structural formula is:



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

Aprepitant is a structurally novel substance P neurokinin 1 (NK<sub>1</sub>) receptor antagonist, chemically described as 5-[[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one.

Its empirical formula is C<sub>23</sub>H<sub>21</sub>F<sub>7</sub>N<sub>4</sub>O<sub>3</sub>, and its structural formula is:



Aprepitant is a white to off-white crystalline solid, with a molecular weight of 534.43. It is practically insoluble in water. Aprepitant is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile.

### Active Ingredients

EMEND IV is available as a 150 mg and 115 mg IV for infusion. Each vial of EMEND IV 115 mg for CINV intravenous administration contains 188 mg of fosaprepitant dimeglumine equivalent to 115 mg of fosaprepitant free acid. Each vial of EMEND IV 150 mg for CINV intravenous administration contains 245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg of fosaprepitant free acid.

### Inactive Ingredients

Each vial of EMEND IV 115 mg for CINV contains the following inactive ingredients: edetate disodium, polysorbate 80 (57.5 mg), lactose anhydrous, sodium hydroxide and/or hydrochloric acid (for pH adjustment). Each vial of EMEND IV 150 mg for CINV contains the following inactive ingredients: edetate disodium, polysorbate 80 (75 mg), lactose anhydrous, sodium hydroxide and/or hydrochloric acid (for pH adjustment).

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### Date of Preparation

13 July 2011

WPC-MK0517-IV-032011

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