PRODUCT MONOGRAPH

Pr FOSAPREPITANT

Fosaprepitant for Injection

150 mg fosaprepitant /vial

(as fosaprepitant dimeglumine)

Professed

Neurokinin 1 (NK_1) receptor antagonist

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9
Control Number: 167490

DATE OF PREPARATION:
January 8, 2015

Table of Contents

Pr FOSAPREPITANT
Fosaprepitant for Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Intravenous	Lyophilized powder / 150 mg per vial	Edetate disodium, Lactose anhydrous , Polysorbate 80 and Sodium hydroxide and/or Hydrochloric acid (for pH adjustment)

INDICATIONS AND CLINICAL USE

FOSAPREPITANT (fosaprepitant dimeglumine), in combination with a 5-HT_3 antagonist class of antiemetics and dexamethasone, is indicated for the:

1. prevention of acute and delayed nausea and vomiting due to highly emetogenic cancer chemotherapy.

2. prevention of nausea and vomiting in women due to treatment with moderately emetogenic cancer chemotherapy.

The clinical effectiveness of single day fosaprepitant in the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy is based on demonstration of non-inferiority with a three day oral aprepitant regimen in patients receiving highly emetogenic chemotherapy. Despite differences in concomitant antiemetic dosing regimens employed with highly emetogenic chemotherapy and moderately emetogenic chemotherapy, efficacy results from the highly emetogenic chemotherapy setting have been extrapolated to the moderately emetogenic chemotherapy setting (see CLINICAL TRIALS).

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

Pediatrics (<18 years of age): No data available.

CONTRAINDICATIONS

- Patients who are hypersensitive to fosaprepitant, aprepitant, polysorbate 80, or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

- FOSAPREPITANT 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).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Drug interactions with:
- Medicinal products, including chemotherapeutic agents, that are metabolized through CYP3A4 (see DRUG INTERACTIONS)
- Warfarin (see DRUG INTERACTIONS)
- Hormonal contraception (see DRUG INTERACTIONS)

The following are clinically significant adverse events:
- Immediate hypersensitivity reactions (see Hypersensitivity Reactions)

Hypersensitivity Reactions

Isolated reports of immediate hypersensitivity reactions including flushing, erythema, and dyspnea have occurred during infusion of fosaprepitant. These hypersensitivity reactions have generally responded to discontinuation of the infusion and administration of appropriate therapy. The infusion should not be reinitiated in patients who experience hypersensitivity reactions (see CONTRAINDICATIONS).

Drug Interactions

CYP3A4 substrates: fosaprepitant is a weak inhibitor of CYP3A4. Caution should be used when fosaprepitant is co-administered with CYP3A4 substrates, including chemotherapeutic agents (see **DRUG INTERACTIONS**).

Serious post-marketing reports of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported in patients after oral aprepitant and ifosfamide co-administration. Caution and careful monitoring are advised. Refer to IFEX (ifosfamide for injection) product monograph. (see **ADVERSE REACTIONS / Post-Market Adverse Drug Reactions** and **DRUG INTERACTIONS**).

Warfarin: Co-administration of fosaprepitant with warfarin may cause a clinically significant decrease in the INR. 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**).

Hormonal contraception: Fosaprepitant may reduce the efficacy of hormonal contraception. Alternative or backup methods should be used during and for 1 month following the last dose of FOSAPREPITANT (see **DRUG INTERACTIONS**).

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women; therefore, FOSAPREPITANT are not recommended for use during pregnancy unless clearly necessary (see TOXICOLOGY, Reproduction and Development).

Nursing Women: Fosaprepitant, 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; therefore, breastfeeding is not recommended during treatment with FOSAPREPITANT.

Pediatrics (<18 years of age): Safety and effectiveness of fosaprepitant in pediatric patients have not been established.

Geriatrics (≥65 years of age): In 2 well-controlled clinical studies, of the total number of patients (N=544) treated with aprepitant, 31% were 65 and over, while 5% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment in the elderly is not necessary.

Hepatic Impairment: There are no clinical data or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score >9). FOSAPREPITANT should be used with caution in these patients (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

ADVERSE REACTIONS

Clinical Trial Adverse Experiences

Since fosaprepitant is converted to aprepitant, those adverse reactions associated with aprepitant are to be expected to occur with FOSAPREPITANT. The overall safety of fosaprepitant was evaluated in approximately 1100 individuals and the overall safety of aprepitant was evaluated in approximately 6500 individuals. Injection site adverse reactions can also be expected with fosaprepitant.

Oral Aprepitant

Highly Emetogenic Chemotherapy (HEC)

In 2 well-controlled clinical trials in patients receiving cisplatin-based 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 and was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.

In Cycle 1, clinical adverse experiences were reported in approximately 74% of patients treated with the aprepitant regimen compared with approximately 72% of patients treated with standard therapy.

Table 1 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3%.

Table 1 – All adverse experiences, regardless of causality, (incidence ≥3%) occurring in patients receiving highly emetogenic chemotherapy who were treated with the aprepitant regimen for chemotherapy induced nausea and vomiting (CINV) in clinical studies (cycle 1)

	Aprepitant Regimen N = 544 %	**Standard Therapy** N = 550 %
General Disorders and Administration Site Conditions		
Asthenia	10.1	7.1
Fatigue	8.8	5.8
Pyrexia	2.4	3.1
Gastrointestinal Disorders		
Abdominal Pain	4.2	3.1
Abdominal Pain Upper	3.7	3.3
Constipation	10.8	12.7
Diarrhea	10.3	7.5
Dyspepsia	8.3	6.9
Gastritis	3.9	2.9
Nausea	12.7	11.8
Stomatitis	2.2	3.1
Vomiting	7.5	7.5
Ear and Labyrinth Disorders		
Tinnitus	3.7	3.6
Metabolism and Nutrition Disorders		
Decreased appetite	11.8	10.0
Dehydration	5.5	4.7
Nervous System Disorders		
Dizziness	6.3	4.4
Headache	8.3	8.4
Psychiatric Disorders		
Insomnia	2.9	3.1
Respiratory Thoracic and Mediastinal Disorders		
Hiccups	10.8	5.6

In addition, isolated cases of serious adverse experiences, regardless of causality, of bradycardia, disorientation, and perforating duodenal ulcer were reported in highly emetogenic CINV clinical studies.

In an additional active-controlled clinical study (study P017L) 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)

During Cycle 1 of 2 moderately emetogenic chemotherapy studies, 868 patients were treated with the aprepitant regimen and 686 of these patients continued into extensions for up to 4 cycles of chemotherapy. In the combined analysis of Cycle 1 data for these 2 studies, adverse

experiences were reported in approximately 69% of patients treated with the aprepitant regimen compared with approximately 72% of patients treated with standard therapy.

In the combined analysis of Cycle 1 data for these 2 studies, the adverse experience profile in the moderately emetogenic chemotherapy studies was generally comparable to the highly emetogenic chemotherapy studies. Table 2 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3%.

Table 2 – All adverse experiences, regardless of causality, (incidence ≥3%) occurring in patients receiving moderately emetogenic chemotherapy who were treated with the aprepitant regimen for CINV in clinical studies (cycle 1)

	Aprepitant Regimen N=868 %	**Standard Therapy** N=846 %
Blood and Lymphatic System Disorders		
Neutropenia	5.8	5.6
Metabolism and Nutrition Disorders		
Decreased appetite	7.6	8.5
Psychiatric Disorders		
Insomnia	2.6	3.7
Nervous System Disorders		
Dizziness	2.8	3.4
Headache	13.2	14.3
Gastrointestinal Disorders		
Constipation	10.3	15.5
Diarrhea	7.9	8.9
Dyspepsia	5.8	3.8
Nausea	5.8	5.1
Stomatitis	3.1	2.7
Skin and Subcutaneous Tissue Disorders		
Alopecia	12.4	11.9
General Disorders and General Administration Site Conditions		
Asthenia	4.7	4.6
Fatigue	15.4	15.6

In a combined analysis of these two studies, isolated cases of serious adverse experiences were similar in the two treatment groups.

Additional Clinical Trial Adverse Experiences (>0.5% and greater than standard therapy), Regardless of Causality, Occurring in Patients Receiving Highly and Moderately Emetogenic Chemotherapy

Blood and lymphatic system disorders: anemia, febrile neutropenia, neutropenia, thrombocytopenia.

Cardiac disorders: myocardial infarction, palpitations, tachycardia.

Eye disorders: conjunctivitis.

Gastrointestinal disorders: dry mouth, dysphagia, epigastric discomfort, eructation, flatulence, gastroesophageal reflux disease, odynophagia, salivary hypersecretion.

General disorders and administrative site conditions: chest pain, edema peripheral, malaise, pain.

Infections and infestations: oral candidiasis, pharyngitis, septic shock.

Investigations: weight decreased.

Metabolism and nutrition disorders: diabetes mellitus, hypokalemia.

Musculoskeletal and connective tissue disorders: musculoskeletal pain.

Nervous system disorders: dysgeusia, peripheral neuropathy, peripheral sensory neuropathy.

Psychiatric disorders: anxiety, confusion, depression.

Renal and urinary disorders: dysuria, renal insufficiency.

Respiratory, thoracic and mediastinal disorders: cough, dyspnea, oropharyngeal pain, pneumonitis, pulmonary embolism, respiratory insufficiency, vocal disturbance.

Skin and subcutaneous tissue disorders: hyperhidrosis, acne, rash.

Vascular disorders: deep venous thrombosis, flushing, hot flush, hypertension, hypotension.

Other Clinical Trials

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

Abnormal Hematologic and Clinical Chemistry Findings

Table 3 shows the percent of patients with laboratory adverse experiences reported at an incidence ≥3% in patients receiving highly emetogenic chemotherapy.

Table 3 – All laboratory abnormalities, regardless of causality, (incidence ≥3%) occurring in patients receiving highly emetogenic chemotherapy who were treated with the aprepitant regimen for CINV in clinical studies (cycle 1)

	Aprepitant Regimen N=544 %	**Standard Therapy** N=550 %
ALT increased	5.9	3.8
Blood urea increased	4.6	3.5
Blood creatinine increased	3.7	3.8
Protein urine present	6.1	4.5

Table 4 shows the percent of patients with laboratory adverse experiences reported at an incidence ≥3% in patients receiving moderately emetogenic chemotherapy.

Table 4 - Percent of Patients Receiving Moderately Emetogenic Chemotherapy with Laboratory Adverse Experiences (Incidence ≥3%) — Cycle 1

	Aprepitant Regimen (N = 868)	Standard Therapy (N = 846)
Neutrophil Count Decreased	4.6	4.6
White Blood Cell Count Decreased	5.1	4.7

Other Abnormal Hematological and Clinical Chemistry Findings Observed in Clinical Trials

The following additional laboratory adverse experiences, regardless of causality, were reported in patients treated with aprepitant regimen: AST increased, blood alkaline phosphatase increased, blood glucose increased, blood sodium decreased, white blood cell count increased, red blood cell urine positive, white blood cell urine positive. The adverse experiences of increased AST and ALT were generally mild and transient.

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

Fosaprepitant (150 mg intravenous formulation)

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

However, infusion-site reactions occurred at a higher incidence in the fosaprepitant group (3.0%) compared to those in the aprepitant group (0.5%), and there were significantly more cases of infusion-associated thrombophlebitis and infusion-site pain in the fosaprepitant group compared to those in the aprepitant group (thrombophlebitis: 0.8% vs. 0.1%; infusion-site pain: 1.4% vs. 0.1%). Infusion-site reactions included infusion-site erythema, infusion-site pruritus, infusion-site pain, infusion-site induration, and infusion-site thrombophlebitis.

In addition, there were more patients with adverse events of hypertension in the fosaprepitant group (1.5%) than in the aprepitant group (0.6%), as well as more patients with potential hypersensitivity adverse events in the fosaprepitant group (3.7%) than in the aprepitant group (3.1%).

Table 5 shows the percent of patients with clinical adverse experiences reported with fosaprepitant at an incidence > 3%, regardless of causality.

Table 5 - All adverse experiences, regardless of causality, (incidence ≥3%) occurring in patients receiving highly emetogenic chemotherapy who were treated with fosaprepitant for CINV in a clinical study

	Fosaprepitant Regimen N=1143 %	Aprepitant Regimen N=1169 %
Blood and lymphatic system disorders		
Neutropenia	3.9	3.3
Gastrointestinal disorders		
Abdominal pain	3.1	3.3

	Fosaprepitant Regimen N=1143 %	Aprepitant Regimen N=1169 %
Abdominal pain upper	4.0	2.6
Constipation	10.6	9.6
Diarrhea	7.8	8.7
Dyspepsia	4.4	3.3
Nausea	5.9	6.9
Vomiting	6.6	5.6
General disorders and administration site conditions		
Asthenia	8.6	11.6
Fatigue	4.6	4.9
Metabolism and nutrition disorders		
Anorexia	6.6	9.1
Nervous system disorders		
Dizziness	3.3	3.0
Headache	4.0	4.1
Respiratory, thoracic, and mediastinal disorders		
Hiccups	5.6	6.3

Clinically significant laboratory analysis 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%).

Post-Market Adverse Drug Reactions

Regardless of causality with aprepitant the following adverse events have been reported rarely or very rarely and occur with multiple confounding factors: loss of consciousness, depressed level of consciousness, convulsion, somnolence, paresthesia, syndrome of inappropriate antidiuretic hormone, hallucination, pruritus, rash, urticaria, Stevens-Johnson syndrome/toxic epidermal necrolysis, and hypersensitivity reactions including anaphylactic reactions.

Serious post-marketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported in patients after oral aprepitant and ifosfamide co-administration including acute psychosis, encephalopathy, toxic encephalopathy, delirium, convulsion, decreased level of consciousness and hallucination (see **DRUG INTERACTIONS**).

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

DRUG INTERACTIONS

Following the infusion of fosaprepitant 150 mg, a higher aprepitant C_{max} (~ 2.6-fold) was observed compared to oral aprepitant (125 mg). A theoretical risk for increased adverse experiences due to a higher peak aprepitant exposure cannot be ruled out.

Serious Drug Interactions

- Fosaprepitant is rapidly converted to aprepitant, which is an inhibitor of CYP3A4. Fosaprepitant should be used with caution in patients receiving concomitant medicinal products that are primarily metabolized through CYP3A4 and CYP2C9, including chemotherapy agents. 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. Induction of CYP2C9 by aprepitant could result in decreased plasma concentrations of these concomitant medicinal products (see **CONTRAINDICATIONS** and **Drug-Drug Interactions** below).

- 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.

- Coadministration of oral aprepitant with warfarin results in decreased prothrombin time, reported as International Normalized Ratio (INR). 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 (see **Drug-Drug Interactions** below).

- 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 (see **Drug-Drug Interactions** below).

Overview

Drug interactions following administration of fosaprepitant are likely to occur with drugs that interact with oral aprepitant. The following information was derived from studies conducted with oral aprepitant and studies conducted with fosaprepitant coadministered with dexamethasone, midazolam or diltiazem.

Aprepitant is a substrate, a moderate inhibitor, and an inducer of CYP3A4 when administered as a 3-day antiemetic dosing regimen for CINV. Aprepitant is also an inducer of CYP2C9.

Fosaprepitant 150 mg, given as a single dose, is a weak inhibitor of CYP3A4, and does not induce CYP3A4.

Chronic continuous use of fosaprepitant is not recommended because it has not been studied and because the drug interaction profile may change during chronic dosing.

Effect of fosaprepitant/aprepitant on the pharmacokinetics of other agents

Aprepitant, as a moderate inhibitor of CYP3A4, and fosaprepitant 150 mg, as a weak inhibitor of CYP3A4, can increase plasma concentrations of orally coadministered medicinal products that are metabolized through CYP3A4 (see CONTRAINDICATIONS). Aprepitant may increase the plasma concentration of orally administered CYP3A4 substrates to a greater extent than if the substrate was administered intravenously.

Aprepitant has been shown to induce the metabolism of S(-) warfarin and tolbutamide, which are metabolized through CYP2C9. Coadministration of fosaprepitant or oral aprepitant 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.

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. Moderate CYP3A4 inhibitors (e.g., diltiazem) resulted in a 2-fold increase in plasma concentrations of aprepitant; therefore, 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.

Drug-Drug Interactions
Chemotherapeutic agents: Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. In clinical studies, the oral aprepitant regimen was administered commonly with etoposide, vinorelbine, paclitaxel and cyclophosphamide. The doses of these agents were not adjusted to account for potential drug interactions.

In separate pharmacokinetic studies, oral aprepitant did not influence the pharmacokinetics of IV administered vinorelbine or docetaxel. However, fosaprepitant may increase the plasma concentration of oral CYP3A4 substrates to a greater extent than if the substrates were administered intravenously. No additional drug-drug interaction studies with chemotherapeutic agents metabolized by CYP3A4 were carried out.

Serious post-marketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported in patients after oral aprepitant and ifosfamide co-administration. Refer to IFEX (ifosfamide for injection) product monograph.

Caution and careful monitoring are advised in patients receiving chemotherapy agents metabolized by CYP3A4, particularly those that were not studied in the clinical trials. (see **WARNINGS AND PRECAUTIONS**).

Established or potential drug-drug interactions

Proper name	Ref	Effect	Clinical comment
pimozide	T	↑ pimozide concentration	Potentially causing serious or life-threatening reactions.
terfenadine	T	↑ terfenadine concentration	Potentially causing serious or life-threatening reactions.
Astemizole	T	↑ astemizole concentration	Potentially causing serious or life-threatening reactions.
Cisapride	T	↑ cisapride concentration	Potentially causing serious or life-threatening reactions.
Warfarin	CT	↓ Warfarin concentration ↓ INR	In patients on chronic warfarin therapy, the INR should be closely monitored in the 2-

Proper name	Ref	Effect	Clinical comment
			week period, particularly at 7 to 10 days, following initiation of fosaprepitant with each chemotherapy cycle (see WARNINGS AND PRECAUTIONS and DETAILED PHARMACOLOGY).
tolbutamide	CT	↓ tolbutamide concentration	Aprepitant induces the metabolism of drug metabolized by CYP2C9 (see DETAILED PHARMACOLOGY).
Phenytoin	T	↓ phenytoin concentration	Aprepitant induces the metabolism of drug metabolized by CYP2C9.
dexamethasone	CT	↑ dexamethasone concentration	The usual oral dexamethasone dose on Days 1 and 2 should be reduced by approximately 50% when coadministered with fosaprepitant 150 mg IV on Day 1 to achieve exposures of dexamethasone similar to those obtained when it is given without fosaprepitant 150 mg (see DETAILED PHARMACOLOGY).
methylprednisolone	CT	↑ methylprednisolone concentration	See DETAILED PHARMACOLOGY.
hormone contraceptives with all routes of administration	CT	↓ hormone concentration	The efficacy of hormonal contraceptives during and for 28 days after administration fosaprepitant may be reduced. Alternative or back-up methods of contraception should be used during treatment with fosaprepitant and for 1 month following administration (see WARNINGS AND PRECAUTIONS and DETAILED PHARMACOLOGY).
Midazolam oral and IV	CT	↑ midazolam concentration	The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these agents with fosaprepitant. Fosaprepitant 150 mg IV as a single dose is a weak CYP3A4 inhibitor on Day 1 with no evidence of inhibition or induction of CYP3A4 observed on Day 4 (see DETAILED PHARMACOLOGY).
ketoconazole	CT	↑ aprepitant concentration	Concomitant administration of fosaprepitant with strong CYP3A4 inhibitors should be approached cautiously (see DETAILED PHARMACOLOGY).
Rifampin	CT	↓ aprepitant concentration	Coadministration of fosaprepitant with drugs that induce CYP3A4 activity may result in reduced plasma concentrations and

Proper name	Ref	Effect	Clinical comment
			decreased efficacy of fosaprepitant (see DETAILED PHARMACOLOGY).
Diltiazem	CT	↑ aprepitant and diltiazem concentration	No clinically meaningful changes in ECG, heart rate, PR interval or blood pressure beyond those changes induced by diltiazem alone (see DETAILED PHARMACOLOGY).
paroxetine	CT	↓ aprepitant and paroxetine concentration	See DETAILED PHARMACOLOGY.

Legend: CT = Clinical Trial; T = Theoretical

5-HT_3 antagonists: In clinical drug interaction studies, oral aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron administered intravenously, granisetron administered orally, or hydrodolasetron (the active metabolite of dolasetron) following oral administration of dolasetron.

P-glycoprotein transporter substrates: 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 in a clinical drug interaction study.

Drug-Food Interactions
Fosaprepitant may be administered with or without food.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Consideration
FOSAPREPITANT is available as a 150 mg for IV infusion.

FOSAPREPITANT has not been demonstrated to be effective as a single anti-emetic agent and must be administered with other anti-emetic agents.

Recommended Dose and Dosage Adjustment
FOSAPREPITANT 150 mg is administered on Day 1 only as an infusion **over 20 – 30 minutes** initiated approximately 30 minutes prior to chemotherapy. FOSAPREPITANT should be administered in conjunction with a corticosteroid and a 5-HT_3 antagonist as specified in the tables below. The package insert for the co-administered 5-HT_3 antagonist must be consulted prior to initiation of treatment with FOSAPREPITANT 150 mg.

Table 7: Recommended dosing for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy:

	Day 1	Day 2	Day 3	Day 4
FOSAPREPITANT	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.

Table 8: Recommended dosing for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy:

	Day 1 Only
FOSAPREPITANT	150 mg IV
Dexamethasone*	12 mg orally
5-HT_3 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.

For highly emetogenic chemotherapy, there is only limited efficacy data with aprepitant or fosaprepitant in combination with oral ondansetron or other 5-HT_3 antagonist class of antiemetics and dexamethasone. In the highly emetogenic chemotherapy clinical trials, the 5-HT_3 antagonist studied was ondansetron administered by intravenous route. However, the dose was 32 mg and is no longer a recommended dose due to the dose-dependent risk of QTc prolongation (see the package insert for ondansetron for additional details).

For moderately emetogenic chemotherapy, there is only limited efficacy data with aprepitant in combination with other 5-HT_3 antagonist class of antiemetics and dexamethasone. In the moderately emetogenic trials, the 5-HT_3 antagonist studied was ondansetron administered by the oral route.

Dosage Adjustment
See DRUG INTERACTIONS for additional information on the administration of fosaprepitant or aprepitant with corticosteroids.

Refer to each product's respective Product Monograph for additional information on 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).

Administration

FOSAPREPITANT is for IV infusion only, upon reconstitution and dilution and for single use only.

Instructions for reconstitution and dilution

1. Aseptically inject 5 mL 0.9% Sodium Chloride for injection (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. Aseptically prepare an infusion bag filled with **145 mL** 0.9% NaCl for injection.
3. Aseptically 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** and a final concentration of approximately 1 mg fosaprepitant/mL. Gently invert the bag 2-3 times.

The reconstituted and diluted solutions should be used immediately; however, after reconstitution and dilution the final drug solution is stable for 24 hours at ambient room temperature (at or below 25°C).

Reconstituted and diluted solutions should be inspected for discoloration, cloudiness and particulate matter before administration whenever solution and container permit. Discard unused portion.

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

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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, FOSAPREPITANT 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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_1) receptors. Counter-screening assays showed that aprepitant was at least 3,000-fold selective for the NK_1 receptor over other enzyme, transporter, ion channel and receptor sites including the dopamine and serotonin receptors that are targets for existing chemotherapy induced nausea and vomiting (CINV) therapies.

NK_1-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_1 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_3-receptor antagonist ondansetron and the corticosteroid dexamethasone against cisplatin-induced emesis.

Pharmacokinetics

Table 9 - Summary of pharmacokinetic parameters of aprepitant in healthy subjects

	C_{max} (µg/mL)	$AUC_{0\text{-}24hr}$ (µg•hr/mL)
Day 1 oral dose aprepitant 125 mg	1.5	19.5
Day 3 oral dose aprepitant 80 mg	1.4	20.1

Absorption: Following a single intravenous 150-mg dose of fosaprepitant administered as a 20-minute infusion to healthy volunteers, the mean $AUC_{0\text{-}\infty}$ of aprepitant was 37.38 (±14.75) mcg•hr/mL and the mean maximal aprepitant concentration was 4.15 (± 1.15) mcg/mL.

The mean absolute oral bioavailability of aprepitant is approximately 60 to 65% and the mean peak plasma concentration (C_{max}) of aprepitant occurred at approximately 4 hours (T_{max}). Oral administration of the capsule with a standard breakfast had no clinically meaningful effect on the bioavailability of aprepitant.

The pharmacokinetics of aprepitant are non-linear across the clinical dose range. In healthy young adults, the increase in $AUC_{0\text{-}\infty}$ was 26% greater than dose proportional between 80-mg and 125-mg single doses administered in the fed state.

Following oral administration of a single 125-mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 and 3, the $AUC_{0\text{-}24hr}$ was approximately 19.5 µg•hr/mL and 20.1 µg•hr/mL on

Day 1 and Day 3, respectively. The C_{max} of 1.5 µg/mL and 1.4 µg/mL were reached in approximately 4 hours (T_{max}) on Day 1 and Day 3, respectively.

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 (Vd_{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 ACTION AND CLINICAL PHARMACOLOGY).

Metabolism: Fosaprepitant was rapidly converted to aprepitant in *in vitro* 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 [^{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 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 [^{14}C]-fosaprepitant dose were also observed following an oral dose of [^{14}C]-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.

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

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

Pharmacodynamics

NK_1 Receptor Occupancy: A positron emission tomography study in healthy young men administered a single intravenous dose of 150 mg fosaprepitant (N=8) with coadministration of 32 mg IV ondansetron on Day 1 and oral dexamethasone (12/8/16/16-mg) on Days 1, 2, 3, and 4 demonstrated mean brain NK_1 receptor occupancy values (%) and corresponding mean

aprepitant plasma concentrations (μg/mL) at T_{max}, 24, 48, and 120 hours postdose, as shown below in Table 10.

Table 10 - Brain NK_1-Receptor Occupancy (%) and Aprepitant Plasma Concentration (μg/mL) Following Intravenous Administration of 150 mg Fosaprepitant

Postdose Time Points	N	Brain NK_1-Receptor Occupancy Arithmetic Mean (%)	Aprepitant Plasma Concentration Arithmetic Mean (μg/mL)
T_{max}	2	100	2.4
24 hours	5	100	0.8
48 hours	4	99	0.3
120 hours	3	62	BLOQ
BLOQ: Below the Limit of Quantitation of the Assay (<0.01 μg/mL).			

However, the relationship between NK_1 receptor occupancy and the clinical efficacy of aprepitant has not been established.

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

Special Populations and Conditions

Pediatrics: The pharmacokinetics of aprepitant and FOSAPREPITANT have not been evaluated in patients below 18 years of age.

Geriatrics: 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 $AUC_{0\text{-}24hr}$ of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (≥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 for aprepitant is necessary in elderly patients.

Gender: Following oral administration of a single dose of aprepitant, the $AUC_{0\text{-}24hr}$ and C_{max} 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 T_{max} occurs at approximately the same time. No dosage adjustment is necessary based on gender.

Race: Following oral administration of a single dose of aprepitant, there was no difference in the $AUC_{0\text{-}24hr}$ or C_{max} between Caucasians and Blacks. Single dose administration of oral aprepitant in Hispanics resulted in a 27% and 19% increase in $AUC_{0\text{-}24hr}$ and C_{max}, respectively, as compared to Caucasions. Single dose administration of oral aprepitant in Asians resulted in a 74% and 47% increase in $AUC_{0\text{-}24hr}$ and C_{max}, respectively, as compared to Caucasians. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on race.

Body Mass Index (BMI): For every 5 kg/m^2 increase in BMI, $AUC_{0\text{-}24h}$ decreased by 8.5% and C_{max} decreased by 10.2%. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on BMI.

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 $AUC_{0\text{-}24hr}$ 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 $AUC_{0\text{-}24hr}$ 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 $AUC_{0\text{-}24hr}$ 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 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 $AUC_{0\text{-}\infty}$ of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects. In patients with ESRD undergoing hemodialysis, the $AUC_{0\text{-}\infty}$ of total aprepitant decreased by 42% and C_{max} decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal insufficiency compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

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

STORAGE AND STABILITY

Vials: store at 2-8°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

FOSAPREPITANT is available as a 150 mg single dose per 10 mL glass vial as a white lyophilized powder or cake to be administered intravenously as an infusion, upon reconstitution and dilution. One vial per carton.

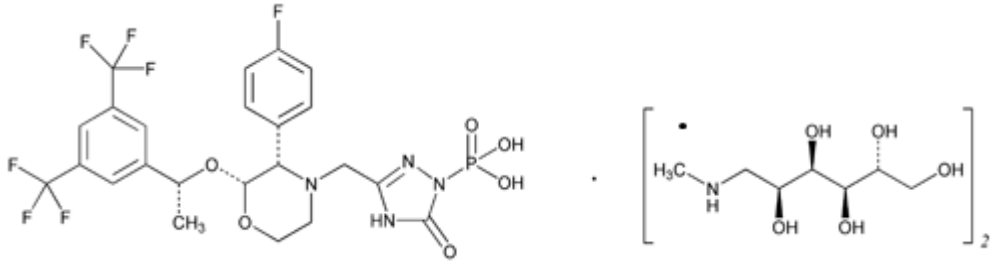
Active ingredients:
Each vial of FOSAPREPITANT 150 mg for intravenous administration contains 245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg of fosaprepitant free acid.

Inactive ingredients:
Each vial of FOSAPREPITANT for intravenous administration contains the following inactive ingredients: edetate disodium, lactose anhydrous, polysorbate 80 and sodium hydroxide and/or hydrochloric acid (for pH adjustment).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name:	Fosaprepitant dimeglumine
Chemical name:	Fosaprepitant dimeglumine is a prodrug of aprepitant and is chemically described as 1-Deoxy-1-(methylamino)-D-glucitol [3-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5- bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]phosphonate (2:1) (salt).
Molecular formula:	$C_{23}H_{22}F_7N_4O_6P \bullet 2 (C_7H_{17}NO_5)$
Molecular mass:	1004.83
Structural formula:	
Physicochemical properties:	Description: Fosaprepitant dimeglumine is a white to off-white powder. Solubilities: It is freely soluble in water, soluble in N, N-Dimethylsufoxide and insoluble in n-hexane. pH (1 % w/v Aqueous solution): Between 6.5 and 8.5. pKa: 5.40.

CLINICAL TRIALS

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

The pivotal efficacy studies were conducted with oral aprepitant. Oral administration of aprepitant in combination with ondansetron and dexamethasone has been shown to prevent nausea and vomiting associated with highly emetogenic and moderately emetogenic chemotherapy in well-controlled clinical studies. An active-controlled non-inferiority study comparing fosaprepitant 150 mg with oral aprepitant demonstrated efficacy of fosaprepitant 150 mg in the prevention of nausea and vomiting associated with highly emetogenic chemotherapy.

Study Demographics and Trial Design

Table 11 - Summary of patient demographics for clinical trials in highly emetogenic and moderately emetogenic chemotherapy (HEC and MEC)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
P017L1* (HEC)	Randomized, double-blind, active-controlled, parallel group, non-inferiority	Fosaprepitant 150 mg on Day 1 in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg on Day 1, 8 mg on Day 2, and 8 mg twice daily on Days 3 and 4. OR Aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg on Day 1 and 8 mg once daily on Days 2 through 4.	2322	55 (19-86)	Male:1470 Female: 852
052* (HEC)	Randomized, double-blind, placebo-controlled, parallel-group	Aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg on Day 1 and 8 mg once daily on Days 2 through 4. OR Standard therapy which consisted of placebo in	534	14-84	Male: 266 Female: 268

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
		combination with ondansetron 32 mg IV on Day 1 and dexamethasone 20 mg on Day 1 and 8 mg twice daily on Days 2 through 4.			
054* (HEC)	Randomized, double-blind, placebo-controlled, parallel-group	Aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg on Day 1 and 8 mg once daily on Days 2 through 4. OR Standard therapy which consisted of placebo in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 20 mg on Day 1 and 8 mg twice daily on Days 2 through 4.	569	18-82	Male: 283 Female: 286
071 (MEC)	Randomized, double-blind, parallel-group, standard therapy	Aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1 Standard Therapy consisted of placebo in combination with ondansetron 8 mg orally (twice on Day 1, and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.	866	52 (23-78)	Female: 864 Male: 2
130 (MEC)	Randomized, double-blind, parallel-group	Aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1 Standard	848	56 (19-87)	Female: 652 Male: 196

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
		Therapy consisted of placebo in combination with ondansetron 8 mg orally (twice on Day 1, and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1			

*Although a 32 mg IV dose of ondansetron was used in clinical trials, this is no longer a recommended dose due to the dose-dependent risk of QTc prolongation (see the package insert for ondansetron for additional details).

1-Day Regimen of fosaprepitant for injection

Highly Emetogenic Chemotherapy (HEC)

Study P017L1

In a randomized, parallel, double-blind, active-controlled non-inferiority study, fosaprepitant 150 mg (N=1147) was compared with a 3-day aprepitant regimen (N=1175) in patients receiving a highly emetogenic chemotherapy regimen that included cisplatin (≥70 mg/m^2). Other concomitant chemotherapy agents were administered similar to those in prior HEC studies described above. The fosaprepitant regimen consisted of fosaprepitant 150 mg on Day 1 in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg on Day 1, 8 mg on Day 2, and 8 mg twice daily on Days 3 and 4. The aprepitant regimen consisted of aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg on Day 1 and 8 mg daily on Days 2 through 4. Fosaprepitant placebo, aprepitant placebo, and dexamethasone placebo (in the evenings on Days 3 and 4) were used to maintain blinding. Although a 32 mg IV dose of ondansetron was used in clinical trials, this is no longer a recommended dose due to the dose-dependent risk of QTc prolongation (see the package insert for ondansetron for additional details).

Efficacy was based on the evaluation of the following composite measures: complete response in both the overall and delayed phases and no vomiting in the overall phase. The pre-specified non-inferiority margins were as follows: complete response in the overall phase -7 percentage points; complete response in the delayed phase -7.3 percentage points; and no vomiting in the overall phase -8.2 percentage points. Fosaprepitant 150 mg was shown to be non-inferior to that of the 3-day regimen of aprepitant. A summary of the results is shown in Table 12.

Table 12 - Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase — Cycle 1			
ENDPOINTS*	Fosaprepitant Regimen (N =1106) ** %	Aprepitant Regimen (N =1134) ** %	Difference[†] (95% CI)
Complete Response[‡]			
Overall[§]	71.9	72.3	-0.4 (-4.1, 3.3)
Delayed phase[§§]	74.3	74.2	0.1 (-3.5, 3.7)
No Vomiting			
Overall[§]	72.9	74.6	-1.7 (-5.3, 2.0)

*Primary endpoint is bolded.
**N: Number of patients included in the primary analysis of complete response.
[†]Difference and confidence interval (CI) were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.
[‡]Complete Response: no vomiting and no use of rescue therapy.
[§]Overall: 0 to 120 hours post-initiation of cisplatin chemotherapy.
[§§]Delayed phase: 25 to 120 hours post-initiation of cisplatin chemotherapy.

3-Day Regimen of aprepitant

Oral administration of aprepitant in combination with ondansetron and dexamethasone has been shown to prevent nausea and vomiting associated with highly emetogenic chemotherapy in well-controlled clinical studies.

Highly Emetogenic Chemotherapy (HEC)

Studies 052 and 054

In the clinical studies 052 and 054 above, all enrolled patients received high-dose cisplatin ≥70 mg/m^2. Approximately 95% of the patients in the aprepitant group received a concomitant chemotherapeutic agent. The most common chemotherapeutic agents and the number of aprepitant patients exposed follows: etoposide (106), fluorouracil (100), gemcitabine (89), vinorelbine (82), paclitaxel (52), cyclophosphamide (50), doxorubicin (38), docetaxel (11). The efficacy of aprepitant has not been investigated in highly emetogenic chemotherapy clinical trials without cisplatin.

The antiemetic activity of aprepitant was evaluated during the acute phase (0 to 24 hours post-cisplatin treatment), the delayed phase (25 to 120 hours post-cisplatin treatment) and overall (0 to 120 hours post-cisplatin treatment) in Cycle 1. Efficacy was based on evaluation of the following endpoints:

Primary endpoint:
- complete response (defined as no emetic episodes and no use of rescue therapy)

Other prespecified endpoints:
- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score <25 mm on a 0 to 100 mm scale)
- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no nausea (maximum VAS <5 mm on a 0 to 100 mm scale)
- no significant nausea (maximum VAS <25 mm on a 0 to 100 mm scale)

A summary of the key study results from each individual study analysis is shown in Table 13 and in Table 14.

Table 13 – Percent of patients receiving highly emetogenic chemotherapy responding by treatment group and phase for study 1 – Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)[†] %	Standard Therapy (N = 261)[†] %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall[‡]	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[§]	89	78	<0.001
Delayed phase[‖]	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

[†] N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
[‡] Overall: 0 to 120 hours post-cisplatin treatment.
[§] Acute phase: 0 to 24 hours post-cisplatin treatment.
[‖] Delayed phase: 25 to 120 hours post-cisplatin treatment.
* Not statistically significant when adjusted for multiple comparisons.
** Not statistically significant.
Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

Table 14 – Percent of patients receiving highly emetogenic chemotherapy responding by treatment group and phase for study 2 – Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 261)[†] %	Standard Therapy (N = 263)[†] %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall[‡]	63	43	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[§]	83	68	<0.001
Delayed phase[‖]	68	47	<0.001
Complete Protection			
Overall	56	41	<0.001
Acute phase	80	65	<0.001
Delayed phase	61	44	<0.001
No Emesis			
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
No Nausea			
Overall	49	39	NS*
Delayed phase	53	40	NS*
No Significant Nausea			
Overall	71	64	NS**
Delayed phase	73	65	NS**

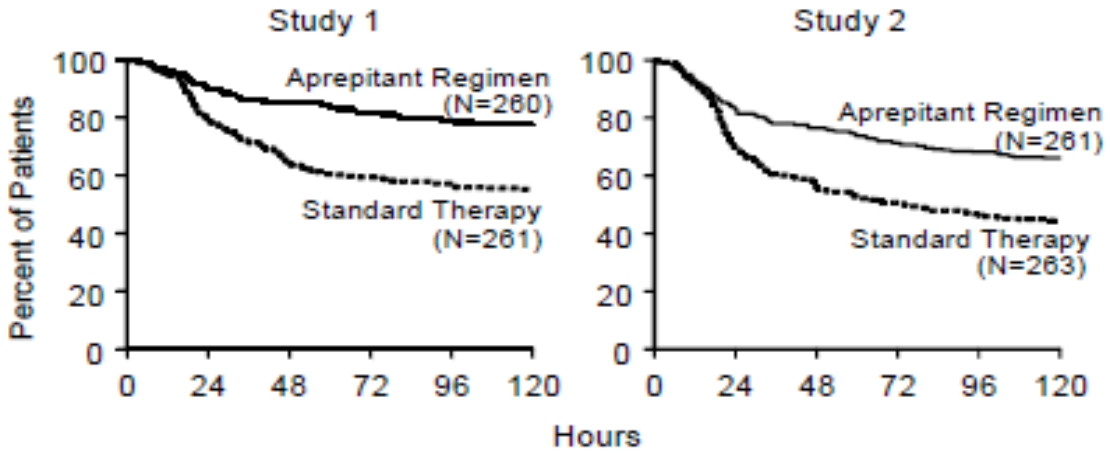
[†] N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
[‡] Overall: 0 to 120 hours post-cisplatin treatment.
[§] Acute phase: 0 to 24 hours post-cisplatin treatment.
[‖] Delayed phase: 25 to 120 hours post-cisplatin treatment.
* Not statistically significant when adjusted for multiple comparisons.
** Not statistically significant.
Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

In both studies, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response (primary endpoint), compared with patients receiving standard therapy. A statistically significant difference in complete response in favor of the aprepitant regimen was also observed when the acute phase and the delayed phase were analyzed separately.

In both studies, the estimated time to first emesis after initiation of cisplatin treatment was longer with the aprepitant regimen, and the incidence of first emesis was reduced in the aprepitant

regimen group compared with standard therapy group as depicted in the Kaplan-Meier curves in Figure 1.

Figure 1 - Percent of patients receiving highly emetogenic chemotherapy who remain emesis free over time – Cycle 1



p-Value <0.001 based on a log rank test for Study 1 and Study 2; nominal p-values not adjusted for multiplicity.

Patient-Reported Outcomes: The impact of nausea and vomiting on patients' daily lives was assessed in Cycle 1 of both Phase III studies using the Functional Living Index–Emesis (FLIE), a validated nausea and vomiting-specific patient-reported outcome measure. Minimal or no impact of nausea and vomiting on patients' daily lives is defined as a FLIE total score >108. In each of the 2 studies, a higher proportion of patients receiving the aprepitant regimen reported minimal or no impact of nausea and vomiting on daily life (Study 1: 74% versus 64%; Study 2: 75% versus 64%).

Multiple-Cycle Extension: In the same 2 clinical studies, 851 patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. The efficacy of the aprepitant regimen was maintained during all cycles.

Moderately Emetogenic Chemotherapy (MEC)

Study 071

The first MEC study (P071) enrolled breast cancer patients (99% women) receiving a chemotherapy regimen that included cyclophosphamide 750-1500 mg/m^2; or cyclophosphamide 500-1500 mg/m^2 and doxorubicin (≤60 mg/m^2) or epirubicin (≤100 mg/m^2). Some patients also received other chemotherapeutic agents such as fluorouracil, methotrexate, docetaxel or paclitaxel. In this study (P071), the most common combinations were cyclophosphamide + doxorubicin (60.6%); and cyclophosphamide + epirubicin +fluorouracil (21.6%).

In the first MEC study (P071), the antiemetic activity of aprepitant was evaluated during the acute phase (0 to 24 hours post-chemotherapy treatment), the delayed phase (25 to 120 hours post-chemotherapy treatment) and overall (0 to 120 hours post-chemotherapy treatment) in Cycle

1. The antiemetic activity of aprepitant was evaluated based on the following endpoints:

Primary endpoint:
- complete response (defined as no emetic episodes and no use of rescue therapy) in the overall phase (0 to 120 hours post-chemotherapy)

Other prespecified endpoints:
- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no nausea (maximum VAS <5 mm on a 0 to 100 mm scale)
- no significant nausea (maximum VAS <25 mm on a 0 to 100 mm scale)
- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score <25 mm on a 0 to 100 mm scale)
- complete response during the acute and delayed phases

A summary of the key results from this study is shown in Table 15.

Table 15 – Percent of patients receiving moderately emetogenic chemotherapy responding by treatment group and phase – Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 433)† %	Standard Therapy (N = 424)† %	p-Value
PRIMARY ENDPOINT			
Complete Response‡	51	42	0.015
OTHER PRESPECIFIED ENDPOINTS			
No Emesis	76	59	NS*
No Nausea	33	33	NS
No Significant Nausea	61	56	NS
No Rescue Therapy	59	56	NS
Complete Protection	43	37	NS

† N: Number of patients included in the primary analysis of complete response.
‡ Overall: 0 to 120 hours post-chemotherapy treatment.
* NS when adjusted for prespecified multiple comparisons rule; unadjusted p-value <0.001.

In this study, a statistically significantly (p=0.015) higher proportion of patients receiving the aprepitant regimen (51%) in Cycle 1 had a complete response (primary endpoint) during the overall phase compared with patients receiving standard therapy (42%). The difference between treatment groups was primarily driven by the "No Emesis Endpoint", a principal component of this composite primary endpoint. In addition, a higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response during the acute (0-24 hours) and delayed (25-120 hours) phases compared with patients receiving standard therapy; however, the treatment group differences failed to reach statistical significance, after multiplicity adjustments.

Patient-Reported Outcomes: In a phase III study in patients receiving moderately emetogenic chemotherapy, the impact of nausea and vomiting on patients' daily lives was assessed in Cycle 1 using the FLIE. A higher proportion of patients receiving the aprepitant regimen reported minimal or no impact on daily life (64% versus 56%). This difference between treatment groups was primarily driven by the "No Vomiting Domain" of this composite endpoint.

Multiple-Cycle Extension: A total of 744 patients receiving moderately emetogenic cancer chemotherapy continued into the Multiple-Cycle extension for up to 4 cycles of chemotherapy. The efficacy of the aprepitant regimen was maintained during all cycles.

Study 130
In a second multicenter, randomized, double-blind, parallel-group, clinical study (130), the aprepitant regimen was compared with standard therapy in 848 patients receiving a MEC regimen that included any IV dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin; cyclophosphamide IV (<1500 mg/m^2); or cytarabine IV (>1 g/m^2). Patients who were randomized to receive the aprepitant regimen consisted of 76% women and 24% men. Patients receiving the aprepitant regimen were receiving chemotherapy for a variety of tumor types including 52% with breast cancer, 21% with gastrointestinal cancers including colorectal cancer, 13% with lung cancer and 6% with gynecological cancers. In this study, 48% of patients received AC therapy, defined as anthracycline (doxorubicin, epirubicin) + cyclophosphamide chemotherapy regimen and 52% received non-AC therapy.

The aprepitant regimen consisted of aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1. Standard therapy consisted of placebo in combination with ondansetron 8 mg orally (twice on Day 1, and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

The antiemetic activity of aprepitant was evaluated during the overall phase (0 to 120 hours post-chemotherapy treatment) in Cycle 1. Efficacy was based on the evaluation of the following endpoints:

Primary endpoint:
- no vomiting in the overall period (0 to 120 hours post-chemotherapy).

Other prespecified endpoints:
- complete response (defined as no vomiting and no use of rescue therapy) in the overall period (0 to 120 hours post-chemotherapy).
- time to first vomiting episode overall (0 to 120 hours post-chemotherapy)
- no vomiting – Acute (0 to 24 hours following initiation of chemotherapy infusion) and Delayed (25 to 120 hours following initiation of chemotherapy infusion)
- complete response - Acute and Delayed, as defined above
- no use of rescue therapy – Overall, Acute, and Delayed, as defined above
- no Impact on Daily Life (Functional Living Index-Emesis [FLIE] total score >108) – Overall, as defined above
- no vomiting and no significant nausea (VAS <25 mm) – Overall, as defined above

A summary of the key study results is shown in Table 16.

Table 16 - Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 2 – Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 430)[†] %	Standard Therapy (N = 418)[†] %	p-Value
PRIMARY ENDPOINT			
No Vomiting			
Overall	76	62	<0.0001
KEY SECONDARY ENDPOINT			
Complete Response			
Overall	69	56	0.0003
OTHER SECONDARY ENDPOINTS			
No Vomiting			
Acute phase	92	84	0.0002
Delayed phase	78	67	0.0005
No Impact on Daily Life (FLIE total score >108)			
Overall	73	66	0.035
Complete Response			
Acute phase	89	80	0.0005
Delayed phase	71	61	0.0042
No Use of Rescue Therapy			
Overall	81	75	0.0427[ß]
Acute phase	95	91	0.0179[ß]
Delayed phase	84	79	0.0922[ß]
No Vomiting and No Significant Nausea (VAS <25 mm)			
Overall	65	53	0.0011

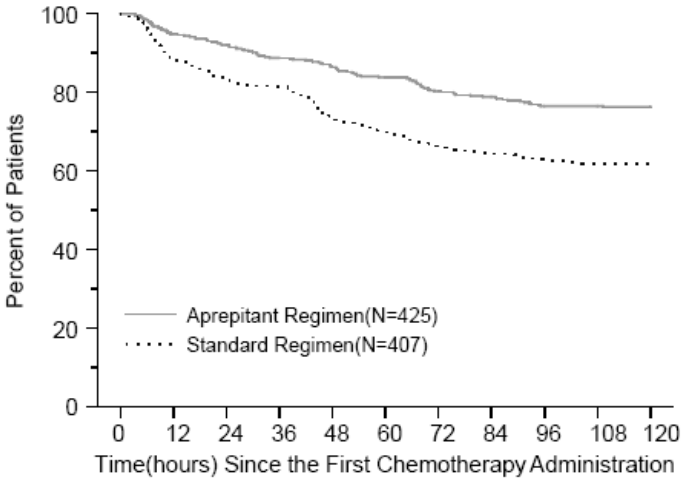
[†]N=Number of patients who received chemotherapy treatment, study drug, and had at least one post-treatment efficacy evaluation.
[ß]Not statistically significant after adjustment for multiplicity.
Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

In this study, a statistically significantly (p<0.0001) higher proportion of patients receiving the aprepitant regimen (76%) in Cycle 1 had no vomiting (primary endpoint) during the overall phase compared with patients receiving standard therapy (62%). In addition, a higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response in the overall phase (0-120 hours) compared with patients receiving standard therapy. Aprepitant was numerically superior versus standard therapy regardless of age, gender, chemotherapy regimen, or tumor type (breast, gastrointestinal, lung or other) as assessed by the No Vomiting and Complete Response endpoints. However, the proportion of patients with no vomiting and complete response in the standard therapy group, as well as the size of the difference in no vomiting and complete response between the treatment groups, differed by gender and chemotherapy regimen. During the overall phase, complete response to the aprepitant regimen and standard therapy, respectively, was reached in 209/324 (65%) and 161/320 (50%) in

women and 83/101 (82%) and 68/87 (78%) of men. No vomiting in the aprepitant regimen and standard therapy, respectively, was reached in 235/324 (73%) and 181/319 (57%) in women and 89/101 (88%) and 71/87 (82%) in men. During the overall phase, complete response to the aprepitant regimen and standard therapy, respectively, was reached in 125/199 (63%) and 96/204 (47%) in AC therapy and 167/226 (74%) and 133/203 (66%) in non-AC therapy. No vomiting in the aprepitant regimen and standard therapy, respectively, was reached in 136/199 (68%) and 108/204 (53%) in AC-therapy and 188/226 (83%) and 144/202 (71%) in non-AC therapy.

In this study, the estimated time to first vomiting after initiation of chemotherapy treatment was longer with the aprepitant regimen, and the incidence was reduced in the aprepitant regimen group compared with standard therapy group as depicted in the Kaplan-Meier curves in Figure 2.

Figure 2: Kaplan-Meier Curves for Time to First Vomiting Episode From Start of Chemotherapy Administration in the Overall Phase – Cycle 1 (Full Analysis Set Patient Population)



In this study, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 reported no impact of nausea and vomiting on daily life, as measured by a FLIE total score >108, compared with patients receiving standard therapy.

DETAILED PHARMACOLOGY

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant, a substance P/neurokinin 1 (NK_1) receptor antagonist. Plasma concentrations of fosaprepitant are below the limits of quantification (10 ng/mL) within 30 minutes of the completion of infusion.

Dexamethasone: Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the $AUC_{0\text{-}24hr}$ of dexamethasone, a CYP3A4 substrate, by approximately 2.01, 1.86 and 1.18-fold on Days 1, 2 and 3 respectively 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 by approximately 50% when coadministered 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 coadministered orally as 20 mg on Day 1, and oral aprepitant when given as 80 mg/day with dexamethasone coadministered 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 daily dose of dexamethasone administered in clinical CINV 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 coadministered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3.

Warfarin: A single 125-mg dose of aprepitant was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were stabilized on chronic warfarin therapy. Although there was no effect of oral aprepitant on the plasma AUC of R(+) or S(-) warfarin determined on Day 3, there was a 34% decrease in S(-) warfarin (a CYP2C9 substrate) trough concentration accompanied by a 14% decrease in the prothrombin time (reported as International Normalized Ratio or INR) 5 days after completion of dosing with oral aprepitant. 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 (see WARNINGS AND PRECAUTIONS).

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%; therefore 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 (see WARNINGS AND PRECAUTIONS).

Midazolam: Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the $AUC_{0-\infty}$ of midazolam by approximately 1.8-fold on Day 1 and had no effect (1.0-fold) on Day 4 when midazolam was coadministered 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.

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 coadministered 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 metabolized via CYP3A4 (alprazolam, triazolam) should be considered when coadministering 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. Depending on clinical situations (e.g., elderly patients) and degree of monitoring available, dosage adjustment for intravenous midazolam may be necessary when it is coadministered with aprepitant for the chemotherapy induced nausea and vomiting indication (125 mg on Day 1 followed by 80 mg on Days 2 and 3).

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

Diltiazem: In a study in 10 patients with mild to moderate hypertension, intravenous infusion of 100 mg of 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. It also resulted in a small but clinically meaningful further maximum decrease in diastolic blood pressure [mean (SD) of 24.3 (± 10.2) mm Hg with fosaprepitant versus 15.6 (± 4.1) mm Hg without fosaprepitant] and resulted in a small further maximum decrease in systolic blood pressure [mean (SD) of 29.5 (± 7.9) mm Hg with fosaprepitant versus 23.8 (± 4.8) mm Hg without fosaprepitant], which may be clinically meaningful, but did not result in a clinically meaningful further change in heart rate or PR interval, beyond those changes induced by diltiazem alone.

In patients with mild to moderate hypertension, 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: 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 by approximately 25% and C_{max} by approximately 20% of both aprepitant and paroxetine.

TOXICOLOGY

Animal Toxicology

Acute Toxicity

The approximate oral LD_{50} of aprepitant was >2000 mg/kg in female mice and rats. The approximate intraperitoneal LD_{50} of aprepitant was >800 mg/kg, but <2000 mg/kg in female rats and >2000 mg/kg in female mice.

The approximate LD_{50} 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 ≥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 characterized 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 ≥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.

Local Tolerance

In rabbits, fosaprepitant caused initial focal acute inflammation when administered intravenously, paravenously, and subcutaneously. Focal skeletal muscle degeneration and necrosis with associated neutrophilic inflammation were noted with intramuscular injection. At the end of the follow-up period (post-dose day 8), paravenous injection sites showed focal subacute inflammation. Intramuscular injection site changes consisted of focal skeletal muscle necrosis and mineralization bordered by subacute inflammation and focal skeletal muscle regeneration.

Carcinogenesis
Carcinogenicity studies were conducted in mice and rats for approximately 2 years with oral aprepitant. In mice, aprepitant was not carcinogenic at doses up to 500 mg/kg/day (approximately 2 times the adult human dose based on systemic exposure). Rats developed hepatocellular adenomas at a dose of 25 mg/kg twice daily (females) and 125 mg/kg twice daily (females and males), thyroid follicular cell adenomas at a dose of 125 mg/kg twice daily (females and males), and thyroid follicular cell carcinomas at a dose of 125 mg/kg twice daily (males). Systemic exposures at these doses in rats were approximately equivalent to or lower than exposures in humans at the recommended dose. Tumors of these types 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. 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/fetal 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/fetal 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/fetal survival, fetal body weight, and fetal external, visceral, and skeletal morphology. Placental transfer of aprepitant occurred in rats and rabbits at these doses.

Concentrations of aprepitant in fetal 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 drug concentration was 90% of the mean maternal plasma concentration.

REFERENCES

1. MRL Clinical Study Report: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety, Tolerability, and Efficacy of MK–0869 for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated With High-Dose Cisplatin (Protocol 052).

2. MRL Clinical Study Report: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety, Tolerability, and Efficacy of MK–0869 for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated With High-Dose Cisplatin (Protocol 054).

3. MRL Clinical Study Report, Multicenter Study: A Randomized, Double-Blind, Parallel- Group Study Conducted Under In-House Blinding Conditions to Determine the Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated With Moderately Emetogenic Chemotherapy (Protocol 071).

4. MRL Clinical Study Report, A Randomized, Double-Blind, Parallel-Group Study Conducted Under In-House Blinding Conditions to Determine the Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated With Moderately Emetogenic Chemotherapy (Protocol 130).

5. MRL Clinical Study Report, Multicenter Study: A Randomized, Double-Blind, Parallel- Group Study Conducted Under In-House Blinding Conditions to Examine the Safety, Tolerability, and Efficacy of a Single Dose of MK-0517 for the Prevention of Chemotherapy- Induced Nausea and Vomiting (CINV) Associated With Cisplatin Chemotherapy (Protocol 017L).

6. de Wit R, Herrstedt J, Rapoport B, Carides AD, Guoguang-Ma J, Elmer M et al. The oral NK(1) antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomised, placebo-controlled phase III clinical trials. Eur J Cancer 2004;40:403–10.

7. Gralla RJ, de Wit R, Herrstedt J. Carides AD, Ianus J, Guoguang-Ma J et al. Antiemetic Efficacy of the Neurokinin-1 Antagonist, Aprepitant, Plus a $5HT_3$ Antagonist and a Corticosteroid in Patients Receiving Anthracyclines or Cyclophosphamide in Addition to High-Dose Cisplatin. Cancer 2005 Aug 15;104(4):864-8.

8. Hesketh PJ, Grunberg SM, Gralla RJ, Warr DG, Roila F, de Wit R et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. J Clin Oncol 2003;21:4112–9.

9. Hesketh PJ, Grunberg, SM, Herrstedt J, de Wit R, Gralla RJ, Carides AD. Combined data from two phase III trials of the NK1 antagonist aprepitant plus a $5HT_3$ antagonist and a corticosteroid for prevention of chemotherapy-induced nausea and vomiting: effect of gender on treatment response. Support Care Cancer 2006;14:354–60.

10. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Guoguang-Ma J, Eldridge K, Hipple A et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy

improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 2003;97:3090–8.

11. Rapoport BL, Jordan K, Boice JA, Taylor A, Brown C, Hardwick JS et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double blind study. Support Care Cancer 2009 Jul 01; published on line.

12. Warr DG, Hesketh PJ, Gralla RJ, Muss HB, Herrstedt J, Eisenbert PD et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after one cycle of moderately emetogenic chemotherapy. J Clin Oncol 2005;23:2822–30.

13. Product Monograph – PrEMEND® IV (fosaprepitant for injection) 150 mg fosaprepitant/vial (as fosaprepitant dimeglumine) (Merck Canada Inc.), Date of Revision: January 22, 2014, control number: 168157.

PART III: CONSUMER INFORMATION

[Pr]FOSAPREPITANT
Fosaprepitant for Injection
(as fosaprepitant dimeglumine)

This leaflet is part III of a three-part "Product Monograph" published when FOSAPREPITANT was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FOSAPREPITANT. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this leaflet carefully before you start to take your medicine, even if you have just refilled your prescription. Some of the information in the previous leaflet may have changed.

Remember that your doctor has prescribed this medicine only for you. Never give it to anyone else.

ABOUT THIS MEDICATION

What the medication is used for:
FOSAPREPITANT, in combination with 5-HT_3 antagonists and dexamethasone is indicated for the prevention of nausea and vomiting associated with your cancer chemotherapy treatment.

What it does:
FOSAPREPITANT is a member of a class of medicines called neurokinin 1 (NK_1) receptor antagonists. Fosaprepitant when administered intravenously is rapidly converted to aprepitant. Aprepitant works by blocking neurokinin, a substance in the brain that causes nausea and vomiting.

When it should not be used:
Do not take FOSAPREPITANT if you are allergic to fosaprepitant dimeglumine, aprepitant or any of the other ingredients of FOSAPREPITANT.

Do not take FOSAPREPITANT with pimozide, terfenadine, astemizole, or cisapride. Taking FOSAPREPITANT with these medications could result in **serious or life-threatening problems.**

What the medicinal ingredient is:
Fosaprepitant dimeglumine

What the important non-medicinal ingredients are:
edetate disodium, lactose anhydrous, polysorbate 80 and sodium hydroxide and/or hydrochloric acid (for pH adjustment).

What dosage forms it comes in:
Powder for injection. Each vial contains 150 mg of fosaprepitant.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Drug interactions with:
- Medicines that are likely to be broken down mainly by the liver
- Warfarin
- Hormonal contraception (birth control medicines)

Possible serious side effects:
- Severe allergic (hypersensitivity) reactions during infusion

BEFORE you use FOSAPREPITANT talk to your doctor or pharmacist if:
- you have any past or present medical problems
- you have liver problems
- you have any allergies
- you drive a car or operate machinery
- you are pregnant or plan to become pregnant
- you are breast-feeding or plan to breast-feed

Use in children
FOSAPREPITANT should not be given to children under 18 years of age.

Use in the elderly
No dosage adjustment is necessary.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all medicines that you are taking or plan to take, even those you can get without a prescription or herbal products.

Your doctor may check that your medicines are working properly together if you are taking other medicines such as:
- anti-anxiety drugs (such as alprazolam, midazolam)
- birth control medicines (which may not work as well)
- ketoconazole (an antifungal)
- rifampin (an antibiotic)
- paroxetine (a medicine used to treat a certain type of depression)
- diltiazem (a medicine used to treat high blood pressure)
- dexamethasone, methylprednisolone (steroid medicines used for a variety of conditions)
- warfarin (a blood thinner)
- tolbutamide (a medicine used to treat diabetes)
- phenytoin (a medicine used to treat seizures)
- some chemotherapy medications such as ifosfamide

Following the infusion of FOSAPREPITANT, the early concentration of aprepitant in the blood is double that

of an aprepitant capsule (125 mg); therefore, a possible risk for increased side effects cannot be ruled out.

PROPER USE OF THIS MEDICATION

FOSAPREPITANT may be taken with or without food.

Usual dose:
FOSAPREPITANT 150 mg given on Day 1 only.

- Day of chemotherapy: FOSAPREPITANT 150 mg will be given to you intravenously approximately 30 minutes before you start your chemotherapy treatment.

Overdose:

In case of a drug overdose, contact a health care practitioner, hospital emergency department or Regional Poison Control Centre, immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Any medicine may have unintended or undesirable effects, so-called side effects.

Like all prescription drugs, FOSAPREPITANT may cause side effects. The most common side effects included diarrhea, stomach pain, upset stomach, vomiting, dizziness, hiccups, fatigue, weakness, constipation, headache, hair loss and loss of appetite.

Infusion-site reactions included pain, hardening, swelling of a vein caused by a blood clot, redness, and/or itching at the infusion site.

Other side effects may also occur rarely, which include: anxiousness, fever with increased risk of infection, dry mouth, conjunctivitis (eye discharge and itching), excessive sweating, flushing, painful burning urination, muscle cramp or pain, taste disturbance, high blood pressure, ringing in the ear (tinnitus) and low blood pressure.

Allergic reactions, which may be sudden and/or serious, and may include hives, rash, itching, redness of the face/skin, and cause difficulty in breathing or swallowing.

Ask your doctor or pharmacist for more information. Both have a more complete list of side effects. Tell your doctor or pharmacist promptly about these or any other unusual symptoms.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms/Effects		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Allergic reactions/ Angioedema (swelling of the face, eyes, lips, tongue, throat, difficulty in breathing or swallowing)		√	
Uncommon	Stevens-Johnson syndrome/toxic epidermal necrolysis (severe skin reactions, blistering)		√	
Uncommon	Urticaria (severe rash, itching, swelling of the hands and feet)		√	

This is not a complete list of side effects. For any unexpected effects while taking FOSAPREPITANT, contact your doctor or pharmacist.

HOW TO STORE IT

Vials: Sterile powder for intravenous use. Store at 2-8°C.

Keep FOSAPREPITANT and all medicines safely away from children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service at:

1-800-667-4708

This leaflet can also be found at: http://www.apotex.ca/products.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last revised: January 8, 2015