PRODUCT INFORMATION

EMEND IV

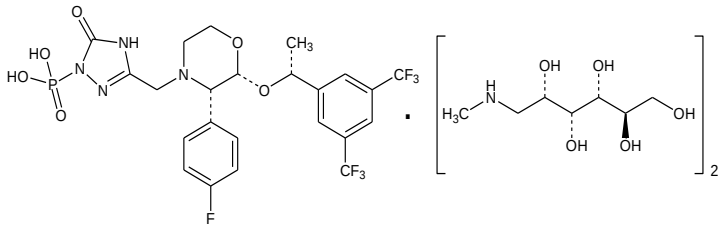
NAME OF THE MEDICINE

fosaprepitant dimeglumine

Chemical Structure

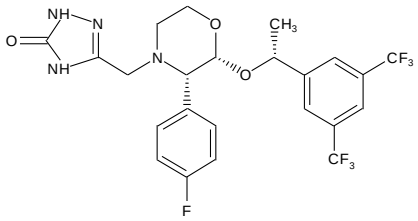
Fosaprepitant dimeglumine is a prodrug of aprepitant and is chemically described as 1-Deoxy-1-(methylamino)-D-glucitol [3-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]phosphonate (2:1) (salt).

Its empirical formula is $C_{23}H_{22}F_7N_4O_6P \cdot 2(C_7H_{17}NO_5)$ and its structural formula is:



Aprepitant is a structurally novel substance P neurokinin 1 (NK_1) receptor antagonist, chemically described as 5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one.

Its empirical formula is $C_{23}H_{21}F_7N_4O_3$, and its structural formula is:



CAS Number

The CAS No. is 265121-04-8.

DESCRIPTION

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

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

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

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

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 the targets of existing therapy for chemotherapy-induced nausea and vomiting (CINV).

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

Aprepitant after Fosaprepitant Administration

Following a single intravenous 150-mg dose of fosaprepitant administered as a 20-minute infusion to healthy volunteers the mean $AUC_{0-\infty}$ of aprepitant was 35.0 mcg•hr/mL and the mean maximal aprepitant concentration was 4.01 mcg/mL.

Distribution

Fosaprepitant is rapidly converted to aprepitant.

Aprepitant is greater than 95% bound to plasma proteins. The geometric mean apparent volume of distribution at steady state (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 PHARMACOLOGY, *Mechanism of Action*).

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 metabolised primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19, and no metabolism by CYP2D6, CYP2C9, or CYP2E1.

All metabolites observed in urine, faeces and plasma following an intravenous 100-mg [^{14}C]-fosaprepitant dose were also observed following an oral dose of [^{14}C]-aprepitant. Upon conversion of 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 faeces.

Aprepitant is eliminated primarily by metabolism. No aprepitant is excreted unchanged in the urine. 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 faeces.

The mean apparent terminal half-life of aprepitant following fosaprepitant administration was approximately 14 hours.

Special Populations

Gender

Following oral administration of a single 125-mg dose of aprepitant, the C_{max} for aprepitant is 16% higher in females as compared with males. The half-life of aprepitant is 25% lower in females as compared with males and its T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on gender.

Elderly

Following oral administration of a single 125-mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 through 5, the $AUC_{0\text{-}24hr}$ 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 is necessary in elderly patients.

Race

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

Renal Insufficiency

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

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 haemodialysis, 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. Haemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

No dosage adjustment for EMEND IV is necessary for patients with severe renal insufficiency or for patients with ESRD undergoing haemodialysis, based on the pharmacokinetics of aprepitant in these patients, although no clinical studies have been conducted to determine whether efficacy is affected.

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).

Paediatric Patients

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

Pharmacodynamics

Cardiac Electrophysiology

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

Brain NK1 Receptor Occupancy Assessed by Positron Emission Tomography

A positron emission tomography study in healthy young men administered a single intravenous dose of 150 mg fosaprepitant (N=8) demonstrated brain NK_1 receptor occupancy of ≥100% at $T_{max,}$ and 24 hours, ≥97% at 48 hours, and between 41% and 75% at 120 hours, following dosing. Occupancy of brain NK_1 receptors, in this study, correlate well with aprepitant plasma concentrations.

CLINICAL STUDIES

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

3-Day Regimen of EMEND

Oral administration of aprepitant in combination with ondansetron and dexamethasone has been shown to prevent acute and delayed nausea and vomiting associated with highly and moderately emetogenic chemotherapy (HEC and MEC) in well-controlled clinical studies.

Highly Emetogenic Chemotherapy (HEC)

In 2 multicentre, randomised, parallel, double-blind, controlled clinical studies, the aprepitant regimen was compared with standard therapy in 1094 patients receiving a chemotherapy regimen that included cisplatin ≥70 mg/m^2. Some patients also received additional chemotherapeutic agents such as gemcitabine, etoposide, fluorouracil, vinorelbine tartrate, doxorubicin, cyclophosphamide, paclitaxel, or docetaxel. The aprepitant regimen consisted of oral 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. Standard therapy 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. Although a 32mg IV dose of ondansetron was used in clinical trials, this may no longer be the currently recommended dose. See the package insert for ondansetron for appropriate dosing information.

The antiemetic activity of oral 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 composite measures:

- complete response (defined as no emetic episodes and no use of rescue therapy)
- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score <25 mm)
- impact of nausea and vomiting on daily life (Functional Living Index-Emesis [FLIE] total score >108).

Efficacy was also based on the following individual efficacy measures:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy)

- no significant nausea (maximum VAS <25 mm).

The results were evaluated for each individual study and for the 2 studies combined.

A summary of the key study results from each individual study analysis is shown in Table 1 and in Table 2.

Table 1 Percent of Patients 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 (SECONDARY AND EXPLORATORY) 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	0.005
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	>0.050
Delayed phase	51	48	>0.050
No Significant Nausea			
Overall	73	66	>0.050
Delayed phase	75	69	>0.050

†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.
Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.
Table 1 includes nominal p-values not adjusted for multiplicity.

Table 2 Percent of Patients Responding by Treatment Group and Phase for Study 2 – Cycle 1

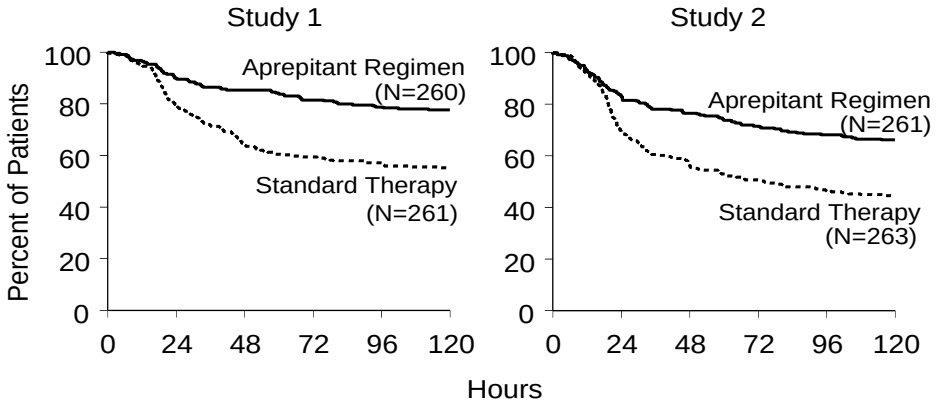
ENDPOINTS	Aprepitant Regimen (N=261)† %	Standard Therapy (N=263)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	63	43	<0.001
OTHER PRESPECIFIED (SECONDARY AND EXPLORATORY) ENDPOINTS			
Complete Response			
Acute phase§	83	68	<0.001
Delayed phase‖	68	47	<0.001
Complete Protection			
Overall	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	0.021
Delayed phase	53	40	0.004
No Significant Nausea			
Overall	71	64	>0.050
Delayed phase	73	65	>0.050

†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.
Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.
Table 2 includes nominal p-values not adjusted for multiplicity.

In both studies, a statistically significant, 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 favour of the aprepitant regimen was also observed when the acute phase and the delayed phase were analysed 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 Who Remain Emesis Free Over Time – Cycle 1

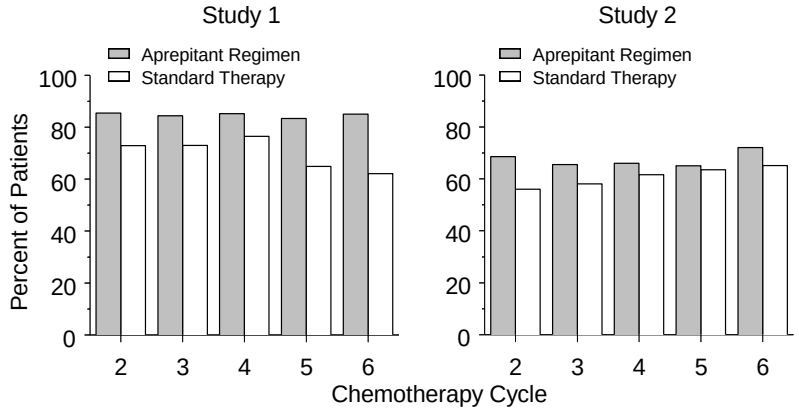


p-Value <0.001 based on a log rank test for Study 1 and Study 2; nominal p-values not adjusted for multiplicity.

Patient Reported Outcomes: The impact of nausea and vomiting on patients' daily lives was assessed in Cycle 1 of both Phase II 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 (Study1: 74% versus 64%; Study 2: 75% versus 64%).

Multiple-Cycle Extension: In the same 2 clinical studies, patients continued into the Multiple-Cycle extension for up to 5 additional cycles of chemotherapy. The proportion of patients with no emesis and no significant nausea by treatment group at each cycle is depicted in Figure 2. Antiemetic effectiveness for patients receiving the aprepitant regimen is maintained throughout the repeat cycles for those patients continuing in each of the multiple cycles.

Figure 2: Proportion of Patients with No Emesis and No Significant Nausea by Treatment Group and Cycle



	Study 1					Study 2				
Aprepitant (N)	158	122	81	54	40	191	148	103	63	43
Standard (N)	177	111	68	37	**29**	216	167	112	74	**43**

Moderately Emetogenic Chemotherapy (MEC)

In a multicentre, randomised, double-blind, parallel-group, clinical study, the aprepitant regimen was compared with standard therapy in 866 breast cancer patients 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. The aprepitant regimen consisted of oral aprepitant (EMEND) 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. Refer to the table below:

Treatment Regimen	Day 1	Days 2 and 3
Aprepitant	Aprepitant 125mg Ondansetron 16mg (2x8mg) Dexamethasone12mg	Aprepitant 80mg Ondansetron placebo (every 12 hours)
Standard	Aprepitant placebo Ondansetron 16 mg (2x8mg) Dexamethasone 20mg	Aprepitant placebo daily Ondansetron 8mg daily (every 12 hours)

The antiemetic activity of oral aprepitant (EMEND) 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. Efficacy was based on evaluation of the following composite measures:

- complete response (defined as no emetic episodes and no use of rescue therapy)
- impact of nausea and vomiting on daily life (Functional Living Index-Emesis [FLIE] total score >108).

Efficacy was also based on the following individual efficacy measures:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no rescue therapy.

A summary of the key study results is shown in Table 3.

Table 3: Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group and Phase — Cycle 1

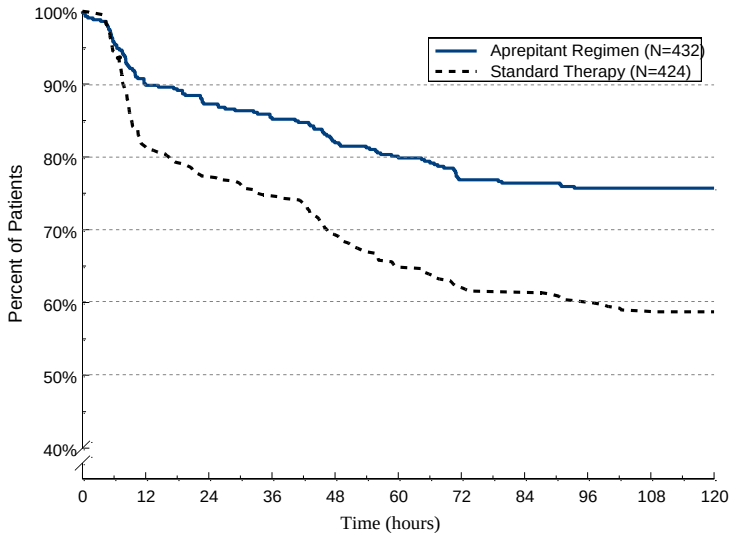
COMPOSITE MEASURES	Aprepitant Regimen* (N = 433)† %	Standard Therapy** (N = 424)† %	p-Value
Complete Response (no emesis and no rescue therapy)			
Overall‡	51	42	0.015
Acute phase§	76	69	0.034
Delayed phase‖	55	49	0.064
No Impact on Daily Life (Functional Living Index-Emesis [FLIE] total score >108)			
Overall	64	56	0.019
INDIVIDUAL MEASURES			
No Emesis			
Overall	76	59	<0.001
Acute phase	88	77	<0.001
Delayed phase	81	69	<0.001
No Rescue Therapy			
Overall	59	56	0.480
Acute phase	83	80	0.366
Delayed phase	63	60	0.407
No Significant Nausea			
Overall	61	56	0.116
Acute phase	80	78	0.699
Delayed phase	65	62	0.219

*Aprepitant Regimen: oral aprepitant 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.
**Standard Therapy: Placebo plus 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.
†N: Number of patients included in the primary analysis of complete response.
‡Overall: 0 to 120 hours post-chemotherapy treatment.
§Acute phase: 0 to 24 hours post-chemotherapy treatment.
‖Delayed phase: 25 to 120 hours post-chemotherapy treatment.

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 unadjusted absolute difference in complete response (8.3%) represents a 20% relative improvement (relative risk ratio = 1.2, aprepitant regimen over standard therapy).

In this study, the estimated time to first emesis after initiation of chemotherapy treatment was significantly (p<0.001) longer with the aprepitant regimen, and the incidence of first emesis was reduced in the aprepitant regimen group compared with the standard therapy group as depicted in Figure 3.

Figure 3: Percent of Patients Receiving Moderately Emetogenic Chemotherapy Who Remain Emesis Free Over Time—Cycle 1

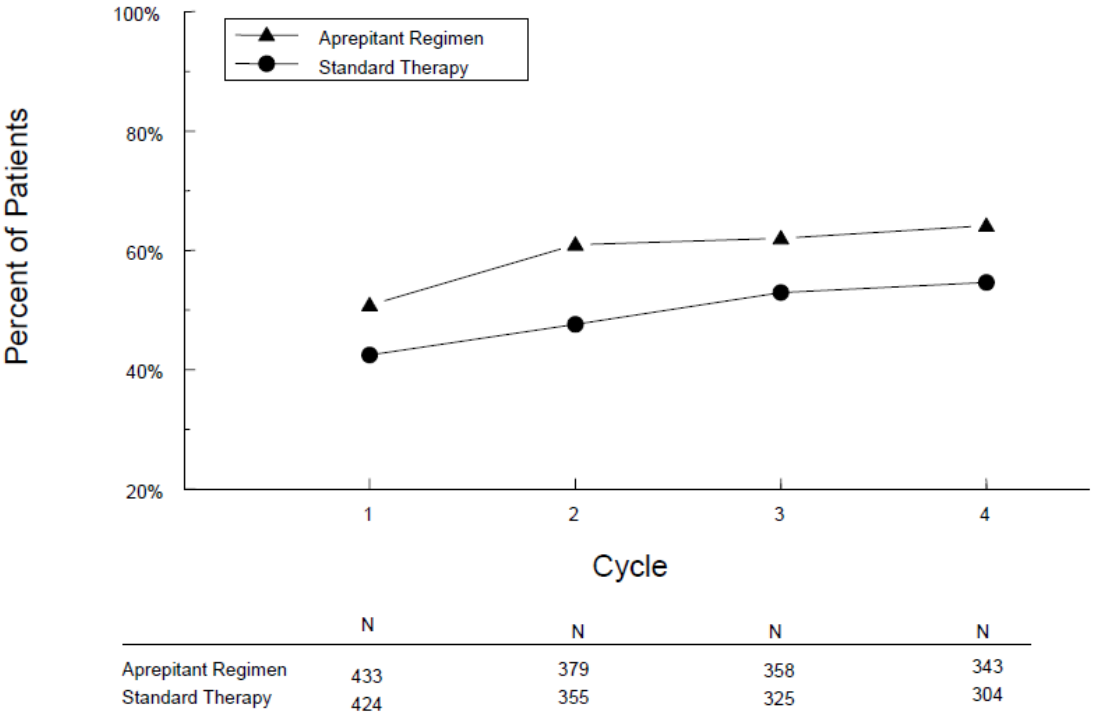


Aprepitant Regimen: oral aprepitant 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.
Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

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.

Multiple-Cycle Extension: A total of 744 patients receiving MEC continued into the Multiple-Cycle extension for up to 4 cycles of chemotherapy. The efficacy of the aprepitant regimen was maintained during all cycles. The response rates are depicted in Figure 4.

Figure 4: Percent of Patients Receiving Moderately Emetogenic Chemotherapy With No Emesis and No Rescue Therapy by Treatment Group and Cycle



	N	N	N	N
Aprepitant Regimen	433	379	358	343
Standard Therapy	424	355	325	304

Aprepitant Regimen: oral aprepitant 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.
Standard Therapy: Placebo plus 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.

In a second multicentre, randomised, double-blind, parallel-group, clinical study, the aprepitant regimen was compared with standard therapy in 848 patients receiving a chemotherapy 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 randomised 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. The aprepitant regimen consisted of EMEND 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 EMEND 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 pre-specified 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 4.

Table 4: 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 phaseÞ	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	0.0427ß
Acute phase			0.0179ß
Maleà	97	100	
Femaleà	95	88	
Delayed phase	84	79	0.0922ß
No Vomiting and No Significant Nausea (VAS <25 mm)			
Overall	65	53	0.0011

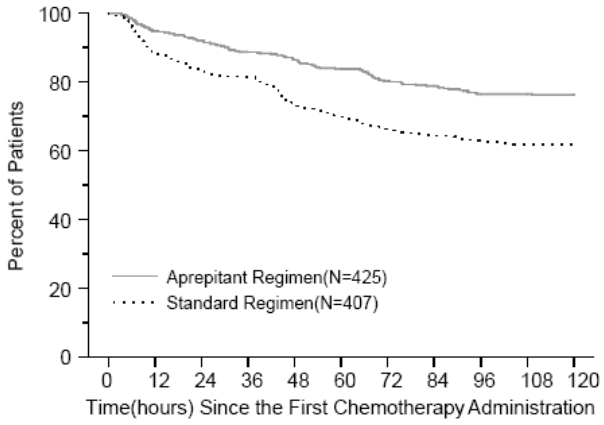
*Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.
**Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.
†N = Number of patients who received chemotherapy treatment, study drug, and had at least one

post-treatment efficacy evaluation.
‡Hochberg's procedure was used as a multiplicity adjustment when testing secondary endpoints for significance.
§Overall: 0 to 120 hours post chemotherapy treatment.
¶Complete Response = No Vomiting with no rescue therapy
Acute phase: 0 to 24 hours following initiation of chemotherapy infusion.
Þ Delayed phase: 25 to 120 hours following initiation of chemotherapy infusion.
ßNot statistically significant.
àData are shown separately for males and females per prespecified analytic plan
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, or tumor type (breast, gastrointestinal, lung or other) as assessed by the No Vomiting and Complete Response endpoints.

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 5.

Figure 5: 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.

1-Day Regimen of EMEND IV

In a randomised, parallel, double-blind, active-controlled 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 32mg IV dose of ondansetron was used in clinical trials, this may no longer be the currently recommended dose. See the package insert for ondansetron for appropriate dosing information.

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. EMEND IV 150 mg was shown to be non-inferior to that of the 3-day regimen of aprepitant. A summary of the primary and secondary endpoints is shown in Table 5.

Table 5 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.

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

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

INDICATIONS

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

- highly emetogenic cancer chemotherapy (see DOSAGE AND ADMINISTRATION)
- moderately emetogenic cancer chemotherapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

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

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

PRECAUTIONS

Since fosaprepitant is rapidly converted to aprepitant, which is a dose dependent inhibitor of CYP3A4, fosaprepitant should be used with caution in patients receiving concomitant orally administered medicinal products that are primarily metabolized through CYP3A4; some chemotherapy agents are metabolized by CYP3A4 (see INTERACTIONS WITH OTHER MEDICINES). Weak inhibition of CYP3A4 by fosaprepitant 150 mg could result in elevated plasma concentrations of these concomitant medicinal products (see INTERACTIONS WITH OTHER MEDICINES).

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

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

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

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

Carcinogenicity

Carcinogenicity studies were not conducted with fosaprepitant but studies were conducted with aprepitant in mice and rats for approximately 2 years. 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 (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. Tumours of these types are considered to be a 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. Consideration of the mechanisms involved in the development of these tumour types suggest that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of fosaprepitant or aprepitant.

Genotoxicity

Fosaprepitant and aprepitant were both negative in the following genotoxicity assays: *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.

Effects on Fertility

Fosaprepitant, when administered intravenously, is rapidly converted to aprepitant, particularly in rats. The effect of fosaprepitant on fertility has not been established at exposures expected with clinical use of the drug. 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 male or female rats at oral doses up to 1,000 mg/kg twice daily (approximately 1.5 times the adult human dose based on systemic exposure following oral aprepitant 125 mg in females, or lower than the adult human dose in males) had no effects on mating performance, fertility, or embryonic/foetal survival. Sperm count and motility were unaffected in males.

Use in Pregnancy (Category B2)

Fosaprepitant, when administered intravenously, is rapidly converted to aprepitant, particularly in the species used in the reproductive toxicity studies and the potential teratogenicity of fosaprepitant at exposures equivalent to those expected with clinical use has not been established. In the teratology studies conducted with fosaprepitant and aprepitant, the highest systemic exposures to aprepitant were obtained following oral administration of aprepitant.

Reproductive studies with oral aprepitant have been performed in rats and rabbits at doses up to 1.5 times the systemic exposure at the adult human dose following oral aprepitant 125 mg and have revealed no evidence of harm to the foetus. Given that there are no adequate and well-controlled studies in pregnant women and that the potential teratogenicity of fosaprepitant at exposures equivalent to those expected with clinical use has not been established, this drug should not be used during

pregnancy unless the clinical benefit to the mother outweighs any potential harm to the foetus.

Use in Lactation

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

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

INTERACTIONS WITH OTHER MEDICINES

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

Aprepitant is a substrate and an inhibitor of CYP3A4. During treatment for CINV, the 3-day 125 mg/80 mg regimen of aprepitant is a moderate inhibitor of CYP3A4. After the end of treatment with the 3-day CINV regimen, aprepitant causes transient moderate induction of CYP2C9 and a transient mild induction of CYP3A4 and glucuronidation.

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

Effect of fosaprepitant/aprepitant on the pharmacokinetics of other agents

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

Fosaprepitant should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions (see CONTRAINDICATIONS). Caution should be exercised in using aprepitant concurrently with drugs which have a narrow therapeutic index and are known to be metabolised primarily by CYP3A4, such as cyclosporine, sirolimus and tacrolimus.

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

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

5-HT_3 antagonists:

In clinical drug interaction studies, aprepitant when given as a regimen of 125 mg on Day 1 and 80 mg on Days 2 and 3, did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Corticosteroids:

Dexamethasone: Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the $AUC_{0\text{-}24hr}$ of dexamethasone, a CYP3A4 substrate, by approximately 2.0-fold on Days 1 and 2 when dexamethasone was coadministered as a single 8 mg oral dose on Days 1, 2, and 3. The oral dexamethasone dose on Days 1 and 2 should be reduced 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 (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.

Chemotherapeutic agents:

Chemotherapy agents that are known to be metabolised by the CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. In clinical studies, oral aprepitant (125 mg/80 mg regimen) was administered commonly with etoposide, vinorelbine, and paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions. Adequate data are not available on interactions between aprepitant and other chemotherapy agents primarily metabolised by CYP3A4.Particular caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolised primarily by CYP3A4. Post-marketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosfamide coadministration (see PRECAUTIONS).

Docetaxel: In an interaction study, oral aprepitant (125 mg/80 mg regimen) did not influence the pharmacokinetics of docetaxel.

Vinorelbine: In a separate pharmacokinetic study, oral aprepitant (125 mg/80 mg regimen) did not influence the pharmacokinetics of vinorelbine.

Formal interaction studies have not been conducted with other chemotherapy agents.

Warfarin:

A single 125-mg dose of oral aprepitant was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were 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.

Tolbutamide:

Oral aprepitant, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide (a CYP2C9 substrate) by 23% on Day 4, 28% on Day 8, and 15% on Day 15, when a single dose of tolbutamide 500 mg was administered orally prior to the administration of the 3-day regimen of oral aprepitant and on Days 4, 8, and 15.

Oral contraceptives:

Aprepitant, when given once daily for 14 days as a 100-mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol by 43%, and decreased the AUC of norethindrone by 8%.

In another study, a single dose of an oral contraceptive containing ethinyl estradiol and norethindrone was administered on Days 1 through 21 with oral aprepitant, given as a regimen of 125 mg on Day 8 and 80 mg/day on Days 9 and 10 with ondansetron 32 mg IV on Day 8 and oral dexamethasone given as 12 mg on Day 8 and 8 mg/day on Days 9, 10, and 11. In the study, the AUC of ethinyl estradiol decreased by 19% on Day 10 and there was as much as a 64% decrease in ethinyl estradiol trough concentrations during Days 9 through 21. While there was no effect of oral aprepitant on the AUC of norethindrone on Day 10, there was as much as a 60% decrease in norethindrone trough concentrations during Days 9 through 21.

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

Midazolam:

Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the $AUC_{0-\infty}$ 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.

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) should be approached cautiously; but concomitant administration of aprepitant with moderate CYP3A4 inhibitors (e.g., diltiazem) does not result in clinically meaningful changes in plasma concentrations of aprepitant.

Aprepitant is a substrate for CYP3A4; therefore, coadministration of fosaprepitant with drugs that strongly induce CYP3A4 activity (e.g., rifampin) may result in reduced plasma concentrations and decreased efficacy. Concomitant administration of fosaprepitant with St. John's Wort is not recommended.

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.

Rifampicin:

When a single 375-mg dose of oral aprepitant was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampicin, 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.

Additional interactions

Diltiazem: In patients with mild to moderate hypertension, infusion of 100 mg fosaprepitant over 15 minutes with diltiazem 120-mg 3 times daily, resulted in a 1.5-fold increase of aprepitant AUC and a 1.4 fold increase in diltiazem AUC. The pharmacokinetic effects resulted in a small but clinically meaningful decrease in diastolic blood pressure (decrease of 16.8 mm Hg with fosaprepitant versus 10.5 mm Hg without fosaprepitant) and may result in a small but clinically meaningful decrease in systolic blood pressure (decrease of 24.4 mm Hg with fosaprepitant versus 18.8 mm Hg without fosaprepitant), but did not result in a clinically meaningful change in heart rate, or PR interval, beyond those changes induced by diltiazem alone.

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

Paroxetine: 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.

ADVERSE EFFECTS

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

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

PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)

Oral Aprepitant

In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy (HEC), 544 patients were treated with 3-day oral aprepitant regimen during Cycle 1 of chemotherapy and 413 of these patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. In 2 well-controlled clinical trials in patients receiving moderately emetogenic cancer chemotherapy (MEC), 868 patients were treated with the 3-day oral aprepitant during Cycle 1 of chemotherapy and 686 of these patients continued into the extensions for up to 4 cycles of chemotherapy. The 3-day oral aprepitant regimen 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.

Highly Emetogenic Chemotherapy (HEC)

In Cycle 1 in patients receiving HEC, drug-related clinical adverse experiences were reported in approximately 19% of patients treated with the 3-day oral aprepitant regimen compared with approximately 14% of patients treated with standard therapy. Treatment was discontinued due to drug-related clinical adverse experiences in 0.6% of patients treated with the 3-day oral aprepitant regimen compared with 0.4% of patients treated with standard therapy. Table 6 shows the drug-related adverse experiences reported at an incidence ≥0.5% (and at a greater incidence than standard therapy) in patients treated with the 3-day oral aprepitant regimen.

Table 6: Drug-Related Adverse Experiences (Incidence ≥0.5% and Greater Than Standard Therapy) Occurring in Patients Receiving Highly Emetogenic Chemotherapy Who Were Treated With the 3-Day Oral Aprepitant Regimen for CINV in Clinical Studies

	Aprepitant Regimen* (N = 544)	**Standard Therapy**** (N = 550)
Blood and Lymphatic System Disorders		
Anaemia	0.6	0.0
Metabolism and Nutrition Disorders		
Decreased appetite	2.0	0.5
Nervous System Disorders		
Dizziness	0.9	0.7
Headache	2.0	1.8
Respiratory, Thoracic and Mediastinal Disorders		
Hiccups	4.6	2.9
Gastrointestinal Disorders		
Abdominal Pain	0.9	0.5
Constipation	2.4	2.0
Diarrhoea	1.1	0.9
Dyspepsia	2.6	2.0
Gastroesophageal reflux disease	0.7	0.2
Nausea†	0.7	0.0
General Disorders and Administrative Site Conditions		
Asthenia	1.5	0.2
Investigations		
ALT increased	2.8	1.1
AST increased	1.1	0.7
Blood alkaline Phosphatase increased	0.7	0.2

*Aprepitant Regimen: oral aprepitant 125 mg orally on Day 1 and 80 mg orally once daily on Days 2 and 3 plus Ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg orally on Day 1 and 8 mg orally once daily on Days 2 to 4.

**Standard Therapy: Placebo plus Ondansetron 32 mg IV on Day 1 and dexamethasone 20 mg orally on Day 1 and 8 mg orally twice daily on Days 2 to 4.

†These adverse experiences of nausea occurred 2 or 3 days after the last dose of study drug (Study Day 6 or greater; i.e., after the period in which efficacy was assessed).

In an additional active-controlled clinical study in 1169 patients receiving the 3-day oral aprepitant regimen and HEC, the adverse experience profile was generally similar to that seen in the other HEC studies with the 3-day oral aprepitant regimen.

Moderately Emetogenic Chemotherapy (MEC)

In the combined analysis of Cycle 1 data in patients receiving MEC, drug-related adverse experiences were reported in approximately 14% of patients treated with the 3-day oral aprepitant regimen compared with approximately 15% of patients treated with standard therapy. Treatment was discontinued due to drug-related adverse experiences in 0.7% of patients treated with the 3-day oral aprepitant regimen compared with 0.2% of patients treated with standard therapy. Table 7 shows the drug-related adverse experiences reported at an incidence ≥0.5% and at a greater incidence than standard therapy in patients treated with the 3-day oral aprepitant regimen.

Table 7: Drug-Related Adverse Experiences (Incidence ≥0.5% and Greater Than Standard Therapy) Occurring in Patients Receiving Moderately Emetogenic Chemotherapy Who Were Treated With the 3-Day Oral Aprepitant Regimen for CINV in Clinical Studies

	Aprepitant Regimen* (N = 868)	Standard Therapy** (N = 846)
Psychiatric Disorders		
Anxiety	0.5	0.0
Nervous System Disorders		
Dizziness	0.7	0.6
Somnolence	0.6	0.2
Respiratory, Thoracic and Mediastinal Disorders		
Hiccups	0.5	0.2
Gastrointestinal Disorders		
Dyspepsia	0.8	0.4
Eructation	1.0	0.1
General Disorders and Administration Site Conditions		
Fatigue	1.4	0.9

*Aprepitant Regimen: oral aprepitant 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.
**Standard Therapy: Placebo plus 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.

Highly and Moderately Emetogenic Chemotherapy

In a pooled analysis of the HEC and MEC studies the following drug-related adverse experiences were reported in patients treated with the 3-day aprepitant regimen at a greater incidence than standard therapy and not described above:

Infection and infestations: candidiasis, staphylococcal infection.
Blood and lymphatic system disorders: febrile neutropenia.
Metabolism and nutrition disorders: polydipsia
Psychiatric disorders: disorientation, euphoric mood.
Nervous system disorders: cognitive disorder, lethargy, dysgeusia.
Eye disorders: conjunctivitis.
Ear and labyrinth disorders: tinnitus.
Cardiac disorders: cardiovascular disorder, bradycardia, palpitations.
Vascular disorders: hot flush.
Respiratory, thoracic and mediastinal disorders: cough, oropharyngeal pain, postnasal drip, sneezing, throat irritation.
Gastrointestinal disorders: abdominal distension, dry mouth, faeces hard, flatulence, neutropenic colitis, duodenal ulcer perforation, stomatitis, vomiting.
Skin and subcutaneous tissue disorders: acne, hyperhidrosis, seborrhoea, photosensitivity reaction, rash pruritic, rash, skin lesion.
Musculoskeletal and connective tissue disorders: muscular weakness, muscle spasms.
Renal and urinary disorders: dysuria, pollakiuria.
General disorders and administration site conditions: chest discomfort, oedema, gait disturbance, malaise.
Investigations: blood sodium decreased, red blood cells urine positive, neutrophil count decreased, weight decreased, glucose urine present, urine output increased.

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

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

Fosaprepitant

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

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

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

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

Investigations:
Uncommon: blood pressure increased.

Skin and subcutaneous tissue disorders:
Uncommon: erythema.

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

OTHER STUDIES

Prevention of Postoperative Nausea and Vomiting (PONV)

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

Clinical adverse experiences were reported in approximately 60% of patients treated with 40 mg aprepitant compared with approximately 64% of patients treated with 4 mg ondansetron IV. Table 8 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3% of the combined studies.

Table 8 Percent of Patients Receiving General Anesthesia With Clinical Adverse Experiences (Incidence ≥3%)

	Aprepitant 40 mg (N = 564)	Ondansetron (N = 538)
Infections and Infestations		
Urinary Tract Infection	2.3	3.2
Blood and Lymphatic System Disorders		
Anaemia	3.0	4.3
Psychiatric Disorders		
Insomnia	2.1	3.3
Nervous System Disorders		
Headache	5.0	6.5
Cardiac Disorders		
Bradycardia	4.4	3.9
Vascular Disorders		
Hypertension	2.1	3.2
Hypotension	5.7	4.6
Gastrointestinal Disorders		
Constipation	8.5	7.6
Flatulence	4.1	5.8
Nausea	8.5	8.6
Vomiting	2.5	3.9
Skin and Subcutaneous Tissue Disorders		
Pruritus	7.6	8.4
General Disorders and General Administration Site Conditions		
Pyrexia	5.9	10.6

The following additional clinical adverse experiences (incidence >0.5% and greater than ondansetron), regardless of causality, were reported in patients treated with aprepitant:

Infections and infestations: postoperative infection
Metabolism and nutrition disorders: hypokalaemia, hypovolaemia.
Nervous system disorders: dizziness, hypoesthesia, syncope.
Vascular disorders: haematoma
Respiratory, thoracic and mediastinal disorders: dyspnea, hypoxia, respiratory depression.
Gastrointestinal disorders: abdominal pain, abdominal pain upper, dry mouth, dyspepsia.
Skin and subcutaneous tissue disorders: urticaria
General disorders and administrative site conditions: hypothermia, pain.
Investigations: blood pressure decreased
Injury, poisoning and procedural complications: operative haemorrhage, wound dehiscence.

Other adverse experiences (incidence ≤0.5%) reported in patients treated with aprepitant 40 mg for postoperative nausea and vomiting included:

Nervous system disorders: dysarthria, sensory disturbance.
Eye disorders: miosis, visual acuity reduced.

Respiratory, thoracic and mediastinal disorders: wheezing
Gastrointestinal disorders: bowel sounds abnormal, stomach discomfort.

In addition, two serious drug-related adverse experiences were reported in postoperative nausea and vomiting clinical studies in patients taking a higher dose of aprepitant: one case of constipation, and one case of subileus.

Laboratory Adverse Experiences with Postoperative Nausea and Vomiting

One laboratory adverse experience, haemoglobin decreased (40 mg aprepitant), was reported, regardless of causality, at an incidence ≥3% in a patient receiving general anaesthesia.

The following additional laboratory adverse experiences (incidence >0.5% and greater than ondansetron), regardless of causality, were reported in patients treated with aprepitant 40 mg: blood albumin decreased, blood bilirubin increased, blood glucose increased, blood potassium decreased, glucose urine present.

The adverse experience of ALT increased, occurred with similar incidence in patients treated with aprepitant 40 mg (1.1%) as in patients treated with ondansetron 4 mg (1.0%).

Other Studies

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

Post-Marketing Experience:

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

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

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

Immediate hypersensitivity or anaphylactic reactions have been observed during the infusion of fosaprepitant which may include the following: flushing, erythema, rash, chest tightness, wheezing, dyspnoea (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Dosage Recommendations

EMEND IV, for administration by intravenous infusion, is a lyophilised prodrug of aprepitant (EMEND) containing polysorbate 80 (PS80).

EMEND IV 150 mg

EMEND IV 150 mg is administered on Day 1 as an infusion **over 20 – 30 minutes** initiated approximately 30 minutes prior to chemotherapy. EMEND IV should be administered in conjunction with a corticosteroid and a 5-HT_3 antagonist as specified in the tables below.

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

	Day 1	Day 2	Day 3	Day 4
EMEND IV	150 mg IV	none	none	none
Dexamethasone**	12 mg orally	8 mg orally	**8 mg orally bid**	**8 mg orally bid**
Ondansetron	See the package insert for ondansetron for appropriate dosing information.	none	none	none

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

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

	Day 1
EMEND IV	150 mg IV
Dexamethasone**	12 mg orally
Ondansetron	See the package insert for ondansetron for appropriate dosing information.

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

Preparation of EMEND IV for Injection 150 mg

1. Inject 5 mL saline into the vial. Assure that saline is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and jetting saline into the vial.

2. Prepare an infusion bag filled with **145 mL** of saline.

3. Withdraw the entire volume from the vial and transfer it into an infusion bag containing 145 mL of saline to **yield a total volume of 150 mL**. Gently invert the bag 2-3 times.*

4. To avoid microbiolgical hazard, the EMEND IV solution should be used as soon as practicable after reconstitution and further dilution. If storage is unavoidable, the solution should be held at 2-8°C for not more than 24 hours.

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

permit.

6. EMEND IV 150 mg should only be administered as an infusion **over 20-30 minutes**.

Product is for single use in one patient only. Discard any residue.

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

* Please Note: there is a 5% overage in each vial to account for non-withdrawable losses and to ensure that the labelled dose of 150 mg is deliverable after reconstitution.

GENERAL INFORMATION

See INTERACTIONS WITH OTHER MEDICINES for additional information on the administration of EMEND IV with corticosteroids.

Refer to the full prescribing information for coadministered antiemetic agents.

No dosage adjustment is necessary for the elderly.

No dosage adjustment is necessary based on age, gender, or race.

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

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

OVERDOSAGE

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, EMEND IV 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 haemodialysis.

PRESENTATION AND STORAGE CONDITIONS

Presentation

EMEND IV is a white to off white solid powder.

EMEND IV 150 mg is available as a single dose vial containing 150 mg of fosaprepitant free acid, in cartons containing 1 vial.

Storage

Store refrigerated at 2-8°C (36-46°F). Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

MERCK SHARP & DOHME (AUSTRALIA) PTY LIMITED
LEVEL 1, BUILDING A, 26 TALAVERA RD
MACQUARIE PARK NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

20 August 2007

DATE OF MOST RECENT AMENDMENT

07 September 2017