Attachment 1: Product information for AusPAR Emend Aprepitant Merck, Sharp & Dohme PM-2011-00237-3-4 Final 12 November 2012. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

EMEND ®

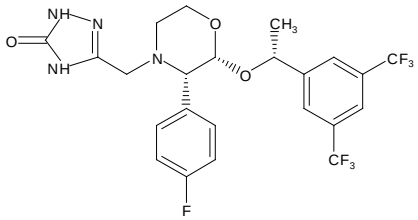
(aprepitant)

(i) NAME OF THE MEDICINE

EMEND (aprepitant) capsules

EMEND is a substance P neurokinin 1 (NK_1) receptor antagonist.

Aprepitant is 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.



Molecular formula: $C_{23}H_{21}F_7N_4O_3$
Molecular mass: 534.43
CAS number: 170729-80-3

(ii) DESCRIPTION

Aprepitant is a white to off-white crystalline solid. It is practically insoluble in water. Aprepitant is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile.

Each capsule of EMEND for oral administration contains 40 mg, 80 mg, 125 mg or 165 mg of aprepitant.

Each capsule of EMEND contains the following inactive ingredients: sucrose, microcrystalline cellulose, hydroxypropyl cellulose and sodium lauryl sulfate. The hard gelatin capsules contain the following inactive ingredients: gelatin and titanium dioxide CI 77891, and may also contain sodium lauryl sulfate and silicon dioxide. The 40-mg capsule shell also contains iron oxide yellow CI 77492, the 125-mg capsule shell also contains iron oxide red CI 77491 and iron oxide yellow CI 77492, and the 165-mg capsule shell also contains indigo carmine. The capsules are printed with ink containing iron oxide black CI 77499.

(iii) PHARMACOLOGY

Mechanism of Action

Aprepitant is a selective high affinity antagonist at human substance-P neurokinin-1 (NK_1) receptors. Aprepitant showed at least 3,000-fold selectivity for the NK_1 receptor over other

enzyme, transporter, ion-channel and receptor sites, including the dopamine and serotonin ($5HT_3$) receptors that are targets for existing chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV) therapies.

Aprepitant has been shown in animal models 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 $5HT_3$-receptor antagonist ondansetron, and the corticosteroid dexamethasone against cisplatin-induced emesis.

Pharmacokinetics

Absorption
The mean absolute oral bioavailability of aprepitant (125 or 80 mg capsules) is approximately 60% to 65% and the mean peak plasma concentration (C_{max}) of aprepitant occurred at approximately 4 hours (T_{max}).

Following oral administration of a single 125-mg dose of EMEND 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**.**

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

Oral administration of the capsule with a standard breakfast had no clinically meaningful effect on the bioavailability of aprepitant.

Following oral administration of a single 40-mg dose of EMEND in the fasted state, the $AUC_{0\text{-}¥}$ was 7.8 µg•hr/mL, the C_{max}, 0.7 µg/mL, the T_{max}, 3 hours, and the half-life 9 hours.

A separate clinical study in healthy young adults demonstrated that there is no clinically important effect of food on the pharmacokinetics of a single 40-mg dose of EMEND.

As shown in the table below, following oral administration of a single 165-mg dose of EMEND, in the fasted state, the $AUC_{0\text{-}\infty}$ of aprepitant was 32.5 µg·hr/mL and the mean maximal aprepitant concentration (C_{max}) was 1.67 µg/mL, as compared to aprepitant exposures in the fed state when a single 165-mg dose of EMEND was given with a standard light (low-fat) breakfast, and when given with a standard high-fat breakfast.

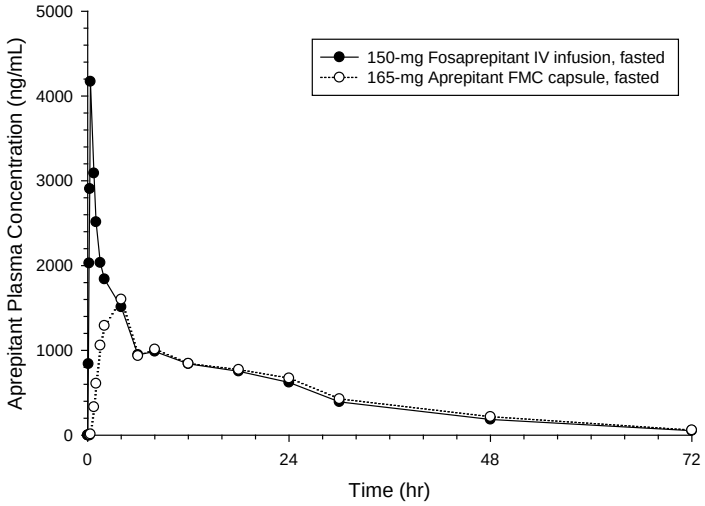
Plasma Aprepitant Pharmacokinetic Parameters	Fasted State	Fed State	
		Light (low-fat) Breakfast	High-fat Breakfast
$AUC_{0\text{-}\infty}$ (µg·hr/mL)	32.5	35.2	47.8

C_{max} (µg/mL)	1.67	1.73	2.21

Oral administration of the 165 mg dose of EMEND with a standard light (low-fat) breakfast and a high-fat breakfast resulted in up to an 8% and 47% increase in $AUC_{0-\infty}$ of aprepitant, respectively. It is recommended that EMEND 165 mg be taken fasted or with a light (low fat) meal to minimise the potential for drug interactions (see INTERACTIONS WITH OTHER MEDICINES).

The geometric mean ratio (GMR) and nominal 95% confidence interval (CI) for aprepitant $AUC_{0-\infty}$ for 165 mg oral aprepitant / 150 mg IV fosaprepitant was 0.93 (0.84, 1.02) which demonstrated that a single 165-mg dose of EMEND taken in the fasted state was $AUC_{0-¥}$-equivalent to a single 150-mg dose (1 mg/mL) of the IV prodrug, fosaprepitant, when infused over 20 minutes. Mean plasma concentrations following single doses are depicted in Figure 1.

Figure 1: Mean Plasma Concentration of Aprepitant Following 165-mg Oral Aprepitant and 150-mg IV Fosaprepitant



Distribution

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 rabbits, 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

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.

Excretion
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 faeces.

The apparent plasma clearance of aprepitant ranged from approximately 60 to 84 mL/min. The apparent terminal half-life ranged from approximately 9 to 13 hours.

Special Populations
EMEND 165 mg pharmacokinetics have not been evaluated in special populations. No clinically relevant differences in aprepitant pharmacokinetics are expected.

Gender
Following oral administration of a single 125-mg dose of EMEND, 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 for EMEND is necessary based on gender.

Elderly
Following oral administration of a single 125-mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 through 5, the AUC_{0-24hr} of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (³ 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 EMEND is necessary in elderly patients.

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

Renal Insufficiency
A single 240-mg dose of EMEND 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 $AUC_{0-¥}$ 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 $AUC_{0-¥}$ of total aprepitant decreased by 42% and C_{max} decreased by 32%. However, due to decreases in protein binding of aprepitant in ESRD patients, the AUC of pharmacologically active unbound drug was not significantly affected as 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 is necessary in patients with severe renal insufficiency or in 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
EMEND was well tolerated in patients with mild to moderate hepatic insufficiency. Following administration of a single 125-mg dose of EMEND 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 for EMEND 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
The pharmacokinetics of EMEND have not been evaluated in patients below 18 years of age.

Pharmacodynamics

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

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 NK_1 Receptor Occupancy Assessed by Positron Emission Tomography
A positron emission tomography study in healthy young men administered a single oral dose of 165 mg aprepitant or a single intravenous dose of 150 mg fosaprepitant demonstrated similar brain NK_1 receptor occupancy at $T_{max,}$ (≥ 99 %), 24 hours (≥ 99 %), 48 hours (≥ 97 %), and 120 hours (37 to 76 %) following dosing. Following administration of a single oral dose of 165 mg aprepitant or a single intravenous dose of 150 mg fosaprepitant, T_{max} was approximately 4 hours or 30 minutes post dose, respectively. Occupancy of brain NK_1 receptors by aprepitant correlate well with aprepitant plasma concentrations.

(iv) CLINICAL TRIALS

PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)

3-Day Regimen of EMEND

Oral administration of EMEND 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 ³70 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 EMEND 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.

The antiemetic activity of EMEND 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).

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

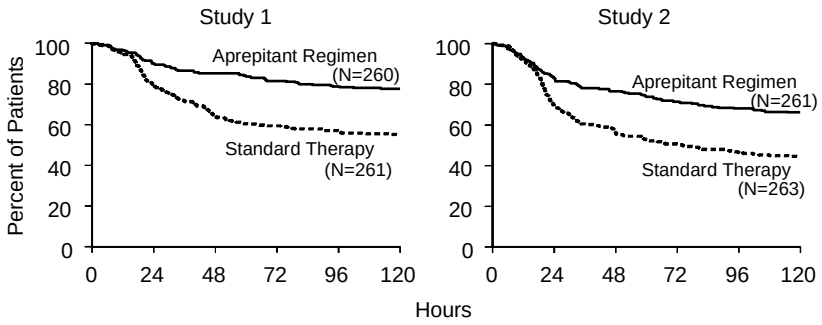
ENDPOINTS	Aprepitant Regimen (N=261)[†] %	Standard Therapy (N=263)[†] %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall[‡]	63	43	<0.001
OTHER PRESPECIFIED (SECONDARY AND EXPLORATORY) ENDPOINTS			
Complete Response			
Acute phase[§]	83	68	<0.001
Delayed phase[‖]	68	47	<0.001
Complete Protection			
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 2.

Figure 2: Percent of Patients Who Remain Emesis Free Over Time - Cycle 1

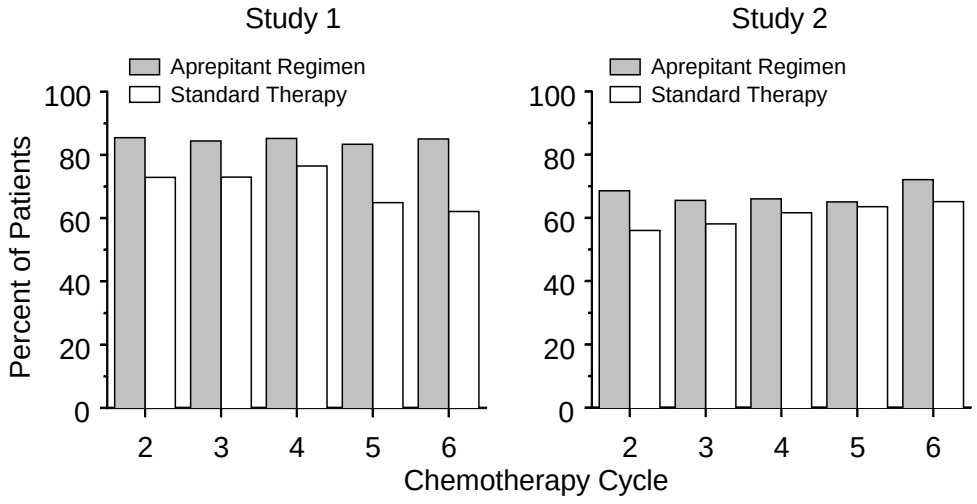


p-Value <0.001 based on a log rank test for Study 1 and Study 2; nominal p-values not adjusted for multiplicity

Patient-Reported Outcomes: The impact of nausea and vomiting on patients' daily lives was assessed in Cycle 1 of both Phase 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, 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 3. Antiemetic effectiveness for the patients receiving the aprepitant regimen is maintained throughout the repeat cycles for those patients continuing in each of the multiple cycles.

Figure 3: Proportion of Patients with No Emesis and No Significant Nausea By Treatment Group and Cycle



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 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 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			

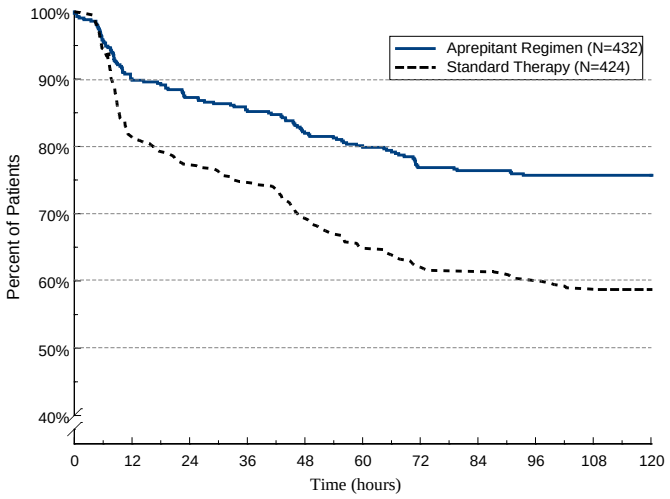
Overall	59	56	0.480
Acute phase	83	80	0.366
Delayed phase	63	60	0.407
No Significant Nausea			
Overall	61	56	0.116
Acute phase	80	78	0.699
Delayed phase	65	62	0.219

*Aprepitant Regimen: 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 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 4.

Figure 4: Percent of Patients Receiving Moderately Emetogenic Chemotherapy Who Remain Emesis Free Over Time—Cycle 1

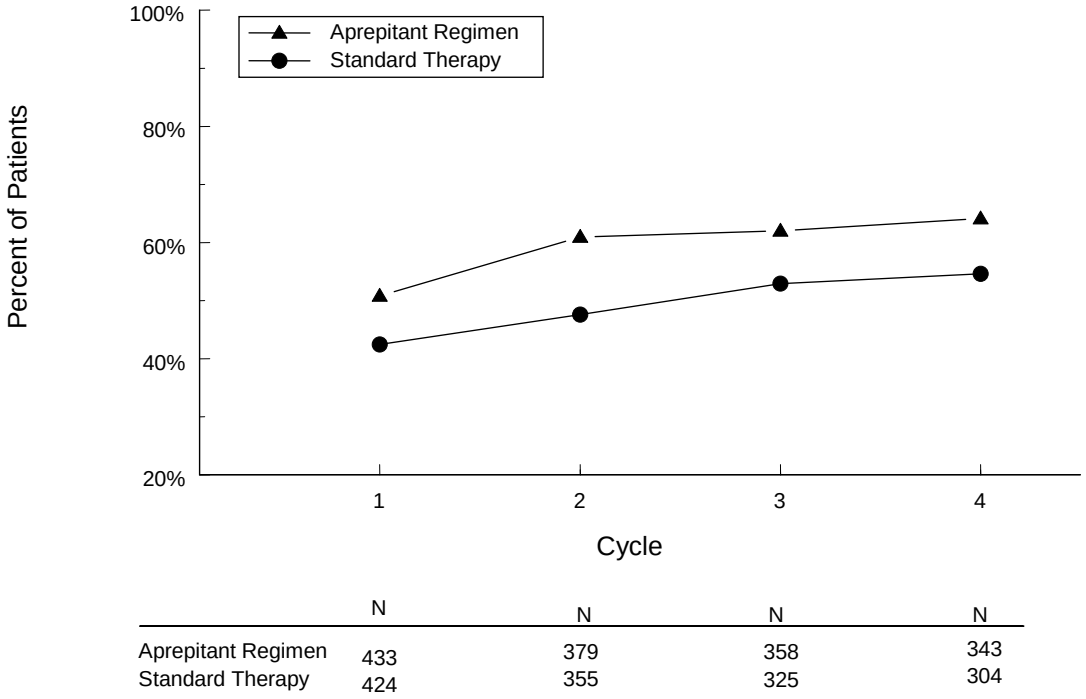


Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.
Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally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

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 5.

Figure 5: 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: 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.

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 tumour types including 52% with breast cancer, 21% with gastrointestinal cancers including colorectal cancer, 13% with lung cancer and 6% with gynaecological 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 phase[Þ]	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			0.0179[ß]
Male[à]	97	100	
Female[à]	95	88	
Delayed phase	84	79	0.0922[ß]
No Vomiting and No Significant Nausea (VAS <25 mm)			
Overall	65	53	0.0011

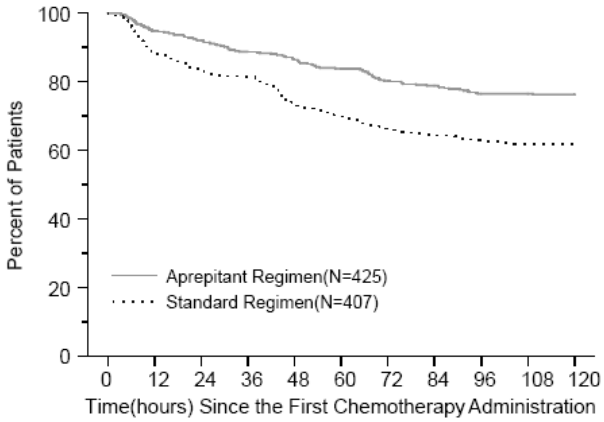
*Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.
**Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg 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.
[ß]Not statistically significant.
[à]Data 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 6.

Figure 6: 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 Fosaprepitant

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant. Based on a comparable pharmacokinetic/pharmacodynamic profile, the 1-day oral regimen of EMEND 165 mg is anticipated to have a similar efficacy profile to that of the 1-day regimen of fosaprepitant 150 mg and 3-day regimen of oral aprepitant (see PHARMACOLOGY).

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.

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.

PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING (PONV)

In two multicentre, randomised, double-blind, active comparator-controlled, parallel-group clinical studies, aprepitant was compared with ondansetron for the prevention of postoperative nausea and vomiting in 1658 adult patients undergoing open abdominal surgery. The majority of patients were women (>90%), mainly undergoing gynaecological surgery. Patients were randomised to receive 40 mg aprepitant, 125 mg aprepitant, or 4 mg ondansetron. Aprepitant was given orally with 50 mL of water 1 to 3 hours before anaesthesia. Ondansetron was given intravenously immediately before induction of anaesthesia.

The antiemetic activity of EMEND was evaluated during the 0 to 48 hour period following the end of surgery. Efficacy measures included:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy) in the 0 to 24 hours following the end of surgery (primary)
- complete response (defined as no emetic episodes and no use of rescue therapy) in the 0 to 24 hours following the end of surgery (primary)
- no emesis (defined as no emetic episodes regardless of use of rescue therapy) in the 0 to 48 hours following the end of surgery (secondary)

- no use of rescue therapy in the 0 to 24 hours following the end of surgery (exploratory)
- nausea severity (measured on a verbal rating score/VRS) in the 0 to 24 hours following the end of surgery (exploratory)
- time to first emesis in the 0 to 48 hours following the end of surgery (exploratory)

A closed testing procedure was applied to control the type I error for the primary end points.

The results demonstrate that a higher percentage of post-surgical patients will experience complete response (no emesis and no use of rescue) with aprepitant 40 mg than with ondansetron 4 mg (lower bound of C.I. is 0.0 indicating borderline significance) as described in Table 6.

Table 6
Percent of Post-Operative Patients Responding by Treatment Group
Modified-Intent-to-Treat population
Studies 090 - 091

Study 090	Aprepitant 40 mg PO (N=248)		Ondansetron 4 mg IV (N=246)		Aprepitant vs Ondansetron	
	n/m	(%)	n/m	(%)	OR	95% C.I.
Complete Response (0-24 hours) †	111/248	(44.8)	104/246	(42.3)	1.1	(0.77; 1.57)
No Vomiting (0-24 Hours)	223/248	(89.9)	181/246	(73.6)	3.2	p-val < 0.001
Study 091	Aprepitant 40 mg PO (N=293)		Ondansetron 4 mg IV (N=280)		Aprepitant vs Ondansetron	
	n/m	(%)	n/m	(%)	OR	95% C.I.
Complete Response (0-24 hours) †	187/293	(63.8)	154/280	(55.0)	1.4	(1.02; 2.01)
No Vomiting (0-24 Hours)	246/293	(84.0)	200/280	(71.4)	2.1	p-val < 0.001

† Complete Response = No vomiting and no use of rescue.

‡ Estimated odds ratio for Aprepitant 40 mg versus Ondansetron 4 mg. The lower bound of CI > 0.65 means that Aprepitant 40 mg is non-inferior to Ondansetron 4 mg. A value of >1 means that Aprepitant 40 mg is better than Ondansetron4 mg.

The model included terms for treatment and investigative sites.

n/m= Number of patients with desired response/number of patients included in analysis.

CI = Confidence Interval.

Results presented in the table were obtained by use of a logistics model with terms for treatment and investigative sites. For the No Vomiting endpoint, an additional analysis was performed for time to first event, where patients who received rescue medication were censored at the time of rescue. In study 090, results of this analysis show that the reduction in risk for a vomiting episode over the 0 to 24 hour period with aprepitant 40 mg relative to ondansetron 4 mg was 61.9% (95% C.I.: **32.1%, 78.6%).** In study 091, results of this analysis show that reduction in risk for a vomiting episode over the 0 to 24 hour period with aprepitant 40 mg relative to ondansetron 4 mg was 48.7% (95% C.I.: **23.6%, 65.5%)**.

(v) INDICATIONS

EMEND, 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.
- moderately emetogenic cancer chemotherapy

EMEND is indicated for the prevention of postoperative nausea and vomiting.

(vi) CONTRAINDICATIONS

EMEND is contraindicated in patients who are hypersensitive to any component of the product.

EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Dose-dependent 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.

(vii) PRECAUTIONS

EMEND, a dose-dependent inhibitor of CYP3A4, should be used with caution in patients receiving concomitant orally administered medicinal products that are primarily metabolised through CYP3A4; some chemotherapy agents are metabolised by CYP3A4 (see INTERACTIONS WITH OTHER MEDICINES). Moderate inhibition of CYP3A4, by aprepitant (125 mg/80 mg 3-day oral regimen or 165 mg single dose) could result in elevated plasma concentrations of these concomitant medicinal products (see INTERACTIONS WITH OTHER MEDICINES). Weak inhibition of CYP3A4 by a single 40 mg dose of aprepitant is not expected to alter the plasma concentrations of these concomitant medicinal products to a clinically significant degree. The effect of EMEND on the pharmacokinetics of orally administered CYP3A4 substrates is greater than the effect of EMEND on the pharmacokinetics of intravenously administered CYP3A4 substrates (see INTERACTIONS WITH OTHER MEDICINES).

Coadministration of EMEND with warfarin may result in a clinically significant decrease in International Normalised Ratio (INR) of prothrombin time. In patients on chronic warfarin therapy, the INR should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND (125 mg/80 mg) or administration of a single 165 mg dose of EMEND with each chemotherapy cycle or following administration of a single 40 mg dose of EMEND for the prevention of postoperative nausea and vomiting (PONV) (see INTERACTIONS WITH OTHER MEDICINES).

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

Effects on Fertility

Aprepitant administered to male or female rats at doses up to 1000 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 B1)

Reproductive studies performed in rats and rabbits at doses up to about 1.5 times the systemic exposure at the adult human dose following oral aprepitant 125 mg have revealed no evidence of

harm to the foetus due to aprepitant. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Use in Lactation

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 EMEND 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.

Paediatric Use

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

Use in the Elderly

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

Genotoxicity

Aprepitant was not genotoxic in the *in vitro* microbial and TK6 human lymphoblastoid cell mutagenesis assays, alkaline elution/rat hepatocyte DNA strand break test and chromosomal aberration assay in Chinese hamster ovary cells or in the *in vivo* mouse micronucleus assay.

Carcinogenicity

Carcinogenicity studies of approximately 2 years duration were conducted in mice and rats 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 (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 suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of aprepitant.

(viii) INTERACTIONS WITH OTHER MEDICINES

General

Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor and inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. During treatment, the single 40 mg dose of aprepitant recommended for PONV results in a weak inhibition of CYP3A4. Aprepitant has been studied at higher doses. During treatment for chemotherapy induced nausea and vomiting (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, EMEND causes a transient moderate induction of CYP2C9 and a transient mild induction of CYP3A4 and glucuronidation. The effects of induction by a single 40 mg dose of aprepitant have not been studied, but it is unlikely that a 40 mg single dose will cause any clinically relevant induction.

Effect of aprepitant on the pharmacokinetics of other agents

As a weak (40 mg) to moderate (125 mg/80 mg, 165 mg) inhibitor of CYP3A4, aprepitant can increase plasma concentrations of orally coadministered medicinal products that are metabolised through CYP3A4. Aprepitant can increase plasma concentrations of intravenously coadministered medicinal products metabolised through CYP3A4 to a lesser extent.

Caution should be exercised in using EMEND 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 metabolised through CYP2C9. Coadministration of EMEND with these drugs or other drugs that are known to be metabolised by CYP2C9, such as phenytoin, may result in lower plasma concentrations of these drugs.

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

5-HT_3 antagonists: In clinical drug interaction studies, EMEND 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: EMEND, when given as a regimen of 125 mg with dexamethasone coadministered orally as 20 mg on Day 1, and EMEND 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 usual oral dexamethasone doses should be reduced by approximately 50% when coadministered with EMEND (125 mg/80 mg regimen) to achieve exposures of dexamethasone similar to those obtained when it is given without EMEND. The daily dose of dexamethasone administered in clinical chemotherapy induced nausea and vomiting studies with EMEND reflects an approximate 50% reduction of the dose of dexamethasone (see DOSAGE AND ADMINISTRATION).

Aprepitant, when given as a single dose of 200 mg in the fed state (standard light breakfast) on Day 1 with oral dexamethasone coadministered orally as 12 mg on Day 1 and 8 mg on Days 2 through 4, increased the AUC of dexamethasone by 2.1- and 2.3-fold on Days 1 and 2, to a lesser extent (1.4-fold increase) on Day 3, and had no effect on Day 4 (1.1-fold increase). The daily dose of dexamethasone on Days 1 and 2 should be reduced by approximately 50% when coadministered with EMEND 165 mg on Day 1 to achieve exposures of dexamethasone similar to those obtained when given without EMEND 165 mg.

Methylprednisolone: EMEND, 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. The usual IV methylprednisolone dose should be reduced by approximately 25%, and the usual oral methylprednisolone dose should be reduced by approximately 50% when coadministered with EMEND (125 mg/80 mg regimen), to achieve exposures of methylprednisolone similar to those obtained when it is given without EMEND.

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, EMEND (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 EMEND and other chemotherapy agents primarily metabolised by CYP3A4, and particular caution and careful monitoring are advised in patients receiving these agents (see PRECAUTIONS).

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

Vinorelbine: In a separate pharmacokinetic study, EMEND (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 EMEND was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were stabilised on chronic warfarin therapy. Although there was no effect of EMEND 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 Normalised Ratio or INR) 5 days after completion of dosing with EMEND.

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 the 3-day regimen (125 mg/80 mg) or administration of a single 165 mg dose of EMEND with each chemotherapy cycle, or following administration of a single 40 mg dose of EMEND for the prevention of PONV.

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 EMEND, 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 EMEND 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 EMEND may be reduced. Alternative or back-up methods of contraception should be used during treatment with EMEND and for one month following the last dose of EMEND.

Tolbutamide: EMEND, when given as 125mg on Day 1 and 80mg/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 500mg was administered orally prior to the administration of the 3-day regimen of EMEND and on Days 4, 8 and 15.

Midazolam: EMEND 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 EMEND 125 mg on Day 1 and 80 mg/day on Days 2 through 5. A single dose of aprepitant 200 mg in the fed state (standard light breakfast) coadministered orally with 2 mg midazolam increased the AUC of midazolam by 3.2-fold on Day 1. No clinically important effect resulted on Day 4 (midazolam AUC 1.2-fold increase) and a slight change in midazolam AUC was observed on Day 8 (35% decrease). The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these agents with EMEND (125 mg/80 mg or 165 mg).

In another study with intravenous administration of midazolam, EMEND 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 EMEND and on Days 4, 8, and 15. EMEND 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 EMEND 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 EMEND. Intravenous midazolam 2 mg was given 1 hour after oral administration of a single dose of EMEND 125 mg. The plasma AUC of midazolam was increased by 1.5-fold. This effect was not considered clinically important.

Effect of other agents on the pharmacokinetics of aprepitant

Aprepitant is a substrate for CYP3A4; therefore, coadministration of EMEND with drugs that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of EMEND with strong CYP3A4 inhibitors (e.g., ketoconazole) should be approached cautiously; but concomitant administration of EMEND 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 EMEND with drugs that strongly induce CYP3A4 activity (e.g. rifampicin) may result in reduced plasma concentrations of aprepitant that may result in decreased efficacy of EMEND.

Concomitant administration of EMEND with St. John's wort is not recommended.

Ketoconazole: When a single 125-mg dose of EMEND 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 EMEND with strong CYP3A4 inhibitors should be approached cautiously.

Rifampicin: When a single 375-mg dose of EMEND 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 EMEND with drugs that induce CYP3A4 activity may result in reduced plasma concentrations and decreased efficacy of EMEND.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Additional interactions

Diltiazem: 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.

(ix) ADVERSE EFFECTS

The overall safety of aprepitant was evaluated in approximately 6500 individuals.

PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)

In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy (HEC), 544 patients were treated with the 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, 868 patients were treated with the 3-day oral aprepitant regimen during Cycle 1 of chemotherapy and 686 of these patients continued into the Multiple-Cycle extensions for up to 4 cycles of chemotherapy. The 3-day oral EMEND 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 7 shows the drug-related adverse experiences reported at an incidence ³ 0.5% (and at a greater incidence than standard therapy) in patients treated with the 3-day oral aprepitant regimen.

Attachment 1: Product information for AusPAR Emend Aprepitant Merck, Sharp & Dohme PM-2011-00237-3-4 Final 12 November 2012. This Product Information was approved at the time this AusPAR was published.

Table 7

Drug-Related Adverse Experiences (Incidence ³ 0.5% and Greater Than Standard Therapy) Occurring in Patients Receiving HEC 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: EMEND 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 8

shows the drug-related adverse experiences reported at an incidence ³ 0.5% and at a greater incidence than standard therapy in patients treated with the 3-day oral aprepitant regimen.

Table 8

Drug-Related Adverse Experiences (Incidence ³ 0.5% and Greater Than Standard Therapy) Occurring in Patients Receiving MEC 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: 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.

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 oral aprepitant regimen at a greater incidence than standard therapy and not described above:

Blood and lymphatic system disorders: febrile neutropenia
Infection and infestations: candidiasis, staphylococcal infection.
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.

In other clinical studies, isolated cases of serious adverse experiences were reported. In another chemotherapy induced nausea and vomiting (CINV) study, Stevens-Johnson syndrome was reported as a serious adverse experience in a patient receiving aprepitant with cancer chemotherapy. Angioedema and urticaria were reported in a patient receiving aprepitant in a non-CINV study.

Oral administration of a single 165-mg dose of aprepitant was generally well tolerated in healthy adults.

Based on a comparable pharmacokinetic/pharmacodynamic profile, the 1-day oral regimen of EMEND 165 mg administered in the fasted state or with a light (low fat) meal is anticipated to have a similar safety and tolerability profile to that of the 1-day regimen of fosaprepitant 150 mg and the 3-day oral aprepitant regimen in chemotherapy patients (see PHARMACOLOGY).

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. EMEND 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 9 shows the percent of patients with clinical adverse experiences reported at an incidence ³ 3% of the combined studies.

Table 9

Percent of Patients Receiving General Anesthesia With Clinical Adverse Experiences (Incidence ³ 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, hypoaesthesia, syncope.
Vascular disorders*:* haematoma
Respiratory, thoracic and mediastinal disorders*:* dyspnoea, 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 PONV 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 PONV clinical studies in patients taking a higher dose of aprepitant: one case of constipation, and one case of subileus.

Laboratory Adverse Experiences

One laboratory adverse experience, haemoglobin decreased (40 mg aprepitant 3.8%, ondansetron 4.2%), was reported at an incidence ³ 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 of aprepitant. 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, Stevens-Johnson syndrome/toxic epidermal necrolysis
Immune system disorders: hypersensitivity reactions including anaphylactic reactions.

(x) DOSAGE AND ADMINISTRATION

PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)

EMEND is given for 1 day or 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist.

1-Day Regimen of EMEND:

The recommended dose of EMEND for the 1-day oral regimen is 165 mg orally 1 hour prior to chemotherapy treatment on Day 1 only.

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

	Day 1	Day 2	Day 3	Day 4
EMEND	165 mg orally	none	none	none
Dexamethasone**	12 mg orally	8 mg orally	**8 mg orally twice daily**	**8 mg orally twice daily**
Ondansetron†	32 mg I.V.	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.

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

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

	Day 1 Only
EMEND	165 mg orally
Dexamethasone**	12 mg orally
Ondansetron†	2 x 8 mg orally

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

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

3-Day Regimen of EMEND:

The recommended dose of EMEND for the 3-day oral regimen is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg orally once daily in the morning on Days 2 and 3.

In clinical studies, the following regimen was used for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy:

	Day 1	Day 2	Day 3	Day 4
EMEND*	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally	8 mg orally
Ondansetron†	32 mg IV	none	none	none

*EMEND was administered orally 1 hour prior to chemotherapy treatment on Day 1 and in the morning on Days 2 and 3.
**Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The dose of dexamethasone was chosen to account for drug interactions.
†Ondansetron was administered 30 minutes prior to chemotherapy treatment on Day 1. The dose of ondansetron in the clinical studies exceeds the recommended dose of ondansetron in the Australian Product Information.

In a clinical study, the following regimen was used for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy:

	Day 1	Day 2	Day 3
EMEND*	125 mg orally	80 mg orally	80 mg orally
Dexamethasone**	12 mg orally	none	none
Ondansetron†	2 x 8 mg orally	none	none

*EMEND was administered orally 1 hour prior to chemotherapy treatment on Day 1 and in the morning on Days 2 and 3.
**Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone was chosen to account for drug interactions.
†Ondansetron 8-mg capsule was administered 30 to 60 minutes prior to chemotherapy treatment and one 8-mg capsule was administered 8 hours after the first dose on Day 1.

EMEND IV 115 mg and 150 mg (fosaprepitant), a lyophilized prodrug of aprepitant for intravenous administration, are also available. EMEND IV 115 mg can be substituted for EMEND 125 mg on Day 1 only of the 3-day regimen. Capsules of EMEND 80 mg are administered on Days 2 and 3. EMEND IV 150 mg is available as a single dose and may be used as an alternative to oral EMEND 165 mg. EMEND IV 150 mg is administered on Day 1 only with no capsules of EMEND administered on Days 2 and 3.

PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING (PONV)

The recommended oral dosage of EMEND is 40 mg within 3 hours prior to induction of anaesthesia.

General Information

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

Refer to the full Product Information for coadministered antiemetic agents.

EMEND may be taken with or without food. It is recommended that EMEND 165 mg be taken with or without a light (low fat) meal, as administration with a high fat meal results in a 47% increase in systemic exposure of aprepitant (see PHARMACOKINETICS).

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).

(xi) OVERDOSAGE

No specific information is available on the treatment of overdosage with EMEND. Single doses up to 600 mg of aprepitant were generally well tolerated in healthy subjects. 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 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.

(xii) PRESENTATION AND STORAGE CONDITIONS

EMEND is available in a 165 mg, 125 mg, 80 mg and 40 mg capsule.

The EMEND 165 mg capsules are opaque with a white body and light blue cap with “466” and “165 mg” printed radially in black ink on the body with Merck logo on the side opposite the printing.

The EMEND 125 mg capsules are opaque with a white body and pink cap with “462” and “125 mg” printed radially in black ink on the body.

The EMEND 80 mg capsules are opaque with a white body and cap with “461” and “80 mg” printed radially in black ink on the body.

The EMEND 40 mg capsules are white and mustard yellow coloured, with “464” and “40 mg” printed in black on the capsule.”

EMEND capsules should be stored below 30°C in their original packaging.

EMEND comes in pack sizes containing:

1x 165 mg capsules*
6x 165 mg capsules*
1x 125mg + 2x 80 mg capsules
1x 125mg capsule *
1x 80mg capsule *
2x 80mg capsule
1x40mg capsule*

***** These pack sizes not currently available in Australia

(xiii) NAME AND ADDRESS OF THE SPONSOR

MERCK SHARP & DOHME (AUSTRALIA) PTY LIMITED
54-68 FERNDELL STREET
SOUTH GRANVILLE NSW 2142

(xiv) POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

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

This document was first approved by the Therapeutic Goods Administration on 13 April 2004.

(xvi) DATE OF MOST RECENT AMENDMENT

6 June 2012