

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 6, 2003

FROM: Brian Strongin, R.Ph., M.B.A., Project Manager, *for*
Robert L. Justice, M.D., M.S., Director
Division of Gastrointestinal and Coagulation Drug Products,
HFD-180

SUBJECT: Briefing Document for the March 6, 2003 Meeting of the
Gastrointestinal Drugs Advisory Committee

MEETING TIME: 8:30AM – 5:00PM

MEETING LOCATION: Holiday Inn, The Ballroom, 2 Montgomery Village Avenue,
Gaithersburg, MD

Please find enclosed the following items:

Attachment One: Medical Officer’s Summary Page 3

Attachment Two: Clinical Pharmacology and Biopharmaceutics Summary Page 34

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often includes initial reviews and/or preliminary conclusions and recommendations written by individual FDA reviewers. These conclusions and recommendations do not necessarily represent the final position of the individual reviewer, nor to they necessarily represent the final position of the FDA. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized.

NDA 21-549 Emend (aprepitant)
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ATTACHMENT ONE

MEDICAL OFFICER'S SUMMARY

MEMORANDUM

Date: February 5, 2003

From: Division of Gastrointestinal and Coagulation Drug Products
Gary Della’Zanna D.O. M.Sc. (Medical Officer)
Wen-Jen Chen PhD (Bio-Statistician)

To: Advisory Committee Members

Subject: Background Package for Advisory Committee Meeting on March 6, 2003

Drug Name: EMEND[®] (aprepitant)

I. Subject of Advisory Committee Meeting

Merck & Co., Inc. submitted a New Drug Application (21-549) on September 27, 2002 for aprepitant. Aprepitant (previously known as MK-0869 and L-754030) is a New Molecular Entity that is the first in a new therapeutic class: NK₁-receptor antagonist. The Applicant has requested an indication for “the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy”. Aprepitant would be the first drug to be granted an indication that included the delayed phase of chemotherapy-induced nausea and vomiting.

The FDA is requesting the Advisory Committee members to provide us views on the following:

Proposed Indication:

- Do the data support the prevention of nausea and vomiting in the delayed, acute and overall phases?
- Do the data support the prevention of nausea?
- Did subjects receive “highly emetogenic chemotherapy”?
- Do the data support the use of any 5-HT₃ antagonist as part of the aprepitant regimen?
- Do the data support the use of any steroid as part of the aprepitant regimen?
- Do the data support the Applicant’s proposed indication?

Drug-Drug Interaction:

- What concerns does the Committee have regarding drug-drug interactions with other chemotherapeutic agents?
- What concerns does the Committee have in regard to other drug-drug interactions?

II. Agency’s Comments Regarding Study Design and Analysis

The Applicant submitted two Phase III trials in support of the proposed indication of prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of high-dose cisplatin either alone or with concomitant chemotherapy. (Study 052 and Study 054). The two Phase III trials were identical in design, except Study 052 contained a protocol amendment to allow for the inclusion of four adolescent patients. The treatment regimens are listed in Table 1.

Table 1
Treatment Regimens

Treatment Regimen	Day 1	Day 2 to 4
MK-0869	MK-0869 125 mg PO Dexamethasone 12 mg PO Ondansetron 32 mg IV	MK-0869 80 mg PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning) Dexamethasone Placebo PO Daily (evening)
Standard Therapy	MK-0869 Placebo PO Dexamethasone 20 mg PO Ondansetron 32 mg IV	MK-0869 Placebo PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning) Dexamethasone 8 mg PO Daily (evening)

In adolescent patients (12 and <18 years of age and =40 kg body weight), ondansetron was administered in three intravenous doses of 0.15 mg/kg; the first dose was given 30 minutes prior to cisplatin, and the subsequent doses were given at 4 and 8 hours after first dosing.

A. Efficacy Results

Primary Endpoint: Complete Response (Overall Phase)

The Agency has verified the Applicant’s data and concurs with the results of the major analysis. The primary endpoint for both studies was complete response in the overall phase (0-120 hours post cisplatin administration). Complete response was defined as no emesis and no rescue therapy. The Applicant defined complete response for the acute (0 to 24 hours) and delayed (25 to 120 hours) phases as secondary endpoints. The primary endpoint did not evaluate nausea, however, it is part of the requested treatment indication.

Analysis of the data by the Agency demonstrated the aprepitant regimen was statistically superior to standard therapy for the primary endpoint of complete response in the overall phase as well as the secondary endpoints of complete response for the

acute and delayed phases. (Table 2) In study 052, 72.7% of the patients in the aprepitant group were responders for the primary endpoint compared to 52.3% in the standard therapy group ($p < 0.0001$). Similar results were achieved for study 054 with 62.7% of the patients in the aprepitant group were responders for the primary endpoint compared to 43.3% in the standard therapy group ($p < 0.0001$). The following table displays the efficacy results for both pivotal studies.

Table 2
Efficacy Summary

	Aprepitant Regimen n/m (%)	Standard Therapy n/m (%)
Complete Response (no emetic episodes and no rescue therapy)		
Study 052		
Overall Phase	189/260 (72.7)** (p < 0.0001)	136/260 (52.3)
Acute Phase	231/259 (89.2)** (p = 0.0009)	203/260 (78.1)
Delayed Phase	196 / 260 (75.4)** (p < 0.0001)	145/260 (55.8)
Study 054		
Overall Phase	163 / 260 (62.7)** (p < 0.0001)	114/263 (43.3)
Acute Phase	216 / 261 (82.8)** (p = 0.0001)	180/263 (68.4)
Delayed Phase	176 / 260 (67.7)** (p < 0.0001)	123/263 (46.8)
No Nausea (maximum nausea VAS < 5)		
Study 052		
Overall Phase	122 /257 (47.5) (p = 0.48)	115 / 260 (44.2)
Acute Phase	185/256 (72.3) (p = 0.48)	179/ 259 (69.1)
Delayed Phase	132/259 (51.0) (p = 0.46)	124 / 260 (47.7)
Study 054		
Overall Phase	127 / 260 (48.8)* (p = 0.021)	102 / 263 (38.8)
Acute Phase	176 / 260 (67.7) (p = 0.71)	174 / 263 (66.2)
Delayed Phase	137 / 260 (52.7)** (p = 0.003)	105 / 263 (39.9)
No Significant Nausea (maximum nausea VAS < 25)		
Study 052		
Overall Phase	188 / 257 (73.2) (p = 0.09)	171 / 259 (66.0)
Acute Phase	232 /256 (91.0) (p = 0.16)	224 / 259 (86.5)
Delayed Phase	195 / 259 (75.3) (p = 0.09)	178 /260 (68.5)
Study 054		
Overall Phase	185 / 260 (71.2) (p = 0.08)	168 / 263 (63.9)
Acute Phase	235 / 260 (90.4)* (p = 0.011)	218 / 263 (82.3)
Delayed Phase	189 / 260 (72.7) (p = 0.07)	172 / 263 (65.4)

** p < 0.01 when compared with Standard Therapy; * p < 0.05 when compared with Standard Therapy
n/m = Number of patients with desired response/number of patients included in time point.

With regard to the definitions for the acute and delayed phases, the Applicant's terminology is consistent with medical literature. This is the first time the Agency will be granting an indication for the delayed phase and would like the committee's opinion.

The Applicant pre-specified multiple secondary and exploratory endpoints (including emesis, nausea, and significant nausea) in the protocol. When analyses were performed for the nausea endpoints independently (i.e. no nausea, and no significant nausea), only in Study 054 did some of the results reach statistical significance. The significant results for the nausea endpoints failed to be replicated in Study 052. (Table 2) Furthermore, since several secondary and exploratory endpoints were analyzed, the nominally significant results can not be taken quite at face value due to multiple comparisons.

Therefore, the statistical significance of the no nausea endpoints is not persuasive when evaluated independently.

The Agency acknowledges that the results of the nausea endpoints may have been effected by the use of antiemetic “rescue” therapy. A higher proportion of patients in the standard therapy group than aprepitant group utilized rescue therapy. (27.6% vs 18.0% respectively)

The Agency seeks guidance on whether the data supports the proposed indication; specifically, regarding the delayed phase and the prevention of nausea and vomiting.

B. Highly Emetogenic Chemotherapy

The Applicant proposes the aprepitant regimen will prevent chemotherapy induced nausea and vomiting associated with highly emetogenic chemotherapy. The Applicant has studied safety and efficacy only with highly emetogenic doses of cisplatin with or without other concomitant chemotherapy. The safety and efficacy of the aprepitant regimen with other chemotherapeutic agents at highly emetogenic doses have not been evaluated.

The Phase III protocols defined a highly emetogenic dose of cisplatin as ≥ 70 mg/m². However, approximately 20% of the patients received less than the protocol dose and were included in efficacy analysis. The Applicant states all patients received a highly emetogenic dose of cisplatin (> 50 mg/m²) and submitted the Hesketh Classification in support of this dose.

The Applicant reportedly modeled the primary endpoint on the protocol used in the approval of ondansetron. However, when ondansetron was approved, the highly emetogenic cisplatin dose was 100 and 120 mg/m². The cisplatin dose range of 50-80 mg/m² is described as a moderate emetogenic dose in label. The defined dose of highly emetogenic cisplatin has varied since the approval of ondansetron. The Kytril label describes a highly emetogenic cisplatin dose as ≥ 80 mg/m² and the Anzemet label describes a highly emetogenic cisplatin dose as ≥ 70 mg/m² in one study and 80 mg/m²

in another.

The number of patients who received less than 70 mg/m² cisplatin were balanced between treatment groups and should not affect the primary endpoint analysis. However, the Agency is interested in the Committee's opinion on whether 50-70 mg/m² of cisplatin is highly emetogenic.

III. Safety

A. 5-HT₃ Antagonists:

The aprepitant regimen, as defined by the proposed label, states that a corticosteroid and a 5-HT₃ antagonists be used in the treatment. The Applicant has provided exposure data only for ondansetron and granisetron. During the phase II trials 332 patients were treated with a regimen that included the combination of aprepitant with granisetron, and 520 patients received aprepitant with ondansetron. During the Phase III trials only ondansetron was utilized in the protocol. A total of 549 patients received aprepitant in combination with intravenous ondansetron.

The NDA submission included pharmacokinetic data for intravenous ondansetron and oral granisetron. In these drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of the specific drug formulations studied. The Agency does not have drug interaction studies for the oral formulation of ondansetron or the intravenous formulation of granisetron. The Agency has no exposure safety data on the use of aprepitant with dolasetron.

Because of first pass metabolism, one cannot extrapolate PK results from intravenous studies to oral formulations. The CYP3A4 inhibitory effect of aprepitant is not as pronounced when CYP3A4 substrates are administered intravenously. For example, when the same dose of aprepitant (125 mg) was administered prior to IV methylprednisolone compared to oral dexamethasone (both CYP3A4 substrates), aprepitant increased the AUC of methylprednisolone 1.3-fold, and the AUC of dexamethasone 2.3-fold increase. Since the Applicant studied the "worse case" situation with granisetron (oral formulation), additional PK information is not needed for granisetron. However, there are no PK studies for the oral formulation of odansetron and one needs to consider that the oral formulations may be utilized as rescue therapy. This may result in higher plasma concentrations of odansetron.

Within the class of 5-HT₃ antagonists, there are differences in metabolic pathways. Both ondansetron and granisetron are predominately metabolized by CYP3A4. Dolasetron, however, is metabolized by carbonyl reductase to hydrodolasetron. CYP2D6 is primarily responsible for the subsequent hydroxylation of hydrodolasetron and both CYP3A4 and flavin monooxygenase are responsible for the N-oxidation of

hydrodolasetron. Furthermore, dolasetron is the only drug in the class to have QTc and cardiac warnings in its label.

Since there is no exposure data on the use of aprepitant with dolasetron and it has a different metabolic pathway, the Agency seeks advice as to whether the regimen proposed in the label should specify only the 5-HT₃ antagonists that have been studied. The Agency would like the committee's opinion on whether or not additional PK studies are required on the oral formulation of ondansetron.

B. Drug-Drug Interactions (General)

Aprepitant is a substrate and a moderate inhibitor of CYP3A4 and may affect the pharmacokinetics of drugs that are metabolized by CYP3A4. In addition, administration of aprepitant for 28 days has shown aprepitant is also an inducer of CYP3A4. Aprepitant was also shown to be an inducer of CYP2C9. This was characterized by a drug interaction study with S-warfarin, whose metabolism is mediated almost exclusively by CYP2C9. Consequently, aprepitant might also affect the pharmacokinetics of drugs that are CYP2C9 substrates. Please refer to Clinical Pharmacology and Biopharmaceutics section for a detailed review.

During the Phase IIb studies a drug-drug interaction was identified between aprepitant and dexamethasone that resulted in a 2-fold increase in plasma concentrations of dexamethasone. This finding resulted in the adjustment of dexamethasone in the aprepitant group in the Phase III protocols. During these Phase IIb studies the incidences of febrile neutropenia and serious infections were higher in the aprepitant groups than the standard therapy group. The Applicant attributes these adverse events to the increased exposure to dexamethasone. The adverse events reported during the Phase II trials are presented in Table 3.

Table 3

Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence ≥2% in One or More Combined Treatment Groups)
by Body System—CINV Phase II Studies (Cycle 1)

	Aprepitant Capsules						Aprepitant Tablets and/or L-758298 (N=518)	Ondansetron or Granisetron +/- Dexamethasone (N=460)		
	40 mg (N=120)		125 mg (N=241)		375 mg (N=36)					
	n	(%)	n	(%)	n	(%)				
Sinus tachycardia	2	(1.7)	1	(0.4)	1	(2.8)	11	(2.1)	9	(2.0)
Tachycardia	2	(1.7)	3	(1.2)	0	(0.0)	23	(4.4)	8	(1.7)
Digestive System	55	(45.8)	117	(48.5)	20	(55.6)	307	(59.3)	225	(48.9)
Constipation	14	(11.7)	31	(12.9)	6	(16.7)	81	(15.6)	74	(16.1)
Dental Pain	0	(0.0)	2	(0.8)	1	(2.8)	0	(0.0)	0	(0.0)
Diarrhea	13	(10.8)	25	(10.4)	4	(11.1)	148	(28.6)	63	(13.7)
Digestive gas symptoms	2	(1.7)	9	(3.7)	3	(8.3)	18	(3.5)	4	(0.9)
Dry mouth	0	(0.0)	1	(0.4)	0	(0.0)	18	(3.5)	6	(1.3)
Dysgeusia	2	(1.7)	6	(2.5)	1	(2.8)	14	(2.7)	9	(2.0)
Dyspepsia	4	(3.3)	11	(4.6)	2	(5.6)	24	(4.6)	23	(5.0)
Dysphagia	3	(2.5)	5	(2.1)	1	(2.8)	9	(1.7)	4	(0.9)
Epigastric discomfort	4	(3.3)	9	(3.7)	0	(0.0)	19	(3.7)	18	(3.9)
Gastritis	2	(1.7)	5	(2.1)	2	(5.6)	7	(1.4)	6	(1.3)
Heartburn	5	(4.2)	11	(4.6)	2	(5.6)	35	(6.8)	22	(4.8)
Nausea	14	(11.7)	34	(14.1)	7	(19.4)	59	(11.4)	58	(12.6)
Obstipation	3	(2.5)	0	(0.0)	0	(0.0)	1	(0.2)	2	(0.4)
Oral candidiasis	4	(3.3)	6	(2.5)	3	(8.3)	14	(2.7)	5	(1.1)
Perforating duodenal ulcer	0	(0.0)	0	(0.0)	1	(2.8)	0	(0.0)	0	(0.0)
Salivation increased	2	(1.7)	3	(1.2)	0	(0.0)	12	(2.3)	10	(2.2)
Stomatitis	4	(3.3)	4	(1.7)	1	(2.8)	9	(1.7)	7	(1.5)
Taste loss	0	(0.0)	2	(0.8)	1	(2.8)	5	(1.0)	3	(0.7)
Vomiting	7	(5.8)	15	(6.2)	1	(2.8)	30	(5.8)	42	(9.1)
Eyes, Ears, Nose, and Throat	16	(13.3)	23	(9.5)	8	(22.2)	77	(14.9)	55	(12.0)
Epistaxis	4	(3.3)	1	(0.4)	2	(5.6)	0	(0.0)	6	(1.3)
Pharyngeal ulcer	0	(0.0)	0	(0.0)	1	(2.8)	0	(0.0)	0	(0.0)
Pharyngitis	4	(3.3)	8	(3.3)	3	(8.3)	17	(3.3)	13	(2.8)
Retinal infarction	0	(0.0)	0	(0.0)	1	(2.8)	0	(0.0)	0	(0.0)
Sinusitis	0	(0.0)	0	(0.0)	1	(2.8)	4	(0.8)	4	(0.9)
Tinnitus	4	(3.3)	4	(1.7)	0	(0.0)	20	(3.9)	14	(3.0)
Visual disturbance	0	(0.0)	1	(0.4)	1	(2.8)	2	(0.4)	0	(0.0)
Vocal disturbance	3	(2.5)	1	(0.4)	0	(0.0)	4	(0.8)	2	(0.4)
Hemic and Lymphatic System	13	(10.8)	34	(14.1)	5	(13.9)	17	(3.3)	32	(7.0)
Anemia	5	(4.2)	12	(5.0)	1	(2.8)	16	(3.1)	16	(3.5)
Febrile neutropenia	9	(7.5)	14	(5.8)	2	(5.6)	0	(0.0)	8	(1.7)
Leukopenia	1	(0.8)	6	(2.5)	0	(0.0)	1	(0.2)	2	(0.4)
Neutropenia	2	(1.7)	11	(4.6)	4	(11.1)	0	(0.0)	13	(2.8)
Thrombocytopenia	3	(2.5)	2	(0.8)	1	(2.8)	0	(0.0)	6	(1.3)

Table 3 (cont)

Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence $\geq 2\%$ in One or More Combined Treatment Groups)
by Body System—CINV Phase II Studies (Cycle 1)

	Aprepitant Capsules						Aprepitant Tablets and/or L-758298 (N=518)		Ondansetron or Granisetron +/- Dexamethasone (N=460)	
	40 mg (N=120)		125 mg (N=241)		375 mg (N=36)		n	(%)	n	(%)
	n	(%)	n	(%)	n	(%)				
Metabolism and Nutrition	20	(16.7)	44	(18.3)	4	(11.1)	106	(20.5)	94	(20.4)
Anorexia	7	(5.8)	27	(11.2)	0	(0.0)	63	(12.2)	58	(12.6)
Appetite decreased	1	(0.8)	8	(3.3)	2	(5.6)	28	(5.4)	17	(3.7)
Hyperglycemia	1	(0.8)	1	(0.4)	1	(2.8)	0	(0.0)	0	(0.0)
Hypokalemia	3	(2.5)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Weight loss	7	(5.8)	17	(7.1)	1	(2.8)	12	(2.3)	16	(3.5)
Musculoskeletal System	12	(10.0)	15	(6.2)	2	(5.6)	79	(15.3)	59	(12.8)
Back pain	2	(1.7)	2	(0.8)	0	(0.0)	16	(3.1)	8	(1.7)
Leg pain	1	(0.8)	1	(0.4)	1	(2.8)	9	(1.7)	5	(1.1)
Muscular weakness	7	(5.8)	7	(2.9)	1	(2.8)	34	(6.6)	19	(4.1)
Nervous System	16	(13.3)	48	(19.9)	7	(19.4)	170	(32.8)	132	(28.7)
Akathisia	0	(0.0)	1	(0.4)	1	(2.8)	1	(0.2)	3	(0.7)
Coma	0	(0.0)	0	(0.0)	1	(2.8)	0	(0.0)	0	(0.0)
Headache	9	(7.5)	27	(11.2)	3	(8.3)	121	(23.4)	85	(18.5)
Insomnia	6	(5.0)	6	(2.5)	2	(5.6)	33	(6.4)	31	(6.7)
Somnolence	0	(0.0)	2	(0.8)	0	(0.0)	23	(4.4)	9	(2.0)
Tremor	1	(0.8)	1	(0.4)	1	(2.8)	5	(1.0)	6	(1.3)
Psychiatric Disorder	6	(5.0)	18	(7.5)	2	(5.6)	19	(3.7)	26	(5.7)
Anxiety	3	(2.5)	9	(3.7)	1	(2.8)	15	(2.9)	11	(2.4)
Depression	1	(0.8)	4	(1.7)	1	(2.8)	1	(0.2)	4	(0.9)
Respiratory System	22	(18.3)	50	(20.7)	5	(13.9)	142	(27.4)	90	(19.6)
Chronic obstructive pulmonary disease	0	(0.0)	0	(0.0)	1	(2.8)	0	(0.0)	1	(0.2)
Cough	1	(0.8)	9	(3.7)	1	(2.8)	17	(3.3)	10	(2.2)
Dyspnea	2	(1.7)	7	(2.9)	1	(2.8)	24	(4.6)	22	(4.8)
Hiccups	19	(15.8)	26	(10.8)	3	(8.3)	88	(17.0)	45	(9.8)
Pneumonia	1	(0.8)	4	(1.7)	2	(5.6)	7	(1.4)	5	(1.1)
Respiratory failure	0	(0.0)	0	(0.0)	1	(2.8)	1	(0.2)	0	(0.0)
Respiratory insufficiency	0	(0.0)	2	(0.8)	1	(2.8)	5	(1.0)	2	(0.4)
Skin and Skin Appendages	9	(7.5)	27	(11.2)	4	(11.1)	45	(8.7)	43	(9.3)
Acne	0	(0.0)	3	(1.2)	1	(2.8)	1	(0.2)	1	(0.2)
Alopecia	2	(1.7)	9	(3.7)	0	(0.0)	20	(3.9)	15	(3.3)
Furuncle	0	(0.0)	0	(0.0)	1	(2.8)	0	(0.0)	0	(0.0)
Rash	2	(1.7)	4	(1.7)	3	(8.3)	6	(1.2)	5	(1.1)

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

CINV = Chemotherapy-induced nausea and vomiting.

(Ref Table E-37 ISS.pdf)

Based on the Phase II data, several adverse experiences were identified as being of special interest: fever, febrile neutropenia, infections, leukopenia, neutropenia, anemia, thrombocytopenia, hypertension, hyperglycemia, hypokalemia, and dehydration.

The Agency has concerns regarding the potential for aprepitant to alter the pharmacokinetics of therapeutic agents via CYP3A4 interaction. There are no PK data available regarding the drug-drug interaction of the aprepitant regimen on chemotherapeutic agents metabolized by CYP3A4. Therefore, the focus of the remainder of this review will be on the safety data from the Phase III Studies in regard to concomitant chemotherapeutic agents.

C. Drug-Drug Interactions (Chemotherapy)

The most common concomitant chemotherapeutic agents used during the Phase III trials were cyclophosphamide, etoposide, fluorouracil, gemcitabine, paclitaxel, and vinorelbine tartrate (Table 4). The Applicant performed additional safety analyses for these concomitant chemotherapeutic agents. Limited safety data is available for the remaining chemotherapeutic agents.

Table 4

Number (%) of Patients With Specific Antineoplastic Agents
(Incidence >0% in One or More Treatment Groups) by Drug Category—
CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=547)		Standard Therapy (N=552)	
	n	(%)	n	(%)
Patients with one or more concomitant antineoplastic agents	520	(95.1)	530	(96.0)
Patients with no concomitant antineoplastic agent	27	(4.9)	22	(4.0)
Antineoplastic and Immunomodulating Agents				
Antineoplastic Agent	520	(95.1)	530	(96.0)
Bleomycin	21	(3.8)	23	(4.2)
Capecitabine	1	(0.2)	1	(0.2)
Carboplatin	0	(0.0)	1	(0.2)
Cyclophosphamide	50	(9.1)	43	(7.8)
Cytarabine	1	(0.2)	0	(0.0)
Dacarbazine	4	(0.7)	4	(0.7)
Docetaxel	11	(2.0)	14	(2.5)
Doxorubicin	38	(6.9)	44	(8.0)
Epirubicin	4	(0.7)	7	(1.3)
Etoposide	106	(19.4)	92	(16.7)
Fluorouracil	100	(18.3)	93	(16.8)
Gemcitabine	89	(16.3)	101	(18.3)
Ifosfamide	2	(0.4)	1	(0.2)
Irinotecan hydrochloride	0	(0.0)	1	(0.2)
Melphalan	0	(0.0)	1	(0.2)
Methotrexate	5	(0.9)	4	(0.7)
Mitomycin	14	(2.6)	5	(0.9)
Paclitaxel	52	(9.5)	58	(10.5)
Raltitrexed	2	(0.4)	3	(0.5)
Trastuzumab	1	(0.2)	3	(0.5)
Vinblastine	11	(2.0)	12	(2.2)
Vincristine	2	(0.4)	0	(0.0)
Vinorelbine tartrate	84	(15.4)	80	(14.5)
<p>Although a patient may have had 2 or more antineoplastic agents, the patient is counted only once within a category. The same patient may appear in different categories.</p> <p>Aprepitant Regimen = Aprepitant 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.</p> <p>Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.</p> <p>CINV = Chemotherapy-induced nausea and vomiting. P.O. = By mouth. IV = Intravenous. N = Number of adult patients.</p>				

(Ref Table E-60 ISS.pdf)

D. Drug-Drug Interactions (Chemotherapy CYP3A4 substrates)

The Applicant identified the following chemotherapies as CYP3A4 substrates: etoposide, vinca alkaloids (vinblastine, vincristine, and vinorelbine tartrate), Taxanes (docetaxel and paclitaxel), irinotecan, and ifosfamide. The adverse events for patients who received cisplatin in combination with a concomitant chemotherapy metabolized by CYP3A4 are listed in the table below. (Table 5)

Table 5

Number (%) of Patients With Specific Serious Clinical Adverse Experiences
(Incidence >0% in One or More Treatment Groups) by Body System—
Concomitant Chemotherapy Metabolized by CYP3A4—
CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=266)		Standard Therapy (N=251)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	40	(15.0)	34	(13.5)
Patients with no adverse experience	226	(85.0)	217	(86.5)
Body as a Whole/Site Unspecified	17	(6.4)	8	(3.2)
Abdominal pain	2	(0.8)	0	(0.0)
Abnormal consciousness	0	(0.0)	1	(0.4)
Collapse	0	(0.0)	1	(0.4)
Dehydration	6	(2.3)	1	(0.4)
Dizziness	0	(0.0)	1	(0.4)
Fever	3	(1.1)	1	(0.4)
Fistula	1	(0.4)	0	(0.0)
Infection	0	(0.0)	1	(0.4)
Malignant neoplasm	2	(0.8)	0	(0.0)
Metastatic neoplasm of known primary	1	(0.4)	0	(0.0)
Sepsis	1	(0.4)	0	(0.0)
Septic shock	3	(1.1)	0	(0.0)
Syncope	1	(0.4)	2	(0.8)
Unknown cause of death	0	(0.0)	1	(0.4)
Upper respiratory infection	1	(0.4)	0	(0.0)
Cardiovascular System	6	(2.3)	9	(3.6)
Angina pectoris	0	(0.0)	1	(0.4)
Arterial thrombosis	0	(0.0)	1	(0.4)
Atrial fibrillation	1	(0.4)	1	(0.4)
Cardiac arrest	1	(0.4)	2	(0.8)
Cerebrovascular accident	1	(0.4)	0	(0.0)
Deep venous thrombosis	0	(0.0)	1	(0.4)
Hemorrhage	0	(0.0)	1	(0.4)
Myocardial infarction	1	(0.4)	0	(0.0)
Orthostatic hypotension	0	(0.0)	1	(0.4)
Pulmonary edema	1	(0.4)	0	(0.0)
Pulmonary embolism	2	(0.8)	2	(0.8)
Venous thrombosis	1	(0.4)	1	(0.4)

Table 5 (cont)

Number (%) of Patients With Specific Serious Clinical Adverse Experiences
(Incidence >0% in One or More Treatment Groups) by Body System—
Concomitant Chemotherapy Metabolized by CYP3A4—
CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=266)		Standard Therapy (N=251)	
	n	(%)	n	(%)
Digestive System	6	(2.3)	9	(3.6)
Diarrhea	3	(1.1)	1	(0.4)
Esophageal malignant neoplasm	0	(0.0)	1	(0.4)
Esophagitis	0	(0.0)	1	(0.4)
Gastrointestinal perforation	1	(0.4)	1	(0.4)
Necrotizing enterocolitis	1	(0.4)	0	(0.0)
Pancreatitis	0	(0.0)	1	(0.4)
Paralytic ileus	1	(0.4)	0	(0.0)
Pseudomembranous enterocolitis	0	(0.0)	1	(0.4)
Stomatitis	0	(0.0)	1	(0.4)
Upper gastrointestinal hemorrhage	0	(0.0)	2	(0.8)
Vomiting	0	(0.0)	2	(0.8)
Endocrine System	2	(0.8)	0	(0.0)
Diabetes mellitus	1	(0.4)	0	(0.0)
Syndrome of inappropriate antidiuretic hormone	1	(0.4)	0	(0.0)
Hemic and Lymphatic System	15	(5.6)	8	(3.2)
Anemia	1	(0.4)	0	(0.0)
Febrile neutropenia	6	(2.3)	4	(1.6)
Leukopenia	1	(0.4)	2	(0.8)
Neutropenia	8	(3.0)	2	(0.8)
Pancytopenia	0	(0.0)	1	(0.4)
Thrombocytopenia	1	(0.4)	0	(0.0)
Metabolism and Nutrition	1	(0.4)	3	(1.2)
Hyperglycemia	0	(0.0)	1	(0.4)
Hypokalemia	0	(0.0)	1	(0.4)
Hyponatremia	1	(0.4)	2	(0.8)
Musculoskeletal System	0	(0.0)	1	(0.4)
Bone pain	0	(0.0)	1	(0.4)
Nervous System	0	(0.0)	1	(0.4)
Spinal cord compression	0	(0.0)	1	(0.4)

Table 5 (cont)
Number (%) of Patients With Specific Serious Clinical Adverse Experiences
(Incidence >0% in One or More Treatment Groups) by Body System—
Concomitant Chemotherapy Metabolized by CYP3A4—
CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=266)		Standard Therapy (N=251)	
	n	(%)	n	(%)
Respiratory System	13	(4.9)	7	(2.8)
Aspiration pneumonia	1	(0.4)	0	(0.0)
Chronic obstructive pulmonary disease	1	(0.4)	0	(0.0)
Dyspnea	3	(1.1)	1	(0.4)
Hemoptysis	0	(0.0)	1	(0.4)
Lung carcinoma	0	(0.0)	1	(0.4)
Lung malignant neoplasm	2	(0.8)	0	(0.0)
Non-small cell lung carcinoma	2	(0.8)	1	(0.4)
Pleural effusion	0	(0.0)	1	(0.4)
Pneumonia	3	(1.1)	2	(0.8)
Pneumonitis	0	(0.0)	1	(0.4)
Pneumothorax	1	(0.4)	0	(0.0)
Respiratory insufficiency	5	(1.9)	1	(0.4)
Skin and Skin Appendages	2	(0.8)	0	(0.0)
Catheter site infection	1	(0.4)	0	(0.0)
Herpes zoster	1	(0.4)	0	(0.0)
Urogenital System	5	(1.9)	4	(1.6)
Acute renal failure	1	(0.4)	0	(0.0)
Breast cellulitis	1	(0.4)	0	(0.0)
Nephrotoxicity	1	(0.4)	1	(0.4)
Renal insufficiency	2	(0.8)	0	(0.0)
Testicular malignant neoplasm	0	(0.0)	1	(0.4)
Urinary tract infection	0	(0.0)	2	(0.8)

* The same patient may appear more than once in different categories.

(Ref Table E-113 ISS.pdf)

Two hundred sixty-six patients in the aprepitant group and 251 patients in the standard therapy group received, in addition to cisplatin, a concomitant chemotherapy metabolized by CYP3A4. Overall, the incidence of serious adverse experiences in this subpopulation

was slightly higher in the aprepitant group than the standard therapy group (15.0% Vs 13.5% respectively).

There were more infection related serious adverse events reported in the aprepitant group. In the aprepitant group, septic shock was reported in 3 patients, sepsis in one patient and upper respiratory infection in the 1 patient. In the corresponding standard therapy group there were no reports of these serious adverse events.

A higher incidence of hematologic serious adverse events was also seen in this subpopulation. Neutropenia was reported as a serious adverse event in 8 of the 266 patients receiving the aprepitant regimen, compared to 2 of the 251 patients in the corresponding standard therapy group. The incidence of anemia, febrile neutropenia and thrombocytopenia were generally similar between treatment groups with a difference between treatment groups less than 1 %.

E. Drug-Drug Interactions (Most Common Chemotherapy)

The applicant performed additional safety analysis for the most common concomitant chemotherapy (both CYP3A4 and non- CYP3A4) utilized during the Phase III trials. These results are discussed below.

As previously stated, several adverse experiences (serious and non-serious) were identified as being of special interest: fever, febrile neutropenia, infections, leukopenia, neutropenia, anemia, thrombocytopenia, hypertension, hyperglycemia, hypokalemia, and dehydration. In order to focus on the Agency's concerns, the incidence of these as serious adverse events will be discussed.

Etoposide (CYP3A4 substrate)

One hundred ninety seven patients received etoposide in combination with cisplatin (106 patients in the aprepitant group and 91 patients in the standard therapy group). The following table displays the serious adverse events by body system for patients who received etoposide in combination with cisplatin.

Table 6

Number (%) of Patients Treated With Etoposide With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System—CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=106)		Standard Therapy (N=91)	
	n	(%)	n	(%)
Patients with one or more serious adverse experiences	16	(15.1)	14	(15.4)
Patients with no serious adverse experience	90	(84.9)	77	(84.6)
Body as a Whole/Site Unspecified	6	(5.7)	3	(3.3)
Abnormal consciousness	0	(0.0)	1	(1.1)
Collapse	0	(0.0)	1	(1.1)
Dehydration	3	(2.8)	0	(0.0)
Dizziness	0	(0.0)	1	(1.1)
Fever	1	(0.9)	0	(0.0)
Septic shock	1	(0.9)	0	(0.0)
Upper respiratory infection	1	(0.9)	0	(0.0)
Cardiovascular System	2	(1.9)	5	(5.5)
Angina pectoris	0	(0.0)	1	(1.1)
Atrial fibrillation	1	(0.9)	0	(0.0)
Cardiac arrest	0	(0.0)	1	(1.1)
Orthostatic hypotension	0	(0.0)	1	(1.1)
Pulmonary embolism	2	(1.9)	1	(1.1)
Venous thrombosis	0	(0.0)	1	(1.1)
Digestive System	2	(1.9)	2	(2.2)
Diarrhea	1	(0.9)	0	(0.0)
Necrotizing enterocolitis	1	(0.9)	0	(0.0)
Stomatitis	0	(0.0)	1	(1.1)
Vomiting	0	(0.0)	1	(1.1)
Endocrine System	1	(0.9)	0	(0.0)
Diabetes mellitus	1	(0.9)	0	(0.0)
Hemic and Lymphatic System	9	(8.5)	3	(3.3)
Anemia	1	(0.9)	0	(0.0)
Febrile neutropenia	4	(3.8)	2	(2.2)
Leukopenia	0	(0.0)	2	(2.2)
Neutropenia	4	(3.8)	0	(0.0)
Thrombocytopenia	1	(0.9)	0	(0.0)

(Ref Table E-127 ISS.pdf)

Table 6 (cont)

Number (%) of Patients Treated With Etoposide With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System—CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=106)		Standard Therapy (N=91)	
	n	(%)	n	(%)
Patients with one or more serious adverse experiences	16	(15.1)	14	(15.4)
Patients with no serious adverse experience	90	(84.9)	77	(84.6)
Metabolism and Nutrition	1	(0.9)	1	(1.1)
Hyponatremia	1	(0.9)	1	(1.1)
Musculoskeletal System	0	(0.0)	1	(1.1)
Bone pain	0	(0.0)	1	(1.1)
Respiratory System	6	(5.7)	4	(4.4)
Aspiration pneumonia	1	(0.9)	0	(0.0)
Dyspnea	2	(1.9)	1	(1.1)
Hemoptysis	0	(0.0)	1	(1.1)
Lung malignant neoplasm	1	(0.9)	0	(0.0)
Non-small cell lung carcinoma	1	(0.9)	1	(1.1)
Pneumonia	1	(0.9)	0	(0.0)
Pneumonitis	0	(0.0)	1	(1.1)
Respiratory insufficiency	1	(0.9)	1	(1.1)
Skin and Skin Appendages	1	(0.9)	0	(0.0)
Herpes Zoster	1	(0.9)	0	(0.0)
Urogenital System	1	(0.9)	2	(2.2)
Acute renal failure	1	(0.9)	0	(0.0)
Nephrotoxicity	0	(0.0)	1	(1.1)
Testicular malignant neoplasm	0	(0.0)	1	(1.1)

Although a patient may have had 2 or more serious clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

(Ref Table E-127 ISS.pdf)

Overall, the incidence of serious adverse experiences in this subpopulation was similar between treatment groups. Serious adverse experiences were reported in 16 out of 106 aprepitant patients (15.1%) and 14 out of 91 patients (15.4%) receiving standard therapy. Analysis of serious adverse events by body system, however, demonstrates three times as many hematologic serious adverse events occurred in the aprepitant group. Nine out of 106 patients (8.5%) in the aprepitant group compared to 3 out of 91 patients (3.3%) in the standard therapy group developed a serious hematologic adverse event. Neutropenia was reported as a serious adverse event in 4 of the 106 patients receiving the aprepitant regimen in combination with etoposide and cisplatin, compared to none in the corresponding standard therapy group. Febrile neutropenia was described as a serious adverse event in twice as many patients in the aprepitant group. This was reported in 4 of the 106 patients in the aprepitant group compared to 2 cases in the standard therapy group.

Infection was reported as an adverse event (serious and non-serious) in more than twice as many patients in the aprepitant group. It was reported in 19 patients (17.9%) in the aprepitant group compared to 8 patients (8.8%) in the standard therapy group. Although the incidence of fever, septic shock and upper respiratory infection as serious

adverse events were small, they were only reported in the aprepitant group.

On analyzing the data, there was a notable difference in the incidence of serious hematologic and serious infection related adverse events for patients receiving concomitant etoposide.

Fluorouracil

One hundred ninety three patients (100 patients in the aprepitant group and 93 patients in the standard therapy group) received fluorouracil in combination with cisplatin. The following table displays the serious adverse events by body system for patients who received fluorouracil in combination with cisplatin.

Table 7

Number (%) of Patients Treated With Fluorouracil With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System—CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=100)		Standard Therapy (N=93)	
	n	(%)	n	(%)
Patients with one or more serious adverse experiences	14	(14.0)	21	(22.6)
Patients with no serious adverse experience	86	(86.0)	72	(77.4)
Body as a Whole/Site Unspecified	6	(6.0)	7	(7.5)
Asthenia/fatigue	0	(0.0)	1	(1.1)
Cardiopulmonary failure	1	(1.0)	3	(3.2)
Dehydration	2	(2.0)	2	(2.2)
Fever	0	(0.0)	1	(1.1)
Metastatic neoplasm of known primary	1	(1.0)	0	(0.0)
Sepsis	1	(1.0)	0	(0.0)
Septic shock	0	(0.0)	1	(1.1)
Syncope	1	(1.0)	0	(0.0)
Unknown cause of death	1	(1.0)	0	(0.0)
Cardiovascular System	4	(4.0)	6	(6.5)
Angina pectoris	1	(1.0)	0	(0.0)
Arrhythmia	0	(0.0)	1	(1.1)
Cardiac arrest	0	(0.0)	1	(1.1)
Cardiogenic shock	0	(0.0)	1	(1.1)
Cerebrovascular accident	0	(0.0)	1	(1.1)
Deep venous thrombosis	2	(2.0)	1	(1.1)
Hypovolemic shock	0	(0.0)	1	(1.1)
Myocardial infarction	1	(1.0)	0	(0.0)
Pulmonary embolism	0	(0.0)	1	(1.1)
Vascular stenosis	0	(0.0)	1	(1.1)
Venous infusion infection	1	(1.0)	0	(0.0)
Digestive System	1	(1.0)	5	(5.4)
Constipation	0	(0.0)	1	(1.1)
Diarrhea	0	(0.0)	1	(1.1)
Esophagitis	0	(0.0)	1	(1.1)
Oral candidiasis	0	(0.0)	1	(1.1)
Perforating duodenal ulcer	1	(1.0)	0	(0.0)
Stomatitis	0	(0.0)	1	(1.1)
Upper gastrointestinal hemorrhage	0	(0.0)	1	(1.1)

(Ref Table E-129 ISS.pdf)

Table 7 (cont)

Number (%) of Patients Treated With Fluorouracil With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System—CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=100)		Standard Therapy (N=93)	
	n	(%)	n	(%)
Patients with one or more serious adverse experiences	14	(14.0)	21	(22.6)
Patients with no serious adverse experience	86	(86.0)	72	(77.4)
Endocrine System	0	(0.0)	1	(1.1)
Carcinoid syndrome	0	(0.0)	1	(1.1)
Hemic and Lymphatic System	4	(4.0)	7	(7.5)
Febrile neutropenia	1	(1.0)	3	(3.2)
Leukopenia	0	(0.0)	1	(1.1)
Neutropenia	2	(2.0)	3	(3.2)
Pancytopenia	1	(1.0)	2	(2.2)
Thrombocytopenia	1	(1.0)	1	(1.1)
Metabolism and Nutrition	1	(1.0)	2	(2.2)
Hypoglycemia	0	(0.0)	1	(1.1)
Hypokalemia	1	(1.0)	1	(1.1)
Musculoskeletal System	1	(1.0)	1	(1.1)
Leg pain	0	(0.0)	1	(1.1)
Muscular weakness	1	(1.0)	1	(1.1)
Nervous System	0	(0.0)	1	(1.1)
Head trauma	0	(0.0)	1	(1.1)
Psychiatric Disorder	1	(1.0)	0	(0.0)
Disorientation	1	(1.0)	0	(0.0)
Respiratory System	0	(0.0)	4	(4.3)
Airway obstruction	0	(0.0)	1	(1.1)
Bacterial pneumonia	0	(0.0)	1	(1.1)
Dyspnea	0	(0.0)	1	(1.1)
Pneumonia	0	(0.0)	1	(1.1)
Pulmonary hemorrhage	0	(0.0)	1	(1.1)
Urogenital System	0	(0.0)	3	(3.2)
Nephrotoxicity	0	(0.0)	1	(1.1)
Renal failure	0	(0.0)	1	(1.1)
Uremia	0	(0.0)	1	(1.1)

Although a patient may have had 2 or more serious clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

(Ref Table E-129 ISS.pdf)

The incidence of serious adverse experiences was smaller in the aprepitant group than the standard therapy group (14.0% vs 22.6% respectively). Serious hematologic adverse events occurred less frequently in the aprepitant group as well.

The incidence of neutropenia was similar in both treatment groups. It was reported as a serious adverse event in 2 of the 100 patients in the aprepitant group who received fluorouracil in combination with cisplatin, compared to 3 patients receiving standard therapy. The incidence of febrile neutropenia was also smaller in the aprepitant group. It

was reported as a serious adverse event in 1 of the 100 patients in the aprepitant group compared to 3 in the standard therapy group.

The incidences of fever, sepsis and septic shock as a serious adverse event were small and similar between treatment groups. Overall, the incidence of infection was similar between treatment groups.

On analyzing the data, there was little difference seen in the safety profile of fluorouracil between treatment groups.

Gemcitabine

A total of 190 patients were treated with gemcitabine in combination with cisplatin: 89 in the aprepitant group and 101 in the standard therapy group. Sixteen out of 89 patients (18.0%) in the aprepitant group had a serious adverse experience compared with 14 out of 101 patients (13.9%) in the standard therapy group. The following table displays the serious adverse events by body system for patients who received gemcitabine in combination with cisplatin.

Table 8

Number (%) of Patients Treated With Gemcitabine With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System—CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=89)		Standard Therapy (N=101)	
	n	(%)	n	(%)
Patients with one or more serious clinical adverse experiences	16	(18.0)	14	(13.9)
Patients with no serious clinical adverse experience	73	(82.0)	87	(86.1)
Body as a Whole/Site Unspecified	4	(4.5)	4	(4.0)
Chills	0	(0.0)	1	(1.0)
Dehydration	2	(2.2)	1	(1.0)
Dizziness	1	(1.1)	0	(0.0)
Drug overdose	0	(0.0)	1	(1.0)
Infection	2	(2.2)	0	(0.0)
Septic shock	0	(0.0)	1	(1.0)
Cardiovascular System	5	(5.6)	2	(2.0)
Acute myocardial infarction	0	(0.0)	1	(1.0)
Atrial fibrillation	1	(1.1)	0	(0.0)
Cardiac arrest	1	(1.1)	0	(0.0)
Cerebral infarction	0	(0.0)	1	(1.0)
Deep venous thrombosis	1	(1.1)	0	(0.0)
Pulmonary embolism	2	(2.2)	0	(0.0)
Digestive System	2	(2.2)	2	(2.0)
Candida esophagitis	1	(1.1)	0	(0.0)
Duodenitis	1	(1.1)	0	(0.0)
Esophageal tear	1	(1.1)	0	(0.0)
Gastritis	1	(1.1)	0	(0.0)
Gastrointestinal perforation	0	(0.0)	1	(1.0)
Intestinal obstruction	0	(0.0)	1	(1.0)
Nausea	1	(1.1)	0	(0.0)
Vomiting	1	(1.1)	0	(0.0)
Endocrine System	0	(0.0)	1	(1.0)
Diabetic ketoacidosis	0	(0.0)	1	(1.0)
Hemic and Lymphatic System	3	(3.4)	1	(1.0)
Febrile neutropenia	1	(1.1)	0	(0.0)
Leukopenia	0	(0.0)	1	(1.0)
Neutropenia	1	(1.1)	1	(1.0)
Thrombocytopenia	1	(1.1)	0	(0.0)
Metabolism and Nutrition	0	(0.0)	1	(1.0)
Hyponatremia	0	(0.0)	1	(1.0)
Musculoskeletal System	0	(0.0)	1	(1.0)
Leg pain	0	(0.0)	1	(1.0)
Psychiatric Disorder	1	(1.1)	0	(0.0)
Confusion	1	(1.1)	0	(0.0)
Respiratory System	1	(1.1)	2	(2.0)
Lower respiratory infection	0	(0.0)	1	(1.0)
Pleural effusion	0	(0.0)	1	(1.0)
Pneumonia	1	(1.1)	0	(0.0)
Skin and Skin Appendages	1	(1.1)	0	(0.0)
Catheter site infection	1	(1.1)	0	(0.0)
Urogenital System	2	(2.2)	3	(3.0)
Cystitis	0	(0.0)	1	(1.0)
Hematuria	0	(0.0)	1	(1.0)
Renal insufficiency	1	(1.1)	0	(0.0)
Urinary retention	1	(1.1)	0	(0.0)
Urinary tract infection	0	(0.0)	1	(1.0)

Although a patient may have had 2 or more serious clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

(Ref Table E-131 ISS.pdf)

Overall, the incidence of serious adverse experiences in this subpopulation was similar between treatment groups. Neutropenia was reported as a serious adverse event in 1 patient from each group. Although the incidences of febrile neutropenia and thrombocytopenia as serious adverse events were small, they were only reported in the aprepitant group.

On analyzing the data, there was little difference seen in the safety profile of gemcitabine between treatment groups.

Vinorelbine tartrate (CYP3A4 substrate)

A total of 158 patients were treated with vinorelbine tartrate in combination with cisplatin: 82 in the aprepitant group and 76 in the standard therapy group. Thirteen out of 82 patients (15.9%) in the aprepitant group had serious adverse experiences compared to 8 out of 76 patients (10.5%) in the standard therapy group. The following table displays the serious adverse events by body system for patients who received vinorelbine tartrate in combination with cisplatin.

Table 9

Number (%) of Patients Treated With Vinorelbine Tartrate With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System—CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=82)		Standard Therapy (N=76)	
	n	(%)	n	(%)
Patients with one or more serious clinical adverse experiences	13	(15.9)	8	(10.5)
Patients with no serious clinical adverse experience	69	(84.1)	68	(89.5)
Body as a Whole/Site Unspecified	7	(8.5)	5	(6.6)
Abdominal pain	1	(1.2)	0	(0.0)
Dehydration	2	(2.4)	1	(1.3)
Fever	0	(0.0)	1	(1.3)
Fistula	1	(1.2)	0	(0.0)
Infection	0	(0.0)	1	(1.3)
Malignant neoplasm	1	(1.2)	0	(0.0)
Metastatic neoplasm of known primary	1	(1.2)	0	(0.0)
Sepsis	1	(1.2)	0	(0.0)
Septic shock	2	(2.4)	0	(0.0)
Syncope	0	(0.0)	2	(2.6)
Unknown cause of death	0	(0.0)	1	(1.3)
Cardiovascular System	3	(3.7)	3	(3.9)
Arterial thrombosis	0	(0.0)	1	(1.3)
Atrial fibrillation	0	(0.0)	1	(1.3)
Cardiac arrest	1	(1.2)	0	(0.0)
Cerebrovascular accident	1	(1.2)	0	(0.0)
Deep venous thrombosis	0	(0.0)	1	(1.3)
Pulmonary edema	1	(1.2)	0	(0.0)
Pulmonary embolism	0	(0.0)	1	(1.3)
Venous thrombosis	1	(1.2)	0	(0.0)
Digestive System	1	(1.2)	1	(1.3)
Gastrointestinal perforation	0	(0.0)	1	(1.3)
Paralytic ileus	1	(1.2)	0	(0.0)

(Ref Table E-133 ISS.pdf)

Table 9 (cont)

Number (%) of Patients Treated With Vinorelbine Tartrate With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System—CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=82)		Standard Therapy (N=76)	
	n	(%)	n	(%)
Patients with one or more serious clinical adverse experiences	13	(15.9)	8	(10.5)
Patients with no serious clinical adverse experience	69	(84.1)	68	(89.5)
Hemic and Lymphatic System	2	(2.4)	1	(1.3)
Leukopenia	1	(1.2)	0	(0.0)
Neutropenia	2	(2.4)	1	(1.3)
Metabolism and Nutrition	0	(0.0)	1	(1.3)
Hypokalemia	0	(0.0)	1	(1.3)
Hyponatremia	0	(0.0)	1	(1.3)
Respiratory System	6	(7.3)	1	(1.3)
Chronic obstructive pulmonary disease	1	(1.2)	0	(0.0)
Dyspnea	1	(1.2)	0	(0.0)
Lung malignant neoplasm	1	(1.2)	0	(0.0)
Non-small cell lung carcinoma	1	(1.2)	0	(0.0)
Pleural effusion	0	(0.0)	1	(1.3)
Pneumonia	1	(1.2)	1	(1.3)
Pneumothorax	1	(1.2)	0	(0.0)
Respiratory insufficiency	4	(4.9)	0	(0.0)
Urogenital System	2	(2.4)	0	(0.0)
Renal insufficiency	2	(2.4)	0	(0.0)

Although a patient may have had 2 or more serious clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

(Ref Table E-133 ISS.pdf)

The incidence of serious adverse experiences were higher in the aprepitant group than the standard therapy group (15.9% VS 10.5% respectively).

The incidences of serious hematologic adverse events were similar in both treatment groups. Neutropenia was reported as a serious adverse event in 2 patients in the aprepitant group compared to 1 in the standard therapy group.

Febrile neutropenia and thrombocytopenia were not reported as a serious adverse event in either group.

Infection was reported in 15 out of 82 patients (18.3%) and 9 out of 76 patients (11.8%) in the aprepitant and standard therapy groups, respectively. Of these adverse experiences of infections, 6 were described as serious: 4 (4.9%) in the aprepitant group and 2 (2.6%) in the standard therapy group.

The incidence of fever as serious adverse event was smaller in the aprepitant group than the standard therapy group. Only one patient (1.3%) in the standard therapy group reported a serious adverse experience of fever.

Review of the data demonstrated a notable difference in the incidence of serious adverse events involving the respiratory system. Six of 82 patients (7.3%) in the aprepitant group compared to 1 out of 76 patients (1.3%) in the standard therapy group

experienced a serious adverse event involving the respiratory system.

None of the patient receiving standard therapy reported respiratory insufficiency, whereas 4 patients in the aprepitant group developed a fatal respiratory insufficiency. These 4 patients (ANs 5097, 5109, 5114, and 6088) were randomized at the same study site (Site 018 in Protocol 054). The Applicant conducted an audit. The investigator reported that the cases of respiratory insufficiency represented progression of underlying malignant disease (lung cancer) and did not consider the events to be drug related. Analyzing the data suggests that these deaths were not related to the patient developing either pneumonia or pleural effusions.

In addition to these four fatalities, 3 additional deaths (7) occurred in the aprepitant group. There were 2 fatalities in the corresponding standard therapy group.

Analysis of the data does not suggest that the aprepitant regimen increased the hematologic toxicity of vinorelbine tartrate. However, twice as many patients in the aprepitant regime developed a serious infection. There were 3 reported cases of sepsis or septic shock as serious adverse events in the aprepitant group compared to no cases in the standard therapy.

The Agency noted that the aprepitant regimen may have increased the pulmonary toxicity of vinorelbine tartrate, since all the fatal cases of respiratory insufficiency occurred in the aprepitant group. Given that no formal drug-drug interaction PK study was completed for vinorelbine tartrate (CYP3A4 substrate), the Agency seeks the opinion of the Committee whether PK studies should be performed.

Paclitaxel (CYP3A4 substrate)

A total of 110 patients were treated with Paclitaxel in combination with cisplatin: 52 in the aprepitant group and 58 in the standard therapy group. Seven out of 52 patients (13.5%) in the aprepitant group had serious adverse experiences compared to 6 out of 58 patients (10.3%) in the standard therapy group. The following table displays the serious adverse events by body system for patients who received Paclitaxel in combination with cisplatin.

Table 10

Number (%) of Patients Treated With Paclitaxel With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System—CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=52)		Standard Therapy (N=58)	
	n	(%)	n	(%)
Patients with one or more serious adverse experiences	7	(13.5)	6	(10.3)
Patients with no serious adverse experience	45	(86.5)	52	(89.7)
Body as a Whole/Site Unspecified	2	(3.8)	0	(0.0)
Fever	1	(1.9)	0	(0.0)
Malignant neoplasm	1	(1.9)	0	(0.0)
Syncope	1	(1.9)	0	(0.0)
Cardiovascular System	1	(1.9)	1	(1.7)
Cardiac arrest	0	(0.0)	1	(1.7)
Hemorrhage	0	(0.0)	1	(1.7)
Myocardial infarction	1	(1.9)	0	(0.0)
Digestive System	1	(1.9)	3	(5.2)
Esophageal malignant neoplasm	0	(0.0)	1	(1.7)
Gastrointestinal perforation	1	(1.9)	0	(0.0)
Pseudomembranous enterocolitis	0	(0.0)	1	(1.7)
Upper gastrointestinal hemorrhage	0	(0.0)	1	(1.7)
Vomiting	0	(0.0)	1	(1.7)
Endocrine System	1	(1.9)	0	(0.0)
Syndrome of inappropriate antidiuretic hormone	1	(1.9)	0	(0.0)
Hemic and Lymphatic System	1	(1.9)	1	(1.7)
Febrile neutropenia	1	(1.9)	1	(1.7)
Respiratory System	1	(1.9)	1	(1.7)
Pneumonia	1	(1.9)	1	(1.7)
Skin and Skin Appendages	1	(1.9)	0	(0.0)
Catheter site infection	1	(1.9)	0	(0.0)
Urogenital System	1	(1.9)	1	(1.7)
Nephrotoxicity	1	(1.9)	0	(0.0)
Urinary tract infection	0	(0.0)	1	(1.7)

Although a patient may have had 2 or more serious clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

(Ref Table E-135 ISS.pdf)

The incidences of serious hematologic adverse events were small and similar in both treatment groups. The only serious hematologic adverse event reported was febrile neutropenia, which occurred in one patient from each group.

Incidences of prespecified adverse experiences were generally similar between treatment groups. Six out of 52 patients (11.5%) in the aprepitant group compared to 7 of the 58 patients (12.1%) receiving standard therapy reported infection as an adverse event.

On analyzing the data, there was little difference seen in the safety profile of paclitaxel between treatment groups.

Cyclophosphamide

A total of 93 patients were treated with cyclophosphamide in combination with cisplatin: 50 in the aprepitant group and 43 in the standard therapy group. Three out of 50 patients (6.0%) in the aprepitant group had serious adverse experiences compared to 3 out of 43 patients (7.0%) in the standard therapy group. The following table displays the serious adverse events by body system for patients who received cyclophosphamide in combination with cisplatin.

Table 11

Number (%) of Patients Treated With Cyclophosphamide With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System—CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=50)		Standard Therapy (N=43)	
	n	(%)	n	(%)
Patients with one or more serious clinical adverse experiences	3	(6.0)	3	(7.0)
Patients with no serious clinical adverse experience	47	(94.0)	40	(93.0)
Body as a Whole/Site Unspecified	0	(0.0)	1	(2.3)
Dehydration	0	(0.0)	1	(2.3)
Cardiovascular System	1	(2.0)	0	(0.0)
Arrhythmia	1	(2.0)	0	(0.0)
Digestive System	0	(0.0)	1	(2.3)
Nausea	0	(0.0)	1	(2.3)
Vomiting	0	(0.0)	1	(2.3)
Endocrine System	0	(0.0)	1	(2.3)
Diabetes mellitus	0	(0.0)	1	(2.3)
Hemic and Lymphatic System	2	(4.0)	0	(0.0)
Anemia	1	(2.0)	0	(0.0)
Febrile neutropenia	1	(2.0)	0	(0.0)
Neutropenia	1	(2.0)	0	(0.0)
Thrombocytopenia	1	(2.0)	0	(0.0)
Metabolism and Nutrition	1	(2.0)	0	(0.0)
Hypokalemia	1	(2.0)	0	(0.0)
Urogenital System	1	(2.0)	0	(0.0)
Renal failure	1	(2.0)	0	(0.0)

Although a patient may have had 2 or more serious clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

(Ref Table E-137 ISS.pdf)

Overall, the incidences of serious and non-serious adverse experiences were similar between treatment groups. However, serious and non-serious hematologic adverse events were more common in the aprepitant group. Four patients in the aprepitant group compared to 1 patient receiving standard therapy reported a hematologic adverse event. The only serious hematologic adverse events in this population were reported in the aprepitant group (2 patients, 4.0%).

Incidences of prespecified adverse experiences were similar between treatment groups. Eleven of the 50 patients (22.0%) in the aprepitant group compared to 12 of the 43

patients (27.9%) in the standard therapy group reported an adverse experience. The most frequently reported prespecified adverse experience was infection.

Four out of 50 patients (8.0%) in the aprepitant group compared to 8 of the 43 patients (18.6%) in the standard therapy group experienced an adverse experience of infection. None of these infections were reported as serious adverse experiences.

On analyzing the data, the number of patients with hematologic adverse events are small, but the possibility of a small signal can not ruled out. Over all, there was little difference seen in the safety profile of cyclophosphamide between treatment groups.

Doxorubicin

Eighty-one patients were treated with doxorubicin in combination with cisplatin: 38 in the aprepitant group and 43 in the standard therapy group. The following table displays the serious adverse events by body system for patients who received doxorubicin in combination with cisplatin.

Table 12

Number (%) of Patients Treated With Doxorubicin With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System—CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=38)		Standard Therapy (N=43)	
	n	(%)	n	(%)
Patients with one or more serious clinical adverse experiences	1	(2.6)	5	(11.6)
Patients with no adverse experience	37	(97.4)	38	(88.4)
Body as a Whole/Site Unspecified	0	(0.0)	1	(2.3)
Metastatic neoplasm of known primary	0	(0.0)	1	(2.3)
Digestive System	1	(2.6)	0	(0.0)
Erosive esophagitis	1	(2.6)	0	(0.0)
Hiatal hernia	1	(2.6)	0	(0.0)
Hemic and Lymphatic System	0	(0.0)	2	(4.7)
Febrile neutropenia	0	(0.0)	1	(2.3)
Pancytopenia	0	(0.0)	1	(2.3)
Nervous System	0	(0.0)	1	(2.3)
Encephalopathy	0	(0.0)	1	(2.3)
Respiratory System	0	(0.0)	1	(2.3)
Hypoxia	0	(0.0)	1	(2.3)
Urogenital System	0	(0.0)	1	(2.3)
Urinary tract infection	0	(0.0)	1	(2.3)

Although a patient may have had 2 or more serious clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

(Ref Table E-139 ISS.pdf)

Out of these 81 patients, 14 out of 38 patients (36.8%) in the aprepitant group and 15 out of 43 patients (34.9%) in the standard therapy group had one or more prespecified

adverse experiences.

The incidences of infection were similar between treatment groups. Six out of 38 patients (15.8%) in the aprepitant group compared to 7 of the 43 patients (16.3%) in the standard therapy group. Similarly, the incidence of neutropenia was higher in the standard therapy group. Neutropenia was reported as an adverse event in 1 of the 38 patients in the aprepitant group (2.6%) compared to 6 of the 43 patients (14.0%) receiving standard therapy. The incidence of hematologic serious adverse events were only reported in the standard therapy group (2 patients, 4.7%). Overall, the incidence of serious adverse experiences was less in the aprepitant group than in the standard therapy group. Only 1 of 38 patients (2.6%) in the aprepitant group had serious adverse experiences compared to 5 out of 43 patients (7.0%) in the standard therapy group.

The number of patients included in this analysis was small. However, on analyzing the data, there was little difference seen in the safety profile of doxorubicin between treatment groups.

Docetaxel (CYP3A4 substrate)

A total of 24 patients were treated with docetaxel in combination with cisplatin: 11 in the aprepitant group and 13 in the standard therapy group. The following table displays the serious adverse events by body system for patients who received docetaxel in combination with cisplatin.

Table 13

Number (%) of Patients Treated With Docetaxel With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System—CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=11)		Standard Therapy (N=13)	
	n	(%)	n	(%)
Patients with one or more serious clinical adverse experiences	3	(27.3)	5	(38.5)
Patients with no serious clinical adverse experience	8	(72.7)	8	(61.5)
Body as a Whole/Site Unspecified	1	(9.1)	0	(0.0)
Dehydration	1	(9.1)	0	(0.0)
Fever	1	(9.1)	0	(0.0)
Digestive System	2	(18.2)	3	(23.1)
Diarrhea	2	(18.2)	1	(7.7)
Esophagitis	0	(0.0)	1	(7.7)
Pancreatitis	0	(0.0)	1	(7.7)
Upper gastrointestinal hemorrhage	0	(0.0)	1	(7.7)
Hemic and Lymphatic System	2	(18.2)	2	(15.4)
Febrile neutropenia	1	(9.1)	1	(7.7)
Neutropenia	1	(9.1)	1	(7.7)
Metabolism and Nutrition	0	(0.0)	1	(7.7)
Hyperglycemia	0	(0.0)	1	(7.7)
Nervous System	0	(0.0)	1	(7.7)
Spinal cord compression	0	(0.0)	1	(7.7)
Respiratory System	0	(0.0)	1	(7.7)
Lung carcinoma	0	(0.0)	1	(7.7)

Although a patient may have had 2 or more serious clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

(Ref Table E-141 ISS.pdf)

Three of the 11 patients (27.3%) in the aprepitant group and 5 out of the 13 patients (38.5%) in the standard therapy group reported a serious adverse experience.

The incidences of hematologic serious adverse events were balanced between treatment groups. Two patients from each group experienced a serious hematologic adverse event.

The numbers of patients in this sub-population were too small to permit a meaningful analysis. Overall, the data does not suggest that the aprepitant regimen in combination with cisplatin adversely affected the safety profile of docetaxel.

Summary

The incidences of prespecified adverse experiences in the subgroup of patients who, in addition to cisplatin, received concomitant chemotherapy metabolized by CYP3A4, were generally similar in the 2 treatment groups (30.1% and 28.3% in the aprepitant and standard therapy group, respectively). However, the incidence of infections was higher in the aprepitant group (15.4%) compared with the standard therapy group (10.0%).

Overall, analysis of adverse events of individual chemotherapeutic agents did not

identify a definite signal. There were small differences in the incidence of infection and hematologic adverse events that may represent a signal. The number of patients studied was too small to draw any definite conclusions. A possible concern identified during the review is the increased pulmonary adverse events associated with concomitant use of the aprepitant regimen and vinorelbine tartrate.

ATTACHMENT TWO

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
SUMMARY**

Clinical Pharmacology and Biopharmaceutics

1.1. Formulation: The development program for aprepitant utilized several different formulations of this drug including three tablet formulations of aprepitant and an intravenous (IV) formulation of a prodrug of aprepitant (L-758298) that were used in early clinical studies. However the tablet formulations have low oral bioavailability due to poor solubility of the drug. Subsequently, a nanoparticle capsule formulation with enhanced bioavailability was developed for marketing purposes. This nanoparticle capsule formulation was used in late Phase IIb and all Phase III clinical studies. Critical drug interaction studies were also conducted with this final formulation.

1.2. Pharmacokinetics:

1.2.1. Absorption

The absolute bioavailability of aprepitant from the nanoparticle capsule formulation of 125 mg and 80 mg doses is 59% and 67%, respectively. Plasma concentrations of aprepitant reach peak levels at 4 hours. The pharmacokinetics are slightly nonlinear with approximately 25% higher AUC at the 125 mg dose compared to the 80 mg dose. The pharmacokinetics of aprepitant administered as a 3- or 5-day regimen (125 mg on Day 1 and 80 mg/day on subsequent days) show that plasma concentrations of aprepitant are similar (for 3 –Day) or slightly higher (for 5-Day) on the last day of dosing compared to Day 1. Following multiple dosing of fixed doses (125 mg or 375 mg) over 28 days, the plasma concentrations of aprepitant accumulate over the first 7 days and then decline from Day 7 to Day 28. The later decline in plasma concentrations may be due to auto induction of cytochrome P450 3A4 enzyme by aprepitant.

Food effect

The capsule formulation did not have a significant food effect.

1.2.2. Distribution

Following intravenous administration, aprepitant had a mean apparent volume of distribution of 66 L. It is more than 95% bound to plasma proteins in healthy subjects.

1.2.3. Metabolism

Aprepitant undergoes extensive metabolism, primarily via - CYP3A4 mediated oxidation. Seven metabolites have been identified in human plasma following oral administration of [¹⁴C]-aprepitant. The metabolites are not likely to contribute significantly to the efficacy of aprepitant because these metabolites are either inactive or weakly active or are present at low levels relative to aprepitant.

1.2.4. Elimination

After IV administration of the prodrug, [¹⁴C]-L-758298 in humans, approximately 45% and 58% of total radioactivity was excreted in feces and urine respectively as metabolites of aprepitant. The prodrug was shown to be completely and rapidly converted to aprepitant, *in vivo*. No unchanged aprepitant was detected in urine. Overall, it appears that aprepitant undergoes extensive metabolism and was primarily eliminated via excretion of metabolites. Following intravenous administration, aprepitant had mean plasma clearance of 84 mL/minute, and terminal half-life of about 13 hours.

The half-life was similar after oral administration.

1.2.5. Special Populations:

Elderly

Compared to young adults (≤ 45 years), elderly subjects (≥ 65 years) showed small increases of 36% and 24% in AUC and C_{\max} , respectively.

Gender

Compared to men, women had slightly lower (up to 16%) AUC and slightly higher (up to 27%) C_{\max} .

Race

Slightly higher (20 to 30%) plasma concentrations of aprepitant were noted in hispanic subjects compared to white or black subjects.

These differences in elderly, gender, and race were concluded as not clinically significant by the sponsor and no dosage adjustment is recommended in these groups.

Renal Insufficiency

Systemic exposure (AUC) of total aprepitant is lower (20 to 40%) in patients with severe renal insufficiency and end stage renal disease compared to healthy subjects with normal renal function.

Since unbound drug concentrations of aprepitant are similar in patients with renal insufficiency compared to healthy subjects with normal renal function, sponsor concluded that dosage adjustment is not necessary.

Hepatic Insufficiency

An increase of up to 20% in AUC was noted in patients with moderate hepatic impairment compared to age matched control subjects with normal hepatic function. No dosage adjustment is recommended for patients with mild and moderate hepatic impairment. Pharmacokinetics of aprepitant in patients with severe hepatic impairment were not studied.

1.3. Drug-Drug Interactions:

Aprepitant is extensively metabolized by CYP3A4. *In vitro* metabolism studies and *in vivo* pharmacokinetic studies have shown that aprepitant inhibits CYP3A4 on short term dosing (up to 5 days) and induces CYP3A4 on chronic dosing (over 28 days). Several drug interaction studies were conducted to investigate 1) The potential of aprepitant to affect the pharmacokinetics of drugs metabolized by CYP3A4, CYP2C9, or CYP2D6, 2) The potential of aprepitant to affect P-glycoprotein (P-gp) mediated transport, 3) The effect of potent CYP3A4 inhibitors and inducers on the pharmacokinetics of aprepitant. The results of the drug interactions submitted in the NDA are briefly summarized in the following table.

Table 1. Drug Interactions of aprepitant (AP).

Drug	Mean ratio of AUC*	Mean ratio of C_{max}*
Effect on aprepitant	4.8 ↑	1.5 ↑
Ketoconazole (potent 3A4 inhibitor)	2.0 ↑	2.0 ↑
Diltiazem with 300 mg AP (moderate 3A4 inhibitor)	1.5 ↑	1.2 ↑
Diltiazem with 100 mg IV L-758298	0.09 ↓	0.4 ↓
Rifampin (potent inducer)	1.3 ↑ (day 1)	
Dexamethasone (3A4 substrate)	0.98 ↓ (Day 5)	
Effect of aprepitant		
<u>On CYP3A4 substrates</u>		
Midazolam	2.3 ↑ (day 1)	1.5 ↑ (day 1)
	3.3 ↑ (day 5)	1.9 ↑ (day 5)
	1.7 ↑	1.5 ↑
Diltiazem	2.2 ↑	
Dexamethasone		
	2.5 ↑	1.5 ↑
Methylprednisolone (oral)	1.34 ↑	
Methylprednisolone (IV)	0.59 ↓	0.64 ↓
	0.91 ↓	0.81 ↓
Ethinyl estradiol (with 14 days of AP)		
Norethindrone (with 14 days of AP)	No effect	No effect
	No effect	No effect
Ondansetron (IV)		
Granisetron (oral)		
<u>Other isozymes</u>		
Warfarin (CYP2C9 substrate)	0.89 ↓ INR (day 8)	
	0.75 ↓	
Paroxetine (CYP2D6 substrate)		
	No effect	
Digoxin (P-gp substrate)		No effect

*Ratio of AUC or C_{max} with and without the interacting drug, ↑ denotes increase, ↓ denotes decrease.

The following are the main conclusions from the drug interaction studies:

Conclusions relevant to the short term administration (up to 5 days)-

- Aprepitant, upon short term administration (for 5 days) is an inhibitor of CYP3A4 and results in 2 to 3 fold increase in mean AUC of orally coadministered midazolam, a sensitive CYP3A4 substrate. In contrast, ketoconazole, a potent inhibitor of CYP 3A4 is known to increase the AUC of midazolam by 9 to 16 fold.
- Aprepitant also increases the AUC of orally administered diltiazem and methyl prednisolone (not so highly specific substrates!) by about two fold.
- Concomitant administration of aprepitant increased dexamethasone AUC by 2 fold. Therefore, dexamethasone dose in the clinical trials for the aprepitant (active) treatment group was approximately half of that used in the standard therapy (comparator) group.
- Coadministration of aprepitant did not significantly affect the pharmacokinetics of intravenously administered ondansetron or orally administered granisetron. Drug interaction data with dolasetron is unavailable. However, dolasetron is known to be metabolized by multiple pathways including CYP2D6 and CYP3A4. Blood levels of hydrodolasetron (active metabolite of dolasetron) increased 24% when dolasetron was coadministered with cimetidine (nonselective inhibitor of cytochrome P-450) for 7 days, and decreased 28% with coadministration of rifampin (potent inducer of cytochrome P-450) for 7 days.
- Potent CYP3A4 inhibitor, ketoconazole, inhibited the metabolism of aprepitant significantly resulting in a 5-fold mean increase in AUC of aprepitant, while a moderate CYP3A4 inhibitor, diltiazem resulted in about two fold increase. However, since all the three drugs in the aprepitant regimen are CYP3A4 substrates, coadministration of CYP3A4 inhibitors may result in increased concentrations of these drugs.
- Potent CYP3A4 inducer, rifampin, reduced the plasma concentration of coadministered aprepitant by 90%. However, since all the three drugs in the aprepitant regimen are CYP3A4 substrates, coadministration of CYP3A4 inducers may result in decreased concentrations of these drugs.
- Aprepitant is an inducer of CYP2C9; the ratio of International Normalized Ratio (INR) fold-change from baseline decreased by about 11% on Day 8 following concomitant administration of aprepitant 125 mg/80 mg three day regimen. The S-warfarin trough plasma concentration decreased by up to 34% by Day 8.
- Aprepitant does not have significant effect on P-gp mediated transport as evidenced by no change in the pharmacokinetics of coadministered digoxin, a substrate of P-gp transporter.

Conclusions relevant to the long term administration (more than 7 days)-

- On chronic administration, aprepitant is an inducer of CYP3A4 and resulted in a 40% reduction in levels of ethinyl estradiol (CYP3A4 substrate).
- Concomitant administration of two weeks of aprepitant tablet formulation (approximately comparable to 85 to 170 mg of the market formulation), resulted in slightly decreased (25%) AUC of paroxetine (CYP2D6 substrate). Mechanism for lowering of paroxetine concentrations is not understood because CYP2D6 isozyme is not known to be inducible enzyme. However, these results indicate the aprepitant does not inhibit the metabolism of CYP2D6 substrates.

1.3.1. Potential of aprepitant to interact with chemotherapeutic agents that are metabolized by CYP3A4 isozyme:

The drug interaction study results in the NDA have shown that aprepitant is an inhibitor of CYP3A4 on short term administration. Aprepitant administered as 5 day regimen (125 mg on Day 1, 80 mg/day from Day 2 to 5) showed significant inhibition of CYP 3A4, as seen by 2 to 3 fold mean increase in midazolam (highly specific substrate) AUC. Aprepitant also resulted in a two fold increase in AUC of dexamethasone and diltiazem, not so highly specific substrate of CYP3A4. Thus it is possible that aprepitant (at the doses recommended in Emend) may result in a two to three fold mean increase in the plasma levels of coadministered drugs that are primarily metabolized by CYP 3A4.

There are many chemotherapeutic agents for which CYP 3A4 plays an important role in their metabolism. Increase in chemotherapeutic agent's plasma concentration due to inhibition of its metabolism by aprepitant may result in significant toxicity of these agents. Some of the chemotherapeutic agents that are known or suspected to be metabolized by CYP3A4 isozyme include: docetaxel, paclitaxel, irinotecan, etoposide, vinorelbine, vinblastine, vincristine, ifosfamide, cyclophosphamide, and imatinib. Unfortunately, adequate information regarding drug-drug interactions is not available for many of these agents either from sponsor's studies or published literature. Based on the sponsor's background package for the AC meeting, there is an ongoing drug interaction study which investigates the effect of aprepitant on docetaxel (given intravenously), a chemotherapeutic drug primarily metabolized by CYP3A4. Preliminary results with five patients suggest no clinically significant interaction.

One study reported in the literature showed that ketoconazole increased the exposure to SN-38, the active metabolite of irinotecan by 109% and the article recommends up to four-fold reduction in dosage. Due to lack of data from the controlled drug interaction study(ies) between Emend and chemotherapeutic drugs and lack of sufficient information in the literature about the effect of CYP3A inhibitors on chemotherapeutic drugs, it is difficult to recommend any dosage adjustments/appropriate precaution/warning in the label. However, clinical trial database consists of patients who were administered some of these chemotherapy agents metabolized by CYP3A4. For discussion on the safety database in the Phase III clinical studies, please refer to the clinical review section.

1.4. QT analysis in Clinical Pharmacology studies:

There was no prospectively planned, controlled clinical study to evaluate the effect of aprepitant on QT interval. A comprehensive analysis of the effect of aprepitant on QT_c interval was performed on the EKG data collected in several clinical pharmacology studies.

Most of the QT interval readings consisted of automatic readings measured at either one to two time points (4, or 8 hours) with capsule formulation or more frequently with tablet or IV formulation (e.g., 0.5, 1, 2, 4, 8, and 24 hours).

Only 4 subjects in each of nanoparticle capsule clinical dose (4 of 86 subjects; 4.7%), nanoparticle capsule higher than clinical dose (4 of 43 subjects, 9.3%) and placebo treatment groups (4 of 43

subjects; 9.3%) had QT_c interval increases from baseline ≥ 30 and ≤ 60 msec.

QT_c interval increases from baseline ≥ 30 and ≤ 60 msec were slightly higher (8 subjects, 11.6%) for the early tablet formulation compared to capsule formulation. For the L-758298 IV treatment, 9 subjects (of 80 subjects; 11.3%) and 1 subject (of 40; 2.5%) on placebo had QT_c interval changes ≥ 30 and ≤ 60 msec.

Only one subject had QT_c interval > 500 msec at 24 hours following administration of 800 mg tablet formulation. This subject also received a single dose of 1200 mg with no prolongation of QT_c.

In summary, the sponsor concluded that there were few, if any, outliers of clinical concern and many of the subjects who are outliers had subsequent higher doses of L-758298 or oral aprepitant with no changes in QT_c.

1.5. Exposure-Response (PK/PD) information:

The correlation between plasma concentrations of aprepitant and the binding to brain NK₁ receptors (measured by using positron emission tomography (PET)) was assessed in two clinical pharmacology studies in healthy young men. Based on the data from the two studies, there is good correlation between plasma trough concentrations of aprepitant and its binding to brain NK₁ receptors. Based on the correlation, trough concentrations of 10 ng/ml and 100 ng/ml produce NK₁ receptor occupancy of about 50% and 90%, respectively.

In Phase IIb dose ranging studies of CINV, submaximal antiemetic efficacy was achieved at 40-mg/25 mg regimen, while maximum efficacy was achieved with 125 mg/80 mg regimen and there was no apparent benefit at the highest dose regimen of 375 mg/250 mg. Based on the pharmacokinetic pharmacodynamic (PK/PD) correlation, trough concentrations from 375mg /250 mg and 125-mg/80-mg regimens are predicted to provide $>95\%$ NK₁ receptor blockade, while 40 mg/25 mg results in approximately 80 to 89% receptor occupancy. Based on the Phase IIb dose ranging studies and the PK/PD relationship, the sponsor concluded that nearly complete ($>95\%$) NK₁ receptor blockade is required to obtain maximum antiemetic efficacy of aprepitant and NK₁ receptor blockade of 80 to 90% still provides significant but less than maximal antiemetic efficacy.