CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-549/S-008

Trade Name: EMEND Capsules, 80 mg and 125 mg.

Generic Name: Aprepitant

Sponsor: MERCK & CO., Inc.,

Approval Date: October 28, 2005

Indications: The use of Emend™ (aprepitant) in the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

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APPLICATION NUMBER:

21-549/S-008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-549/S-008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-549/S-008

Merck & Co., Inc.
Attention: Vijay Tammara, Ph.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tammara:

Please refer to your supplemental new drug application dated September 29, 2004, received September 29, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Emend™ (aprepitant) Capsules, 80 mg and 125 mg.

We acknowledge receipt of your submissions dated September 29 and December 17, 2004, as well as your submissions dated January 5, January 28, May 20, June 14, June 15, June 16, June 20, and July 22, 2005.

We also acknowledge receipt of your submission dated October 27, 2005 sent via email containing your currently approved packaging components.

This supplemental new drug application provides for the use of Emend™ (aprepitant) in the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert and the text for the patient package insert, (package insert submitted via email October 25, 2005 and patient package insert submitted via email October 18, 2005). In addition, the FPL must be identical to the packaging components submitted via email October 27, 2005, as follows: Trade-Tri-Fold 80-125 mg, Sample Tri-Fold 80-125 mg, HUD carton 125 mg, HUD Blister 80 mg, HUD carton 80 mg, HUD Blister 125 mg, Sample carton 80 mg, Sample Foil 80 mg, Sample Carton 125 mg, and Sample Foil 125 mg.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-549/S-008.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 to less than 6 months of age and deferring pediatric studies for ages 6 months to less than 17 years of age for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the use of Emend ™ (aprepitant) in the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in pediatric patients 6 months to less than 17 years of age.

   Final Report Submission: December 31, 2007

We also remind you of your postmarketing study commitment submitted October 25, 2005 via email and agreed-upon in an October 25, 2005 teleconference between you and this Division. This commitment is listed below.

2. Conduct an appropriately powered randomized controlled clinical trial, in patients receiving moderately emetogenic chemotherapy (MEC), designed to document generalizability among various chemotherapies and an evaluation of efficacy in male patients.

Protocol Submission:	by March 31, 2006
Study Start:	by December 31, 2006
Final Report Submssion:	by December 31, 2008

Submit final study reports to this NDA. For administrative purposes, all submissions related to the pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitment**."

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Betsy Scroggs, Regulatory Project Manager, at (301) 796-0991.

Sincerely,

{See appended electronic signature page}

Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joyce Korvick

10/28/2005 01:28:43 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-549/S-008

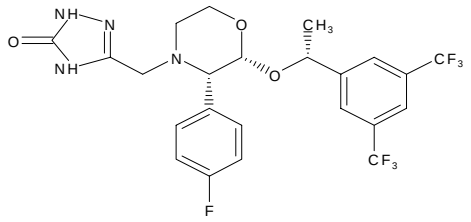
LABELING

EMEND®
(aprepitant)
CAPSULES

DESCRIPTION

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

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



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

Each capsule of EMEND for oral administration contains either 80 mg or 125 mg of aprepitant and the following inactive ingredients: sucrose, microcrystalline cellulose, hydroxypropyl cellulose and sodium lauryl sulfate. The capsule shell excipients are gelatin, titanium dioxide, and may contain sodium lauryl sulfate and silicon dioxide. The 125-mg capsule also contains red ferric oxide and yellow ferric oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK_1) receptors. Aprepitant has little or no affinity for serotonin ($5\text{-}HT_3$), dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CINV).

Aprepitant has been shown in animal models to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Animal and human Positron Emission Tomography (PET) studies with aprepitant have shown that it crosses the blood brain barrier and occupies brain NK_1 receptors. Animal and human studies show that aprepitant augments the antiemetic activity of the $5\text{-}HT_3$-receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis.

Pharmacokinetics

Absorption

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

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

Following oral administration of a single 125-mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 and 3, the $AUC_{0\text{-}24hr}$ was approximately 19.6 mcg•hr/mL and 21.2 mcg•hr/mL on Day 1 and Day 3, respectively. The C_{max} of 1.6 mcg/mL and 1.4 mcg/mL were reached in approximately 4 hours (T_{max}) on Day 1 and Day 3, respectively.

Distribution

Aprepitant is greater than 95% bound to plasma proteins. The mean apparent volume of distribution at steady state (Vd_{ss}) is approximately 70 L in humans.

Aprepitant crosses the placenta in rats and rabbits and crosses the blood brain barrier in humans (see CLINICAL PHARMACOLOGY, *Mechanism of Action*).

Metabolism

Aprepitant undergoes extensive metabolism. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism is largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6, CYP2C9, or CYP2E1 was detected. 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.

Excretion

Following administration of a single IV 100-mg dose of [^{14}C]-aprepitant prodrug to healthy subjects, 57% of the radioactivity was recovered in urine and 45% in feces. A study was not conducted with radiolabeled capsule formulation. The results after oral administration may differ.

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. The apparent plasma clearance of aprepitant ranged from approximately 62 to 90 mL/min. The apparent terminal half-life ranged from approximately 9 to 13 hours.

Special Populations

Gender

Following oral administration of a single 125-mg dose of EMEND, no difference in $AUC_{0\text{-}24hr}$ was observed between males and females. 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 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.

Geriatric

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 $AUC_{0\text{-}24hr}$ of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (≥65 years) relative to younger adults. The C_{max} was 10% higher on Day 1 and 24% higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful. No dosage adjustment for EMEND is necessary in elderly patients.

Pediatric

The pharmacokinetics of EMEND have not been evaluated in patients below 18 years of age.

Race

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

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) (see PRECAUTIONS).

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 hemodialysis.

In patients with severe renal insufficiency, the $AUC_{0\text{-}\infty}$ of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects. In patients with ESRD undergoing hemodialysis, the $AUC_{0\text{-}\infty}$ of total aprepitant decreased by 42% and C_{max} decreased by 32%.

Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal insufficiency compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

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

Clinical Studies

Oral administration of EMEND in combination with ondansetron and dexamethasone (aprepitant regimen) has been shown to prevent acute and delayed nausea and vomiting associated with highly emetogenic chemotherapy including high-dose cisplatin, and nausea and vomiting associated with moderately emetogenic chemotherapy.

Highly Emetogenic Chemotherapy

In 2 multicenter, randomized, parallel, double-blind, controlled clinical studies, the aprepitant regimen (see table below) was compared with standard therapy in patients receiving a chemotherapy regimen that included cisplatin >50 mg/m^2 (mean cisplatin dose = 80.2 mg/m^2). Of the 550 patients who were randomized to receive the aprepitant regimen, 42% were women, 58% men, 59% White, 3% Asian, 5% Black, 12% Hispanic American, and 21% Multi-Racial. The aprepitant-treated patients in these clinical studies ranged from 14 to 84 years of age, with a mean age of 56 years. 170 patients were 65 years or older, with 29 patients being 75 years or older.

Patients (N = 1105) were randomized to either the aprepitant regimen (N = 550) or standard therapy (N = 555). The treatment regimens are defined in the table below.

Treatment Regimens
Highly Emetogenic Chemotherapy Trials

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

Aprepitant placebo and dexamethasone placebo were used to maintain blinding.

During these studies 95% of the patients in the aprepitant group received a concomitant chemotherapeutic agent in addition to protocol-mandated cisplatin. The most common chemotherapeutic agents and the number of aprepitant patients exposed follows: etoposide (106), fluorouracil (100), gemcitabine (89), vinorelbine (82), paclitaxel (52), cyclophosphamide (50), doxorubicin (38), docetaxel (11).

The 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 endpoints:

Primary endpoint:

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

Other prespecified endpoints:

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

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

Table 1

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)[†] %	Standard Therapy (N = 261)[†] %	p-Value

PRIMARY ENDPOINT			
Complete Response			
Overall[‡]	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[§]	89	78	<0.001
Delayed phase[‖]	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

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

Table 2

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 2 — Cycle 1

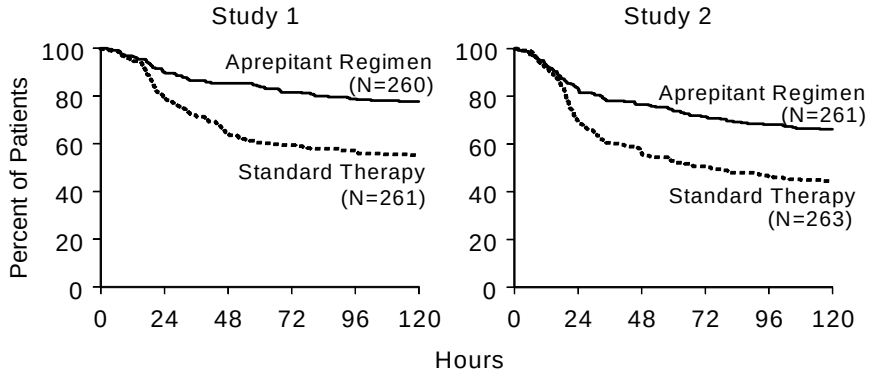
ENDPOINTS	Aprepitant Regimen (N = 261)[†] %	Standard Therapy (N = 263)[†] %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall[‡]	63	43	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[§]	83	68	<0.001
Delayed phase[‖]	68	47	<0.001
Complete Protection			
Overall	56	41	<0.001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

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

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

In both studies, the estimated time to first emesis after initiation of cisplatin treatment was longer with the aprepitant regimen, and the incidence of first emesis was reduced in the aprepitant regimen group compared with standard therapy group as depicted in the Kaplan-Meier curves in Figure 1.

Figure 1: Percent of Patients Receiving Highly Emetogenic Chemotherapy Who Remain Emesis Free Over Time – Cycle 1

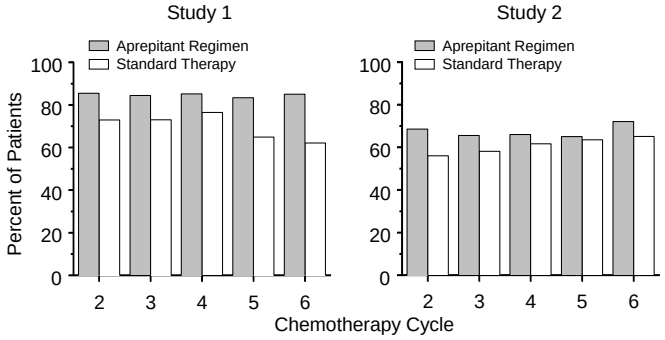


p-Value <0.001 based on a log rank test for Study 1 and Study 2; nominal p-values not adjusted for multiplicity.

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

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

Figure 2: Proportion of Patients Receiving Highly Emetogenic Chemotherapy 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

In a multicenter, randomized, double-blind, parallel-group, clinical study in breast cancer patients, the aprepitant regimen (see table that follows) was compared with a standard of care therapy in patients receiving a moderately emetogenic 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).

In this study, the most common combinations were cyclophosphamide + doxorubicin (60.6%); and cyclophosphamide + epirubicin + fluorouracil (21.6%).

Of the 438 patients who were randomized to receive the aprepitant regimen, 99.5% were women. Of these, approximately 80% were White, 8% Black, 8% Asian, 4% Hispanic, and <1% Other. The aprepitant-treated patients in this clinical study ranged from 25 to 78 years of age, with a mean age of 53 years; 70 patients were 65 years or older, with 12 patients being over 74 years.

Patients (N = 866) were randomized to either the aprepitant regimen (N = 438) or standard therapy (N = 428). The treatment regimens are defined in the table that follows.

Treatment Regimens
Moderately Emetogenic Chemotherapy Trial

Treatment Regimen	Day 1	Days 2 to 3
Aprepitant	Aprepitant 125 mg PO[†] Dexamethasone 12 mg PO[‡] Ondansetron 8 mg PO x 2 doses[§]	Aprepitant 80 mg PO Daily
Standard Therapy	Dexamethasone 20 mg PO Ondansetron 8 mg PO x 2 doses	Ondansetron 8 mg PO Daily (every 12 hours)

Aprepitant placebo and dexamethasone placebo were used to maintain blinding.
[†]1 hour prior to chemotherapy.
[‡]30 minutes prior to chemotherapy.
[§]30 to 60 minutes prior to chemotherapy and 8 hours after first ondansetron dose.

The antiemetic activity of EMEND was evaluated based on the following endpoints:

Primary endpoint:

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

Other prespecified endpoints:

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

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

Table 3

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

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

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

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

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

Multiple-Cycle Extension: Patients receiving moderately emetogenic chemotherapy were permitted to continue into the Multiple-Cycle extension of the study for up to 3 additional cycles of chemotherapy. Antiemetic effect for patients receiving the aprepitant regimen is maintained during all cycles.

INDICATIONS AND USAGE

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 including high dose cisplatin
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

EMEND is a moderate CYP3A4 inhibitor. EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions (see PRECAUTIONS, *Drug Interactions*).

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

PRECAUTIONS

General

EMEND should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents that are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these concomitant medicinal products. The effect of EMEND on the pharmacokinetics of orally administered CYP3A4 substrates is expected to be greater than the effect of EMEND on the pharmacokinetics of intravenously administered CYP3A4 substrates (see PRECAUTIONS, *Drug Interactions*).

Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. In clinical studies, EMEND was administered commonly with etoposide, vinorelbine, or paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions.

In a separate pharmacokinetic study in patients receiving docetaxel, which is also metabolized by CYP3A4, EMEND did not influence the pharmacokinetics of docetaxel.

Due to the small number of patients in clinical studies who received the CYP3A4 substrates vinblastine, vincristine, or ifosfamide, particular caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4 that were not studied (see PRECAUTIONS, *Drug Interactions*).

Chronic continuous use of EMEND for prevention of nausea and vomiting is not recommended because it has not been studied and because the drug interaction profile may change during chronic continuous use.

Coadministration of EMEND with warfarin may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time. In patients on chronic warfarin therapy, the INR should be

closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND with each chemotherapy cycle (see PRECAUTIONS, *Drug Interactions*).

Upon coadministration with EMEND, the efficacy of hormonal contraceptives during and for 28 days following the last dose of EMEND may be reduced. Alternative or back-up methods of contraception should be used during treatment with EMEND and for 1 month following the last dose of EMEND (see PRECAUTIONS, *Drug Interactions*).

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9). Therefore, caution should be exercised when EMEND is administered in these patients (see CLINICAL PHARMACOLOGY, *Special Populations, Hepatic Insufficiency* and DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians should instruct their patients to read the patient package insert before starting therapy with EMEND and to reread it each time the prescription is renewed.

Patients should be instructed to take EMEND only as prescribed. Patients should be advised to take their first dose (125 mg) of EMEND 1 hour prior to chemotherapy treatment.

EMEND may interact with some drugs including chemotherapy; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products.

Patients on chronic warfarin therapy should be instructed to have their clotting status closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND with each chemotherapy cycle.

Administration of EMEND may reduce the efficacy of hormonal contraceptives. Patients should be advised to use alternative or back-up methods of contraception during treatment with EMEND and for 1 month following the last dose of EMEND.

Drug Interactions

Aprepitant is a substrate, a moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

Effect of aprepitant on the pharmacokinetics of other agents

As a moderate inhibitor of CYP3A4, aprepitant can increase plasma concentrations of coadministered medicinal products that are metabolized through CYP3A4 (see CONTRAINDICATIONS).

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

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, aprepitant 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 oral dexamethasone doses should be reduced by approximately 50% when coadministered with EMEND, to achieve exposures of dexamethasone similar to those obtained when it is given without EMEND. The daily dose of dexamethasone administered in clinical studies with EMEND reflects an approximate 50% reduction of the dose of dexamethasone (see DOSAGE AND ADMINISTRATION).

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 1.34-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 IV methylprednisolone dose should be reduced by approximately 25%, and the oral methylprednisolone dose should be reduced by approximately 50% when coadministered with EMEND to achieve exposures of methylprednisolone similar to those obtained when it is given without EMEND.

Chemotherapeutic agents: See PRECAUTIONS, *General*.

Docetaxel: In a pharmacokinetic study, EMEND did not influence the pharmacokinetics of docetaxel.

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 stabilized 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 Normalized 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 of EMEND with each chemotherapy cycle.

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

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

In another study, a daily dose of an oral contraceptive containing ethinyl estradiol and norethindrone was administered on Days 1 through 21, and EMEND was given as a 3-day 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 coadministration of EMEND may reduce the efficacy of hormonal contraceptives during and for 28 days after administration of the last dose of EMEND. Alternative or back-up methods of contraception should be used during treatment with EMEND and for 1 month following the last dose of EMEND.

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. The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these agents with EMEND.

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.

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, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir) should be approached with caution. Because moderate CYP3A4 inhibitors (e.g., diltiazem) result in a 2-fold increase in plasma concentrations of aprepitant, concomitant administration should also be approached with caution.

Aprepitant is a substrate for CYP3A4; therefore, coadministration of EMEND with drugs that strongly induce CYP3A4 activity (e.g., rifampin, carbamazepine, phenytoin) may result in reduced plasma concentrations of aprepitant that may result in decreased efficacy of EMEND.

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.

Rifampin: When a single 375-mg dose of EMEND was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampin, a strong CYP3A4 inducer, the AUC of aprepitant decreased approximately 11-fold and the mean terminal half-life decreased approximately 3-fold.

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

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Three 2-year carcinogenicity studies of aprepitant (two in Sprague-Dawley rats and one in CD-1 mice) were conducted with aprepitant. Dose selection for the studies was based on saturation of absorption in both species. In the rat carcinogenicity studies, animals were treated with oral doses of 0.05, 0.25, 1, 5, 25, 125 mg/kg twice daily. The highest dose tested produced a systemic exposure to aprepitant (plasma $AUC_{0\text{-}24hr}$) of 0.4 to 1.4 times the human exposure ($AUC_{0\text{-}24hr}$ = 19.6 mcg•hr/mL) at the recommended dose of 125 mg/day. Treatment with aprepitant at doses of 5 to 125 mg/kg twice per day produced thyroid follicular cell adenomas and carcinomas in male rats. In female rats, it produced increased incidences of hepatocellular adenoma at 25 and 125 mg/kg twice daily, and thyroid follicular adenoma at the 125 mg/kg twice daily dose. In the mouse carcinogenicity study, animals were treated with oral doses of 2.5, 25, 125, and 500 mg/kg/day. The highest tested dose produced a systemic exposure of about 2.2 to 2.7 times the human exposure at the recommended dose. Treatment with aprepitant produced skin fibrosarcomas in male mice of 125 and 500 mg/kg/day groups.

Aprepitant was not genotoxic in the Ames test, the human lymphoblastoid cell (TK6) mutagenesis test, the rat hepatocyte DNA strand break test, the Chinese hamster ovary (CHO) cell chromosome aberration test and the mouse micronucleus test.

Aprepitant did not affect the fertility or general reproductive performance of male or female rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the recommended human dose and exposure in female rats at about 1.6 times the human exposure).

Pregnancy. Teratogenic Effects: Category B. Teratology studies have been performed in rats at oral doses up to 1000 mg/kg twice daily (plasma $AUC_{0\text{-}24hr}$ of 31.3 mcg•hr/mL, about 1.6 times the human exposure at the recommended dose) and in rabbits at oral doses up to 25 mg/kg/day (plasma $AUC_{0\text{-}24hr}$ of 26.9 mcg•hr/mL, about 1.4 times the human exposure at the recommended dose) and have revealed no evidence of impaired fertility or harm to the fetus 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.

Nursing Mothers

Aprepitant is excreted in the milk of 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 potential for possible serious adverse reactions in nursing infants from aprepitant and because of the potential for tumorigenicity shown for aprepitant in rodent carcinogenicity studies, 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.

Pediatric Use

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

Geriatric Use

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

ADVERSE REACTIONS

The overall safety of aprepitant was evaluated in approximately 3800 individuals.

Highly Emetogenic Chemotherapy

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

In Cycle 1, clinical adverse experiences were reported in approximately 69% of patients treated with the aprepitant regimen compared with approximately 68% of patients treated with standard therapy. Table 4 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3%.

Table 4

Percent of Patients Receiving Highly Emetogenic Chemotherapy With Clinical Adverse Experiences (Incidence ≥3%) — Cycle 1

	Aprepitant Regimen (N = 544)	Standard Therapy (N = 550)
Body as a Whole/ Site Unspecified		
Abdominal Pain	4.6	3.3
Asthenia/Fatigue	17.8	11.8
Dehydration	5.9	5.1
Dizziness	6.6	4.4
Fever	2.9	3.5
Mucous Membrane Disorder	2.6	3.1
Digestive System		
Constipation	10.3	12.2
Diarrhea	10.3	7.5
Epigastric Discomfort	4.0	3.1
Gastritis	4.2	3.1
Heartburn	5.3	4.9
Nausea	12.7	11.8
Vomiting	7.5	7.6
Eyes, Ears, Nose, and Throat		
Tinnitus	3.7	3.8
Hemic and Lymphatic System		
Neutropenia	3.1	2.9
Metabolism and Nutrition		
Anorexia	10.1	9.5
Nervous System		
Headache	8.5	8.7
Insomnia	2.9	3.1
Respiratory System		
Hiccups	10.8	5.6

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

Moderately Emetogenic Chemotherapy

During Cycle 1 of a moderately emetogenic chemotherapy study, 438 patients were treated with the aprepitant regimen and 385 of these patients continued into the Multiple-Cycle extension for up to 4 cycles of chemotherapy. In Cycle 1, clinical adverse experiences were reported in approximately 73% of patients treated with the aprepitant regimen compared with approximately 75% of patients treated with standard therapy.

The adverse experience profile in the moderately emetogenic chemotherapy study was generally comparable to the highly emetogenic chemotherapy studies. Table 5 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3%.

Table 5

Percent of Patients Receiving Moderately Emetogenic Chemotherapy With Clinical Adverse Experiences (Incidence ≥3%) — Cycle 1

	Aprepitant Regimen (N = 438)	Standard Therapy (N = 428)
Blood and Lymphatic System Disorders		
Neutropenia	8.9	8.4
Metabolism and Nutrition Disorders		
Anorexia	4.3	5.8
Psychiatric Disorders		
Insomnia	4.1	5.6
Nervous System Disorders		
Dizziness	3.4	4.2
Headache	16.4	16.4
Vascular Disorders		
Hot Flush	3.0	1.4
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngolaryngeal pain	3.0	2.3
Gastrointestinal Disorders		
Constipation	12.3	18.0

Diarrhea	5.5	6.3
Dyspepsia	8.4	4.9
Nausea	7.1	7.5
Stomatitis	5.3	4.4
Skin and Subcutaneous Tissue Disorders		
Alopecia	24.0	22.2
General Disorders and General Administration Site Conditions		
Asthenia	3.4	3.7
Fatigue	21.9	21.5
Mucosal inflammation	2.5	3.5

Isolated cases of serious adverse experiences, regardless of causality, of dehydration, enterocolitis, febrile neutropenia, hypertension, hypoesthesia, neutropenic sepsis, pneumonia, and sinus tachycardia were reported in the moderately emetogenic CINV clinical study.

Highly and Moderately Emetogenic Chemotherapy

The following additional clinical adverse experiences (incidence >0.5% and greater than standard therapy), regardless of causality, were reported in patients treated with aprepitant regimen:
Infections and infestations: candidiasis, herpes simplex, lower respiratory infection, pharyngitis, septic shock, upper respiratory infection, urinary tract infection.
Neoplasms benign, malignant and unspecified (including cysts and polyps): malignant neoplasm, non-small cell lung carcinoma.
Blood and lymphatic system disorders: anemia, febrile neutropenia, thrombocytopenia.
Metabolism and nutrition disorders: appetite decreased, diabetes mellitus, hypokalemia.
Psychiatric disorders: anxiety disorder, confusion, depression.
Nervous system disorders: peripheral neuropathy, sensory neuropathy, taste disturbance, tremor.
Eye disorders: conjunctivitis.
Cardiac disorders: myocardial infarction, palpitations, tachycardia.
Vascular disorders: deep venous thrombosis, flushing, hypertension, hypotension.
Respiratory, thoracic and mediastinal disorders: cough, dyspnea, nasal secretion, pneumonitis, pulmonary embolism, respiratory insufficiency, vocal disturbance.
Gastrointestinal disorders: acid reflux, deglutition disorder, dry mouth, dysgeusia, dysphagia, eructation, flatulence, obstipation, salivation increased.
Skin and subcutaneous tissue disorders: acne, diaphoresis, rash.
Musculoskeletal and connective tissue disorders: arthralgia, back pain, muscular weakness, musculoskeletal pain, myalgia.
Renal and urinary disorders: dysuria, renal insufficiency.
Reproductive system and breast disorders: pelvic pain.
General disorders and administrative site conditions: edema, malaise, rigors.
Investigations: weight loss.

Laboratory Adverse Experiences Table 6 shows the percent of patients with laboratory adverse experiences reported at an incidence ≥3% in patients receiving highly emetogenic chemotherapy.

Table 6

Percent of Patients Receiving Highly Emetogenic Chemotherapy With Laboratory Adverse Experiences (Incidence ≥3%) — Cycle 1

	Aprepitant Regimen (N = 544)	Standard Therapy (N = 550)
ALT Increased	6.0	4.3
AST Increased	3.0	1.3
Blood Urea Nitrogen Increased	4.7	3.5
Serum Creatinine Increased	3.7	4.3
Proteinuria	6.8	5.3

The following additional laboratory adverse experiences (incidence >0.5% and greater than standard therapy), regardless of causality, were reported in patients treated with aprepitant regimen: alkaline phosphatase increased, hyperglycemia, hyponatremia, leukocytes increased, erythrocyturia, leukocyturia.

The adverse experiences of increased AST and ALT were generally mild and transient.

The following laboratory adverse experiences were reported at an incidence ≥3% during Cycle 1 of the moderately emetogenic chemotherapy study in patients treated with the aprepitant regimen or

standard therapy, respectively: decreased hemoglobin (2.3%, 4.7%) and decreased white blood cell count (9.3%, 9.0%).

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

Stevens-Johnson syndrome was reported in a patient receiving aprepitant with cancer chemotherapy in another CINV study. Angioedema and urticaria were reported in a patient receiving aprepitant in a non-CINV study.

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 hemodialysis.

DOSAGE AND ADMINISTRATION

EMEND is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist. The recommended dose of EMEND is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg 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	80 mg	80 mg	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 chemo herapy treatment on Day 1.

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	80 mg	80 mg
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 has not been studied for the treatment of established nausea and vomiting.

Chronic continuous administration is not recommended (see PRECAUTIONS).

See PRECAUTIONS, *Drug Interactions* for additional information on dose adjustment for corticosteroids when coadministered with EMEND.

Refer to the full prescribing information for coadministered antiemetic agents.

EMEND may be taken with or without food.

No dosage adjustment is necessary for the elderly.

No dosage adjustment is necessary for patients with renal insufficiency or for patients with end stage renal disease undergoing hemodialysis.

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

HOW SUPPLIED

No. 3854 — 80 mg capsules: White, opaque, hard gelatin capsule with “461” and “80 mg” printed radially in black ink on the body. They are supplied as follows:

NDC 0006-0461-30 bottles of 30 (with desiccant)

NDC 0006-0461-05 unit-dose packages of 5.

No. 3855 — 125 mg capsules: Opaque, hard gelatin capsule with white body and pink cap with “462” and “125 mg” printed radially in black ink on the body. They are supplied as follows:

NDC 0006-0462-30 bottles of 30 (with desiccant)

NDC 0006-0462-05 unit-dose packages of 5.

No. 3862 — Unit-of-use tri-fold pack containing one 125 mg capsule and two 80 mg capsules.

NDC 0006-3862-03.

Storage

Bottles: Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature]. The desiccant should remain in the original bottle.

Blisters: Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].

Rx only

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued ~~March 2005~~
Printed in USA

Patient Information
EMEND® (EE mend)
(aprepitant) Capsules

You should read this information before you start taking EMEND*. Also, read the leaflet each time you refill your prescription, in case any information has changed. This leaflet provides only a summary of certain information about EMEND. Your doctor or pharmacist can give you an additional leaflet that is written for health professionals that contains more complete information. This leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss EMEND when you start taking your medicine.

What is EMEND?

EMEND is an antiemetic medicine for use in adult patients. An antiemetic is a medicine used to prevent and control nausea and vomiting. EMEND is always used WITH OTHER MEDICINES to prevent and control nausea and vomiting caused by your chemotherapy treatment. EMEND is not used to treat nausea and vomiting that you already have.

Who should not take EMEND?**

Do not take EMEND if you:

- are taking any of the following medicines:
  - ORAP® (pimozide)
  - SELDANE® (terfenadine)
  - HISMANAL® (astemizole)
  - PROPULSID® (cisapride)

Taking EMEND with these medicines could cause serious or life-threatening problems.

- are allergic to any of the ingredients in EMEND. The active ingredient is aprepitant. See the end of this leaflet for a list of all the ingredients in EMEND.

What should I tell my doctor before and during treatment with EMEND?

Tell your doctor:

- if you are pregnant or plan to become pregnant. It is not known if EMEND can harm your unborn baby.
- if you are breast-feeding. It is not known if EMEND passes into your milk and if it can harm your baby.
- if you have liver problems.
- about all your medical problems.
- about all the medicines that you are taking or plan to take, prescription and nonprescription medicines, vitamins, and herbal supplements. EMEND may cause **serious life-threatening reactions** if used with certain medicines (see the section **Who should not take EMEND?**). Some medicines can affect EMEND. EMEND may also affect some medicines, including chemotherapy, causing them to work differently in your body.

Your doctor may check to make sure your other medicines are working, while you are taking EMEND. Patients who take COUMADIN® (warfarin) may need to have blood tests after each 3-day treatment with EMEND to check their blood clotting.

*Registered trademark of MERCK & CO., Inc.

** The brands listed are the registered trademarks of their respective owners and are not trademarks of Merck & Co., Inc.

Women who use birth control medicines during treatment with EMEND and for up to 1 month after using EMEND should also use a back-up method of contraception to avoid pregnancy.

How should I take EMEND?

- Take EMEND exactly as prescribed.
- EMEND is a capsule that you swallow with a drink.

The recommended dose of EMEND is:
- Take one 125-mg capsule (white/pink) by mouth 1 hour before you start your chemotherapy treatment;
  AND
- Take one 80-mg capsule (white) each morning for the 2 days following your chemotherapy treatment.

- EMEND may be taken with or without food.
- Do not start taking EMEND if you already have nausea and vomiting. Ask your doctor what to do.
- If you take too much EMEND, call your doctor, local emergency room or poison control center right away.

What are the possible side effects of EMEND?

The most common side effects with EMEND are:

- tiredness
- nausea
- hiccups
- constipation
- diarrhea
- loss of appetite
- headache
- hair loss

These are not all of the possible side effects of EMEND. For further information ask your doctor or pharmacist. Talk to your doctor about any side effect that bothers you.

General information about the use of EMEND

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use EMEND for a condition for which it was not prescribed. Do not give EMEND to other people, even if they have the same symptoms you have. It may harm them. Keep EMEND and all medicines out of the reach of children.

This leaflet summarizes the most important information about EMEND. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for information about EMEND that is written for health professionals.

What are the ingredients in EMEND?

Active ingredient: aprepitant

Inactive ingredients: sucrose, microcrystalline cellulose, hydroxypropyl cellulose and sodium lauryl sulfate. The capsule shell excipients are gelatin, titanium dioxide, and may contain sodium lauryl sulfate and silicon dioxide. The 125-mg capsule shell also contains red ferric oxide and yellow ferric oxide.

Issued 2005

MERCK & CO., Inc.
Whitehouse Station, NJ 08889, USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-549/S-008

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 10/24/05

FROM: Joyce A Korvick, MD, MPH **(Deputy Director)**

DGP/ODE III

SUBJECT: **Approval Comments**
NDA 21-549 S008

APPLICANT: Merck & Co., Inc.

DRUG: Emend® (Aprepitant) 80 mg and 125 mg capsules

REGULATORY RECOMMENDATIONS:
I recommend approval of Aprepitant for:

"the prevention of nausea and vomiting associated with initial and repeat course of moderately emetogenic cancer chemotherapy".

This indication varies from that Merck initially proposed to the Agency:

"The prevention of (b) (4) nausea and vomiting associated with initial and repeat course of moderately emetogenic cancer chemotherapy."

In addition it is important in labeling to represent the primary endpoint for complete response at 120 hours. The additional secondary and exploratory analyses did not achieve statistical significance in the phase 3 trial which was designed to test superiority. Those analyses are supportive of activity (b) (4) The p-value should only be displayed for the primary endpoint; all other comparisons should be designated as N.S. (not significant).

POSTMARKETING COMMITMENT:
Conduct a randomized controlled trial in patients receiving moderately emetogenic chemotherapy addressing the following issues:

1. generalizability among various chemotherapies including an evaluation of the efficacy in male patients.
2. if the distinction of "acute" and delayed" is sought then efficacy must be demonstrated in each time frame. The study analysis and design should be such that these endpoints reach statistical significance.

PEDIATRICS:
The sponsor requested a waiver of pediatric patients less than 2 years of age September 15, 2004. The Division denied this request to be consistent with the pediatric requests made of other drugs marketed for CINV; this included studying patients down to one

month of age. In this case the only formulation currently available is the capsule formulation which would be in appropriate to give to pediatric patients under 6 months of age. For the PREA request then we recommend a partial waiver from birth to under 6 months of age for this formulation, and a deferral for pediatric patients 6 months of age to less than 17 years of age for CINV associated with moderately emetogenic chemotherapy.

Division Director (Deputy) Review:
In my review I will discuss the:

- regulatory history of the CINV (chemotherapy induced nausea and vomiting) indications for the serotonin (5HT3) antagonist class,
- the current application,
- consideration of the various points of view of the review staff, and
- support of my recommendation regarding the alteration of Merck's proposed labeling and the approval of same.

I. BACKGROUND:

Aprepitant is a NK1 receptor antagonist and is approved for the:

"prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy."

The recommended combination dosing regimen is as follows:
Day 1: 125 mg aprepitant /12 mg dexamethasone po /32 mg ondansetron IV;
Day 2 &3: 80 mg aprepitant / 8mg dexamethasone;
Day 4: 8 mg dexamethasone

The indication was supported by 2 double-blind, randomized controlled clinical trials of approximately 500 patients each who were receiving highly emetogenic chemotherapy, mostly cisplatin based. The control arm in these studies included dexamethasone and ondansetron and matching placebo for aprepitant. Therefore, the study design is a placebo controlled trial of aprepitant on the background of standard antiemetic therapy. It is important to note that over the past 20 years as chemotherapeutic regimens changed, so did the anti-emetic therapies used by oncologists. Since 1991 when ondansetron was approved for the prevention of emesis associated with chemotherapy, it has become standard of practice in the oncology community to utilize corticosteroids along with ondansetron, or other 5HT3 receptor antagonists to treat emesis associated with chemotherapy. Thus, the study design could also be viewed as an add-on therapy. These points become important later in this review.

Now I will spend some time describing to the reader the regulatory history of the indication of "prevention of emesis associated with chemotherapy." I have chosen this wording carefully as this is the most "generic" way to describe this indication. The reader is referred to Tables 1 & 2 in the Appendix which outline the approval times and changes in labeled indication and dosages for the approved drugs. With the availability of ondansetron, a significant advance was made in the prevention of emesis associated with chemotherapy. One can see that as subsequent approvals in the 5HT3 class were granted, the indications have evolved as well as the data that support them. Further, as more 5HT3 drug products were developed, sponsors desired to develop a competitive niche in the marketplace, an additional advantage over already marketed drug products, e.g. "highly emetogenic", "moderately emetogenic", "acute" and "delayed". Finally, the development of the 5HT3 antagonists is relevant to the review of aprepitant (NK1 antagonist) (b) (4) The study designs across this class and the NK1 original approval are somewhat similar, but not similar enough to allow complete, direct comparisons across all NDA submissions as I will describe below.

In order to understand this evolution, I have reviewed all of the approval packages for "nausea and vomiting associated with chemotherapy" in detail for ondansetron, granisetron, dolasetron, palanosetron and aprepitant. There was a general approach to the development and approval of these agents; however, there exists nuances for each approval. My subsequent discussion will consider the following characteristics for each of these approvals and the labeled indications in an effort to provide clarity to what has become a somewhat artificially complex drug development process:

1. varying definition of the primary endpoint (no vomiting) and secondary endpoints (nausea, etc.).
2. acute verses delayed indications
3. data supporting the various product labeling.

The following table displays some of these characteristics which are reviewed in subsequent discussion.

Characteristics of Clinical Trials Supporting Approval

Drug	Formulation	1° Endpoint	Time frame	2° Endpoint (Nausea)
Ondansetron	IV (1)	No vomiting*	24 hours	Median Nausea scores were change from baseline at 24 hours (VAS scale (0-100). The rates were reported as undefined if more than if 50% of patients in that treatment group did not have nausea.
	IV (2)	No vomiting*	24 hours	
	Tab (1)	No vomiting*	3 days	
	Tab (2)	No vomiting*	3 days	
	Tab (3)	No vomiting & No rescue	24 hours	
Granisetron	IV	No vomiting & Only mild Nausea (<5 mm VAS)	24 hours	% patients with no more than mild nausea in 24 hours (< 5mm on a 0-100 VAS scale)
	Tab	No vomiting & Only mild nausea & No rescue & No withdrawal	24 hours**	
Dolasetron	IV	No vomiting*	24 hours	Median nausea score 24-hr change from baseline (VAS 0-100)
	Tab	No vomiting & No rescue	24 hours	
Aprepitant	Cap	No vomiting & No rescue	Overall*** 0-120 hours	% no nausea (VAS < 5mm)
Palonosetron	IV	No vomiting & No rescue	Acute (0-24 hours) Delayed (25-120 hours)	Quality of life FLEI including a VAS nausea scale (different scoring system, not numerically comparable with the above)

** includes retching episodes as vomiting.*
*** many of these studies in moderately emetogenic chemotherapy patients were originally designed to study the overall effect of the therapy at 7 to 14 days, however they were amended to 24 hours only. These data were not presented in the NDA.*
**** further defines secondary endpoints as acute (0-24 hours) and delayed (25-120 hours)*

ONDANSETRON

In review of the ondansetron original NDA application and subsequent applications several features can be seen. First, the design of the clinical trials included chemotherapy naive patients, not receiving any rescue medication, single day chemotherapy as well as antiemetic therapy, corticosteroids were prohibited and most importantly the studies were required to include a placebo control arm. Patients receiving cisplatin therapy were difficult to enroll because of the placebo treatment arm. The only other drug labeled for chemotherapy induced emesis was metoclopramide. It was utilized in several studies as an active comparator. The primary endpoint was no vomiting at 24 hours. Another strategy that was utilized in the clinical study of ondansetron was multiple-dose, dose comparison studies, where the effective dose was superior to the lowest dose that was assumed to be equivalent to placebo.

The intravenous label (original approval) does not reflect all of the studies that were submitted in support of this application; however, the studies were selected and displayed to demonstrate the effectiveness of ondansetron in the label. Resulting from the entire NDA data, the labeled indication was simply "Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin." The dose recommended was ondansetron 0.15 mg/kg x 3 during on the first day of chemotherapy.

Ondansetron tablets have a more complicated developmental history. The initial development was for the "prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy." The first approved label recommended a dose of ondansetron 8 mg three times per day for 3 days. In these studies the chemotherapy regimen was administered on the first day and the ondansetron was administered each day for 3 days. It is important to note that while the label does not distinguish a time frame of "acute", "delayed" or "overall" in the labeled indication, constructs that appear in recent labels, the data supported the efficacy as measured by day 3, "no vomiting" as the primary endpoint. The second supplement retained the same indication but demonstrated that a regimen of 8 mg bid was equally efficacious compared to the tid regimen.

The development of ondansetron tablets for highly emetogenic cancer chemotherapy, including cisplatin > 50 mg/m2 was accomplished in 2 clinical trials. The dose comparison study utilized ondansetron at 8 mg bid, 24mg qd, and 32 mg qd (no vomiting at 24 hours: 68/124 [55%] vs. 76/116 [66%] vs. 64/117 [55%]). The p-value for the 8 mg bid vs. 24 qd was 0.053. A second study was conducted to confirm this effect comparing ondansetron 24 mg qd orally to 10ug/kg intravenously. The no vomiting results were 106/184 (58%) vs. 95/186 (51%) (p-value – N.S) favoring the ondansetron 24 mg per day dose compared to the intravenous dose respectively. These data were compared to historical placebos from other concurrent controlled trials by the sponsor. This data in sum was considered adequate to allow a change in the labeling to include this dosing regimen as well as to change the indication to the: "Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy." In the dosage and administration section of the label it is of interest to note that following the recommendation for the 24 mg single day dose, it states "that multi-day, single-dose administration has not been studied."

The above was a very brief description of the development of ondansetron for the currently marketed indication of nausea and vomiting associated with chemotherapy. This reader's conclusion from review of the action packages is what one might expect for the development program of a first in class drug. There were many studies supporting this indication. For the intravenous dosing, it was concluded that while the Metoclopramide comparison (an approved drug) was not statistically superior an additional study was needed and this was considered supportive.

Suffice it to say, that the approval of ondansetron was based upon many different studies, which were based upon NO vomiting at 24 hours as the primary endpoint (except as noted above for Tab 1 &2 studies in moderate patients). Nausea is a more difficult endpoint to study and may be on a continuum in the mechanism for vomiting in these patients. When one looks at this endpoint as it is represented in the label it is displayed as the median change in VAS at 24 hours. It is important to note that the differences were highly significant in studies of highly emetogenic therapy, but were less dramatic in moderately emetogenic or regimens that do not contain cisplatin. Finally, one has to ask, if the analysis was statistically significant, was the difference in VAS scores clinically meaningful. The reporting of nausea as a secondary endpoint varies across studies of other drugs. Generally it was supportive of nausea; older studies do not adjust as rigorously as we do today for multiplicity analyses.

Finally, it will be important for the reader to recall that ondansetron 8 mg bid is approved in moderately emetogenic chemotherapy based upon the primary endpoint of no nausea by day 3 of a 3 day regimen.

GRANISETRON

In general, during the development of granisetron the sponsors state that a placebo controlled study is not ethically nor practically achieved at this point in time. If one looks at the timeline for the development of granisetron and ondansetron one also notes that the development and approvals were overlapping in time. Because of the difficulties with placebo design, the granisetron development plan relied on multi-dose, dose comparison studies as described above and presentation of historical placebo rates in order to demonstrate efficacy. In addition comparators included chlorpromazine, historical comparisons to prochlorpromazine, and historical placebo.

Both the intravenous and oral labeled indications are simply for the "prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy including high-dose cisplatin." It should be noted that in the clinical trial section of the intravenous label there is a distinct section for highly emetogenic chemotherapy and moderately emetogenic chemotherapy which is not more specifically stated in the labeled indication. For the moderately emetogenic studies, one finds that the comparative study was to a regimen of chlorpromazine plus dexamethasone 12 mg vs. granisetron 40 mcg/kg. The result for complete response, was 68% (N=133) vs. 47% (N=133), p-value < 0.001, favoring granisetron. It should be noted that the definition for the primary endpoint is somewhat different than that used for the ondansetron approvals (see table above). In addition, the nausea evaluation, which is presented as a rate for "no more than mild nausea", trended in the same direction (77% vs. 59%) as the vomiting result, favoring granisetron. In the same label, one of the pivotal studies for highly emetogenic therapy was broken down by high-dose vs. low dose cisplatin. In the low dose group there was no statistically significant difference across treatment groups for nausea. It may be difficult to distinguish an advantage for the secondary endpoint nausea in active comparator trials when a lesser emetogenic stimulus is used.

It is interesting to note that a recommended dose of granisetron is 10 mcg/kg 30 minutes before chemotherapy on the days that chemotherapy is given. This dose was recommended based upon safety concerns and additional studies in highly emetogenic chemotherapy patients and additional dose escalation studies. It appeared that this dose would have the best benefit-risk ratio. It was not based upon the strict p-value.

DOLASETRON

The intravenous formulation of dolasetron was originally approved for the "prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin" (Dose: 1.8mg/kg 30 minutes prior to chemotherapy; or fixed dose of 100 mg can be given one time). In this application there were three studies of dolasetron for highly emetogenic chemotherapy which demonstrated efficacy. There was one study in moderately emetogenic chemotherapy. This study compared dolasetron to metoclopramide (approved US dosing). The complete response rates were 63% (N=101) vs. 52% (N=104) p-value = 0.12 for dolasetron and metoclopramide, respectively. It was concluded that in patients

with moderately emetogenic chemotherapy, dolasetron was non-inferior to metoclopramide, and it showed a numerical trend (11% difference in rates).

It should be noted that the oral tablet formulation was submitted during the same time period as the intravenous formulation and both NDAs were approved on the same date. The tablet NDA submission focused on the indication of "the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, including initial and repeat courses" (Dose: 100mg within 1 hour prior to chemotherapy). The studies in support of this indication included 3 dose comparison studies, one of which included an ondansetron 8mg QID arm (not approved in the US). All of these showed a linear trend for the "no vomiting" endpoint. There was controversy regarding the recommended 100 mg dosing, some studies showed that 200 mg dose to be somewhat more active, however, due to potential safety concerns the 100mg dose is the recommended dose. It should be noted that across these studies the "no nausea" rates ranged between 40 and 63% for the 100 mg dolasetron dose. As mentioned above, there is a variety in the way nausea was analyzed and expressed in the labels. Dolasetron chose to express nausea as a rate among patients, where as the others tended to express it as the median 24 hour change from baseline.

APREPITANT (original NDA)

The approval of this new NK1 antagonist (March 26, 2003) occurred several years after the previously described 5HT3 antagonist and is contemporary with the approval of palonosetron (July 25, 2003). As mentioned before, regimens for chemotherapy evolved as well as the "standard" of care for emesis. At this time, steroids are part of an anti-emetic regimen and are considered standard of care. It is also important to comment, that up to this point in time the use of the terms "acute" and "delayed" have not been specifically used in the labeled indications. All of the indications avoid this reference since the studies were designed for an assessment of vomiting at 24 hours. Only one label, ondansetron tablets, reports the primary efficacy data at 3 days in the clinical trials section of the label, and was specifically designed as the primary endpoint at 3 days. Thus, one can infer from the label that ondansetron would be effective over 3 days for the prevention of nausea and vomiting. When one looks at the older labels, commented on above, the indication nausea was significant in highly emetogenic therapy, especially cisplatin base regimens, but these studies were not as carefully analyzed for the multiplicity correction for these various secondary endpoints including nausea. Finally, nausea cannot be compared across many of these studies because of the various ways in which it was reported and derived, median 24 h change in VAS score (in some studies this median change was reported as undefined because more than 50% of patients had no nausea), or proportion of patients with NO nausea over 24 hours. Nausea in general, is a more subjective endpoint than vomiting. With these points in mind we will approach the review and labeling of aprepitant and palonosetron below.

Aprepitant is a NK1 receptor antagonist. Although the mechanism of chemotherapy induced emesis is not completely understood, it appears that there is a release of neurokinin peptide substance P after administration of chemotherapy which stimulates the NK1 receptors in the brainstem promoting emesis. The maximal effect appears 2 to 5 days after the initial dose of chemotherapy. Aprepitant blocks this interaction. This is in contrast to the mechanism of action of the 5HT3 antagonists. Here, chemotherapy may promote emesis by increasing serotonin release with subsequent activation of the

receptors (5HT3 receptors) on the vagal afferent neurons in the gastrointestinal tract. When a single dose of chemotherapy is administered this generally peaks within the first 24 hours. Thus, the recommendation for administration of the 5HT3 antagonist class agents prior to chemotherapy.

The indication being sought is similar to those granted the 5HT3 antagonists, several of the design principles were taken from the previous studies, as outlined above, (b) (4)

The study treatment regimens were as follows:

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

This is the approved dosing for ondansetron 32 mg iv for 24hour prevention of nausea and vomiting. Dexamethasone is background therapy adjusted for interactions with aprepitant. Day 2 to 4 can be considered a placebo controlled study on the background of dexamethasone therapy. The results were statistically significant for the primary endpoint (Complete Response: no vomiting, no rescue therapy) for both the acute and delayed portion of the studies in two phase 3 trials. For the secondary endpoint of nausea, one pivotal study in highly emetogenic therapy was statistically significantly better than the standard therapy arm, while aprepitant was only numerically better than the standard arm, trending in the same direction. This second study was conducted outside of the US and it was felt that there may be a difference in reporting the subjective endpoint of nausea based on possible cultural differences. The Division has seen a difference in reporting of the subjective endpoint of nausea between the US and other countries in other studies. It was concluded that this data was sufficient to support the indication.

I will consider the current aprepitant application (S-008) for moderately emetogenic chemotherapy after I finish the review of the regulatory history. Now I turn to palonosetron.

PALONOSETRON

Palonosetron is the most recent drug approved it the 5HT3 class. The terminal elimination half-life of palonosetron is significantly longer than the other 5HT3 antagonists, 40 hours vs. 3.5 to 10 hours, respectively. It was for this reason that the sponsor argued for the relatively new indication of “acute” and “delayed”. In order to gain the indication for the acute and delayed phase the sponsor would have to demonstrate that palonosetron was effective in 24 hours as well as 24-120 hours after initiation of therapy.

Two phase 3 studies were performed in moderately emetogenic chemotherapy patients. One study compared palonosetron to ondansetron 32 mg and the other study compared palonosetron to dolasetron 100 mg. Both of these intravenous formulations are approved

for the 24 hour prevention period. Thus palonosetron was required to be non-inferior to the control groups. The comparison of palonosetron was statistically significantly better than ondansetron, and non-inferior to dolasetron. The complete response rate for palonosetron was greater than dolasetron (63% vs. 53%). It is important to note that in these studies the concomitant use of corticosteroids was only 4-6% and evenly distributed between the treatment groups. In the delayed analysis (25-120 hours) palonosetron was superior to both drugs (neither of which have been labeled for this indication). In thinking about this, one notes that a superior result to an unapproved labeled indication of an approved drug can be viewed as a comparison to placebo. In this case it worked, palonosetron was statistically significantly better than the control groups. Thus, for a moderately emetogenic therapy the longer half-life of palonosetron does seem to afford protection for 120 hours.

For completeness I will review the studies in support of the highly emetogenic chemotherapy patients. For this indication the sponsor submitted two pivotal studies: a large dose comparison study (similar to previously described 5HT3 drugs) as well as a Phase 3 study. There was a linear trend in the dose comparison trial. The phase 3 study compared palonosetron to ondansetron 32 mg IV (approved dose). The phase 3 study demonstrated superiority only in the first 24 hours. Because ondansetron IV 32 mg single dose therapy was not developed beyond the first 24 hours, palonosetron would have to be superior, applying the same reasoning as described above for moderately emetogenic chemotherapy. It was not statistically significantly better than ondansetron. Therefore, in the case of patients receiving a more severe emetogenic stimuli, the longer half-life of palonosetron did not show any advantage over "placebo", i.e. ondansetron. One confounding issue is the fact that in the highly emetogenic chemotherapy study 67% of patients received steroids prophylacticly. This may have been the reason that palonosetron was not able to show a superior difference over ondansetron in 24-120 hours.

In these studies, nausea was a secondary endpoint and was studied in a QOL manner and as severity of nausea on a Likert Scale, which is different that previous studies with ondansetron and dolasetron. In the moderately emetogenic studies there were some statistically significant comparisons, in the highly emetogenic study there were there were none. Finally, the statistical review did consider comparisons to historical controls of ondansetron and dolasetron and found these studies to be similar in results and therefore valid comparisons based on historical considerations as well.

Therefore, the division concluded that in moderately emetogenic chemotherapy palonosetron was effective over the course of therapy up to 120 hours. In addition, for a more severe stimulus (highly emetogenic chemotherapy) there was not enough data for the claim beyond 24 hours, and that the one phase 3 study and the dose comparison study were sufficiently similar to a single iv dose of ondansetorn (non-inferior) that an approval could be given for palonoseton's activity in the first 24 hours only.

II. CURRENT APREPITANT sNDA for Moderately Emetogenic Chemotherapy:

For this sNDA the sponsor submitted 1 large phase 3 study and relied on the highly emetogenic chemotherapy prior approval as supportive evidence for the moderately emetogenic indication. (b) (4) Aprepitant is an add-on therapy in the first 24 hours and is compared directly to ondanseton 8 mg bid on days 2-5 (approved therapy). The study design is displayed below

	Day 1	Days 2 to 3
Aprepitant (N=433)	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 16mg PO	Aprepitant 80 mg PO Daily Ondansetron placebo PO Daily (BID)
Comparator (N=424)	Aprepitant Placebo PO Dexamethasone 20 mg PO Ondansetron 16mg PO	Aprepitant Placebo PO Daily Ondansetron 8 mg PO Daily (BID)

Here aprepitant is administered as daily therapy contrasted with that of most of the 5HT3 which is administered on day one only.

The primary endpoint stated by the sponsor was Complete Response Overall. This was statistically significantly superior compared to the control arm. It would appear that acute is superior but as we will see the multiplicity adjustments render the results NS. The second primary endpoint was the FLEI as stated in the protocol, a quality of life endpoint with vomiting and nausea domains. This was statistically significant on the overall time period. It is interesting that the efficacy in the quality of life instrument appears to be driven by the vomiting domain.

Phase	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Overall Phase (0 to 120 hours)*	220/433 (50.8)	180/424 (42.5)	0.015
Acute phase (0 to 24 hours)ŦŦ	327/432 (75.7)	292/423 (69.0)	0.034¥
Delayed phase (25 to 120 hours) Ŧ	240/433 (55.4)	208/424 (49.1)	N.S.

Ref: Table 3.1.2 , P071.pdf
* Primary Endpoint
ŦExploratory Endpoint
¥ Not Significant after applying the Applicant's multiplicity adjustment
(Confirmed by Agency Statistician, Dr. Wen-Jen Chen, Ph.D.)

Part of the difficulty with evaluating (b) (4) of the indication involves the study design and the rules with which the statistical analyses are performed. It makes clinical and biological sense to study the overall effect of a multi-day therapy on the primary outcome. One would expect the results of the secondary outcomes to support this overall effect.

In this application, the statistical analysis plan designed to protect the p-value against multiplicity was different that that of the original application. Here the sponsor chose a hierarchy procedure. A closed testing procedure was employed by grouping the exploratory efficacy endpoints and testing each group of endpoints in a sequential fashion such that subsequent groups of efficacy endpoints would not be tested unless the prior groups each revealed at least one statistically significant finding. Hochberg's procedure was used to adjust for testing the multiple efficacy endpoints within the group to control the type I error at the 0.05 level.

The groups of efficacy endpoints are listed below in the order in which they were to be tested:

Group 1

- Complete Response in acute and delayed phases;

Group 2

- No Significant Nausea in the overall phase;
- Time to first vomiting episode in the overall phase;
- Complete Protection (no vomiting, no rescue therapy, and no significant nausea) in overall phase.

Group 3

- No vomiting in the delayed phase;
- No Significant Nausea in the delayed phase;
- Complete Protection in the delayed phase.

Group 4

- No vomiting in the acute phase;
- No Significant Nausea in the acute phase;
- Complete Protection in the acute phase.

Group 5

- Total Control (no vomiting, no rescue therapy, and no nausea, i.e., peak VAS < 5 mm) in acute, delayed, and overall phases;
- No Use of Rescue Therapy in the acute and delayed Phases;
- No Nausea in the 0 to 72 hours time frame;
- No Significant Nausea in the 0 to 72 hours time frame; and
- ≥3 vomiting episodes in the Overall phase.
-

The exploratory endpoints were only considered for statistical significance provided the primary and secondary hypotheses were satisfied. The results are listed below.

Exploratory Endpoints	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Complete Response			
Acute phase (0 to 24 hours)	327/432 (75.7)	292/423 (69.0)	0.034**
Delayed phase (25 to 120 hours)	240/433 (55.4)	208/424 (49.1)	N.S.
No Vomiting			
Acute phase	378/432 (87.5)	327/423 (77.3)	<0.001**
Delayed phase	349/432 (80.8)	293/424 (69.1)	<0.001**
No Use of Rescue Therapy			
Acute phase	355/429 (82.8)	336/420 (80.0)	N.S.
Delayed phase	271/432 (62.7)	253/423 (59.8)	N.S.
No Significant Nausea (maximum VAS <25 mm)			
Overall phase	262/430 (60.9)	236/424 (55.7)	N.S.
Acute phase	342/430 (79.5)	331/423 (78.3)	N.S.
Delayed phase	281/430 (65.3)	260/423 (61.5)	N.S.
0 to 72 hours	274/430 (63.7)	254/424 (59.9)	N.S.
No Nausea (maximum VAS <5 mm)			
Overall phase	142/430 (33.0)	140/424 (33.0)	N.S.
Acute phase	261/430 (60.7)	250/423 (59.1)	N.S.
Delayed phase	159/430 (37.0)	154/423 (36.4)	N.S.
0 to 72 hours	167/430 (38.8%)	159/424 (37.5)	N.S.
Complete Protection (no vomiting, no rescue and maximum nausea VAS <25 mm)			
Overall phase	184/433 (42.5)	156/424 (36.8)	N.S.
Acute phase	296/431 (68.7)	272/423 (64.3)	N.S.
Delayed phase	203/433 (46.9)	180/424 (42.5)	N.S.
Total Control (no vomiting, no rescue and maximum nausea VAS <5 mm)			
Overall phase	125/433 (28.9)	115/424 (27.1)	N.S.
Acute phase	241/431 (55.9)	222/423 (52.5)	N.S.
Delayed phase	139/433 (32.1)	132/424 (31.1)	N.S.

Ref: Table 3.1.3, Statistical Review

†: Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group

** Not statically significant after adjusting for multiplicity

VAS = Visual analogue scale.

One can see that while statistical significance cannot given for these secondary endpoints, there was activity. In fact it was either similar to or better than the comparator by rate. If one were to look at this from a non-inferiority position, for the delayed portion, complete response would be well within a 10% bounds. Thus making aprepitant comparable to ondansetron which is approved for the prevention of nausea and vomiting based upon a multiple day endpoint.

III. Summary Discussion and Conclusions:

Review of this application in moderately emetogenic caner chemotherapy patients leads me to the following conclusions:

1. Aprepitant regimen is superior ondansetron regime for "complete response" in the "overall" timeframe compared to the control regimen (ondansetron is approved for multi-day therapy).
2. Aprepitant is comparable to ondansetron for the "acute" and "delayed" complete response but not statistically significantly superior (b) (4)
3. Secondary endpoint comparisons were not statistically significantly different for aprepitant compared to the control regimen, however, the results trend in same direction as the primary endpoint, favoring aprepitant.
4. The statistical significance of the FLIE appears to be driven by the no vomiting endpoint domain.
5. There is no difference in nausea domain when comparing aprepitant to the approved drug, ondansetron.
6. Ondansetron is a valid, active comparator.

The facts of the statistical analysis are agreed upon agreed upon by all of the reviewers, including the medical TL, however, the interpretation and application to labeling differs. I believe that this single study was robust enough to support a claim in moderately emetogenic chemotherapy patients, using the support to the Highly Emetogenic studies as I have described above.

What specific indication could be supported by these data?
I agree that these data do not support the indication (b) (4) In my review of the entire regulatory history, it has been demonstrated that if vomiting associated with highly emetogenic chemotherapy can be prevented, it can be prevented in patients receiving moderately emetogenic therapy. It is biologically plausible, as the MO reviewer states since these are the same mechanism and the stimuli are on a continuum.

Nausea is treated as a secondary endpoint across various applications. In the older studies the statistical analysis was not corrected for multiplicity, and the analysis varied being presented as a rate or a median change or as part of a quality of life scale. Nausea is also a more subjective endpoint than nausea. Overall, in these applications the nausea results appeared to follow vomiting results, sometimes being statistically superior and other times being similar. Again, nausea and vomiting are on a continuum, and therefore the less vomiting one sees, the less significant nausea there should be. Finally, it is similar to ondansetron, an approved drug. I believe that as convention nausea be placed in the proposed indication in moderately emetogenic chemotherapy patients.

Finally, it is important to consider how to represent the patient population that was studied in the label. Review of the regulatory history does show that studies had varying populations of men and women. Some were almost exclusively women. An issue brought up by the MO reviewer comments on a potential gender issue. In the original NDA for highly emetogenic chemotherapy there was a gender interaction in one of the two studies. In this study the primary efficacy result was statistically superior to control

for the female population but only numerically better for the male patient group. The results are as follows:

Complete Response by Stratification Factor by Treatment Group I Highly Emetogenic Patients – Study 052		
	Aprepitant Regimen	Standard Therapy
Female	76/98 (77.6%)	38/98 (38.8%)
Male	113/162 (69.8%)	98/162 (60.5%)

This was not the case in study 054, where there was no by gender interaction. It appeared the aprepitant worked equally well in both males and females. Thus, I believe it is appropriate to label the fact this the moderately emetogenic therapy was performed in breast cancer patients in the clinical trials section of the label for two reasons. It gives the data to the oncologist, and it prevents the indication from becoming more undely complicated than it already is. I intend to ask the sponsor for an additional study to further demonstrate the activity of aprepitant in a broader population of patients receiving a variety of chemotherapies, including more males in these studies as a phase IV commitment. A variety of companion agents that are used with cisplatin therapy were already studied as regimens upon which cisplatin was added in the highly emetogenic chemotherapy studies. This can serve as additional supporting data, but should be confirmed in phase IV studies.

I conclude that these data are sufficient to support an abbreviated indication "the prevention of nausea and vomiting associated with initial and repeat course of moderately emetogenic cancer chemotherapy". This is consistent with the ondansetron tablet label. The negative data will be commented on in the label (see my recommendations interim labeling FAX'd to sponsor 10/18/05).

Given the past regulatory record, current regulatory thinking, the biologic plausibility, previous supportive data in moderately emetogenic chemotherapy studies and the variation in labeling among 5HT3 products in the class, my recommendation is consistent with current CDER review standards.

Comments Addressing the Medical Team Leader Concerns:
Since the medical Team Leader has recommended an approvable action instead of an approval, I will address each one of his concerns, in italics (The addendum of the medical reviewer and the statistical reviewer recommend approval). These concerns are listed in his memo of September 27, 2005.

"First, based on the Division's initial evaluations, addressed in detail in the initial MO Review and the corresponding MTL review [section I of the current memorandum], the data from the single study 071 are not convincing of efficacy. (b) (4) *. For the later, the study was set to demonstrate the aprepitant [alone] is superior to ondansetron [mono therapy]. This is a new use, since the clinical trials for the highly emetogenic chemotherapy indication included dexamethasone, in an add-on approach. Since Study 071,* (b) (4) *, this add on approach was not used. Thus, nowhere in the sponsor's extensive clinical development program there are persuasive*

clinical and statistical data that may be used to demonstrate effectiveness of the new use [aprepitant alone].”

This comment contains several issues which are somewhat overlapping and not clearly evaluated.

a. The “Division” did not conclude that the action should be approvable, but awaited the MO and MTL review of the substantial amendment. At the time of the substantial amendment, the medical officer was recommending approvable because, as he states in his addendum, that he was unsure how to apply the data from the prior approval to this one. In his addendum he addresses this and recommends approval. In subsequent labeling discussions, he felt that the revised proposed labeling is appropriate and is supported by study 071 and the prior approval.
b. The sponsor proposed a single study as their sole study in support of the indication, and the division agreed that if it was robust, it may lead to an approval. Study 071 was the sole study. The primary endpoint was the complete response (no vomiting, no rescue) at 120 hours. Aprepitant was statistically, significantly superior to ondansetron. Ondansetron is an approved, active comparator for this indication. The ondansetron tablet approval was based upon a 3 day no vomiting (including retching) endpoint. The primary result of study 071 is robust.
c. The issue of steroids is bothersome to the MTL. It turns out that this is standard of care in the oncology community today, whereas it was not in the early 1990’s when ondansetron was originally approved. Including steroids on the first day is acceptable. This would control steroid use and make it equivalent among the groups. Grant it, the use of steroids was different in the original approval of aprepitant (every day for 4 days), but this is somewhat irrelevant to the overall endpoint. If aprepitant is a weaker drug than ondansetron, and is not given beyond 24 hours, this might be a more difficult hurdle for aprepitant to surmount. Thus, the significantly superior response is even more clinically significant.
d. In study 071 aprepitant was used as a combination therapy on day one and as a single therapy on day 2 and 3. Though the secondary results for acute and delayed are not statistically significant they are a least as good as those for the comparator arm, i.e. numerically superior. So there is some overlap with both the prior approval of ondansetron and the regimen which gives steroid and aprepitant, both supportive of the approval.

“<u>Second</u>, prior approvals for the moderately emetogenic indication, (b) (4) *. Specifically, after review of the evidence,* (b) (4) *for the use of ondansetron hydrochloride [Glaxo], granisetron hydrochloride [Smith Kline and Beecham, now part of Glaxo], and dolasetron mesylate [Aventis]. Similarly, palonosetron hydrochloride [Helsinn Healthcare] is indicated for the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy and the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy. Thus, approval for use of palonosetron for the highly emetogenic* (b) (4)

It is not clear what issue this comment is addressing. As described above in the palonosetron regulatory history, the sponsor explicitly designed the studies to show both acute and delayed effects. Since the "delayed" indication was a highly sought indication it was felt that it should be statistically significant and supported by 2 studies. In the delayed indication this was not the case for highly emetogenic for the primary endpoint of complete response (no vomiting). The sponsor did not desire the overall claim; however, if both acute and delayed were positive, they were allowed to display the overall outcome in the clinical trials section of the label.

Regarding the ondansetron and granisetron supplements, there was a reference in the granisetron applications which referred to the amended protocols. In this case the complete response would be analyzed for 24 hours only. The original protocols state that the study was over 7-14 days of repeat dose moderately emetogenic chemotherapy. From a read of the administrative record, approval packages, it is not clear why this amendment was made. There are no data in the application which refer to the endpoints beyond 24 hours. As for denying claims, there is no record of this in these applications.

As I have described above, palonosetron has a longer half-life; (b) (4) In that application the statistical analysis was designed differently. Palonosetron was required to show superiority for (b) (4) was the desired one. In the highly emetogenic patients it was not demonstrated so only (b) (4) was given.

"<u>Third</u>, the efficacy results did not support approval of the proposed indication: prevention of nausea and vomiting. The results from Study 071 may have demonstrated a significant advantage over standard therapy for only the vomiting endpoint. Analyses of all nausea related endpoints failed to differentiate aprepitant from the standard therapy comparator. Labeling these negative data is very challenging."

As pointed out in the review of the regulatory history, the nausea endpoint is more subjective than the vomiting endpoint. This secondary endpoint has been either numerically superior to other comparators or statistically significantly better than placebo. Since ondansetron was the only 5HT3 approval based upon placebos, it became harder to show superiority to approved 5HT3 products. Also, analyses of multiple secondary endpoints were not adjusted for multiplicity as we do today. Therefore, what may seem to be a statistically significant p-value may not be when corrections are made. The labeled indication for all of these drugs is "nausea and vomiting' associated with chemotherapy. All of the studies have utilized vomiting as the primary endpoint in the clinical trials. The have demonstrated efficacy on the basis of superiority to placebo, dose comparison studies, and active comparator studies. Nausea was not always statistically significantly better. In this case they failed to show superiority, but they were at least as good as ondansetron, which is an active, approved drug. Please refer to FDA proposed labeling to see how these issues are addressed. It is not as challenging as the MTL suggests.

"<u>Fourth</u>, the analyses of the individual components of the primary and secondary endpoints demonstrated that the success of these endpoints were driven by the No Vomiting variable. The aprepitant regimen had no significant effect on the use of rescue

therapy or the symptoms of nausea ("exploratory endpoints"). Again, labeling these negative data is very challenging."

The response to this issue is covered in my discussion to point number three above.

"Fifth, in addition to the lack of demonstration of efficacy in the acute and the delayed phases separately, there are unsettled clinical issues related to the design and execution of Study 071 and the use of the drug if approved. These constraints include issues regarding generalizability of results since Study 071 only evaluated the safety and efficacy of aprepitant when administered with moderately emetogenic chemotherapeutic regimens used to treat breast cancer. These results may not necessarily be generalizable to other moderate emetogenic chemotherapy regimens. One additional constraint is that the study population consisted almost exclusively of female patients. This means that the safety and efficacy of aprepitant in male patients receiving moderately emetogenic chemotherapy regimens is yet to be demonstrated."

Study 071 was a study of breast cancer patients mostly in female patients. While there may be an issue regarding the generalizability to the male population, we have evidence from the original NDA (as described in regulatory history section) that gives us confidence that aprepitant is effective in male patients. While the regimens for various moderately emetogenic therapies may differ from those given to breast cancer patients, patients with highly emetogenic chemotherapy were given some of these as companion drugs to the cisplatin. For these reasons, the results are plausible and generalizable to the male population. In addition, historically, not all of the combinations of cancer chemotherapy were studied in the studies which lead to approvals in the past. There are studies in predominantly women which did not lead to restrictions in the indication. On the whole this is sufficient data for the indication with wording in the clinical trials section of the label. The sponsor has agreed to the phase 4 commitment. Finally, there are no safety concerns regarding this regimen as the medical officer states in his review.

"Sixth, it seems that it would be very confusing to the reader to include in the labeling so many negative findings or the lack of data assessing the effects of the drug in a variety of unsettled issues."

I agree that it might be confusing to the reader of the label if one where to place all of the secondary endpoints into the label. We generally do not do this, even in the older labels, at times there is only brief review of the primary outcome, complete response, in the label. (b) (4) It is important to note that these are clinically meaningful in light of the fact that ondansetron is approved based on a mulit-day primary endpoint. Finally, this drug is currently marketed, and the other reviewers and statistical staff have agreed with our newly proposed indication and labeling which address the concerns above.

I have addressed each one of the MOTL concerns in a logical manner based upon the written record. He is correct that this is a very complicated area given the past regulatory history; however, some of the "artificial" constructs that have evolved in the labeling language make it so.

APPENDIX

Table 1: Timelines* for serotonin 5HT3 receptor antagonist anti-emesis development

Year		'91		'92		'93		'94		'95		'96		'97		'98		'99		'00		'01		'02		'03	
Ondansetron (Zofran)	CINV	IV			TAB	IV				TAB								HEC									
	PONV					IV				TAB																	
	RINV								TAB																		
Granisetron (Kytril)	CINV						IV			TAB				TAB								sol					
	PONV																								IV		
	RINV																		TAB			sol					
Dolasetron (Anzemet)	CINV														TAB IV												
Aprepitant** (Emend)	CINV																									CAP	
Palonosetron (Aloxi)	CINV																										IV

**years denoted as six month intervals*
***NK1receptor antagonist*

Table 2: CINV Labels		
Drug	Formu-lation*	**Indication/Dosing**
Ondansetron (Zofran)	IV-1	Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin. Dose: 0.15 mg/kg x 3 (studied over 24 hours)
	IV-2	Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin. Efficacy of the 32 mg single dose for longer than on day in these patients has not been established. Dose: 0.15 mg/kg x 3 (studied over 24 hours); or a single 32 mg dose prior to chemotherapy
	TAB-1	Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy Dose: 8 mg 3x per day for 3 days (one dose of chemo on day 1)
	TAB-2	Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy Dose: 8 mg tab every 12 hours for 3 days.
	TAB-3	Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy , including cisplatin > 50 mg/m2 Dose: 24 mg x1 30 mins prior to chemo. Note that multi day, single-dose administration has not been studied.
Granisetron (Kytril)	IV	Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy including high-dose cisplatin Dose: 10 mcg/kg, 30 mins before chemo, and only on the days that chemo is given.
	TAB	Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin. Dose: 2 mg once per day (’97) or 1 mg twice per day (’95), 1hour before RX and for the second dose of 1 mg 12 hours later.
Dolasetron (Anzemet)	IV	Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin Dose: 1.8mg/kg 30 mins prior to chemotherapy; or fixed dose of 100 mg can be given one time.
	TAB	Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, including initial and repeat courses Dose: 100mg within 1 hour prior to chemotherapy.
Aprepitent** (Emend)	CAP	Prevention of acute and delayed nausea and vomiting associated wit initial and repeat courses of highly emetogenic cancer chemotherapy Dose: day 1:Emend 125 mg/12mg dexa/32 mg ondansetron IV; Day 2 &3:emend 80 mg/8mg dexamethasone Day 4: 8 mg dexamethasone Currently seeking indication (b) (4) for moderately emetogenic Dose for moderate is: day 1: Emend 125 mg/12 mg dexamethasone/8 mg bid ondansetron po D2&3: emend 80 mg.
Palonosetron (Aloxi)	IV	Prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and Prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. Dose: Single iv 0.25 mg dose 30 minutes prior

** more than one listing of the formulation indicates change in labeling based on supplemental NDA submission.*

*** NK1receptor antagonist*

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/s/

Joyce Korvick
10/28/2005 11:22:04 AM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Addendum

DATE: ***September 27, 2005***

FROM: Hugo E. Gallo-Torres, MD, PhD, PNS
Division of Gastrointestinal Products [HFD-180]
DGDP/ODE III

SUBJECT: GI Team Leader **AE** Comments
S-NDA 21-549 *[Submitted July 22, 2005]*

APPLICANT: **Merck & Co., Inc.**
West Point, PA 19486

DRUG: **Aprepitant [Selective, neurokinin (NK_1)-receptor antagonist]**

INDICATION: Prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of *moderately* emetogenic cancer [MEC] chemotherapy

GI TEAM LEADER AE RECOMMENDATION:

In his initial review, Dr. Gary DellaZanna, the Medical Officer Reviewer, concluded that results of Study 071 do not support approval for the use of aprepitant for the prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy. As documented in his initial review, the MTL agreed with this conclusion. In an addendum to his review, the MO reviewer recommended approval of the application on the basis of a "related indication" approach, with post-marketing commitments. In the current addendum, the MTL delineates a number of significant constraints that, in his opinion, preclude an AP recommendation using the "related indication" approach.

To resolve outstanding issues, Merck should consider additional Phase III studies assessing the use of the drug in the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic chemotherapy. These future studies should a) enroll both male and female patients; b) not be limited to breast cancer; c) be designed to demonstrate effectiveness in the prevention of *both* nausea and vomiting; d) demonstrate efficacy in *both* the acute and delayed phase time periods, separately; and e) preferentially use aprepitant as an add on therapy. This would be an approach like the one used successfully to demonstrate that the drug is safe and effective in the prevention of acute and delayed nausea and vomiting associated with highly emetogenic chemotherapy.

I. BACKGROUND/INTRODUCTION

EMEND® (aprepitant) is a substance P/neurokinin receptor antagonist with little or no affinity for serotonin (5-HT_3), dopamine, and corticosteroids receptors. Animal and human studies show that aprepitant augments the antiemetic activity of the 5-HT_3- receptor antagonist ondansetron and the corticosteroid dexamethasone**.** Aprepitant was first approved in March 2003 as part of a three day, three drug regimen for the prevention of ***acute*** and ***delayed*** chemotherapy-induced nausea and vomiting associated with initial and repeat courses of ***highly emetogenic*** chemotherapy regimens.

- It is worth noting that the sponsor's approach to testing effects of the drug in the prevention of highly emetogenic chemotherapy consisted of an ***add on*** approach, for both the acute as well as the delayed phase.

Treatment Arms for the Approved Prevention of Nausea and Vomiting Induced by Highly Emetogenic Chemotherapy

	Day 1	Days 2 to 4
Aprepitant	Aprepitant 125 mg PO DEX 12 mg PO Ondansetron 32 mg I.V.	Aprepitant 80 mg PO Daily [Days 2 and 3 only] DEX 8 mg PO Daily (morning)
Standard Therapy	DEX 20 mg PO Ondansetron 32mg I.V.	DEX 8 mg PO Daily (morning) DEX 8 mg PO Daily (evening)

- For the acute indication the backbone of efficacy is due to a 5-HT_3 drug, to which dexamethasone [DEX] and aprepitant are added. For the delayed indication, the clinical trials compared the effect of aprepitant to DEX 8 mg PO daily given in the evening in patients that were receiving DEX 8 mg PO daily in the morning. The reader is invited to note the presence of DEX in both the acute as well as the delayed phase of the trials. Although the precise role of DEX has not been clearly delineated, in the clinic, it is customary to add DEX as part of the antiemetic regimens.

On September 29, 2004, Merck submitted S-NDA 21549/S008 seeking approval for the prevention of (b) (4) nausea and vomiting associated with initial and repeated courses of ***moderately emetogenic*** chemotherapy. The submission consisted of results of a single Phase III multicenter, randomized, double-blind, parallel-group trial (Study # 71) that enrolled patients diagnosed with breast cancer that were scheduled to receive moderately emetogenic chemotherapy.

- It is important to mention that to assess the effect of the drug during the first 24 after administration of the moderately emetogenic chemotherapy stimuli [***acute*** CINV], the sponsor still used the **add on** approach. Aprepitant was added to ondansetron and DEX. However, this add on approach was no longer used for the 25th through the 120th

evaluations [***delayed*** CINV]. Thus, I shown below, the evaluations for the (b) (4) consist of a head-to-head comparison of aprepitant 80 mg PO daily to ondansetron 8 mg PO daily [BID]. During Days 2 to 3 of the trial the aprepitant arm contains ondansetron placebo while the ondansetron standard therapy comparator arm contains aprepitant placebo. The protocol-stipulated primary purpose of this trial in patients receiving moderately emetogenic chemotherapy was to demonstrate that the aprepitant regimen provided ***superior*** prevention of chemotherapy-induced nausea and vomiting when compared to a recognized standard of care. Specifically, for the delayed phase evaluations, Study # 71 was set to show that aprepitant 80 mg PO daily ***is superior*** to ondansetron 8 mg PO daily (BID).

Treatment Arms for the Requested Indication: Prevention of Nausea and Vomiting Induced by Moderately Emetogenic Chemotherapy

	Day 1	Days 2 to 3
Aprepitant	Aprepitant 125 mg PO DEX 12 mg PO Ondansetron 8mg PO (BID)	Aprepitant 80 mg PO Daily Ondansetron placebo PO Daily (BID)
Standard Therapy	Aprepitant Placebo PO DEX 20 mg PO Ondansetron 8mg PO (BID)	Aprepitant Placebo PO Daily Ondansetron 8 mg PO Daily (BID)

- Although in Study 071 a responder was defined as a patient who reported no vomiting and did not require rescue therapy for 0 to 120 h after receiving a dose of moderately emetogenic chemotherapy, this endpoint is inappropriate because it does not allow differentiation of results from the *acute* vs the *delayed* phase. Results of the 0 to 24th h [acute] phase and the 25th to 120th [delayed] phase need to be evaluated separately because one is analyzing the effects of the drug (b) (4). These considerations do not preclude displaying of the results from 0 to 120 hours, such as in the case of palonosetron. But this was done only after efficacy was demonstrated in the acute as well as the delayed phase separately, in those patients being treated with moderately emetogenic chemotherapeutic agents [Aloxi® labeling].

- As displayed in a series of Tables listed in the original MTL (b) (4) . On the other hand, (b) (4)

In his original review, based on the original review of the MO, the MTL considered the efficacy results under the following four headings: Complete response, Complete Response: Overall phase, Additional

Endpoints of Efficacy: Acute vs Delayed Phase and Additional Unsettled Efficacy Issues. Owing to the importance of the MTL recommendation for regulatory action, this information on efficacy is reproduced below. As repeatedly stated by both the MO Reviewer and the MTL, safety is not an issue.

A. Complete Response

Study 071 failed to show that the aprepitant regimen offered any significant advantage over standard therapy for Complete Response in *Acute* and/or *Delayed* phase time periods separately. The therapeutic gains appear to be of doubtful clinical significance [6.7% for the acute, 6.3% for the delayed phase]. In addition, neither of these two differences between the treatment arms was statistically significant.

Study 071: Complete Response
Cycle 1

Phase	Aprepitant Regimen [n = 433]	Standard Regimen [n = 424]	Treatment difference/p-Value
Acute phase (0 to 24 hours)	75.7%	69.0%	6.7% [NS]¥
Delayed phase (25 to 120 hours)	55.4%	49.1%	6.3% [NS]

¥ This p-value of 0.034 becomes not significant after applying the Applicant's multiplicity adjustment (Confirmed by Agency Statistician, Dr. Wen-Jen Chen, Ph.D.)
NOTE: Although the sponsor calls the 0 to 24th h and the 25th "exploratory endpoints" there nothing exploratory about the evaluations (b) (4)

This MTL Table is based, in part, in the data in Table 2 of the MOR of S-NDA 21-549 S-008.

B. Complete Response: Overall Phase

As already mentioned, in the MTL's opinion, this approach of lumping together the results of evaluations of acute and delayed effects is inappropriate because it does not allow differentiation between these two phases. Owing to the design of the trial, this differentiation is critical because results from the acute phase, where effects of **add on therapy** are being tested, may spill over the delayed phase, where, according to the protocol-stipulated purpose of the trial, the effects of aprepitant [alone] are expected to be superior to those of alosetron [alone]. But, as already noted, in Study 071, evaluations for the delayed phase are no longer under add on conditions. This is because each drug is given with the placebo of the other. As pointed out by the MO Reviewer, the analyses of the individual components of the primary and secondary endpoints demonstrated that the success of these endpoints was driven by the No Vomiting variable. The aprepitant regimen had no significant effect on the use of rescue therapy or the symptoms of nausea ("exploratory endpoints", see below).

C. Additional Endpoints of Efficacy: Acute vs Delayed Phase

The following Table, taken from Dr. DellaZanna's review, without modifications, clearly demonstrate that, when results of the acute and the delayed phase are analyzed separately, the aprepitant regimen is not superior [**the object of the clinical trial was to demonstrate superiority**] to the comparator, the

standard regimen. The parameters of efficacy ["Exploratory Endpoints"] included customary endpoints of evaluation of efficacy: Complete Response, No Vomiting, No Use of Rescue Therapy, No Significant Nausea [maximum VAS < 25 mm], No Nausea [maximum VAS < 5 mm]. But disappointing results were also seen using **Complete Protection** [no vomiting, no rescue and maximum nauseas VAS < 25 mm] and **Total Control** [no vomiting, no rescue and maximum nausea VAS < 5 mm] as the parameters of evaluation of efficacy.

Study 071
Results of Exploratory Endpoints of Efficacy (Cycle 1)
mITT Patient Population
Sponsor's Analyses

Exploratory Endpoints	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Complete Response			
Acute phase (0 to 24 hours)	327/432 (75.7)	292/423 (69.0)	N.S. ∓
Delayed phase (25 to 120 hours)	240/433 (55.4)	208/424 (49.1)	N.S.
No Vomiting			
Acute phase	378/432 (87.5)	327/423 (77.3)	N.S. ∓
Delayed phase	349/432 (80.8)	293/424 (69.1)	N.S. ∓
No Use of Rescue Therapy			
Acute phase	355/429 (82.8)	336/420 (80.0)	N.S.
Delayed phase	271/432 (62.7)	253/423 (59.8)	N.S.
No Significant Nausea (maximum VAS <25 mm)			
Overall phase	262/430 (60.9)	236/424 (55.7)	N.S.
Acute phase	342/430 (79.5)	331/423 (78.3)	N.S.
Delayed phase	281/430 (65.3)	260/423 (61.5)	N.S.
0 to 72 hours	274/430 (63.7)	254/424 (59.9)	N.S.
No Nausea (maximum VAS <5 mm)			
Overall phase	142/430 (33.0)	140/424 (33.0)	N.S.
Acute phase	261/430 (60.7)	250/423 (59.1)	N.S.
Delayed phase	159/430 (37.0)	154/423 (36.4)	N.S.
0 to 72 hours	167/430 (38.8%)	159/424 (37.5)	N.S.
Complete Protection (no vomiting, no rescue and maximum nausea VAS <25 mm)			
Overall phase	184/433 (42.5)	156/424 (36.8)	N.S.
Acute phase	296/431 (68.7)	272/423 (64.3)	N.S.
Delayed phase	203/433 (46.9)	180/424 (42.5)	N.S.
Total Control (no vomiting, no rescue and maximum nausea VAS <5 mm)			
Overall phase	125/433 (28.9)	115/424 (27.1)	N.S.
Acute phase	241/431 (55.9)	222/423 (52.5)	N.S.
Delayed phase	139/433 (32.1)	132/424 (31.1)	N.S.

Ref: Table 3.1.3, Statistical Review
†: Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group, investigator group, and age category (<55 years, ≥55 years).
∓ – Not Statically Significant after Applying Merck's Data Analysis Plan
VAS = Visual analogue scale.

D. Additional Unsettled Efficacy Issues

In addition to the lack of demonstration of efficacy in the acute and the delayed phases separately, the MOR identified other clinical issues related to the design and execution of Study 071 and the use of the drug if approved. As noted by Dr. DellaZanna, it is unknown whether the results of Study 071 can be generalized to all patients receiving moderately emetogenic chemotherapy. Greater than 99% of the patients were female. This is an important limitation in the efficacy data since a treatment-by-gender interaction was identified in one of the two pivotal trials submitted with the original NDA. It is unknown whether this gender interaction would be more significant in patients receiving moderate emetogenic agents. Furthermore, Study 071 only evaluated the safety and efficacy of aprepitant when administered with moderately emetogenic chemotherapeutic regimens used to treat breast cancer. As noted by Drs. N. Scher and A. Farrell [Division of Drug Oncology Products], in a Consult review dated 09/23/05, these results may not necessarily be generalizable to other moderate emetogenic chemotherapy regimens.

Based on his review of the above summarized evidence [data from single trial Study Protocol 071 submitted in S-NDA 21-549/S008] Dr. Gary DellaZanna, the Medical Officer Reviewer, concluded that that results of Study 071 do not support approval for the use of aprepitant for the prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy. As documented in his initial memorandum to files, the MTL agreed with this conclusion.

II. MEDICAL OFFICER'S ADDENDUM

Dr. DellaZanna has written an addendum to his review, recommending approval of the application. In the current addendum, the MTL considers this new recommendation for regulatory action.

In his addendum, Dr. DellaZanna mentions that following a detailed discussion of the issues discussed in detail in his review and summarized in the original MTL review and presented in a succinct fashion in Section I. above, the sponsor voiced disagreement with the Division's interpretation of the data and requested an opportunity to respond to the Division's concerns. As a result of these discussions, the Division agreed to review a Major Amendment which would include Merck's justifications regarding the robustness of the data and a post-hoc non-inferiority analysis for the nausea endpoints. This Major Amendment was the focus of Dr. DellaZanna's addendum to his review. Dr. DellaZanna points out that after several internal meetings, which focused on Merck's justifications regarding the robustness of the data, and the level of significance required to grant approval of a new indication based on a single study, "the Review team determined that the results from the original NDA could be considered as supporting evidence for this S-NDA. The two distinct indications, Highly and Moderately emetogenic CINV, are closely related and, from a regulatory viewpoint, may be treated in a similar fashion. The Aprepitant regimen had already succeeded in demonstrating efficacy under experimental conditions using a more potent emetogenic stimulus". The MTL did not disagree with the related indication approach, in principle. There is no question that such an approach offers opportunities that may justify certain

regulatory actions. But it is also true that it is important to identify constraints, if any, associated with such an approach.

Dr. DellaZanna noted that with consideration of the efficacy data from the original NDA (21-549 /000), he now recommended that the S-NDA (21-549 /008) for the Moderately Emetogenic indication be Approved. He arrived at the conclusion that with the supportive evidence from the original NDA (21-549 /000), the information in the initial S-NDA is adequate to support approval of the new indication. He clarified that he initially approached the S-NDA Application as a new indication based on a *single study*. As such, his initial recommendations were based on the need for "robust", highly statistically significant results. It was *originally* the Medical Officer's opinion that, although Study 071 succeeded for its primary and secondary efficacy endpoints, the results from Study 071 were not sufficiently robust to support approval based on a *single study*... The results of the exploratory endpoints were not statistically significant; however, they were all either numerically in favor of aprepitant or equal to the Standard of Care which is widely accepted as effective. According to Dr. DellaZanna, even though the success of the primary and secondary endpoints were driven by the "no vomiting" variable, the results for the nausea related variables are clinically significant, considering the Standard Care comparator is recognized as effective. Dr. DellaZanna states that the single trial, Protocol 071, with the support of the efficacy results from the highly emetogenic application, is *adequate* to grant approval of the proposed new indication(s): "the prevention of (b) (4) *nausea* and *vomiting* associated with initial and repeated courses of moderately emetogenic cancer chemotherapy." The MTL does not agree with this conclusion.

The MO Reviewer also notes that there remain some unanswered questions regarding the generalizability of Study 071. In his opinion, based on the results from the original NDA, these issues can be addressed as a Phase IV commitment. According to Dr. DellaZanna, approval should be contingent on Merck agreeing to perform a study to further evaluate the safety and efficacy of the aprepitant regimen in both male and female patients receiving moderately emetogenic chemotherapy regimens. This study should be designed to demonstrate that the aprepitant regimen is effective in the prevention of both nausea and vomiting, in both the acute and delayed phase time periods.

III. MTL SUMMARY/CONCLUSIONS

The MTL believes that there are too many significant constraints that, taken together, preclude the use of the "related indication" approach.

First, based on the Division's initial evaluations, addressed in detail in the initial MO Review and the corresponding MTL review [Section I of the current memorandum], the data from the single Study 071 are not convincing of efficacy. (b) (4). For the latter, the study was set to demonstrate that aprepitant [alone] is superior to ondansetron [monotherapy]. This is a new use, since the clinical trials for the highly emetogenic indication included DEX, in an add on approach. In Study 071, evaluations of the effect of the drug in the (b) (4) of the moderately emetogenic (b) (4) this add on approach was not used. Thus, nowhere in the sponsor's extensive clinical development program there are persuasive clinical and statistical data that may be used to demonstrate effectiveness of the new use [aprepitant alone].

Second, prior approvals for the moderately emetogenic indication, [redacted], have been denied for lack of data. Specifically, after review of the evidence, the Division [redacted] for the use of ondansetron hydrochloride [Glaxo], granisetron hydrochloride [Smith Kline and Beecham, now part of Glaxo], and dolasetron mesylate [Aventis]. Similarly, palonosetron hydrochloride [Helsinn Healthcare] is indicated for the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy and the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy. [redacted]

Third, the efficacy results did not support approval of the proposed indication: prevention of *nausea and vomiting*. The results from Study 071 may have demonstrated a significant advantage over standard therapy for only the vomiting endpoint. Analyses of all nausea related endpoints failed to differentiate aprepitant from the standard therapy comparator. Labeling these negative data is very challenging.

Fourth, the analyses of the individual components of the primary and secondary endpoints demonstrated that the success of these endpoints were driven by the No Vomiting variable. The aprepitant regimen had no significant effect on the use of rescue therapy or the symptoms of nausea ("exploratory endpoints"). Again, labelling these negative data is very challenging.

Fifth, in addition to the lack of demonstration of efficacy in the acute and the delayed phases separately, there are unsettled clinical issues related to the design and execution of Study 071 and the use of the drug if approved. These constraints include issues regarding generalizability of results since Study 071 only evaluated the safety and efficacy of aprepitant when administered with moderately emetogenic chemotherapeutic regimens used to treat breast cancer. These results may not necessarily be generalizable to other moderate emetogenic chemotherapy regimens. One additional constraint is that the study population consisted almost exclusively of female patients. This means that the safety and efficacy of aprepitant in male patients receiving moderately emetogenic chemotherapy regimens is yet to be demonstrated.

Sixth, it seems that it would be very confusing to the reader to include in the labeling so many negative findings or the lack of data assessing the effects of the drug in a variety of unsettled issues.

IV. MTL's RECOMMENDATIONS FOR REGULATORY ACTION

The totality of evidence in S-NDA 21-549 and its major amendment does not support approval of aprepitant for the prevention of [redacted] nausea and vomiting induced by moderately emetogenic chemotherapy, for reasons delineated in Section III of the current addendum.

As pointed out by the MOR in his original review of the evidence, to resolve outstanding issues, Merck should consider additional Phase III studies assessing the use of the drug in the prevention of [redacted] nausea and vomiting associated with moderately emetogenic chemotherapy. These future studies should a) enroll both male and female patients; b) not be limited to breast cancer; c) be designed

to demonstrate effectiveness in the prevention of *both* nausea and vomiting; d) demonstrate efficacy in *both* the acute and delayed phase time periods, separately; and e) test the efficacy and safety of use aprepitant as an add on therapy. This would be an approach like the one used successfully to demonstrate that the drug is safe and effective in the prevention of acute and delayed nausea and vomiting associated with highly emetogenic chemotherapy.

Hugo E. Gallo-Torres, MD, PhD, PNS
Medical Team Leader
HFD-180

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/s/

Hugo Gallo Torres
9/27/2005 08:26:55 PM
MEDICAL OFFICER

This addendum to the original MTL AE comments on NDA 21-549 addresses recommendations by Dr. Gary DellaZanna, the MO reviewer, in the addendum to his review of S-NDA 21-549.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: **September 20, 2005**

FROM: Hugo E. Gallo-Torres, MD, PhD, PNS
Division of Gastrointestinal Products [HFD-180]
DGDP/ODE III

SUBJECT: GI Team Leader **AE** Comments

S-NDA **21-549** [Submitted July 22, 2005]

APPLICANT: **Merck & Co., Inc.**
West Point, PA 19486

DRUG: **Aprepitant [Selective, neurokinin (NK_1)-receptor antagonist]**

INDICATION: Prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of *moderately* emetogenic cancer [MEC] chemotherapy

GI TEAM LEADER RECOMMENDATION:
This memorandum documents results of my examination of the evidence [data from single trial Study Protocol 071] submitted in S-NDA 21-549 in support of the indication sought and the primary review by the Medical Officer Reviewer [MOR] Dr. Gary DellaZanna. Included is a review of the evidence used in support of the regulatory actions regarding drugs intended for use for the sought indication. The MTL agrees with the MOR' conclusion that results of Study 071 do not support approval for the use of aprepitant for the prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.

As pointed out by the MOR, to resolve outstanding issues, Merck should consider additional Phase III studies assessing the use of the drug in the prevention of (b) (4) nausea and vomiting associated with moderately emetogenic chemotherapy. These future studies should a) enroll both male and female patients; b) not be limited to breast cancer; c) be designed to demonstrate effectiveness in the prevention of *both* nausea and vomiting; d) demonstrate efficacy in *both* the acute and delayed phase time periods, separately; and use aprepitant as an add on therapy. This would be an approach like the one used successfully to demonstrate that the drug is safe and effective in the prevention of acute and delayed nausea and vomiting associated with highly emetogenic chemotherapy.

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I. Background:

Aprepitant was first approved in March 2003 as part of a three day, three drug regimen for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) associated with initial and repeat courses of *highly* emetogenic chemotherapy regimens. Through S-NDA 21549/S008, submitted on September 29, 2004, Merck is seeking approval for the prevention of (b) (4) nausea and vomiting associated with initial and repeated courses of *moderately* emetogenic chemotherapy. The submission consisted of a single Phase III multicenter, randomized, double-blind, parallel-group trial that enrolled patients diagnosed with breast cancer that were scheduled to receive moderately emetogenic chemotherapy. Patients were randomly assigned to one of the following two treatment arms: Aprepitant regimen or Standard Therapy regimen. After reviewing the evidence, the Medical Officer Reviewer concluded that results of the single trial under [Study Protocol 071] did not support the sought indication. As a result of a July 12, 2005 teleconferences with Merck to discuss issues regarding their pending Supplemental NDA the sponsor submitted results of an ad hoc analysis of the data in (S-NDA). After review of this additional evidence, the Medical Officer Reviewer's opinion was the same: results of Study 071 do not support approval of aprepitant for the proposed new indication(s), the prevention of (b) (4) *nausea* and *vomiting* associated with initial and repeated courses of moderate emetogenic chemotherapy.

The MTL provides a brief account of the studies reviewed by the Agency that were the basis for the scientific appraisal of the data and the consequent regulatory action on drug applications intended for drugs for the moderately emetogenic indication. Although a significant number of trials were active-active comparisons, it is not the purpose of this mini Summary Basis of Approval to compare the safety and effectiveness of one drug against the other. This exercise, which provides an overview of the Division's regulatory process through the years, is expected, based on parity and consistency, to facilitate the understanding of the MOR and the MTL's AE recommendations for the moderately emetogenic chemotherapy indication sought in S-NDA 21549/S008.

In addition to the differentiation between highly vs moderately emetogenic indication, another recognized differentiation is between acute [0 to 24 h after chemotherapy administration] and delayed [25 to 120 h after chemotherapy administration]. The prevention of CINV has evolved from monotherapy to the administration of two or three drugs together [add on therapy]. For the highly emetogenic indication, only the first two drugs approved for this indication [ondansetron and granisetron] underwent placebo-controlled studies. Owing to ethical considerations, subsequent drugs [dolasetron, palonosetron, aprepitant] were evaluated in active-active comparison trials. A similar approach [placebo comparator, monotherapy, add on therapy, in sequential fashion] is now being followed for the moderately emetogenic indication. The Tables below display data for the **moderately emetogenic indication only**, as this is the indication for which S-NDA 21549/S008 has been submitted. For simplification purposes, only results of evaluations using **Complete Response** [No emesis, no rescue medication and at the most mild nausea] as the **primary** endpoint of efficacy and nausea scores when available are displayed. Included is also brief information on characterization of the study population as the type of cancers [and the actual chemotherapeutic regimens] and inclusion of male and female patients. Although, also for simplification purposes, the number of patients per cell may not be displayed, the general statement can be made that these numbers were adequate to assess effectiveness of the drugs, draw scientific conclusions and justified the regulatory action resulting in labeling information. Safety-related data are not an issue. Safety is not addressed in this memorandum.

A. Zofran® [0ndansetron hydrochloride] [Tables 1 through 4]

1. Zofran® Injection [Tables 1 and 2]

Table 1
Single-Day Cyclophosphamide Therapy[a]

Endpoint [Response over 24 h]	Zofran Injection [n = 10]	PL [n = 10]	Therapeutic gain	p-value [ITT]
0 Emetic episodes	70%	0%	70%	0.001
Median nausea scores [VAS: 0 to 100]	0	60	60	0.001
a) All patients received cyclophosphamide [500 to 600 mg/m^2], plus other agents including fluorouracil, doxorubicin, methotrexate and vincristine.				

Table 2
Single-Day Medium-dose Cisplatin (50 to 70 mg/m^2)[a]

Endpoint [Response over 24 h]	Ondansetron Dose		Therapeutic gain	p-value [ITT]
	0.15 mg/kg x 3 [n = 101]	32 mg x 1 [n= 93]		
0 Emetic episodes	61%	73%	12%	0.083
Median nausea scores [VAS: 0 to 100]	9	3	6	NS
a) At that time, this cisplatin regimen was considered to be associated with moderately induced Nausea and Vomiting. Nowadays this cisplatin regimen is considered to be highly emetogenic.				

2. Zofran Tablets [Tables 3 and 4]

Table 3
3-Day Study Cyclophosphamide-based Therapy[a]

Endpoint[b] [Response over 3 days]	Ondansetron[c] 8mg bid [n = 33]	PL [n = 34]	Therapeutic gain	p-value [ITT]
0 Emetic episodes	61%	6%	55%	<0.001
Median number of emetic episodes	0	Undefined		

a) All patients received cyclophosphamide [500 to 600 mg/m^2], plus other agents including fluorouracil, doxorubicin, methotrexate and vincristine.
b) Treatment response based on total number of emetic episodes over the 3-day study period.
c) The first dose was administered 30 min before the start of emetogenic chemotherapy, with a subsequent dose 8 h after the first dose. An 8-mg Zofran® Tablet was administered twice a day for 2 days after completion of chemotherapy.

Table 4
3-Day Study Cyclophosphamide-based Chemotherapy[a]

Endpoint [Response over 3 days]	Ondansetron Dose Zofran® Tablets		Therapeutic gain	p-value [ITT]
	8 mg bid [n = 165]	8 mg tid [n= 171]		
0 Emetic episodes	61%	58%	3%	NS
Median nausea scores [VAS: 0 to 100]	6	6		

a) Containing either methotrexate or doxorubicin.
b) Treatment response as per footnote to Table 3.
- This trial demonstrated one regimen not to be inferior to the other.

Ondansetron indication [pertinent section of the labeling]

Zofran® Injection

1. Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin. Efficacy of the 32-mg single dose beyond 24 hours in these patients has not been established.

Zofran® Tablets

1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy including cisplatin $\geq$ 50 mg/m^2. [NOTE: Evidence in support of this indication is not addressed in this MTL review].

2. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

B. Kytril® [granisetron hydrochloride] [Tables 5 through 9]

1. Kytril® Injection [Tables 5 and 6]

Table 5
Single-Day Moderately Emetogenic Chemotherapy[a]

Endpoint [Response over 24 h]	Kytril Injection 40 μg/kg [n = 133]	Chlorpromazine Plus DEX[b] [n = 133]	Therapeutic gain	p-value [ITT]
Complete Response[c]	68%	47%	21%	<0.001
No more than mild nausea	77%	59%	18%	<0.001

a) Included primarily carboplatin > 300 mg/m^2, cisplatin 20 to 50 mg/m^2 and cyclophosphamide > 600 mg/m^2.
b) Chlorpromazine [50 to 200 mg/24 h]; DEX = dexamethasone, 12 mg.
c) No vomiting and no moderate or severe nausea.

Table 6
Single-Day Low-Dose Cisplatin Therapy[a]

Endpoint [Response over 24 hours]	Kytril Injection [μg/kg]				Therapeutic gain/p-value [vs 2 μg/kg]		
	5 [n=42]	**10** [n=41]	**20** [n=40]	**40** [n=46]	**10**	**20**	**40**
Complete Response[b]	29%	56%	58%	41%	27% [0.012]	29% [0.009]	12% [NS]
No nausea	29%	56%	38%	33%	27% [0.012]	9% [NS]	4% [NS]

a) 50 to 79 mg/m^2, at that time, considered moderately emetogenic.
b) No vomiting and no use of rescue medication.

- In other studies of moderately emetogenic chemotherapy, no significant difference in efficacy was found between Kytril® doses of 40 μg/kg and 160 μg/kg.

2. Kytril® Tablets [Tables 7 through 9]

Table 7
Moderately Emetogenic Chemotherapy[a]

Endpoint [Response over 24 h]	Kytril Tablets Dose [mg bid]				Therapeutic gain/p-value [vs 0.25 mg bid]		
	0.25 [n=229]	**0.5** [n=235]	**1** [n=233]	**2** [n=233]	**0.5**	**1[b]**	**2**
Complete Response[b]	61%	70%	81%	72%	9% [<0.01]	20% [<0.01]	11% [<0.01]
No nausea	48%	57%	63%	54%	9% [NS]	15% [<0.01]	6% [NS]

a) Chemotherapy included oral and injectable cyclophosphamide, carboplatin, cisplatin [20 to 50 mg/m^2, dacarbazine, doxorubicin, epirubicin.
b) This drug regimen was also shown to be superior to the 0.5 mg bid [Therapeutic gain = 11%, $p < 0.01$] for Complete Response, but not for the No nausea parameter.
c) No vomiting, no use of rescue medication, no moderate or severe nausea.

Table 8
Moderately Emetogenic Chemotherapy[a]

Endpoint [Response over 24 h]	Kytril Tablets		Prochlorperazine[b]	Therapeutic gain/p-value	
	1 mg bid [n = 354]	**2** mg qd [n = 343]	**10** mg bid [n = 111]	**1**	**2**
Complete Response[c]	69%	64%	41%	28% [< 0.05]	23% [< 0.05]
No nausea	51%	53%	35%	16% [< 0.05]	18% [< 0.05]

a) Moderately emetogenic chemotherapy agents included cisplatin [20 to 50 mg/m^2], oral and intravenous cyclophosphamide, carboplatin, dacarbazine, doxorubicin.
b) Historical control from a previous double-blind Kytril trial.
c) No vomiting, no rescue medication and at the most mild nausea.

- Results from a Kytril Tablets 2mg qd alone treatment arm in a third double-blind, randomized trial, were compared to chlorpromazine [PCPZ], 10 mg bid, derived from a historical control. The 24-hour results for Kytril tablets 2 mg qd were statistically superior to PCPZ for all efficacy parameters [Table 9].

Table 9
Single-Day Moderately Emetogenic Chemotherapy[a]

Endpoint [Response over 24 h]	Kytril Tablets 2 mg qd	PCPZ 10 mg bid	Therapeutic gain	p-value
Complete Response	58%	41%	17%	<0.05
No nausea	51%	35%	16%	<0.05

a) The PCPZ rates are those displayed in Table 8, derived from a historical control.

Granisetron indication [pertinent section of the labeling]

Kytril® Injection

1. Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.

Kytril® Tablets

1. Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.

C. ANZEMET® [Dolasetron mesylate] [Tables 10 through 12]

1. ANZEMET® Injection [Tables 10 and 11]

Table 10
Moderately Emetogenic Chemotherapy[a]

Endpoint [Response over 24 hours]	ANZEMET Injection 1.8 mg/kg [n= 95]	MCP Intravenous[b] [see footnote] [n = 98]	Therapeutic gain	p-value
Complete Response	63%	52%	11%	NS
Nausea score[d]	This information is not listed in the 2005 PDR.			

a) The total number of patients was 309 [96 men, 213 women]. The moderately emetogenic chemotherapy these patients received consisted of cyclophosphamide-based regimens.
b) MCP = Metoclopramide, administered as a 2 mg/kg I.V. bolus followed by 3 mg/kg intravenously over 8 hours.
c) In the ANZEMET® Injection labeling, these results are described as showing that intravenously administered ANZEMET® [1.8 mg/kg] was equivalent to MCP.
d) The Medical Officer's review does not report results of nausea score evaluations. In this European trial, the primary assessment was ITT logistic regression analysis of Complete Response.

- This trial demonstrated ANZEMET not to be inferior to MCP.

Table 11
Cisplatin Chemotherapy [$\geq$ 70 mg/m^2][a]

Endpoint [Response over 24 hours]	ANZEMET Injection 1.8 mg/kg [n = 198]	Ondansetron 32 mg Intravenous [n = 206][b]	Therapeutic gain	p-value
Complete Response[c]	44%	43%	11%	NS
Nausea score[d]	10	16	6	NS

a) At this point in time this cisplatin regimen was considered moderately emetogenic. In addition please see data in Table 2 for granisetron and Table 6 for granisetron.
This trial included ca. the same proportion of men as women [roughly 50% each].
b) Includes 12 patients who received 3 doses of 0.15 mg/kg of ondansetron intravenously.
c) No emetic episodes and no rescue medication.
d) Median 24-h change from baseline nausea score using VAS. Score range: 0 = "None" to 100 = "Nausea as bad as it could be".

2. ANZEMET® Tablets [Table 12]

Table 12
Moderately Emetogenic Chemotherapy[a]

Endpoint [Response over 24 hours]	ANZEMET Tablets [mg]				p-value for Linear Trend
	25 [n = 78]	**50** [n = 83]	**100[b]** [n = 80]	**200** [n = 78]	
Complete Response[c]	31%	41%	**61%**	59%	$p < 0.0001$
Nausea scores[d]	49	10	11	7	$p = 0.0006$

a) This consisted of cyclophosphamide and/or doxorubicin regimens. The total study population [n = 319] included 60 men and 259 women.
b) There was no statistically significant difference between the 100 mg [the recommended dose] and the 200 mg dose.
c) No emetic episodes and no rescue medication.
d) Median 24-h change from baseline nausea score using VAS [See Footnote d to Table 11].

- Another trial also compared single oral ANZEMET doses of 25, 50, 100, and 200 mg in 307 patients receiving moderately emetogenic chemotherapy. In this study, the 100 mg ANZEMET dose [the recommended dose] gave a 73% Complete Response rate.

Dolasetron indication [pertinent section of the labeling]
ANZEMET® Injection
1. Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin.

ANZEMET® Tablets
1. Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, including initial and repeat courses.

D. ALOXI® [palonosetron hydrochloride]

It is worth noting that the drugs discussed under A, B, and C above have been approved for the prevention of *acute* [meaning 0 to 24 hours after chemotherapy administration] nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy. (b) (4) neither ondansetron nor granisetron or dolasetron are approved for the prevention of delayed nausea and vomiting associated with moderately cancer chemotherapy, although these drugs, alone or in combination, especially with dexamethasone, may be used off-label (b) (4)

1. Aloxi ® injection

a. Prevention of *acute* [0 to 24 hours] Moderately CINV]

Table 13
Moderately Emetogenic Chemotherapy [a]

Endpoint [Response over 24 hours]	Aloxi® 0.25 mg [n = 189] [b]	Ondansetron 32 mg I.V. [n = 185]	Therapeutic gain	p-value
Complete Response[c]	81%	69%	12%	0.009
Nausea score[d]	This information is not included in the 2005 PDR.			

a) The majority of patie4nts in this study were women [77%], white [65%] and naïve to previous chemotherapy [54%].
The test medications were administered intravenously 30 minutes prior to moderately emetogenic regimens. The latter included carboplatin, cisplatin $\leq$ 50 mg/m^2, cyclophosphamide < 1500 mg/m^2, doxorubicin > 25 mg/m^2, epirubicin, irinotecan, and methotrexate > 250 mg/m^2.
Concomitant corticosteroids were not administered prophylactically.

b) This study was designed to show non-inferiority. A lower bound greater than -15% demonstrates non-inferiority between Aloxi® and ondansetron.

c) No emetic episodes and no rescue medication.

d) The original Medical Officer's review, carried out by Dr. Narayan Nair, is not presently Available. The file on NDA 21-372 is quarantined because of a threat that these files may contain a virus. Virtual card files [VCFs] are not recoverable.

Table 14
Moderately Emetogenic Chemotherapy [a]

Endpoint [Response over 24 hours]	Aloxi® 0.25 mg [n = 189] [b]	Dolasetron 100mg I.V. [n = 191]	Therapeutic gain	p-value
Complete Response[c]	63%	53%	10%	NS
Nausea score[d]	This information is not included in the 2005 PDR.			

a) The majority of patients in this study were women [77%], white [65%] and naïve to previous chemotherapy [54%].
The test medications were administered intravenously 30 minutes prior to moderately emetogenic regimens. The latter included carboplatin, cisplatin $\leq$ 50 mg/m^2, cyclophosphamide < 1500 mg/m^2, doxorubicin > 25 mg/m^2, epirubicin, irinotecan, and methotrexate > 250 mg/m^2.
Concomitant corticosteroids were used prophylactically by 4 to 6 % of the patients.

b) This study was designed to show non-inferiority. A lower bound greater than -15% demonstrates non-inferiority between Aloxi® and dolasetron.

c) No emetic episodes and no rescue medication.

d) Please see Footnote d) to Table 13.

b. Prevention of ***delayed*** [24 to 120 hours] Moderately CINV

Table 15
Moderately Emetogenic Chemotherapy [a]

Endpoint [Response over 24 to 120 hours]	Aloxi® 0.25 mg [n = 189] [b]	Ondansetron 32 mg I.V. [n = 185]	Therapeutic gain	p-value
Complete Response[c]	74%	55%	19%	<0.001
Nausea score[d]	This information is not included in the 2005 PDR.			

a) This study was designed to test effectiveness of the drug in ***delayed emesis*** [24 to 120 hours after administration of the moderately emetogenic chemotherapy regimen].
The test medications were administered intravenously 30 minutes prior to moderately emetogenic regimens. The latter included carboplatin, cisplatin $\leq$ 50 mg/m^2, cyclophosphamide < 1500 mg/m^2, doxorubicin > 25 mg/m^2, epirubicin, irinotecan, and methotrexate > 250 mg/m^2.
Concomitant corticosteroids were not administered prophylactically.
b) This study was designed to show non-inferiority. A lower bound greater than -15% demonstrates non-inferiority between Aloxi and ondansetron.
c) No emetic episodes and no rescue medication.
d) Please see Footnote d) to Table 13.

Table 16
Moderately Emetogenic Chemotherapy [a]

Endpoint [Response over 24 to 120 hours]	Aloxi® 0.25 mg [n = 189] [b]	Dolasetron 100mg I.V. [n = 191]	Therapeutic gain	p-value
Complete Response[c]	63%	53%	10%	NS
Nausea score[d]	This information is not included in the 2005 PDR.			

a) This study was designed to test effectiveness of the drug in ***delayed emesis*** [24 to 120 hours after administration of the moderately emetogenic chemotherapy regimen].
The test medications were administered intravenously 30 minutes prior to moderately emetogenic regimens. The latter included carboplatin, cisplatin $\leq$ 50 mg/m^2, cyclophosphamide < 1500 mg/m^2, doxorubicin > 25 mg/m^2, epirubicin, irinotecan, and methotrexate > 250 mg/m^2.
Concomitant corticosteroids were used prophylactically by 4 to 6 % of the patients.
b) This study was designed to show non-inferiority. A lower bound greater than -15 % demonstrates non-inferiority between Aloxi® and dolasetron.
c) No emetic episodes and no rescue medication.
d) Please see Footnote d) to Table 13.

Palonosetron indications [pertinent sections of the labeling]
Aloxi® [palonosetron hydrochloride injection]
ALOXI® is indicated for:

1) the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and
2) the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

NOTE: It is important to note that following his review of the evidence, Dr. Narayan Nair, the Medical Officer Reviewer for NDA 21-372 [palonosetron hydrochloride injection] found that palonosetron was not significantly better that the comparator [ondansetron] in preventing *delayed nausea and vomiting* in patients receiving highly emetogenic chemotherapy. In her July 25, 2003 memorandum to NDA 21-372, Dr. Julie Beitz concluded that a claim for *delayed* nausea and vomiting in patients receiving highly emetogenic chemotherapy was not tenable.

II. EMEND® [APREPITANT] capsules

Emend® (aprepitant) is a substance P/neurokinin 1 (NK_1) receptor antagonist with little or no affinity for serotonin (5-HT_3), dopamine and corticosteroid receptors, the targets of therapies summarized under I. above for CINV. Aprepitant was first approved in March 2003 as part of a three day, three drug regimen for the prevention of ***acute*** and ***delayed*** chemotherapy-induced nausea and vomiting associated with initial and repeat courses of ***highly emetogenic*** chemotherapy regimens.

- It is important to mention that the sponsor's approach to testing effects of the drug in the prevention of highly emetogenic chemotherapy indication was an ***add on*** approach. For the acute indication the backbone of efficacy is due to a 5-HT_3 drug, to which dexamethasone [DEX] and aprepitant are added, whereas for the delay indication, the studies compared the effect of aprepitant to DEX 8 mg PO daily given in the evening in patients that were receiving DEX 8 mg PO daily in the morning:

Treatment Arms for the Approved Prevention of Nausea and Vomiting Induced by Highly Emetogenic Chemotherapy

	Day 1	Days 2 to 4
Aprepitant	Aprepitant 125 mg PO DEX 12 mg PO Ondansetron 32 mg I.V.	Aprepitant 80 mg PO Daily [Days 2 and 3 only] DEX 8 mg PO Daily (morning)
Standard Therapy	DEX 20 mg PO Ondansetron 32mg I.V.	DEX 8 mg PO Daily (morning) DEX 8 mg PO Daily (evening)

As explained in detail in the primary Medical Officer Review by Dr. Gary DellaZanna, on September 29, 2004, the sponsor submitted S-NDA 21549/S008 seeking approval for the

prevention of [redacted] nausea and vomiting associated with initial and repeated courses of ***moderately emetogenic*** chemotherapy. The submission consisted of a single Phase III multicenter, randomized, double-blind, parallel-group trial [**Study 071**] that enrolled patients diagnosed with breast cancer who were scheduled to receive moderately emetogenic chemotherapy.

- It is important to mention that to assess the effect of the drug during the first 24 after administration of the moderately emetogenic chemotherapy stimuli [***acute*** CINV], the sponsor still used the add on regimen consisting of ondansetron and DEX. However, this add on approach was no longer used for the 25th through the 120th evaluations [***delayed*** CINV]. [redacted]

  This is because the aprepitant arm contains ondansetron placebo while the ondansetron standard therapy comparator arm contains aprepitant placebo. The protocol-stipulated primary purpose of the trial was to demonstrate that the aprepitant regimen provided *superior prevention of chemotherapy-induced nausea and vomiting* when compared to a recognized standard of care.

Treatment Arms for the Requested Indication: Prevention of Nausea and Vomiting Induced by Moderately Emetogenic Chemotherapy

	Day 1	Days 2 to 3
Aprepitant	Aprepitant 125 mg PO DEX 12 mg PO Ondansetron 8mg PO (BID)	Aprepitant 80 mg PO Daily Ondansetron placebo PO Daily (BID)
Standard Therapy	Aprepitant Placebo PO DEX 20 mg PO Ondansetron 8mg PO (BID)	Aprepitant Placebo PO Daily Ondansetron 8 mg PO Daily (BID)

In Study 071 a responder was defined as a patient who reported no vomiting and did not require rescue therapy for 0 to 120 h after receiving a dose of moderately emetogenic chemotherapy, but this endpoint is **inappropriate** because it does not allow differentiation of results from the *acute* vs the *delayed* phase. Results of the 0 to 24th h [acute] phase and the 25th to 120th [delayed] phase need to be analyzed separately simply [redacted] As displayed in the Tables listed under I. above, this approach has resulted in the [redacted] of ondansetron, granisetron and dolasetron for the [redacted] On the other hand, [redacted]

Summary Results of Efficacy

A. Complete Response

Study 071 failed to show that the aprepitant regimen offered any significant advantage over standard therapy for Complete Response in *Acute* and/or *Delayed* phase time periods separately. The therapeutic gains [6.7% for the acute, 6.3% for the delayed phase], appear to be of doubtful clinical significance.

Study 071: Complete Response
Cycle 1

Phase	Aprepitant Regimen [n = 433]	Standard Regimen [n = 424]	Treatment difference/p-Value
Acute phase (0 to 24 hours)	75.7%	69.0%	6.7% [NS]¥
Delayed phase (25 to 120 hours)	55.4%	49.1%	6.3% [NS]

¥ This p-value of 0.034 becomes not significant after applying the Applicant's multiplicity adjustment (Confirmed by Agency Statistician, Dr. Wen-Jen Chen, Ph.D.)
NOTE: Although the sponsor calls the 0 to 24th h and the 25th "exploratory endpoints" there nothing exploratory about the evaluations (b) (4)

This MTL Table is based, in part, in the data in Table 2 of the MOR of S-NDA 21-549 S-008.

B. Complete Response: Overall Phase

As shown in Table 2 of the MOR, study 071 successfully demonstrated that the aprepitant regimen was significantly more effective than standard therapy for Complete Response in the overall phase. During the 5 days post-chemotherapy administration (Overall Phase), 50.8% of patients in the aprepitant group, compared to 42.5% of the patients receiving standard therapy reported Complete Response. The **unadjusted** absolute difference in Complete Response (8.3%) represents a 20% relative improvement over standard therapy. However, this approach of lumping together the results of evaluations of effects of acute and delayed effects is inappropriate because it does not allow differentiation between these two phases. Owing to the design of the trial, this differentiation is critical because results from the acute phase, where effects of **add on therapy** are being tested, may spill over the delayed phase, where, according to the protocol-stipulated purpose of the trial, the effects of aprepitant are expected to be superior to those of alosetron. But evaluations for the delayed phase are no longer under add on conditions, since each drug is given with the placebo of the other. As pointed out by the MO Reviewer, the analyses of the individual components of the primary and secondary endpoints demonstrated that the success of these endpoints was driven by the No Vomiting variable. The aprepitant regimen had no significant effect on the use of rescue therapy or the symptoms of nausea ("exploratory endpoints", see below).

C. Additional Endpoints of Efficacy: Acute vs Delayed Phase

The following Table, taken from Dr. DellaZanna's review, without modifications, clearly demonstrate that, when results of the acute and the delayed phase are analyzed separately, the aprepitant regimen is not superior [the object of the clinical trial was to demonstrate superiority] to the comparator, the

standard regimen. The parameters of efficacy ["Exploratory Endpoints"] included customary endpoints of evaluation of efficacy: Complete Response, No Vomiting, No Use of Rescue Therapy, No Significant Nausea [maximum VAS < 25 mm], No Nausea [maximum VAS < 5 mm]. But disappointing results were also seen using **Complete Protection** [no vomiting, no rescue and maximum nauseas VAS < 25 mm] and **Total Control** [no vomiting, no rescue and maximum nausea VAS < 5 mm] as the parameters of evaluation of efficacy.

Study 071
Results of Exploratory Endpoints of Efficacy (Cycle 1)
mITT Patient Population
Sponsor's Analyses

Exploratory Endpoints	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Complete Response			
Acute phase (0 to 24 hours)	327/432 (75.7)	292/423 (69.0)	N.S. ∓
Delayed phase (25 to 120 hours)	240/433 (55.4)	208/424 (49.1)	N.S.
No Vomiting			
Acute phase	378/432 (87.5)	327/423 (77.3)	N.S. ∓
Delayed phase	349/432 (80.8)	293/424 (69.1)	N.S. ∓
No Use of Rescue Therapy			
Acute phase	355/429 (82.8)	336/420 (80.0)	N.S.
Delayed phase	271/432 (62.7)	253/423 (59.8)	N.S.
No Significant Nausea (maximum VAS <25 mm)			
Overall phase	262/430 (60.9)	236/424 (55.7)	N.S.
Acute phase	342/430 (79.5)	331/423 (78.3)	N.S.
Delayed phase	281/430 (65.3)	260/423 (61.5)	N.S.
0 to 72 hours	274/430 (63.7)	254/424 (59.9)	N.S.
No Nausea (maximum VAS <5 mm)			
Overall phase	142/430 (33.0)	140/424 (33.0)	N.S.
Acute phase	261/430 (60.7)	250/423 (59.1)	N.S.
Delayed phase	159/430 (37.0)	154/423 (36.4)	N.S.
0 to 72 hours	167/430 (38.8%)	159/424 (37.5)	N.S.
Complete Protection (no vomiting, no rescue and maximum nausea VAS <25 mm)			
Overall phase	184/433 (42.5)	156/424 (36.8)	N.S.
Acute phase	296/431 (68.7)	272/423 (64.3)	N.S.
Delayed phase	203/433 (46.9)	180/424 (42.5)	N.S.
Total Control (no vomiting, no rescue and maximum nausea VAS <5 mm)			
Overall phase	125/433 (28.9)	115/424 (27.1)	N.S.
Acute phase	241/431 (55.9)	222/423 (52.5)	N.S.
Delayed phase	139/433 (32.1)	132/424 (31.1)	N.S.

Ref: Table 3.1.3, Statistical Review
†: Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group, investigator group, and age category (<55 years, ≥55 years).
∓ – Not Statically Significant after Applying Merck's Data Analysis Plan
VAS = Visual analogue scale.

D. Additional Unsettled Efficacy Issues

In addition to the lack of demonstration of efficacy in the acute and the delayed phases separately, the MOR identified other clinical issues related to the design and execution of Study 071 and the use of the drug if approved. As noted by Dr. DellaZanna, it is unknown whether the results of Study 071 can be generalized to all patients receiving moderately emetogenic chemotherapy. Greater than 99% of the patients were female. This is an important limitation in the efficacy data since a treatment-by-gender interaction was identified in one of the two pivotal trials submitted with the original NDA. It is unknown whether this gender interaction would be more significant in patients receiving moderate emetogenic agents. Furthermore, Study 071 only evaluated the safety and efficacy of aprepitant when administered with moderately emetogenic chemotherapeutic regimens used to treat breast cancer. These results may not necessarily be generalizable to other moderate emetogenic chemotherapy regimens.

III. DISCIPLINE REVIEW SUMMARY AND COMMENTARY

The MTL recommends that information on the following disciplines: **OPDRA/DDMAC/DMETS; Chemistry and Manufacturing; Pre-Clinical Pharmacology/Toxicology; Biopharmaceutics; Clinical/Statistical: Efficacy and Pediatric Use** is addressed when management takes an AP regulatory action on S-NDA 21549/S008.

IV. SUMMARY COMMENTS

Documented in this memorandum are results of the MTL examination of the evidence [data from single trial Study Protocol 071] submitted in S-NDA 21-549/S008 in support of the indication prevention of nausea and vomiting induced by moderately emetogenic cancer chemotherapy. The MTL secondary review is primarily based on results of the primary review by the Medical Officer Reviewer [MOR] Dr. Gary DellaZanna.

Included is a review of the evidence used throughout the years in support of the regulatory actions regarding drugs intended for use for the sought indication. The MTL agrees with the MOR' conclusion that results of Study 071 do not support approval for the use of aprepitant for the prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.

As pointed out by the MOR, to resolve outstanding issues, Merck should consider additional Phase III studies assessing the use of the drug in the prevention of (b) (4) nausea and vomiting associated with moderately emetogenic chemotherapy. These future studies should a) enroll both male and female patients; b) not be limited to breast cancer; c) be designed to demonstrate effectiveness in the prevention of *both* nausea and vomiting; d) demonstrate efficacy in *both* the acute and delayed phase time periods, separately; and e) to optimize assessment of the drug's efficacy, use aprepitant as an add on therapy, in a fashion similar to that used for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic already approved indication .

V. LABELING RECOMMENDATIONS: N/A.

Hugo E. Gallo-Torres, MD, PhD, PNS
Medical Team Leader [GI Drugs]
HFD-180

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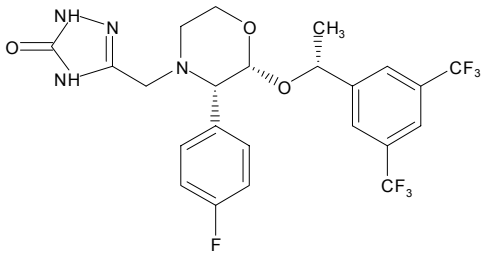
/s/

Hugo Gallo Torres
9/21/2005 10:51:44 AM
MEDICAL OFFICER

This MTL memorandum considers issues addressed in the AE review by Dr. DellaZanna, the MO reviewer of S-008. Dr. DellaZanna has written an adendum to his review, recommending AP. The MTL considers this new recommendation in a separate addendum.

Major Amendment

S-NDA 21-549
Aprepitant



S-NDA:	21-549 /008
Chemical Name:	Aprepitant
Date Received:	July 22, 2005
Indication:	Prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of *moderately* emetogenic cancer (MEC) chemotherapy.
Study:	Phase III
Dose:	125/80mg capsules
Route of Administration:	Oral
Formulation:	Capsule
Category:	neurokinin 1 (NK_1) receptor antagonist
Applicant:	Merck
Documents Reviewed:	Major Amendment Submission
Medical Officer:	Gary Della'Zanna D.O. M.Sc.
Medical Team Leader:	Hugo Gallo-Torres M.D., Ph.D., P.N.S.
Project Manager:	Betsey Scroggs, Pharm. D.

Background:

Aprepitant was first approved in March 2003 as part of a three day, three drug regimen for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) associated with initial and repeat courses of *highly* emetogenic chemotherapy regimens.

On September 29, 2004, Merck submitted S-NDA 21549/S008 seeking approval for the prevention of (b) (4) nausea and vomiting associated with initial and repeated courses of *moderately* emetogenic chemotherapy. The submission consisted of a single Phase III multicenter, randomized, double-blind, parallel-group trial that enrolled patients diagnosed with breast cancer who were scheduled to receive moderately emetogenic chemotherapy. Patients were randomly assigned to one of the following two treatment arms: Aprepitant regimen or Standard Therapy regimen.

Table 1
Treatment Arms

	Day 1	Days 2 to 3
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 8mg PO (BID)	Aprepitant 80 mg PO Daily Ondansetron placebo PO Daily (BID)
Standard Therapy	Aprepitant Placebo PO Dexamethasone 20 mg PO Ondansetron 8mg PO (BID)	Aprepitant Placebo PO Daily Ondansetron 8 mg PO Daily (BID)

On July 12, 2005, the Division initiated a series of teleconferences with Merck to discuss issues regarding their pending Supplemental NDA (S-NDA). It was this Reviewer's opinion that, although Study 071 succeeded for its primary and secondary endpoints, the efficacy results from the *single* study were not sufficiently robust to support approval of the proposed new indication(s), the prevention of (b) (4) *nausea* and *vomiting* associated with initial and repeated courses of moderate emetogenic chemotherapy.

The Division expressed following concerns regarding the efficacy data.

1. (b) (4) Drugs that were found to be safe and effective for acute phase nausea and vomiting were not necessarily effective during the delayed phase. Although Study 071 succeeded in demonstrating statistically significant efficacy in the overall phase, it failed to demonstrate that the aprepitant regimen offered any significant advantage over Standard Therapy for Complete Response in the Acute and/or Delayed phase time periods when analyzed separately.

2. The efficacy results did not support approval of the proposed indication: prevention of *nausea and vomiting*. The results from Study 071 demonstrated a significant advantage over standard therapy for only the vomiting endpoint. Analyses of all nausea related endpoints failed to differentiate aprepitant from the standard therapy comparator.

3. The analyses of the individual components of the primary and secondary endpoints demonstrated that the success of these endpoints were driven by the No Vomiting variable. The aprepitant regimen had no significant effect on the use of rescue therapy or the symptoms of nausea (exploratory endpoints).

4. The results of Study 071 may not be generalizable to all patients receiving moderately emetogenic chemotherapy. Greater than 99% of the patients enrolled in Study 071 were female. This is an important limitation in the efficacy data. During the original NDA approval for the highly emetogenic indication, a significant treatment-by-gender interaction was identified in one of the two pivotal trials. It is unknown whether this gender interaction would be more significant in patients receiving moderate emetogenic agents. At any rate, the safety and efficacy of aprepitant in male patients receiving moderately emetogenic chemotherapy regimens is yet to be demonstrated.

5. Furthermore, Study 071 only evaluated the safety and efficacy of aprepitant when administered with moderately emetogenic chemotherapeutic regimens used to treat breast cancer. These results may not necessarily be generalizable to other moderate emetogenic chemotherapy regimens.

Following a detailed discussion of these issues, Merck voiced disagreement with this Reviewer's interpretation of the data and requested an opportunity to respond to the Division's concerns. As a result of these discussions, the Division agreed to review a Major Amendment which would include Merck's justifications regarding the robustness of the data and a post-hoc non-inferiority analysis for the nausea endpoints. This Major Amendment is the focus of this review.

Conclusions:

After several internal meetings, which focused on Merck's justifications regarding the robustness of the data, and the level of significance required to grant approval of a new indication based on a single study, the Review team determined that the results from the original NDA could be considered as supporting evidence for this S-NDA. The two distinct indications, Highly and Moderately emetogenic CINV, are closely related and, from a regulatory viewpoint, may be treated in a similar fashion. The Aprepitant regimen had already succeeded in demonstrating efficacy under experimental conditions using a more potent emetogenic stimuli.

With consideration of the efficacy data from the original NDA (21-549 /000), this Reviewer now recommends that the S-NDA (21-549 /008) for the Moderately Emetogenic indication be Approved (Appendix A). It is my conclusion that with the supportive evidence from the original

NDA (21-549 /000), the information in the initial S-NDA is adequate to support approval of the new indication.

This Reviewer initially approached the S-NDA Application as a new indication based on a *single study*. As such, this Reviewer's initial recommendations were based on the need for "robust", highly statistically significant results. It was *originally* the Medical Officer's opinion that, although Study 071 succeeded for its primary and secondary efficacy endpoints, the results from Study 071 were not sufficiently robust to support approval based on a *single study* (Table 1). The results of the exploratory endpoints were not statically significant; however, they were all either numerically in favor of aprepitant or equal to the Standard of Care which is widely accepted as effective (Table 2).

Table 1
Study 071
Efficacy Outcomes in Overall Phase
Cycle 1

Efficacy Outcome	Aprepitant Regimen %	Standard Regimen %	Treatment Difference	p-Value
Primary Endpoint				
Complete response*	**50.8%**	**42.5%**	**8.3%**	**0.015**
Secondary Endpoint (Patients with No Impact of CINV on Daily Life)				
Total FLIE Score > 108	**63.5%**	**55.6%**	**7.9%**	**0.019**

* Ref: Table 3.1.2 , P071.pdf
(Confirmed by Agency Statistician, Dr. Wen-Jen Chen, Ph.D.)

Table 2
Exploratory Endpoints (Cycle 1)

Exploratory Endpoints	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Complete Response			
Acute phase (0 to 24 hours)	327/432 (75.7)	292/423 (69.0)	0.034**
Delayed phase (25 to 120 hours)	240/433 (55.4)	208/424 (49.1)	N.S.
No Vomiting			
Acute phase	378/432 (87.5)	327/423 (77.3)	<0.001**
Delayed phase	349/432 (80.8)	293/424 (69.1)	<0.001**
No Use of Rescue Therapy			
Acute phase	355/429 (82.8)	336/420 (80.0)	N.S.
Delayed phase	271/432 (62.7)	253/423 (59.8)	N.S.
No Significant Nausea (maximum VAS <25 mm)			
Overall phase	262/430 (60.9)	236/424 (55.7)	N.S.
Acute phase	342/430 (79.5)	331/423 (78.3)	N.S.
Delayed phase	281/430 (65.3)	260/423 (61.5)	N.S.
0 to 72 hours	274/430 (63.7)	254/424 (59.9)	N.S.
No Nausea (maximum VAS <5 mm)			
Overall phase	142/430 (33.0)	140/424 (33.0)	N.S.
Acute phase	261/430 (60.7)	250/423 (59.1)	N.S.
Delayed phase	159/430 (37.0)	154/423 (36.4)	N.S.
0 to 72 hours	167/430 (38.8%)	159/424 (37.5)	N.S.
Complete Protection (no vomiting, no rescue and maximum nausea VAS <25 mm)			
Overall phase	184/433 (42.5)	156/424 (36.8)	N.S.
Acute phase	296/431 (68.7)	272/423 (64.3)	N.S.
Delayed phase	203/433 (46.9)	180/424 (42.5)	N.S.
Total Control (no vomiting, no rescue and maximum nausea VAS <5 mm)			
Overall phase	125/433 (28.9)	115/424 (27.1)	N.S.
Acute phase	241/431 (55.9)	222/423 (52.5)	N.S.
Delayed phase	139/433 (32.1)	132/424 (31.1)	N.S.

Ref: Table 3.1.3, Statistical Review
†: Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group
** Not statically significant after adjusting for multiplicity
VAS = Visual analogue scale.

Even though the success of the primary and secondary endpoints were driven by the "no vomiting" variable, the results for the nausea related variables are clinically significant, considering the Standard Care comparator is recognized as effective.

Recommendations:

The single trial, Protocol 071, with the support of the efficacy results from the highly emetogenic application, is *adequate* to grant approval of the proposed new indication(s): "the prevention of (b) (4) *nausea* and *vomiting* associated with initial and repeated courses of moderately emetogenic cancer chemotherapy."

There remain some unanswered questions regarding the generalizability of Study 071. However, it is this Reviewer's opinion, based on the results from the original NDA, that these issues can be addressed as a Phase IV commitment. Approval should be contingent on Merck agreeing to perform a study to further evaluate the safety and efficacy of the aprepitant regimen in both male and female patients receiving moderately emetogenic chemotherapy regimens. This study should be designed to demonstrate that the aprepitant regimen is effective in the prevention of both nausea and vomiting, in both the acute and delayed phase time periods.

Appendix A

The following tables are from the highly emetogenic CINV trials submitted with the original NDA.

Table 1
Original NDA 21-549 /000
Summary of Efficacy

	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)**	136/260 (52.3)
Acute Phase	231/259 (89.2)**	203/260 (78.1)
Delayed Phase	196 / 260 (75.4)**	145/260 (55.8)
Study 054		
Overall Phase	163 / 260 (62.7)**	114/263 (43.3)
Acute Phase	216 / 261 (82.8)**	180/263 (68.4)
Delayed Phase	176 / 260 (67.7)**	123/263 (46.8)
Complete Protection (no emetic episodes, no rescue therapy, maximum nausea VAS<25)		
Study 052		
Overall Phase	163 / 257 (63.4)**	128 / 260 (49.2)
Acute Phase	217 / 256 (84.8)**	194 / 260 (74.6)
Delayed Phase	172 / 259 (66.4)**	134 / 260 (51.5)
Study 054		
Overall Phase	145 / 261 (55.6)**	107 / 263 (40.7)
Acute Phase	208 / 260 (80.0)**	170 / 263 (64.6)
Delayed Phase	159 / 261 (60.9)**	116 / 263 (44.1)
Total Control (no emetic episodes, no rescue therapy, maximum nausea VAS<5)		
Study 052		
Overall Phase	117/257 (45.5)	104/260 (40.0)
Acute Phase	181/256 (70.7)	167/260 (64.2)
Delayed Phase	127/259 (49.0)	111/260 (42.7)
Study 054		
Overall Phase	116/261 (44.4)**	84/263 (31.9)
Acute Phase	166/261 (63.6)	149/263 (56.7)
Delayed Phase	130/261 (49.8)**	89/263 (33.8)
Ref: Original NDA Review Modified Tables 2 and 3		

** p<0.01 when compared with Standard Therapy
*p<0.05 when compared with Standard Therapy

Table 2
Original NDA 21-549 /000
Summary of Efficacy

	Aprepitant Regimen n/m (%)	Standard Therapy n/m (%)
No Use of Rescue Medication		
Study 052		
Overall Phase	210/260 (80.8)**	184/260 (70.8)
Acute Phase	244/259 (94.2)*	231/260 (88.8)
Delayed Phase	211/260 (81.2)*	191/260 (73.5)
Study 054		
Overall Phase	214/260 (82.3)**	191/263 (72.6)
Acute Phase	251/261 (96.2)**	236/263 (89.7)
Delayed Phase	216/260 (83.1)*	195/263 (74.1)
No Significant Nausea (maximum nausea VAS<25)		
Study 052		
Overall Phase	188/257 (73.2)	171/259 (66.0)
Delayed Phase	195/259 (75.3)	178/260 (68.5)
Study 054		
Overall Phase	185/260 (71.2)	168/263 (63.9)
Delayed Phase	189/260 (72.7)	172/263 (65.4)
No Nausea (maximum nausea VAS<5)		
Study 052		
Overall Phase	122 / 257 (47.5)	115 / 260 (44.2)
Delayed Phase	132 / 259 (51.0)	124 / 260 (47.7)
Study 054		
Overall Phase	127 / 260 (48.8)*	102 / 263 (38.8)
Delayed Phase	137 / 260 (52.7)**	105 / 263 (39.9)
Ref: Original NDA Review Modified Table 3		

** p<0.01 when compared with Standard Therapy

*p<0.05 when compared with Standard Therapy

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/s/

Gary DellaZanna
9/19/2005 05:10:20 PM
MEDICAL OFFICER

Hugo Gallo Torres
9/19/2005 06:16:20 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	S-NDA
Submission Number	21-549
Submission Code	S-008
Letter Date	September 29, 2004
Stamp Date	September 29, 2004
PDUFA Goal Date	July 29, 2005
Reviewer Name	Gary Della'Zanna D.O., M.Sc.
Review Completion Date	July 18, 2005
Established Name	Aprepitant
Trade Name	Emend®
Therapeutic Class	NK_1 receptor antagonists
Applicant	Merck
Priority Designation	Standard Review
Formulation	Capsule
Dosing Regimen	125/80mg capsules
Indication	Prevention of (b) (4) Nausea and Vomiting Associated with Initial and Repeated courses of Moderately Emetogenic Cancer Chemotherapy
Intended Population	Cancer Patients

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The single trial, Protocol 071, is inadequate to support approval of the proposed new indication(s): "the prevention of (b) (4) *nausea* and *vomiting* associated with initial and repeated courses of moderately emetogenic cancer chemotherapy."

The study only succeeded in demonstrating that the aprepitant regimen was superior to standard therapy for the prevention of vomiting. The study, which included almost exclusively female patients, failed to demonstrate that the aprepitant regimen offered any significant advantage over the standard therapy for control of nausea or the use of rescue therapy. In this Reviewer's opinion the regulatory action should be "Approvable"; the efficacy results are not sufficiently "robust" to support approval of the requested new indications. The Applicant should be asked to carryout a clinical trial addressing these deficiencies.

1.2 Recommendation on Postmarketing Actions

1.2.1 Required Phase 4 Commitments

There are no new Phase IV commitments requested at this time.

During the initial approval the Agency requested several post marketing studies. In a letter dated March 26, 2003, Merck committed to the following Phase IV studies:

Commitment 1:
"Merck will obtain pharmacokinetic interaction data on a total of 10 patients receiving concomitant aprepitant and docetaxel (an IV chemotherapy CYP3A4 substrate)"

Status: Commitment fulfilled.

Commitment 2:
"Merck will conduct a drug interaction study to evaluate the effect of aprepitant on either vinorelbine or irinotecan."

Status: Protocol Submitted

Commitment 3:
"Merck will conduct a drug interaction study in healthy subjects, including some who are CYP2D6 poor metabolizers, to evaluate the effect of aprepitant on dolasetron."

Status: Commitment fulfilled.

Commitment 4:
"Merck will initiate a risk management program as outlined in our submission dated March 18, 2003 to ensure that health care providers understand the approved indication for EMEND and precautions with its use and to address and minimize potential for confusion with AMEN or VFEND and EMEND. Merck will submit all medication error reports relating to trade name confusion, both potential and actual."

Status: Commitment fulfilled.

Commitment 5:
"Merck will submit to FDA a report on the assessment of the inhibitory properties of aprepitant on CYP2C8 and CYP2B6 in vitro in human liver microsomes."

Status: Commitment fulfilled.

Commitment 6:
"Merck commits to justify the use of (b) (4) in the capsule formulation dissolution method, including studies on the surfactant level and RPM for the nanoparticle capsule formulation."

Status: Commitment fulfilled.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Merck submitted results from a single Phase III study (Study 071) to support the approval of the aprepitant regimen for the prevention of (b) (4) nausea and vomiting associated with initial and repeated courses of moderate emetogenic chemotherapy. Study 071 was a worldwide, multicenter, randomized, double-blind, parallel-group trial that enrolled patients diagnosed with breast cancer who were scheduled to receive moderately emetogenic chemotherapy. The primary purpose of the study was to demonstrate that the aprepitant regimen provided *superior* prevention of chemotherapy induced nausea and vomiting when compared to a recognized Standard of Care.

Patients were randomly assigned to one of the following two treatment arms: Aprepitant regimen or Standard Therapy regimen.

Table 1
Treatment Arms

	Day 1	Days 2 to 3
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 16mg PO	Aprepitant 80 mg PO Daily Ondansetron placebo PO Daily (BID)
Standard Therapy	*Aprepitant Placebo PO* Dexamethasone 20 mg PO *Ondansetron 16mg PO*	*Aprepitant Placebo PO Daily* *Ondansetron 8 mg PO Daily (BID)*

1.3.2 Efficacy

Merck is seeking the following new indications: *the prevention of* (b) (4) *nausea and vomiting associated with initial and repeated courses of moderate emetogenic chemotherapy.*

The primary endpoint in Study 071 was Complete Response in the overall phase. A responder was defined as a patient who reported no vomiting and did not require rescue therapy for 0 to 120 hours after receiving a dose of moderately emetogenic chemotherapy.

Study 071 successfully demonstrated that the aprepitant regimen was significantly more effective than standard therapy for Complete Response in the overall phase (primary endpoint). During the 5 days post-chemotherapy administration (Overall Phase), 50.8% of patients in the aprepitant group, compared to 42.5% of the patients receiving standard therapy reported

Complete Response. The unadjusted absolute difference in Complete Response (8.3%) represents a 20% relative improvement over standard therapy (See Table 2).

Although Study 071 succeeded for the primary endpoint, the efficacy results are insufficient to support approval of the proposed new indications. With this single study Merck is seeking approval for two indications: the prevention of (b) (4) nausea and vomiting. (b) (4)

Study 071 failed to show that the aprepitant regimen offered any significant advantage over standard therapy for Complete Response in *Acute* and/or *Delayed* phase time periods separately.

Table 2
Complete Response
Cycle 1

Phase	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Overall Phase (0 to 120 hours)*	220/433 (50.8)	180/424 (42.5)	0.015
Acute phase (0 to 24 hours)ǂ	327/432 (75.7)	292/423 (69.0)	0.034¥
Delayed phase (25 to 120 hours) ǂ	240/433 (55.4)	208/424 (49.1)	N.S.

Ref: Table 3.1.2 , P071.pdf
* Primary Endpoint
ǂ Exploratory Endpoint
¥ Not Significant after applying the Applicant's multiplicity adjustment
(Confirmed by Agency Statistician, Dr. Wen-Jen Chen, Ph.D.)

The results of Complete Response in each time period (exploratory endpoints) failed to reach statical significance. The results for Complete Response in the acute phase (p=0.034) is not statically significant after adjusting for multiplicity. (b) (4)

Furthermore, the efficacy results do not support approval of the proposed indication "the prevention of nausea and vomiting." For approval of the proposed indication, the aprepitant regimen would need to demonstrate significant efficacy for both nausea and vomiting. The results from Study 071 demonstrated a significant advantage over standard therapy for only the vomiting endpoint. Analyses of all nausea related endpoints failed to reach statical significance.

Additionally, the analyses of the individual components of the primary endpoint (No Vomiting and No Rescue therapy), demonstrated the aprepitant regimen had no significant effect on the use of rescue therapy (exploratory endpoint). The success of the primary endpoint, Complete Response (No Vomiting and No Rescue therapy), was driven by the No Vomiting variable.

Table 3
Efficacy Outcomes in Overall Phase
Cycle 1

Efficacy Outcome	Aprepitant Regimen %	Standard Regimen %	Treatment Difference	p-Value
Primary Endpoint				
Complete response	**50.8%**	**42.5%**	**8.3%**	**0.015**
Exploratory Endpoints				
No vomiting	**75.7%**	**58.7%**	**17%**	**<0.001**
No rescue therapy	**58.7%**	**56.2%**	**2.5%**	**N.S.**
No nausea (VAS <5 mm)	**33%**	**33%**	**0**	**N.S.**
No significant nausea (VAS <25 mm)	**60.9%**	**55.7%**	**5.2**	**N.S.**

Ref: clinical-overview.pdf Table 2.5:3
N.S.=not significant after applying the Applicant's multiplicity adjustment
(Confirmed by Agency Statistician, Dr. Wen-Jen Chen, Ph.D.)

Study 071 defined one secondary endpoint: the proportion of patients who reported that their chemotherapy induced *nausea* and vomiting had no impact on their activities of daily life. The effects of nausea and vomiting on a patient's quality of life was assessed using the Functional Living Index—Emesis (FLIE) questionnaire during Cycle 1. The protocol defined "no impact on daily life" as a total FLIE score >108 in the overall phase of Cycle 1. The total score was calculated as the sum of nine nausea specific and nine vomiting specific questions graded on a 7-point scale.

As assessed by the FLIE *total score*, significantly more patients in the aprepitant group than the standard therapy group reported that their CINV had "no impact on daily life" [aprepitant (63.5%) vs standard (55.6%)] (p=0.019)]. However, similar to the results of the primary endpoint, the success of the secondary endpoint "total score" was driven by the vomiting specific questions. For all nausea related questions, the treatment group differences failed to reach statistical significance.

Table 4
Patients with No Impact of CINV on Daily Life

Phase	FLIE Domain or Item Number	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value*
Protocol Defined Secondary Endpoint				
Nausea and Vomiting Specific	**Total Score > 108**	**271/427 63.5%**	**229/412 55.6%**	**0.019**
Related to Secondary Endpoint				
Vomiting Specific	**Vomiting Domain**	**366/427 85.6%**	**296/412 71.8%**	**<0.001**
"ability to enjoy daily meal"	**Item 13**	**392/427 91.8%**	**325/412 78.9%**	**<0.001**
"daily functioning"	**Item 16**	**394/427 92.3%**	**329/413 79.7**	**<0.001**
"hardship on other people"	**Item 18**	**395/427 92.5%**	**330/413 79.9**	**<0.001**
Nausea Specific	**Nausea Domain**	**229/428 53.5%**	**210/416 50.5%**	**N.S.**
"ability to enjoy daily meal"	**Item 4**	**247/428 57.7%**	**228/416 54.9%**	**Not Tested**
"daily functioning"	**Item 7**	**261/428 61.0%**	**234/416 56.3%**	
"hardship on other people"	**Item 8**	**258/428 60.3%**	**233/416 56.0%**	

Ref: Table 3.1.2
Based on a logistic regression model with terms for treatment group, investigator group, and age category (<55 years, ≥55 years).
Shaded cells items not tested since the domain score was not statistically significant.
CINV = Chemotherapy-induced nausea and vomiting.
FLIE = Functional Living Index-Emesis.
n/m = Number of patients with "No Impact of CINV on Daily Life"/number of patients included in the analysis of the item.

In addition to the above analyses, except for complete response in acute phase and no vomiting in both acute and delayed phases, the unadjusted p-values for the rest of the exploratory endpoint analyses were greater than 0.05. Furthermore, after applying the protocol's defined multiplicity adjustments, none of the exploratory endpoints reached statical significance.

Table 5
Exploratory Endpoints (Cycle 1)

Exploratory Endpoints	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Complete Response			
Acute phase (0 to 24 hours)	327/432 (75.7)	292/423 (69.0)	0.034**
Delayed phase (25 to 120 hours)	240/433 (55.4)	208/424 (49.1)	N.S.
No Vomiting			
Acute phase	378/432 (87.5)	327/423 (77.3)	<0.001**
Delayed phase	349/432 (80.8)	293/424 (69.1)	<0.001**
No Use of Rescue Therapy			
Acute phase	355/429 (82.8)	336/420 (80.0)	N.S.
Delayed phase	271/432 (62.7)	253/423 (59.8)	N.S.
No Significant Nausea (maximum VAS <25 mm)			
Overall phase	262/430 (60.9)	236/424 (55.7)	N.S.
Acute phase	342/430 (79.5)	331/423 (78.3)	N.S.
Delayed phase	281/430 (65.3)	260/423 (61.5)	N.S.
0 to 72 hours	274/430 (63.7)	254/424 (59.9)	N.S.
No Nausea (maximum VAS <5 mm)			
Overall phase	142/430 (33.0)	140/424 (33.0)	N.S.
Acute phase	261/430 (60.7)	250/423 (59.1)	N.S.
Delayed phase	159/430 (37.0)	154/423 (36.4)	N.S.
0 to 72 hours	167/430 (38.8%)	159/424 (37.5)	N.S.
Complete Protection (no vomiting, no rescue and maximum nausea VAS <25 mm)			
Overall phase	184/433 (42.5)	156/424 (36.8)	N.S.
Acute phase	296/431 (68.7)	272/423 (64.3)	N.S.
Delayed phase	203/433 (46.9)	180/424 (42.5)	N.S.
Total Control (no vomiting, no rescue and maximum nausea VAS <5 mm)			
Overall phase	125/433 (28.9)	115/424 (27.1)	N.S.
Acute phase	241/431 (55.9)	222/423 (52.5)	N.S.
Delayed phase	139/433 (32.1)	132/424 (31.1)	N.S.

Ref: Table 3.1.3, Statistical Review
†: Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group
** Not statically significant after adjusting for multiplicity
VAS = Visual analogue scale.

In this Reviewer's opinion the success of the "no vomiting" endpoint is not sufficient to grant approval for the prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

1.3.3 Safety

Overall, the aprepitant regimen was generally well tolerated in patients receiving moderately emetogenic chemotherapy. No new safety concerns were identified.

Protocol 071 randomized 866 patients diagnosed with breast cancer [aprepitant (438), standard therapy (428)]. The proportion of the patients who completed Cycle 1 was similar between treatment arms and did not suggest that aprepitant adversely affected the safety profile of the chemotherapy regimens. Four hundred thirty of the 438 patients randomized to the aprepitant regimen completed Cycle 1. This is comparable to the standard therapy group, where 421 of the 428 patients receiving standard therapy completed Cycle 1.

The incidence and type of adverse events were similar between treatment arms. The treatment groups were also similar with respect to the incidence of serious adverse events [aprepitant (3.4%) versus standard therapy (4.2%)], and adverse events that led to discontinuation from the study [aprepitant (1.6%) versus standard therapy (1.2%)]. None of the treatment group differences were statistically significant.

Table 6
Adverse Events Summary Cycle 1
Study 071

Adverse Experience	Treatment Group	
	Aprepitant (N=438) n (%)	Standard (N=428) n (%)
Patients with Adverse Event(s)	320 (73.1)	320 (74.8)
Patients with Serious Adverse Event(s)	15 (3.4)	18 (4.2)
Discontinued from Study due to AE	7 (1.6)	5 (1.2)
Discontinued from Study due to SAE	1 (0.2)	2 (0.5)
Ref: Modified Table 8-7 P071.pdf		

Common adverse events that occurred at a higher incidence in the aprepitant group than standard therapy group included: alopecia (24% versus 22.2%), fatigue (21.9% versus 21.5%), neutropenia (8.9% versus 8.4%), and dyspepsia (8.4% versus 4.9%). Other commonly reported adverse events included headache (16.4% for both groups) and constipation (12.3% versus 18.0%). A review of the severity of these events, based on NCI criteria, did not identify any concerning trends or finding during Cycle 1.

The incidence and type of adverse events reported during Cycles 2 to 4 was similar to that observed in Cycle 1. The most frequently reported adverse events during Cycles 2 to 4 included: fatigue (20.8% versus 17.5%), alopecia (12.7% versus 14.8%), nausea (11.9% versus 11.4%), constipation (9.9% versus 13.6%), headache (9.4% versus 9.2%), and dyspepsia (10.6% versus 7.8%) in the aprepitant group and standard therapy group respectively.

A higher incidence of neutropenia (9.1% vs 5.8%) was observed in the aprepitant group during Cycles 2 to 4. To assess the clinical significance of this treatment group difference, the severity of this adverse event was analyzed in terms of NCI criteria. To be thorough, the incidence of febrile neutropenia was also analyzed in terms of NCI criteria.

With respect to the more severe NCI toxicity, Grade 3/4 neutropenia occurred more frequently in the aprepitant group [27 patients (7.0%)] than the standard therapy group [13 patients (3.6%)]. Additionally, grade 3/4 *febrile* neutropenia also occurred more frequently in the aprepitant group [11 patients (2.9%)] than the standard therapy group [7 patients (1.9%)].

Since these adverse events may be directly related to chemotherapy exposure, these events were then analyzed adjusting for patient exposure to chemotherapy. After adjusting for exposure, the percentage of patient-cycles with Grade 3/4 neutropenia in Cycles 2 to 4 was 2.5% (27/1099) in the aprepitant group versus 1.3% (13/1006) in the standard therapy group. Similarly, the treatment group difference of febrile neutropenia decreased to 1.0% (11/1099) in the aprepitant group versus 0.7% (7/1006) in the standard therapy group. The clinical significance of these small treatment group differences is unknown.

Table 7
Adverse Events Summary Cycle 2 to 4
Adjusted for Patient Exposure (Cycles on Chemotherapy)
Study 071

Adverse Experience	Treatment Group	
	Aprepitant Patient-Cycles (N=1099) n (%)	Standard Patient-Cycles (N=1006) n (%)
Patients with Adverse Event(s)	545 (49.6)	464 (46.1)
Patients with Serious Adverse Event(s)	17 (1.5)	15 (1.5)
Discontinued from Study due to AE	7 (0.6)	4 (0.4)
Discontinued from Study due to SAE	5 (0.5)	0 (0.0)
Ref: Modified Table 8-9 P071.pdf		

1.3.4 Dosing Regimen and Administration

Table 8
Treatment Arms

Treatment Regimen	Day 1	Days 2 to 3
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 16mg PO	Aprepitant 80 mg PO Daily Ondansetron placebo PO Daily (BID)
Standard Therapy	Aprepitant Placebo PO Dexamethasone 20 mg PO Ondansetron 16mg PO	Aprepitant Placebo PO Daily Ondansetron 8 mg PO Daily (BID)

The dose selection for both treatment arms was acceptable for this Phase III study. The 125/80 mg aprepitant dosing regimen, administered for three days, is the currently approved dose. The safety and efficacy of this dosing regimen has been evaluated in several Phase II and III protocols. The Standard Therapy comparator arm is a recognized regimen for the prevention of CINV due to moderately emetogenic cancer chemotherapy.

1.3.5 Drug-Drug Interactions

The current application did not include any new pharmacokinetic or drug interaction studies. The biopharmaceutical portion of this submission was comprised of a single bioequivalence study conducted to bridge Zofran manufactured in the United Kingdom with Zofran manufactured in the United States.

The following is a summary of relevant data submitted with the original NDA.

> Aprepitant is a moderate inhibitor of CYP 3A4 on short-term administration and an inducer of CYP 3A4 on longer administration. When aprepitant was administered as part of a 5 day regimen (125 mg on Day 1, 80 mg/day from Day 2 to 5) it acted as a moderate inhibitor of CYP 3A4, resulting in a 2 to 3 fold mean increase in the AUC of midazolam (highly specific 3A4 substrate) and a two-fold increase in AUC of dexamethasone and diltiazem.
>
> With chronic administration, aprepitant can act as an inducer of CYP 3A4 and can induce its own metabolism. Chronic administration of aprepitant resulted in a 40% reduction in plasma levels of ethinyl estradiol (CYP 3A4 substrate).

Aprepitant has also been shown to be an inducer of CYP 2C9. Patients on warfarin had an 11% decrease in their International Normalized Ratio (INR) on Day 8, following a three day regimen of aprepitant. The S-warfarin trough plasma concentration decreased by as much as 34% by Day 8.

Since the original approval, Merck has completed the following Phase IV drug interaction studies (Ref: Clinical Pharmacology reviews in DFS).

Post marketing Commitment 1:

Drug interaction study with docetaxel, a CYP3A4 substrate.

Findings: administration of aprepitant regiment did not alter the pharmacokinetics of intravenous docetaxel

Post marketing Commitment 3:

Assessment of the inhibitory properties of aprepitant on CYP2C8 and CYP2B6 in vitro in human liver microsomes.

Findings: aprepitant may not cause CYP2B6 or CYP2C8-inhibition related drug interactions.

1.3.6 Special Populations

Supplemental NDA 21-549/008 did not identify any significant treatment-by-age or race interactions for the primary endpoint, Complete Response in the overall phase. The data are insufficient to perform a meaningful treatment by gender analysis; only two of the randomized patients were male (0.2%) and both were in the aprepitant group. This is a very important limitation in the data, considering a significant treatment by gender interaction was identified in one of the two pivotal studies submitted with the original NDA (Study 052).

Table 9
Demographics
Study 071
Cycle 1

Demographics	Treatment Group	
	Aprepitant Regimen (N=438)	Standard Regimen (N=428)
Sex		
Male	2	0
Female	436	428
Race		
Caucasian	79.7%	77.6%
Black	7.8%	8.4%
Hispanic	4.3%	4.9%
Asian	7.5%	8.4%
Other	0.7%	0.7%
Age in Years		
Mean	53.1	52.1
Median	53.0	52.0
Min-Max	25 to 78	23 to 78
<55	55.7%	60.7%
≥55	44.3%	39.3%
65 to 74	13.2%	12.4%
>74	2.7%	1.9%
Ref: P071.pdf, Fig. 6-8, pg. 92		

The following information on Special Populations is based on data submitted with the original application and appears in the current label:

Pediatric

"The pharmacokinetics of EMEND have not been evaluated in patients below 18 years of age."

Analysis by Gender

"Following oral administration of a single 125-mg dose of EMEND, no difference in $AUC_{0\text{-}24hr}$ was observed between males and females. 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 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."

Analysis by Age

"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 (≥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."

Analysis by 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 Whites and Blacks, respectively. The C_{max} is 22% and 31% higher in Hispanics as compared with Whites and Blacks, respectively. These differences are not considered clinically meaningful. There was no difference in AUC_{0-24hr} or C_{max} between Whites and Blacks. No dosage adjustment for EMEND is necessary based on race."

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_{0-24hr} of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the AUC_{0-24hr} of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, as compared with healthy subjects given the same regimen. These differences in AUC_{0-24hr} are not considered clinically meaningful; therefore, no dosage adjustment 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)."

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 hemodialysis.

In patients with severe renal insufficiency, the $AUC_{0-\infty}$ of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects. In patients with ESRD undergoing hemodialysis, the $AUC_{0-\infty}$ of total aprepitant decreased by 42% and C_{max} decreased by 32%.

Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal insufficiency compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

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

2 INTRODUCTION AND BACKGROUND

(b) (4) An oral formulation was then evaluated under IND 50-283 (April 9, 1996). Since the original IND submission aprepitant has undergone several name changes as well as changes in formulation. In the medical literature aprepitant may be referred to as L-754,030, MK-0869, aprepitant, or EMEND®.

Following a GI Advisory Committee meeting on March 6, 2003, aprepitant was approved for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic chemotherapy. (b) (4)

On September 29, 2004, Merck submitted S-NDA 21-549/008 seeking approval for the prevention of (b) (4) nausea and vomiting associated with initial and repeated courses of moderately emetogenic chemotherapy.

2.1 Product Information

The approved formulation of aprepitant is an oral nanoparticle, substance P, neurokinin 1 (NK_1) receptor antagonist. It is currently available in two dose strengths (125mg and 80mg). Aprepitant is approved as part of a three drug, three day regimen that includes a corticosteroid and a 5-HT_3 antagonist. The recommended dose of aprepitant is 125 mg orally 1 hour prior to chemotherapy (Day 1) and 80 mg once daily in the morning on Days 2 and 3.

2.2 Currently Available Treatment for Indications

There are several approved therapies for the prevention of acute nausea and vomiting associated with moderate emetogenic chemotherapy. Currently, palonosetron hydrochloride (ALOXI™) is the only drug approved for the prevention of acute and delayed nausea and vomiting associated with moderate emetogenic chemotherapy.

In clinical practice there are "Standard of Care" regimens that are widely accepted and used in the prevention of acute and *delayed* nausea and vomiting associated with moderately emetogenic chemotherapy. The "Standard of Care" comparator arm used in Study 071, although not FDA approved, is well recognized in the medical literature.

Table 10
Standard of Care
Study 071

	Day 1	Days 2 to 3
Standard Therapy	**Dexamethasone 20 mg PO** **Ondansetron 16mg PO**	**Ondansetron 8 mg PO Daily (BID)**

2.3 Availability of Proposed Active Ingredient in the United States

Aprepitant is available and marketed throughout the United States. There are no reports or concerns of drug shortage at the time of this review.

2.4 Presubmission Regulatory Activity

On September 4, 2003, the Division held a teleconference in response to a Type B meeting request. The purpose of the meeting was to address the firm's questions contained in the August 1, 2003 background package. During this meeting Merck questioned whether a single study would be adequate to support approval. The Division discouraged a single study approach, however, commented that a "single study may suffice if the data are robust."

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Supplemental NDA 21-549/008 did not include any important outstanding CMC issues.

3.2 Animal Pharmacology/Toxicology

Supplemental NDA 21-549/008 did not include any new animal Pharmacology/Toxicology data.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Electronic S-NDA 21-549/008
S-NDA 21-549/008 Safety Update Reports
Original NDA 21-549 Review
GI Advisory Committee Meeting transcript (March 6, 2003)
Phase IV Commitments
Information Requests
Approved and Proposed Package Insert
Electronic Submitted Data Sets
Literature Search

4.2 Tables of Clinical Studies

Table 11
Single Clinical Trial
Protocol 071

Study	Duration	Enrolled	Dose
Phase III (Pivotal)			
071	3 Days Therapy/Cycle (up to 7 Cycles)	866	Aprepitant 125 mg Day 1 Aprepitant 80 mg Days 2 and 3

4.3 Review Strategy

A multi-specialty review of the Supplemental New Drug Application (S-NDA) was performed utilizing the applicant's submitted data. The review team included physicians, statisticians, chemists, biopharmaceutical specialists, and a project manager.

The safety and efficacy data from the single pivotal trial was reviewed and compared with the results reported in the summaries of safety and efficacy. The review included several information requests for material not submitted with the application. The information received from these requests was incorporated into this review.

4.4 Data Quality and Integrity

The quality of the data was discussed in consultation with the Agency's Biostatistical division and was found to be acceptable. The submission was well organized and easy to navigate. During the safety review Case Report Forms (CRFs) were randomly reviewed for completeness and were found to be acceptable.

4.5 Compliance with Good Clinical Practices

Merck certified that the study was conducted in conformance with applicable country and/or local requirements regarding the protection of the rights and welfare of human subjects participating in biomedical research.

4.6 Financial Disclosures

Merck certified that they did not enter into any financial agreement with the clinical investigators whereby the value of their compensation could be affected by the outcome of the studies. Merck also documented that investigators submitted disclosure statements as required by regulations 21 CFR Part 54.

5 CLINICAL PHARMACOLOGY

The current application did not include any new pharmacokinetic or pharmacodynamic studies. The biopharmaceutical portion of this submission was comprised of a single bioequivalence study conducted to bridge Zofran manufactured in UK with Zofran manufactured in US.

5.1 Pharmacokinetics

The following pharmacokinetic and pharmacodynamic information is summarized from the original NDA.

> Drug interaction studies submitted with the original NDA demonstrated that aprepitant, when administered as part of a 5 day regimen (125 mg on Day 1, 80 mg/day from Day 2 to 5), acts as a moderate inhibitor of CYP 3A4. Short term administration of aprepitant resulted in a 2 to 3 fold mean increase in the AUC of midazolam (highly specific 3A4 substrate) and a two-fold increase in AUC of dexamethasone and diltiazem.
>
> Administration of aprepitant for 28 days or longer demonstrated that aprepitant is also an inducer of CYP 3A4 and can auto induces its own metabolism. Chronic administration of aprepitant resulted in a 40% reduction in levels of ethinyl estradiol (CYP 3A4 substrate).

Aprepitant was also shown to be an inducer of CYP 2C9. Patients on warfarin had an 11% decrease in their International Normalized Ratio (INR) on Day 8, following a three day treatment regimen of aprepitant. The S-warfarin trough plasma concentration decreased by as much as 34% by Day 8.

The potential of aprepitant to be a P-glycoprotein (P-gp) substrate and/or inhibitor has been studied in vitro. In these studies aprepitant was found to be a P-gp substrate, probably weaker than vinblastine. It was also an inhibitor of P-gp-mediated transport of vinblastine, with potency similar to that of verapamil. The effect of the aprepitant regimen on digoxin pharmacokinetics was investigated in healthy subjects. Results showed that aprepitant had no effect on the pharmacokinetics of digoxin.

5.2 Pharmacodynamics

Because of first pass metabolism, aprepitant's CYP 3A4 inhibitory effect is greatest when CYP 3A4 substrates are administered orally; aprepitant caused a 2.3-fold increase in the AUC of oral dexamethasone (CYP3A4 substrate) compared to only a 1.3-fold increase in the AUC of I.V. methylprednisolone (CYP3A4 substrate).

5.3 Exposure-Response Relationships

The current application did not include any new exposure-response data.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Merck submitted the results from a single Phase III study to support the approval of the following indication(s): the prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy. In this Reviewer's opinion, approval of this indication requires that the aprepitant regimen demonstrate a significant improvement over standard therapy for both nausea and vomiting in (b) (4)

6.1.1 Methods

A multi-specialty review of the S-NDA was performed utilizing the applicant's submitted data. The review team included physicians, statisticians, chemists, biopharmaceutical specialists, and a project manager.

6.1.2 General Discussion of Endpoints

To interpret the efficacy results and understand the limitations of the primary and secondary endpoints, the following terms need to be defined:

Overall Phase:	0 to 120 hours post initiation of chemotherapy
Acute Phase:	0 to 24 hours post initiation of chemotherapy
Delayed Phase:	>24 to ≤120 hours post initiation of chemotherapy
Complete Response:	No Emesis, No Rescue therapy
No Emesis:	No vomiting or retching or dry heaves (includes patients who received rescue therapy).
No Nausea:	Maximum nausea VAS <5 mm
No Significant Nausea:	Maximum nausea VAS <25 mm
Complete Protection:	No emesis, no rescue therapy, no significant nausea (maximum nausea <25 mm on VAS)
Total Control:	No emesis, no rescue therapy, and no nausea (maximum nausea <5 mm on VAS).

Primary Endpoint:

The primary endpoint in Study 071 was Complete Response in the overall phase. A responder was defined as a patient who reported no vomiting and did not require rescue therapy for 0 to 120 hours after receiving a dose of moderately emetogenic chemotherapy.

Since the primary endpoint did not include a nausea specific assessment, it is this Reviewer's opinion, that for approval of the proposed indication, the efficacy for nausea would need to be supported by the exploratory nausea endpoints.

The primary endpoint evaluated complete response in the overall phase. By definition, the "overall phase" is comprised of the acute phase (0 to 24 hours) and the delayed phase (>24 to ≤ 120 hours) time periods. This distinction between time periods is important when considering the efficacy data, (b) (4) For example, there are several drugs currently approved for the prevention of CINV in the *acute* phase. However, palonosetron is the only approved therapy for the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic chemotherapy.

Secondary Endpoint:

Study 071 defined one secondary endpoint: the proportion of patients who reported that their chemotherapy induced *nausea* and vomiting had no impact on their activities of daily life. The effects of nausea and vomiting on a patient's quality of life was assessed using the Functional Living Index—Emesis (FLIE) questionnaire during Cycle 1. The protocol defined "no impact on daily life" as a total FLIE score >108 in the overall phase of Cycle 1. The total score was calculated as the sum of nine nausea specific and nine vomiting specific questions graded on a 7-point scale.

Again, it is this Reviewer's opinion that for chemotherapy induced *nausea* and vomiting to have "no impact" on a patients activities of daily life, the treatment would need to be effective for both nausea and vomiting.

The Functional Living Index - Emesis (FLIE) questionnaire was reviewed in consultation with the Study Endpoints and Label Development (SEALD) Division to help interpret whether the data support the Applicant's proposed indications. Their review is filed in DFS.

The following is a limited summary of the Study Endpoints and Label Development (SEALD) consult:

1. A single study is generally considered inadequate to meet regulatory requirements for substantial evidence to support statements in labeling or advertising.

2. Analysis of the FLIE *vomiting* scale demonstrated that patients receiving EMEND® were significantly more likely to report scores that could be described as "minimal or no impact of vomiting on daily life". However the FLIE *nausea* scale did not differ between treatment groups. In SEALD opinion, the statement proposed for the revised label would give the false impression that aprepitant significantly improves both nausea and vomiting outcomes.

   Based on the results of Study 071, SEALD questions whether a FLIE total score >108 is appropriate to define symptoms as "minimal or no impact of nausea and vomiting on the patients life".

3. The FLIE was originally developed to assess the impact of chemotherapy-induced nausea and vomiting (CINV) on patients' daily lives over the 3 days following chemotherapy. In this submission the questionnaire was administered at Day 6.

   The SEALD division noted that the 5-day version of the FLIE may not be a valid assessment of what patients experienced over the 5-days post chemotherapy. Published validation of the 5-day recall version of the FLIE focused on discriminant validity and did not address construct validity, recall errors or other concerns raised by extending the recall. The validation study did not compare the original 3-day recall version of the FLIE to the 5-day recall version.

   SEALD discourages patient-reported outcome instruments that require patients to summarize long period of time as this would introduce recall errors and difficulty interpreting responses.

(Note: Based on this Reviewer's interpretation of the FLIE efficacy analyses, the issue of whether the FLIE questionnaire is validated at 5-days post chemotherapy will not impact on my recommendations.)

6.1.3 Study Design

Study 071 was a multi-national, multicenter (109 centers), randomized, double-blind, parallel-group study that evaluated the safety and efficacy of aprepitant in the prevention of chemotherapy induced nausea and vomiting during initial and multiple cycles of moderately emetogenic chemotherapy. A total of 910 patients were screened with 866 randomized into one of two treatment groups [aprepitant group (438), standard therapy (428)].

Table 12
Treatment Arms

Treatment Regimen	Day 1	Days 2 to 3
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 16mg PO	Aprepitant 80 mg PO Daily Ondansetron *Placebo* PO Daily (BID)
Standard Therapy	Aprepitant *Placebo* PO Dexamethasone 20 mg PO Ondansetron 16mg PO	Aprepitant *Placebo* PO Daily Ondansetron 8 mg PO Daily (BID)

Limitations of the Study Design

The protocol enrolled only patients with a diagnosis of breast cancer who were scheduled to receive moderately emetogenic chemotherapeutic agents. This enrollment criterion essentially limited the study to female patients (99.8%) and limited the chemotherapeutic agents to those used to treat breast cancer. These results may not be generalizable to other moderate emetogenic chemotherapy regimens.

This Reviewer is concerned that the results of this single study may not be generalizable to both male and female patients. A significant treatment-by-gender interaction was identified in one of the two pivotal trials submitted with the original aprepitant NDA. In Study 052, the efficacy of the aprepitant regimen was statistically superior to standard therapy in female patients only. It is unknown whether this gender interaction would be more significant in patients receiving moderate emetogenic chemotherapeutic agents.

Table 12
Original NDA
Treatment by Gender
Complete Response Endpoint

Female

	MK-0869 Regimen n/m (%)	Standard Therapy n/m (%)
Overall Phase	76/98 (78)**	38/98 (39)
Acute Phase	88/97 (91)**	66/98 (67)
Delayed Phase	77/98 (79)**	41/98 (42)

Male

	MK-0869 Regimen n/m (%)	Standard Therapy n/m (%)
Overall Phase	113/162 (70)	98/162 (61)
Acute Phase	143/162 (88)	137/162 (85)
Delayed Phase	119/162 (74)	104/162 (64)

**: $p \leq 0.01$ when compared with Standard Therapy; [1]: Complete Response = No emesis with no rescue therapy; n/m = Number of patients with desired response/number of patients included in time point.

Ref: Original NDA, Statical Review, Table 2.2.2.1.1

As a comparison, the approval of palonosetron, the only other drug indicated for the prevention of acute and delayed nausea and vomiting associated with *moderately* emetogenic chemotherapy, was based on *two* multicenter, double-blind, active controlled trials. Each study enrolled greater than 560 patients and included several different types of cancer, including but not limited to: breast, lung, colon, rectal, gastric, prostate and ovarian.

It is not this reviewer's intention to compare the results of the palonosetron trials with the aprepitant trial. The palonosetron trials are being referenced for their study design, enrollment criteria and to emphasize that the approval was based on two well controlled studies (Ref. NDA 21-372, Medical Officer Review June 6, 2003 and Protocol Reviews 99-03 and 99-04, July 2, 2003).

6.1.4 Efficacy Findings

The Division has verified the Applicant's data and concurs with the results of the major efficacy analyses. The primary efficacy analysis was performed on the modified intention to treat (mITT) population. Significantly more patients in the aprepitant group than the standard therapy group reported Complete Response (no vomiting and no rescue therapy) in the overall phase (primary endpoint). During the 5 days post-chemotherapy administration (Overall Phase), 50.8% of patients in the aprepitant group compared to 42.5% of the patients receiving standard therapy reported Complete Response.

Table 13
Complete Response
Cycle 1

Phase	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	Delta	p-Value	Corrected p-Value*
Overall Phase (Primary Endpoint)	**220/433 (50.8)**	**180/424 (42.5)**	**8.3%**	**0.015**	
Acute Phase‡	**327/432 (75.7)**	**292/423 (69.0)**	**6.7%**	**0.034***	**N.S.**
Delayed Phase‡	**240/433 (55.4)**	**208/424 (49.1)**	**6.3%**	**0.064**	**N.S.**

Ref: Table 3.1.2 , P071.pdf
N.S.= not significant
‡ exploratory endpoints
* not significant after multiplicity adjustment

(b) (4)

Analysis of Complete Response during the Acute and Delayed time periods individually (exploratory endpoints) failed to demonstrate that the aprepitant regimen offered any significant improvement over the standard therapy. The treatment group differences were numerically in favor of the aprepitant regimen but were not statistically significant when corrected for multiplicity.

Additionally, the analyses of the individual components of the primary endpoint (No Vomiting and No Rescue therapy), demonstrated that the aprepitant regimen had no significant effect on the use of rescue therapy (exploratory endpoints). Therefore, the success of the primary endpoint, Complete Response (No Vomiting and No Rescue therapy), was driven by the No Vomiting variable.

Table 14
Efficacy Outcomes in Overall Phase
Cycle 1

Efficacy Outcome	Aprepitant Regimen %	Standard Regimen %	Treatment Difference	p-Value
Primary Endpoint				
Complete Response	**50.8%**	**42.5%**	**8.3%**	**0.015**
Exploratory Endpoints				
No Vomiting	**75.7%**	**58.7%**	**17%**	**<0.001**
No Rescue therapy	**58.7%**	**56.2%**	**2.5%**	**N.S.**

Ref: clinical-overview.pdf Table 2.5:3
N.S.=not significant

Since the proposed indication is for the prevention of both *nausea* and vomiting, the exploratory nausea endpoints were analyzed to see if the data supported the proposed indication.

Table 15
Efficacy Outcomes in Overall Phase
Cycle 1

Efficacy Outcome	Aprepitant Regimen %	Standard Regimen %	Treatment Difference	p-Value
Primary Endpoint				
Complete Response	**50.8%**	**42.5%**	**8.3%**	**0.015**
Exploratory Endpoints				
No Vomiting	**75.7%**	**58.7%**	**17%**	**<0.001**
No Nausea (VAS <5 mm)	**33%**	**33%**	**0**	**N.S.**
No Significant Nausea (VAS <25 mm)	**60.9%**	**55.7%**	**5.2**	**N.S.**

Ref: clinical-overview.pdf Table 2.5:3
N.S.=not significant

Significantly more patients in the aprepitant group than standard therapy group reported "no vomiting" in the overall time period. The treatment group differences for all nausea related endpoints failed to reach statical significance. Therefore, the data do not support the proposed indication, "the prevention of nausea and vomiting."

The results of the secondary endpoint followed a similar pattern. Symptoms of nausea and vomiting were described as having *no impact* on a patient's activities of daily life if their total FLIE score was greater than 108 in the overall phase of Cycle 1. The total score was calculated as the sum of both nausea specific and vomiting specific questions. As assessed by the FLIE total score, 63.5% of the patients in the aprepitant regimen group reported "no impact on daily life" compared to 55.6% of the patients receiving standard therapy. The treatment group

difference was statistically significant, in favor of the aprepitant regimen (p=0.019). However, the success of the secondary endpoint was also driven by the "no vomiting" variables.

The analyses of the individual components of the secondary endpoint (Vomiting Domain and Nausea Domain), demonstrated the aprepitant regimen did not significantly effect the patient's symptoms of nausea. The treatment group differences were numerically in favor of the aprepitant regimen but were not statistically significant (p=0.339).

Table 16
Patients with no impact of CINV on daily life

Phase	FLIE Domain or Item Number	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value*
Protocol Defined Secondary Endpoint				
Nausea and Vomiting Specific	**Total Score >108**	**271/427 63.5%**	**229/412 55.6%**	**0.019**
Related to Secondary Endpoint				
Vomiting Specific	**Vomiting Domain**	**366/427 85.6%**	**296/412 71.8%**	**<0.001**
"ability to enjoy daily meal"	**Item 13**	**392/427 91.8%**	**325/412 78.9%**	**<0.001**
"daily functioning"	**Item 16**	**394/427 92.3%**	**329/413 79.7**	**<0.001**
"hardship on other people"	**Item 18**	**395/427 92.5%**	**330/413 79.9**	**<0.001**
Nausea Specific	**Nausea Domain**	**229/428 53.5%**	**210/416 50.5%**	**N.S.**
"ability to enjoy daily meal"	**Item 4**	**247/428 57.7%**	**228/416 54.9%**	**Not Tested**
"daily functioning"	**Item 7**	**261/428 61.0%**	**234/416 56.3%**	
"hardship on other people"	**Item 8**	**258/428 60.3%**	**233/416 56.0%**	

Ref: Table 3.1.2
"No Impact of CINV on Daily Life": defined as a total score >108
Shaded cells items not tested since the domain score was not statistically significant.
CINV = Chemotherapy-induced nausea and vomiting.
FLIE = Functional Living Index-Emesis.
n/m = Number of patients with "No Impact of CINV on Daily Life"/number of patients included in the analysis of the item.

Exploratory Endpoints:

Based on the protocol's data analysis plan, since the primary and secondary efficacy hypotheses were satisfied, additional exploratory efficacy endpoints were tested. In order to address multiplicity in the exploratory efficacy endpoints, Merck employed a closed testing procedure, grouping the exploratory endpoints. Each group was tested in a sequential fashion, such that subsequent groups would not be tested unless the prior group each revealed at least one

statistically significant finding. Hochberg's procedure was used to adjust for testing the multiple efficacy endpoints within the group to control the type I error at the 0.05 level.

Except for the endpoints Complete Response in the acute phase and the No Vomiting endpoints in overall, acute and delayed phases, the uncorrected treatment group differences for all other exploratory endpoints failed to reach statical significance ($p > 0.05$). The aprepitant regimen demonstrated no significant advantage over the standard therapy for any of the nausea endpoints or the use of rescue therapy even before correcting for multiplicity.

Table 17
Exploratory Endpoints Cycle 1

Exploratory Endpoints	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Complete Response			
Acute phase (0 to 24 hours)	327/432 (75.7)	292/423 (69.0)	0.034
Delayed phase (25 to 120 hours)	240/433 (55.4)	208/424 (49.1)	N.S.
No Vomiting			
Acute phase	378/432 (87.5)	327/423 (77.3)	<0.001
Delayed phase	349/432 (80.8)	293/424 (69.1)	<0.001
No Use of Rescue Therapy			
Acute phase	355/429 (82.8)	336/420 (80.0)	N.S.
Delayed phase	271/432 (62.7)	253/423 (59.8)	N.S.
No Significant Nausea (maximum VAS <25 mm)			
Overall phase	262/430 (60.9)	236/424 (55.7)	N.S.
Acute phase	342/430 (79.5)	331/423 (78.3)	N.S.
Delayed phase	281/430 (65.3)	260/423 (61.5)	N.S.
0 to 72 hours	274/430 (63.7)	254/424 (59.9)	N.S.
No Nausea (maximum VAS <5 mm)			
Overall phase	142/430 (33.0)	140/424 (33.0)	N.S.
Acute phase	261/430 (60.7)	250/423 (59.1)	N.S.
Delayed phase	159/430 (37.0)	154/423 (36.4)	N.S.
0 to 72 hours	167/430 (38.8%)	159/424 (37.5)	N.S.
Complete Protection (no vomiting, no rescue and maximum nausea VAS <25 mm)			
Overall phase	184/433 (42.5)	156/424 (36.8)	N.S.
Acute phase	296/431 (68.7)	272/423 (64.3)	N.S.
Delayed phase	203/433 (46.9)	180/424 (42.5)	N.S.
Total Control (no vomiting, no rescue and maximum nausea VAS <5 mm)			
Overall phase	125/433 (28.9)	115/424 (27.1)	N.S.
Acute phase	241/431 (55.9)	222/423 (52.5)	N.S.
Delayed phase	139/433 (32.1)	132/424 (31.1)	N.S.

Ref: Table 3.1.3, Statistical Review
VAS = Visual analogue scale.

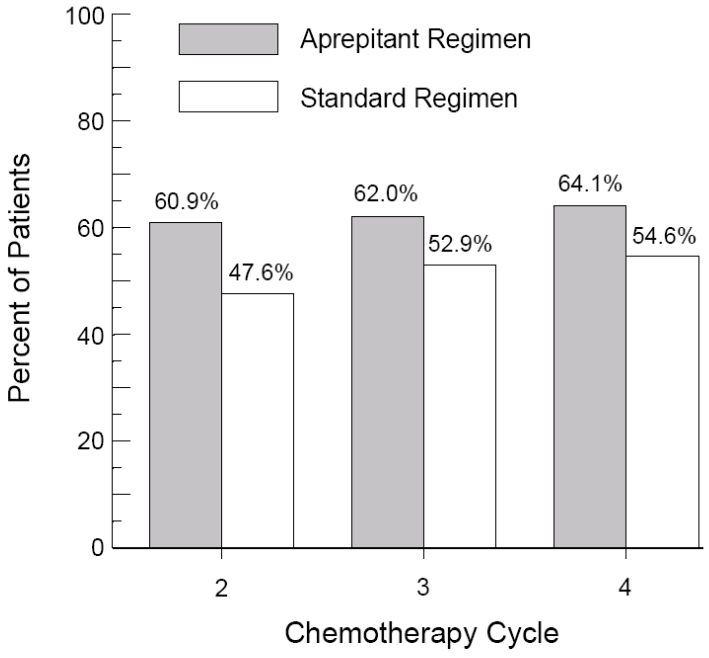
If the Agency strictly follows the protocol's data analysis plan for multiplicity adjustment, then none of the exploratory endpoints reach statistical significance; including the No Vomiting endpoint (see Statical Review, Wen-Jen Chen, Ph.D.).

Efficacy in Multiple Cycles:

During the multiple cycle extension portion of the study, Merck reports that efficacy data collection was "simplified." Only nausea severity was recorded daily for the first 5 days of each cycle. On Day 6, patients answered two "yes/no" questions: 1) whether they experienced any vomiting episodes, 2) whether they used rescue therapy since the most recent administration of chemotherapy.

Based on the protocol definition of Complete Response in the overall phase, Merck reports that the antiemetic effectiveness of the aprepitant regimen was maintained throughout the multiple cycles, as evidenced by the consistent ~10% difference between treatment groups.

Figure 18
Percentage of Patients With a Complete Response
Cycles 2 through 4



Aprepitant (N)	379	358	343
Standard (N)	355	325	304

N = Number of patients with evaluble data.

[Ref. 5.3.5.1; P071]

This Reviewer has already commented on the limitations of this endpoint as an independent indicator of efficacy. Also, due to the defined data analysis plan, the statical significance of this 10% treatment group difference can not be ascertained.

The following tables show the Applicant's exploratory analysis of nausea over Cycles 1 through 4, using the same data analysis as in Cycle 1. Since these results were exploratory in nature, Merck states these results should be considered "only as hypothesis generating and not for making any inference regarding nausea in the multiple cycles."

Table 19
Exploratory Endpoint
No Nausea (Peak VAS<5 mm)
(Cycle 1-4)

Exploratory Endpoints	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Cycle 1			
Overall phase (0 to 120 hours)	142/430 (33.0)	140/424 (33.0)	N.S.
Acute phase (0 to 24 hours)	261/430 (60.7)	250/423 (59.1)	N.S.
Delayed phase (25 to 120 hours)	159/430 (37.0)	154/423 (36.4)	N.S.
Cycle 2			
Overall phase (0 to 120 hours)	137/380 (36.1)	125/357 (35.0)	N.S.
Acute phase (0 to 24 hours)	255/380 (67.1)	210/357 (58.8)	0.024
Delayed phase (25 to 120 hours)	150/380 (39.5)	134/357 (37.5)	N.S.
Cycle 3			
Overall phase (0 to 120 hours)	134/360 (37.2)	136/328 (41.5)	N.S.
Acute phase (0 to 24 hours)	234/359 (65.2)	209/328 (63.7)	N.S.
Delayed phase (25 to 120 hours)	141/360 (39.2)	142/327 (43.4)	N.S.
Cycle 4			
Overall phase	155/344 (45.1)	131/307 (42.7)	N.S.
Acute phase	236/344 (68.6)	206/307 (67.1)	N.S.
Delayed phase	161/343 (46.9)	133/307 (43.3)	N.S.

Ref: Modified Tables 1, 3, 5, 7 Clinical Attachment.pdf
†: Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group, investigator group, and age category (<55 years, ≥55 years).
VAS = Visual analogue scale.

Table 20
Exploratory Endpoint
No Significant Nausea (Peak VAS<25 mm)
(Cycle 1-4)

Exploratory Endpoints	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Cycle 1			
Overall phase (0 to 120 hours)	262/430 (60.9)	236/424 (55.7)	N.S.
Acute phase (0 to 24 hours)	342/430 (79.5)	331/423 (78.3)	N.S.
Delayed phase (25 to 120 hours)	281/430 (65.3)	260/423 (61.5)	N.S.
Cycle 2			
Overall phase (0 to 120 hours)	249/380 (65.5)	203/357 (56.9)	0.020
Acute phase (0 to 24 hours)	324/380 (85.3)	277/357 (77.6)	0.010
Delayed phase (25 to 120 hours)	261/380 (68.7)	217/357 (60.8)	0.028
Cycle 3			
Overall phase (0 to 120 hours)	256/360 (71.1)	213/328 (64.9)	N.S.
Acute phase (0 to 24 hours)	315/359 (87.7)	276/328 (84.1)	N.S.
Delayed phase (25 to 120 hours)	258/360 (71.7)	219/327 (67.0)	N.S.
Cycle 4			
Overall phase	255/344 (74.1)	219/307 (71.3)	N.S.
Acute phase	301/344 (87.5)	263/307 (85.7)	N.S.
Delayed phase	262/343 (76.4)	225/307 (73.3)	N.S.

Ref: Modified Tables 2,4,6,8 Clinical Attachment.pdf
†: Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group, investigator group, and age category (<55 years, ≥55 years).
VAS = Visual analogue scale.

In this Reviewer's opinion, the multiple cycle efficacy data do not support the proposed indication, *the prevention of* (b) (4) *nausea and vomiting.* Based on the Applicant's analysis, the aprepitant regimen did not offer significant improvement over the standard therapy for the symptoms of nausea during Cycles 1 through 4.

The results of the exploratory "No Nausea" endpoint only reached statical significance in the Acute Phase of Cycle 2. The treatment group difference for the "No Nausea" endpoint failed to be statistically significant in the overall and delayed phase of Cycle 2 as well as all three phases during Cycles 1, 3 and 4.

The results for the "No Significant Nausea" endpoint (Peak VAS<25 mm) demonstrated similar findings. The treatment group differences failed to be statistically significant in all three phases of Cycles 1, 3 and 4.

6.1.5 Clinical Microbiology

Not Applicable

6.1.6 Efficacy Conclusions

The efficacy data from the single pivotal trial (071) is not sufficient to support the Applicant's proposed indications, "the prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy."

Study 071 was only successful in demonstrating that the aprepitant regimen was superior to standard therapy for the "no vomiting" endpoint. The aprepitant regimen demonstrated no significant advantage over the standard therapy for any of the nausea endpoints or on the separate analysis of Complete Response in the Acute or Delayed phase time periods separately.

The study failed to demonstrate that the aprepitant regimen offered significant advantage over the standard therapy for any of the exploratory endpoints. In this Reviewer's opinion, the efficacy results in Study 071 are not sufficiently "robust" to support approval of the requested new indications.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

A detailed review of the clinical sections of the S-NDA was performed utilizing applicant submitted data. The safety data was reviewed and outlined. The narratives of all serious adverse events were reviewed. The results of this safety analysis were then compared to the safety data in the original NDA.

7.1.1 Deaths

There were no deaths reported during Cycle 1. One death was reported during the multiple cycle portion of Study 071. A patient in the aprepitant group (AN 179) died as a result of a serious infection/sepsis during Cycle 3.

Case Summary:

> The patient was 58-year-old white female with a past medical history of breast cancer, and a series of co-morbidities that include: asthma, hypertension, depression, hyperlipidemia, obstructive sleep apnea, anemia, diabetes, myocardial infarction, constipation, and neutropenia.

The patient was randomized to the aprepitant arm on 13-Jan-2003 (Relative Day 1 of Cycle 1). The patient's chemotherapy regimen included cyclophosphamide 600 mg/m^2 and doxorubicin hydrochloride 60 mg/m^2 for 1 day.

The patient completed study drug for Cycle 1 on Relative Day 3. On Relative Day 17, the patient developed a "mild infection" which is documented as resolved during Cycle 3, (Relative Day 53). On Relative Day 53, the patient experienced a non-serious adverse event of febrile neutropenia which is reported as resolved on (b) (6). The case summary then reports the patient presented to the emergency room with fever, chills, shortness of breath, hypotension, pneumonia and an infected right breast implant on (b) (6)

The patient was admitted to intensive care on (b) (6) with a diagnosis of sepsis and was treated with broad spectrum antibiotics. The patient's laboratory studies demonstrated: white blood cell count of 4.3 X 109/L (normal range = 3.7 to 11.8 X 109/L) and neutrophil count of 2.9 X 109/L (normal range = 2.0 to 9.0 X 109/L).

The patient status deteriorated into cardiovascular collapse with pulmonary failure. Laboratory results on (b) (6) revealed: white blood cell count of 25.3 X 109/L (normal range = 3.7 to 11.8 X 109/L). Attempts to withdraw vasopressor support and to wean the patient off of a ventilator were unsuccessful. Comfort measures were provided and the vasopressor medications withdrawn at the family's request and the patient expired (b) (6)

Medical Officer Comment:
The primary investigator reported this adverse event as "definitely not" related to the aprepitant regimen. In this Reviewer's opinion there is insufficient information to completely rule out a relationship of this event with the use of aprepitant. However, based on the overall safety data submitted with this application, this event is not in itself suggestive of a safety signal.

The case summary has several conflicting statements, which are mentioned here for accuracy (P071.pdf, page 181). The patient is reported as developing a "mild infection" on Day 17 of Cycle 1, which "resolved on Relative Day 53." The following day (b) (6) the patient was admitted to the ICU with a diagnosis of sepsis. The infection progressed into multisystem failure that did not respond to aggressive therapy and the patient died.

7.1.2 Other Serious Adverse Events

There was an imbalance in exposure to chemotherapy during Cycles 2 to 4. The aprepitant group received 1099 patient-cycles of chemotherapy compared to 1006 patient cycles in the standard therapy group. In general, after adjusting for the imbalance in exposure, the incidence of serious adverse events were balanced between treatment groups for Cycle 1 and Cycles 2 through 4.

Table 21
Serious Adverse Events Summary
Study 071

Serious Adverse Experience	Treatment Group	
	Aprepitant (N=438) n (%)	Standard (N=428) n (%)
Cycle 1		
Patients with Serious Adverse Event(s)	15 (3.4)	18 (4.2)
Cycles 2 to 4 (Not Adjusted for Exposure)		
Patients with Serious Adverse Event(s)	17 (4.4)	13 (3.6)
Ref: Modified Tables 8-7 and 8-8 P071.pdf		

The following table shows the adverse event profile for Cycles 2 to 4 based on a patient-cycle analysis (i.e., each patient-cycle is uniquely counted as opposed to only once per patient).

Table 22
Serious Adverse Events Summary Cycle 2 to 4
Adjusted for Patient Exposure (Cycles on Chemotherapy)
Study 071

Serious Adverse Experience Cycles 2 to 4	Treatment Group	
	Aprepitant Patient-Cycles (N=1099) n (%)	Standard Patient-Cycles (N=1006) n (%)
Patients with Serious Adverse Event(s)	17 (1.5)	15 (1.5)
Ref: Modified Table 8-9 P071.pdf		

Serious Adverse Events by Body System

Cycle 1

The treatment groups were similar with respect to the incidence of serious adverse events. The most frequently occurring serious adverse event during Cycle 1 was febrile neutropenia [aprepitant (1.6%) versus standard therapy (1.9%)].

Table 23
Select Serious Adverse Events by Body System
(Incidence 0%)
Cycle 1

Adverse Experience	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Serious Adverse Event(s)	15 (3.4)	18 (4.2)
Blood and Lymphatic System		
Febrile neutropenia	7 (1.6)	8 (1.9)
Neutropenia	2 (0.5)	3 (0.7)
Gastrointestinal Disorders		
Abdominal Pain	1 (0.2)	2 (0.5)
Enterocolitis	1 (0.2)	0
Vomiting	2 (0.5)	0
General Disorders		
Chest pain	0	1 (0.2)
Pyrexia	0	1 (0.2)
Cardiac Disorders		
Sinus tachycardia	1 (0.2)	0
Infections and Infestations		
Catheter site infection	0	1 (0.2)
Neutropenic sepsis	1 (0.2)	1 (0.2)
Peritonsillar abscess	0	1 (0.2)
Pneumonia	1 (0.2)	
Sinusitis	0	1 (0.2)
Vascular Disorders		
Deep vein thrombosis	0	2 (0.5)
Hypertension	1 (0.2)	0
REF: Modified Table 8-17 p071.pdf		

Cycles 2 to 4

The incidence and type of serious adverse events during Cycles 2 to 4 were similar between treatment groups. The most frequently occurring serious adverse event in Cycles 2 to 4 was febrile neutropenia [aprepitant (1.8%) versus standard (1.4%).

Table 24
Select Serious Adverse Events by Body System
(Incidence 0%)
Cycle 2 to 4

Adverse Experience	Treatment Group	
	Aprepitant N=385 n (%)	Standard N=359 n (%)
Serious Adverse Event(s)	17 (4.4)	13 (3.6)
Blood and Lymphatic System		
Febrile neutropenia	7 (1.8)	5 (1.4)
Neutropenia	1 (0.3)	2 (0.6)
Gastrointestinal Disorders		
Constipation	0	1 (0.3)
Dyspepsia	1 (0.3)	0
Nausea	1 (0.3)	1 (0.3)
Vomiting	0	1 (0.3)
General Disorders		
Chest pain	1 (0.3)	0
Pyrexia	1 (0.3)	0
Impaired healing	0	1 (0.3)
Skin Disorders		
Rash erythematous	1 (0.3)	0
Cardiac Disorders		
Myocardial infarction	1 (0.3)	0
Infections and Infestations		
Bursitis infective	1 (0.3)	0
Cellulitis	0	1 (0.3)
Infection	1 (0.3)	0
Perineal abscess	0	1 (0.3)
Pneumonia	1 (0.3)	1 (0.3)
Sepsis	1 (0.3)	0
Vascular Disorders		
Deep vein thrombosis	1 (0.3)	1 (0.3)
REF: Modified Table 8-19 p071.pdf		

7.1.3 Dropouts and Other Significant Adverse Events

Of the 866 patients randomized, 744 (85.9%) completed Cycle 1 and continued into Cycle 2. The most common reason for not continuing into Cycle 2 was lack of efficacy [aprepitant (3.9%) versus standard (7.2%)]. The second most common reason for not continuing into Cycle 2 was withdrawal of consent [aprepitant (3.7%) versus standard (3.3%)].

7.1.3.1 Overall profile of dropouts

Cycle 1

Overall, the treatment groups were similar with respect to adverse events resulting in discontinuation during Cycle 1. A total of 15 patients discontinued from the study due to an adverse event (serious and non-serious) during Cycle 1 [aprepitant (8), standard (7)].

Cycles 2 to 4

Sixteen (16) patients discontinued from the study due to adverse events (serious and non-serious) during Cycles 2 to 4 [aprepitant (12) versus standard (4)] and one patient in the aprepitant group died. As previously noted, an imbalance in patient exposure to chemotherapy occurred during Cycles 2 to 4. This may have contributed to, but does not fully explain, the higher incidence of adverse events leading to withdrawal in the aprepitant group during Cycles 2 to 4.

Table 25
Discontinued from Study due to Adverse Event

Adverse Experience	Treatment Group	
	Aprepitant (N=438) n (%)	Standard (N=428) n (%)
CYCLE 1		
Discontinued from Study due to AE	7 (1.6)	5 (1.2)
Discontinued from Study due to SAE	1 (0.2)	2 (0.5)
CYCLES 2 through 4 (Not Adjusted for Exposure)		
Discontinued from Study due to AE	7 (1.8)	4 (1.1)
Discontinued from Study due to SAE	5 (1.3)	0 (0.0)
Deaths	1 (0.3)	0 (0.0)
Ref: Modified Tables 8-7 and 8-8 P071.pdf		

After adjusting for the imbalance in chemotherapy exposure the aprepitant group still had a higher incidence of adverse events leading to withdrawal [aprepitant (12) versus standard (4)]. The clinical significance of this finding is uncertain. These adverse events are broken down by system in the following section.

Table 26
Discontinued Due to Adverse Event
Adjusted for Chemotherapy Exposure
Cycle 2 to 4

Adverse Experience	Treatment Group	
	Aprepitant Patient-Cycles (N=1099) n (%)	Standard Patient-Cycles (N=1006) n (%)
Discontinued from Study due to AE	7 (0.6)	4 (0.4)
Discontinued from Study due to SAE	5 (0.5)	0 (0.0)
Ref: Modified Table 8-9 P071.pdf		

7.1.3.2 Adverse events associated with dropouts

Cycle 1

Table 27
Select Adverse Events
Resulting in Discontinuation (Incidence 0%)
Cycle 1

Adverse Experience	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Adverse Event(s)	7 (1.6)	5 (1.2)
Gastrointestinal Disorders		
Diarrhea	0	1 (0.2)
Enterocolitis	1 (0.2)	0
Hematochezia	0	1 (0.2)
Nausea	1 (0.2)	0
Investigations		
Weight decreased	1 (0.2)	0
Metabolism and Nutrition		
Dehydration	1 (0.2)	1 (0.2)
Nervous System Disorders		
Headache	1 (0.2)	1 (0.2)
Migraine	1 (0.2)	0
Respiratory System Disorders		
Dyspnea	0	1 (0.2)
Skin Disorders		
Rash	1 (0.2)	0
Pruritus	1 (0.2)	0
Vascular Disorders		
Deep vein thrombosis	0	1 (0.2)
Flushing	1 (0.2)	0
REF: Modified Table 8-21 p071.pdf		

Table 28
Serious Adverse Events
Resulting in Discontinuation (Incidence 0%)
Cycle 1

Serious Adverse Events	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Serious Adverse Event(s)	1 (0.2)	2 (0.5)
Gastrointestinal Disorders		
Enterocolitis	1 (0.2)	0 (0.0)
Respiratory System Disorders		
Dyspnea	0	1 (0.2)
Vascular Disorders		
Deep vein thrombosis	0	1 (0.2)
REF: Information Request E-mail Response June 15,2005		

Cycles 2 to 4

Table 29
Select Adverse Events
Resulting in Discontinuation (Incidence 0%)
Cycle 2 to 4

Adverse Experience	Treatment Group	
	Aprepitant N=385 n (%)	Standard N=359 n (%)
Adverse Event(s)	7 (1.8)	4 (1.1)
Blood and Lymphatic System		
Febrile neutropenia	2 (0.5)	0
Gastrointestinal Disorders		
Nausea	0	1 (0.3)
General Disorders		
Weight decreased	1 (0.3)	0
Anorexia	1 (0.3)	0
Confusional state	1 (0.3)	0
Asthma	0	1 (0.3)
Dyspnea	1 (0.3)	0
Skin Disorders		
Alopecia	0	1 (0.3)
Rash erythematous	1 (0.3)	0
Cardiac Disorders		
Myocardial infarction	1 (0.3)	0
Immune System Disorders		
Hypersensitivity	0	1 (0.3)
Infections and Infestations		
Infection	1 (0.3)	0
Sepsis	1 (0.3)	0
Vascular Disorders		
Deep vein thrombosis	1 (0.3)	0
REF: Modified Table 8-19 p071.pdf		

Table 30
Serious Adverse Events
Resulting in Discontinuation (Incidence 0%)
Cycle 2 to 4

Serious Adverse Event	Treatment Group	
	Aprepitant N=385 n (%)	Standard N=359 n (%)
Serious Adverse Event(s)	5 (1.3)	0 (0.0)
Blood and Lymphatic System		
Febrile neutropenia	2 (0.5)	0 (0.0)
Cardiac Disorders		
Myocardial infarction	1 (0.3)	0 (0.0)
Infections and Infestations		
Infection	1 (0.3)	0 (0.0)
Sepsis	1 (0.3)	0 (0.0)
Skin Disorders		
Rash erythematous	1 (0.3)	0 (0.0)
Vascular Disorders		
Deep vein thrombosis	1 (0.3)	0 (0.0)
REF: Information Request E-mail Response June 15, 2005		

7.1.4 Common Adverse Events

7.1.4.1 Eliciting adverse events data in the development program

The protocol's safety assessments were acceptable and were adequate for eliciting adverse events.

7.1.4.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were categorized based on MedDRA standards. The severities of most adverse events were also graded based on National Cancer Institute (NCI) Common Toxicity Criteria.

7.1.4.3 Incidence of common adverse events

Cycle 1

Adverse events were reported by 640 of the 866 patients (73.9%). The incidence of adverse events was balanced between treatment arms [aprepitant (73.1%) versus standard therapy (74.8%)]. Overall, the adverse event profile was similar between treatment groups during Cycle 1. The most frequently reported adverse events were alopecia (24.0% versus 22.2%), fatigue (21.9% versus 21.5%), headache (16.4% versus 16.4%), constipation (12.3% versus 18.0%), and neutropenia (8.9% versus 8.4%) in the aprepitant group and standard therapy group respectively. A review of the severity of these events, based on NCI criteria, did not identify any concerning trends during Cycle 1.

Cycles 2 to 4

There was an imbalance in patient exposure to chemotherapy during Cycles 2 to 4. This imbalance may have influenced incidence of adverse events during Cycles 2 to 4. The treatment groups were similar with respect to the incidence of most adverse events during Cycles 2 to 4. The aprepitant group had a slightly higher incidence of adverse events (49.6%) than the standard therapy group (46.1%). The clinical significance of this small treatment group difference in unknown; the difference was not statistically significant.

The most frequently reported adverse events during Cycles 2 to 4 were fatigue (20.8% versus 17.5%), alopecia (12.7% versus 14.8%), nausea (11.9% versus 11.4%), constipation (9.9% versus 13.6%), headache (9.4% versus 9.2%), and dyspepsia (10.6% versus 7.8%) in the aprepitant group and standard therapy group respectively. The aprepitant group also experienced a higher incidence of neutropenia than the standard therapy group [aprepitant (9.1%) versus standard therapy (5.1%)]. The clinical significant of this finding is uncertain. This adverse event is discussed in more detail is Section 7.1.4.6.

7.1.4.4 Common adverse event tables

Cycle 1

Table 31
Select Adverse Events by Body System
(Incidence ≥2%)
Cycle 1

Adverse Experience	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Adverse Event(s)	320 (73.1)	320 (74.8)
Blood and Lymphatic System		
Anemia	12 (2.7)	11 (2.6)
Febrile neutropenia	9 (2.1)	9 (2.1)
Neutropenia	39 (8.9)	36 (8.4)
Gastrointestinal Disorders		
Abdominal pain upper	9 (2.1)	6 (1.4)
Constipation	54 (12.3)	77 (18.0)
Diarrhea	24 (5.5)	27 (6.3)
Nausea	31 (7.1)	32 (7.5)
General Disorders		
Mucosal inflammation	11 (2.5)	15 (3.5)
Pyrexia	7 (1.6)	11 (2.6)
Anorexia	19 (4.3)	25 (5.8)
Headache	72 (16.4)	70 (16.4)
Alopecia	105 (24.0)	95 (22.2)
Rash	12 (2.7)	4 (0.9)
Infections and Infestations		
Nasopharyngitis	3 (0.7)	10 (2.3)
REF: Modified Table 8-10 p071.pdf		

Cycles 2 to 4

Table 32
Select Adverse Events by Body System
(Incidence ≥2%)
Cycles 2 to 4

Adverse Experience	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Adverse Event(s)	308 (80.0)	260 (72.4)
Blood and Lymphatic System		
Anemia	14 (3.6)	20 (5.6)
Febrile neutropenia	11 (2.9)	8 (2.2)
Neutropenia	35 (9.1)	21 (5.8)
Gastrointestinal Disorders		
Constipation	38 (9.9)	49 (13.6)
Diarrhea	33 (8.6)	19 (5.3)
Nausea	46 (11.9)	41 (11.4)
Vomiting	6 (1.6)	9 (2.5)
General Disorders		
Mucosal inflammation	10 (2.6)	22 (6.1)
Pyrexia	11 (2.9)	12 (3.3)
Anorexia	13 (3.4)	14 (3.9)
Headache	36 (9.4)	33 (9.2)
Dizziness	19 (4.9)	10 (2.8)
Alopecia	49 (12.7)	53 (14.8)
Rash	9 (2.3)	8 (2.2)
Infections and Infestations		
Nasopharyngitis	9 (2.3)	11 (3.1)
Upper Respiratory infection	13 (3.4)	14 (3.9)
REF: Modified Table 8-11 p071.pdf		

7.1.4.5 Identifying common and drug-related adverse events

Cycle 1

Overall, the incidence of adverse events that were reported as drug related was similar between treatment groups during Cycle 1 and did not suggest a safety signal. The five most frequently reported *drug-related* adverse events during Cycle 1 were constipation (5.7% versus 7.7%), headache (6.4% versus 7.2%), fatigue (2.5% versus 1.6%), dyspepsia (1.4% versus 0.7%), and flushing (0.9% versus 1.2) in the aprepitant group and standard therapy group, respectively.

Table 33
Select Drug Related Adverse Events by Body System
(Incidence 0%)
Cycle 1
Safety Population Study 071

Adverse Experience	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Adverse Event(s)	94 (21.5)	84 (19.6)
Blood and Lymphatic System		
Febrile neutropenia	2 (0.5)	0 (0.0)
Neutropenia	1 (0.2)	2 (0.5)
Gastrointestinal Disorders		
Abdominal pain	2 (0.5)	1 (0.2)
Constipation	25 (5.7)	33 (7.7)
Diarrhea	3 (0.7)	7 (1.6)
Nausea	3 (0.7)	1 (0.2)
Vomiting	2 (0.5)	0 (0.0)
General Disorders		
Mucosal inflammation	0 (0.0)	2 (0.5)
Pyrexia	0 (0.0)	1 (0.2)
Infections and Infestations		
Candidiasis	1 (0.2)	0 (0.0)
Keratitis herpetic	0 (0.0)	1 (0.2)
Nasopharyngitis	0 (0.0)	1 (0.2)
Staphylococcal infection	1 (0.2)	0 (0.0)
REF: Modified Table 8-11 p071.pdf		

Cycles 2 to 4

The five most frequently reported *drug-related* adverse events during Cycles 2 to 4 were headache (3.9% versus 5.3%), constipation (3.6% versus 4.7%), fatigue (1.3% versus 1.4%), dyspepsia (2.1% versus 0.6%), and nausea (0.5% versus 1.1%) in the aprepitant group and standard therapy group, respectively.

7.1.4.6 Additional analyses and explorations

A higher incidence of neutropenia was observed in the aprepitant group during Cycles 2 to 4 (9.1% versus 5.8%). To assess the clinical significance of this treatment group difference, the severity of this adverse event was analyzed in terms of NCI criteria. To be thorough, the incidence of febrile neutropenia was also analyzed in terms of NCI criteria.

With respect to the more severe NCI toxicity, Grade 3/4 neutropenia occurred more frequently in the aprepitant group [27 patients (7.0%)] than the standard therapy group [13 patients (3.6%)]. Additionally, grade 3/4 *febrile* neutropenia also occurred more frequently in the aprepitant group [11 patients (2.9%)] than the standard therapy group [7 patients (1.9%)].

Since these adverse events may be related to chemotherapy exposure, these events were then analyzed, adjusting for chemotherapy exposure. After adjusting for exposure, the percentage of patient-cycles with Grade 3/4 neutropenia in Cycles 2 to 4 was 2.5% (27/1099) in the aprepitant group versus 1.3% (13/1006) in the standard therapy group. Similarly, the treatment group difference of febrile neutropenia decreased to 1.0% (11/1099) in the aprepitant group versus 0.7% (7/1006) in the standard therapy group. The clinical significance of these small treatment group differences is unknown.

7.1.5 Less Common Adverse Events

A review of the less common adverse events did not identify any specific safety concerns.

7.1.6 Laboratory Findings

7.1.6.1 Overview of laboratory testing in the development program

The following laboratory studies were performed at baseline (-28 to -1 Day), between Days 4 to 6 and during a follow-up visit (Day 14 to 29).

Table 34
Protocol-Specified Laboratory Tests

Hematology	Chemistry	Urinalysis
Hemoglobin	Bicarbonate	pH
Hematocrit	Creatinine	Protein
Total WBC	Total bilirubin	Glucose
Neutrophils	AST (SGOT)	
Lymphocytes	ALT (SGPT)	Microscopy:†
Monocytes	Alkaline phosphatase	WBCs
Eosinophils	Glucose (random)	RBCs
Basophils	Albumin	Epithelial cells
Platelet count	Sodium	Casts (specify)
	Potassium	
	Chloride	
	Urea/BUN (only 1 of the 2 must be done)	
	Calcium	
	Magnesium	
	Prothrombin Time‡ (PT)	
	FSH§	
	β-hCG‖	

† To have been performed only if preceding urinalysis values were abnormal.
‡ For patients on COUMADIN™, PT tests will be performed by a local laboratory.
§ Postmenopausal women only if needed.
‖ Females of childbearing potential.

Ref: P071.pdf , Table 5-5, Page 59

7.1.6.2 Standard analyses and explorations of laboratory data

Criteria for identifying abnormal laboratory values were pre-defined in the protocol.
The analyses of the hematology and chemistry studies revealed no clinically relevant trends associated with the aprepitant regimen. The two most commonly occurring laboratory adverse events during Cycle 1 were decreased white blood cell count (9.3% versus 9.0%) and decreased neutrophil count (8.7% versus 9.6%) in the aprepitant group and standard therapy group respectively.

Cycle 1

Table 35
Specific Laboratory Adverse Events
(Incidence ≥ 2%)
Cycle 1

Event Category	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Laboratory Adverse Event	77 (17.7)	75 (17.6)
Blood Chemistry Test	**18/436 (4.1)**	**22/425 (5.2)**
ALT increased	9/436 (2.1)	7/423 (1.7)
Blood glucose increased	7/436 (1.6)	9/425 (2.1)
Blood urea increased	1/3 (33.3)	0/1 (0.0)
Hematology Laboratory Test	**63/436 (14.4)**	**68/426 (16.0)**
Granulocyte count decreased	0/15 (0.0)	2/9 (22.2)
Hemoglobin decreased	10/432 (2.3)	20/422 (4.7)
Neutrophil count decreased	38/436 (8.7)	41/426 (9.6)
White blood cell count decreased	40/432 (9.3)	38/422 (9.0)
REF: Modified Table 8-27 p071.pdf		

Cycle 2

The incidence of laboratory adverse events during Cycles 2 to 4 was similar between the two treatment groups and did not suggest a safety signal. There was only one report of a serious laboratory adverse event during Cycles 2 to 4 and it occurred in the standard therapy group.

Table 36
Specific Laboratory Adverse Events
(Incidence >= 2%)
Cycles 2 to 4

Event Category	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Laboratory Adverse Event	74 (19.2)	65 (18.1)
Blood Chemistry Test	**26/385 (6.8)**	**23/359 (6.4)**
ALT increased	10/385 (2.6)	8/358 (2.2)
AST increase	5/383 (1.3)	8/358 (2.2)
Blood glucose increased	12/385 (3.1)	7/359 (1.9)
Hematology Laboratory Test	**60/385 (15.6)**	**58/359 (16.2)**
Granulocyte count decreased	0/13 (0.0)	1/9 (11.1)
Hematocrit decreased	7/382 (1.8)	7/355 (2.0)
Hemoglobin decreased	28/382 (7.3)	26/355 (7.3)
Neutrophil count decreased	27/385 (7.0)	23/359 (6.4)
White blood cell count decreased	23/382 (6.0)	23/355 (6.5)
White blood cell count increased	2/382 (0.5)	3/355 (0.8)
REF: Modified Table 8-28 p071.pdf		

7.1.6.2.1 Marked outliers and dropouts for laboratory abnormalities

There were no laboratory adverse events reported as serious or that resulted in discontinuation from the study during Cycle 1. There were no patients discontinued from the study due to a laboratory adverse event during Cycles 2 to 4.

7.1.7 Vital Signs

7.1.7.1 Overview of vital signs testing in the development program

Vital signs, including measurements for systolic and diastolic blood pressure, pulse, temperature, and weight were recorded at baseline and adequately monitored during the clinical trial.

7.1.7.2 Standard analyses and explorations of vital signs data

The protocol defined criteria for identifying Clinically Significant Vital Sign Abnormalities (CSVA). The incidence of CSVA was similar between treatment groups. The most frequently occurring CSVA during Cycle 1 was a respiratory rate >18 rpm [aprepitant (40.5%) versus standard (37.5%)]. The significance of this small difference is unknown.

Table 37
Clinically Significant Vital Sign Abnormality
Cycle 1

Vital Sign	Treatment Group	
	Aprepitant n (%)	Standard n (%)
Systolic Blood Pressure		
≥180 mmHg and ≥20 mmHg Inc.	1/421 (0.2)	1/408 (0.2)
≤90 mmHg and ≥20 mmHg Dec.	2/421 (0.5)	7/408 (1.7)
Diastolic Blood Pressure		
≥105 mmHg and ≥15 mmHg Inc.	1/421 (0.2)	1/408 (0.2)
≤50 mmHg and ≥15 mmHg Dec.	3/421 (0.7)	0/408 (0.0)
Pulse Rate (bpm)		
≥120 bpm and ≥15 bpm Inc.	2/418 (0.5)	3/406 (0.7)
≤50 bpm and ≥15 bpm Dec.	0/418 (0.0)	1/406 (0.2)
Respiratory Rate (rpm)		
>18 rpm	157/388 (40.5)	141/376 (37.5)
>8 rpm	0/388 (0.0)	0/376 (0.0)

REF: Modified Table 8-28 p071.pdf
Inc.=Increase
Dec.=Decrease
n/m = Number of randomized patients in each treatment group with a CSVA/number of randomized Cycle 1 patients in each treatment group with vital sign data.

7.1.7.2.1 Analyses focused on measures of central tendencies

Merck performed an analysis of summary statistics for changes from baseline for blood pressure, pulse rate, and respiratory rate during Cycle 1. The mean and standard deviation for each variable was analyzed and did not suggest any safety signal.

7.1.7.2.2 Marked outliers and dropouts for vital sign abnormalities

There were no vital sign abnormalities reported that resulted in discontinuation from the study during Cycle 1 or Cycles 2 to 4.

7.1.8 Electrocardiograms (ECGs)

7.1.8.1 Overview of ECG testing in the development program, including brief review of preclinical results

The safety data for Study 071 included a twelve-lead electrocardiogram performed at baseline and during the follow-up visit (Day 14 to 29) of each Cycle.

The pre-clinical studies, submitted with the original NDA, did not identify any cardiac rhythm concerns. During the animal studies aprepitant was not associated with an effect on heart rate, PR, QRS or QT interval. Additionally, the safety data from the original NDA did not suggest that aprepitant adversely affected cardiac rhythm in humans.

7.1.8.2 Standard analyses and explorations of ECG data

Summary statistics, mean and standard deviation, were calculated for QTc and the PR interval prior to chemotherapy administration and at the discontinuation visit of Cycle 1.

7.1.8.2.1 Analyses focused on measures of central tendency

The analysis of the ECG summary statistics did not identify any specific safety concerns.

Table 38
Summary Statistics for 12-Lead Electrocardiogram (ECG)

Visit	Treatment	N	Mean	SD
PR Interval (msec)				
Pre-Chemotherapy	**Aprepitant**	**406**	**154.53**	**22.32**
	Standard	**385**	**154.76**	**25.50**
Discontinuation	**Aprepitant**	**341**	**154.03**	**23.18**
	Standard	**344**	**153.21**	**22.40**
QTc Interval (msec)				
Pre-Chemotherapy	**Aprepitant**	**408**	**405.22**	**33.73**
	Standard	**380**	**407.41**	**33.48**
Discontinuation	**Aprepitant**	**342**	**416.32**	**39.88**
	Standard	**347**	**413.93**	**39.47**
Ref: Modified Table 8-39 P071.pdf				

7.1.8.2.2 Marked outliers and dropouts for ECG abnormalities

There were no ECG abnormalities reported that resulted in discontinuation from the study during Cycle 1 or Cycles 2 to 4.

7.1.9 Immunogenicity

Merck did not perform any studies to evaluate the immunogenicity potential of oral aprepitant.

7.1.10 Human Carcinogenicity

S-NDA 21-549/008 did not include human carcinogenicity studies. The carcinogenic potential for aprepitant was assessed in pre-clinical studies for the original approval. The following information is a summary of data submitted with the original NDA.

> The carcinogenic potential of aprepitant was evaluated in a 2-year study in female and male rats at doses that ranged from 0.05 to 125 mg/kg twice daily. Neoplastic changes noted in the liver and thyroids were considered secondary to hepatic cytochrome P-450 enzyme induction. These changes included an increased incidence of hepatocellular adenoma in females (25- and 125-mg/kg twice daily) and in males (125 mg/kg twice daily), thyroid follicular cell adenoma in females and males (125 mg/kg twice daily), thyroid follicular cell carcinoma in males (125 mg/kg twice daily) and uterine carcinoma in females at the highest dose evaluated.
>
> In a 2-year carcinogenicity study in female and male mice, males developed skin fibrosarcoma and in females there was a higher incidence of hepatocellular adenoma and harderian gland adenoma observed. These changes may have been secondary to P-450 enzyme induction. Similar neoplastic and non-neoplastic liver changes have been described in rats treated with compounds known to have potent cytochrome P-450 enzyme induction potential. The thyroid follicular cell adenomas and carcinomas and associated follicular cell hyperplasia may have been related to an altered thyroid hormone milieu.
>
> The available genotoxicity studies did not yield any positive or concerning results.

7.1.11 Special Safety Studies

The application did not include any special safety studies.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

Aprepitant has no known potential for drug abuse or dependence.

7.1.13 Human Reproduction and Pregnancy Data

Pregnant and lactating females were excluded from participation in the aprepitant clinical trials. The current label classifies aprepitant as a Pregnancy Category B; no adequate or well-controlled studies in pregnant women have been performed.

During the pre-clinical studies, aprepitant had no treatment-related effects on the fertility and reproductive performance of the male and female rats at doses up to the maximum feasible oral dose of 1000 mg/kg b.i.d. (2000 mg/kg/day). It was not teratogenic in rats at doses up to the maximum feasible oral dose of 1000 mg/kg b.i.d. (2000 mg/kg/day), or in rabbits at oral doses up to 25 mg/kg/day.

7.1.14 Assessment of Effect on Growth

Merck did not perform any studies to evaluate the effect of oral aprepitant on growth.

7.1.15 Overdose Experience

Merck reports that there is no specific information available on the treatment of an aprepitant overdose. Aprepitant cannot be removed from circulation by hemodialysis. Merck reports that single doses of aprepitant up to 600 mg were generally well tolerated in healthy subjects. Aprepitant was well tolerated when administered as 375 mg once daily for up to 42 days to patients enrolled 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 well tolerated. Drowsiness and headache were reported in one patient who ingested 1440 mg of aprepitant.

7.1.16 Postmarketing Experience

Aprepitant is currently approved in 32 countries. Its marketing has not been suspended, revoked, or withdrawn by any Agency in any country. As of June 21, 2005, the Agency's Adverse Event Reporting System (AERS) received 195 post-marketing cases of patients who experienced one or more adverse events while receiving aprepitant (raw data, may include duplicates). This Reviewer evaluated the type and number of adverse events. These post marketing data are difficult to interpret; however, no specific safety signal was identified

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

S-NDA 21-549/008 included safety data from a single Phase III study (Protocol 071). Study 071 was a worldwide, multicenter, randomized, double-blind, parallel-group study that evaluated the safety and efficacy of aprepitant in the prevention of chemotherapy induced nausea and vomiting during an initial and repeat cycles of moderately emetogenic chemotherapy used to treat breast cancer. A total of 866 patients were randomized in to one of two treatment arms [aprepitant regimen (438) or standard therapy regimen (428).

7.2.1.2 Demographics

The study arms were balanced in terms of age and race. Patients ranged in age from 23 to 78 years with a mean age of 52.6 years. The majority of patients were Caucasian (78.6%). Only two of the 866 patients enrolled were male (0.2%) and both were in the aprepitant group.

Table 39
Demographics
Cycle 1

Demographics	Treatment Group	
	Aprepitant Regimen (N=438)	Standard Regimen (N=428)
Sex		
Male	2	0
Female	436	428
Race		
Caucasian	349	332
Black	34	36
Asian	33	36
Hispanic	19	21
Other	3	3
Age		
Mean	53.1	52.1
Median	53.0	52.0
Min-Max	25 to 78	23 to 78
Age ≥ 65 years	58	53
Ref: P071.pdf, Fig. 6-8, pg. 92		

The study arms were also balanced in terms of malignancy cell type and stage of cancer, with most patients diagnosed with ductal carcinoma (82.3%). In terms of stage of malignancy, a majority of the patients were Stage II (57.7%) followed by Stage I (21.8%), Stage IIIa (11.3%), Stage IIIb (5.1%), and Stage IV (3.3%).

Table 40
Demographics
Type of Malignancy and Stage
Cycle 1

Malignancy	Aprepitant Regimen (N=438)	Standard Regimen (N=428)
Ductal carcinoma	357	356
Ductal carcinoma in situ	24	22
Inflammatory carcinoma	1	0
Lobular carcinoma	38	30
Lobular carcinoma in situ	0	5
Medullary carcinoma	6	5
Mucinous carcinoma	8	4
Papillary carcinoma	1	2
Null	3	4
Stage		
I	21.5%	22.2%
II	57.5%	57.9%
IIIa	11.6%	11.0%
IIIb	5.5%	4.7%
IV	3.4%	3.3%
Null	0.5%	0.9%
Ref: P071.pdf, Fig. 6-8, pg. 92		

The study arms were balanced in terms of type of chemotherapy and duration of cycles. Almost all of the patients received a moderately emetogenic dose of cyclophosphamide (99.9%). The most common chemotherapy regimen included cyclophosphamide + doxorubicin (60.6%) The second most common regimen included cyclophosphamide + epirubicin + fluorouracil (21.6%). The chemotherapies used during Cycles 2 through 4 were similar to those in Cycle 1.

Table 41
Chemotherapy during Cycle 1

Chemotherapy	Treatment Group	
	Aprepitant Regimen (N=438)	Standard Regimen (N=428)
No I.V. Chemotherapy	**0.2%**	**0**
≥ 1 I.V. Chemotherapy	**99.8%**	**100%**
Cyclophosphamide	**99.8%**	**100%**
Docetaxel	0.5%	0.9%
Doxorubicin	69.6%	68.2%
Epirubicin	28.8%	30.8%
Fluorouracil	29.9%	30.4%
Methotrexate	1.4%	0.9%
Paclitaxel	0.5%	0.0%
Ref: P071.pdf, table 6-12, pg. 100		

7.2.1.3 Extent of exposure (dose/duration)

The exposure to study drug was acceptable for this Phase III study. A review of the exposure data did not suggest that a bias in favor of either treatment arm occurred.

Aprepitant Exposure

Cycle 1

During Cycle 1, exposure was calculated as the difference between the number of days between first and last day of therapy and the "actual days on therapy."

All 438 patients randomized to the aprepitant regimen received aprepitant with 434 completing Cycle 1. Two patients received aprepitant for 4 days because their chemotherapy regimen was delayed for one day after receiving aprepitant. Four patients received aprepitant for only one day.

Table 42
Number of Patients on Study Drug by Daily Dose
Aprepitant Exposure Cycle 1

	Days				Total	Range Days of Drug	Mean Days of Drug
	1	2	3	>3			
Aprepitant Regimen							
Any dose	4	0	432	2	438	1 to 4	3.0
80 mg	1	433	0	0	434	1 to 2	2.0
125 mg	435	3	0	0	438	1 to 2	1.0
Ref: Table 8-1 P071.pdf							

Cycle 1 to 4

The range of days on aprepitant (Cycles 1 to 4) was between 1 to 13 days. The mean number of days exposure to aprepitant was 10.4 days (any dose). Of the 438 patients randomized into the aprepitant group, 343 received aprepitant for 11 to 12 days (any dose).

Dexamethasone Exposure

Cycle 1

Of the 438 patients randomized to the aprepitant group, 4 patients did not receive the 12 mg protocol dose of dexamethasone.

Table 43
Number of Patients on Study Drug by Daily Dose
Dexamethasone Exposure Cycle 1

	Days				Total	Range Days of Drug	Mean Days of Drug
	1	2	3	4			
Aprepitant Regimen							
Any dose	435	2	0	0	437	1 to 2	1.0
2.4 mg	1	0	0	0	1	1	1.0
12 mg	434	2	0	0	436	1 to 2	1.0
Standard Regimen							
Any dose	428	0	0	0	428	1	1.0
4 mg	1	0	0	0	1	1	1.0
20 mg	427	0	0	0	427	1	1.0
Ref: Table 8-2 P071.pdf							

Cycle 1 to 4

Of the 865 randomized patients who received dexamethasone during Cycles 1 to 4, the majority received dexamethasone for 4 days. The range of days was between 1 to 5 days. The mean number of days on dexamethasone (any dose) was 3.5 days in the aprepitant group and 3.3 days in the standard therapy group. One patient never received dexamethasone, and 4 patients received a lower dose of dexamethasone than prescribed by the protocol.

Ondansetron Exposure

Cycle 1

Of the 438 patients randomized to the aprepitant group, 12 patients did not receive the appropriate 16-mg ondansetron dose on Day 1.

Table 44
Number of Patients on Study Drug by Daily Dose
Ondansetron Exposure Cycle 1

	Days				Total	Range Days of Drug	Mean Days of Drug
	1	2	3	>3			
Aprepitant Regimen							
Any dose	432	6	0	0	438	1 to 2	1.0
8 mg	6	5	0	0	11	1 to 2	1.5
16 mg	427	0	0	0	427	1	1.0
24 mg	1	0	0	0	1	1	1.0
Standard Regimen							
Any dose	2	4	422	0	428	1 to 3	3.0
8 mg	11	2	0	0	13	1 to 2	1.2
16 mg	7	9	411	0	427	1 to 3	2.9
24 mg	3	0	0	0	3	1	1.0
Ref: Table 8-3 P071.pdf							

Cycle 1 to 4

The range of days on ondansetron was between 1 to 13 days in the standard therapy group and 1 to 7 days in the aprepitant group. The mean number of days on ondansetron was 3.5 days in the aprepitant group versus 9.9 days in the standard therapy group.

One patient in the aprepitant group and 3 patients in the standard therapy group took a dose of ondansetron greater than the protocol specified dose. There were 63 patients [aprepitant (25) vs standard (38)] who took a dose of ondansetron <16 mg (specified daily dose) on one or more days during Cycles 1 to 4.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The safety data from the original NDA were reviewed and compared to the data in the current submission. No other additional clinical data sources were utilized in this safety review.

7.2.2.1 Postmarketing experience

Aprepitant is currently approved in 32 countries. Its marketing has not been suspended, revoked, or withdrawn by an Agency in any country.

As of June 21, 2005, the Agency's Adverse Event Reporting System (AERS) received 195 post-marketing cases of patients who experienced one or more adverse events while receiving aprepitant (raw data, may include duplicates). This Reviewer evaluated the type and number of adverse events. These post marketing data are difficult to interpret; however, no specific safety signal was identified.

7.2.2.2 Literature

Utilizing the Agency's on-line databases and resources, a search of the current literature did not identify any specific safety concerns.

7.2.3 Adequacy of Overall Clinical Experience

The current clinical experience of the aprepitant regimen in the prevention of (b) (4) nausea and vomiting associated with initial and repeated courses of *moderately* emetogenic chemotherapy is not adequate to support approval.

The protocol enrolled only patients with a diagnosis of breast cancer who were scheduled to receive moderately emetogenic chemotherapeutic agents. This enrollment criterion limited the chemotherapeutic agents to those used to treat breast cancer. There are no data on the safety and efficacy of aprepitant in other moderately emetogenic chemotherapeutic regimens.

Additionally, the enrollment criterion essentially limited the study to female patients (99.8%). Considering a significant treatment-by-gender interaction was observed in one of the two pivotal trials submitted with the original NDA (Study P052), the results of this single study may not necessarily reflect the efficacy in male patients.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The Division did not request and this application did not include any new pre-clinical/animal studies.

7.2.5 Adequacy of Routine Clinical Testing

The protocol defined clinical and safety assessments were acceptable for this Phase III study.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The current submission did not include any new metabolic, clearance or drug interaction data. The existing data is acceptable.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The current application did not include any new pharmacokinetic or drug interaction studies. Drug interaction studies submitted with the original NDA demonstrated that aprepitant is a moderate inhibitor of CYP 3A4 on short-term administration and an inducer of CYP 3A4 on longer administration. Aprepitant was also shown to be an inducer of CYP 2C9.

Since the original approval, Merck has conducted Phase IV drug interaction studies which have been outline in this review under Section 1.3.5 (Drug-Drug interactions). The potential for Drug-Drug interactions has been well characterized.

7.2.8 Assessment of Quality and Completeness of Data

Other than the limitations previously discussed (>99% female, limited to breast cancer chemotherapy regimens), the data necessary to perform a through safety review were included and well organized in the NDA. The quality of the efficacy data were discussed in consultation with the Agency's Biostatistical division and found to be acceptable.

7.2.9 Additional Submissions, Including Safety Update

The review of S-NDA 21-549/008 included Safety Update Reports that included results from the open-label extension phase of Study 071. No new safety concerns were identified during the open label portion of the study. In addition to the Safety Update Report, the review included several information requests that were incorporated into this document.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Cycle 1

Overall, the incidence of adverse events that were reported as drug related was similar between treatment groups and did not suggest a safety signal. The five most frequently reported drug-related adverse events during Cycle 1 were constipation (5.7% and 7.7%), headache (6.4% and 7.2%), fatigue (2.5% and 1.6%), dyspepsia (1.4% and 0.7%), and flushing (0.9% and 1.2) in the aprepitant group and standard therapy group, respectively.

Cycles 2 to 4

The five most frequently reported drug-related adverse events during Cycles 2 to 4 were headache (3.9% and 5.3%), constipation (3.6% and 4.7%), fatigue (1.3% and 1.4%), dyspepsia (2.1% and 0.6%), and nausea (0.5% and 1.1%) in the aprepitant group and standard therapy group, respectively.

A review of the drug-related adverse events did not suggest that the aprepitant regimen adversely affected the safety profile of the chemotherapy regimens.

7.4 General Methodology

The review of S-NDA 21-259/008 included becoming familiar with the safety and efficacy data used to support the original NDA approval. Study 071 was reviewed independently and summarized (see Appendix). The Division sent a number of information request which were reviewed and incorporated into this document.

This Reviewer worked closely with the Agency's Statistician to confirm the primary efficacy analysis. The secondary endpoint, FLIE questionnaire, was reviewed in consultation with the Study Endpoints and Label Development (SEALD) Division to help interpret whether the data support the Applicant's proposed indications. Their review is filed in DFS.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The submission included only one pivotal trial; no pooling of data was necessary.

7.4.1.2 Explorations for time dependency for adverse findings

The adverse event profile of Cycle 1 was compared to Cycles 2 to 4. As previously reported, an imbalance in patient exposure to chemotherapy occurred during Cycles 2 to 4 which may have affected the incidence of adverse events.

Overall, the safety data suggest that the aprepitant regimen was well tolerated during Cycles 1 through 4. The increased expose did not appear to significantly affect the safety profile of the aprepitant regimen.

The one concerning finding identified during the safety review was that a higher incidence of neutropenia occurred in the aprepitant group than the standard therapy group during Cycles 2 to 4 (9.1% vs 5.8%). Based on this finding, the incidence of febrile neutropenia was also flagged as an adverse event of interest.

On closer examination, the treatment group differences in neutropenia and febrile neutropenia were small after adjusting for the imbalance in chemotherapy patient-cycles. Adjusting for patient exposure, the percentage of patient-cycles with Grade 3/4 neutropenia in Cycles 2 to 4 was 2.5% (27/1099) in the aprepitant group versus 1.3% (13/1006) in the standard therapy group.

Similarly, the incidence of febrile neutropenia was 1.0% (11/1099) in the aprepitant group versus 0.7% (7/1006) in the standard therapy group adjusting for the imbalance. The clinical significance of this small treatment group difference is unknown.

7.4.1.3 Explorations for drug-demographic interactions

Supplemental NDA 21-549/008 did not identify any significant treatment by treatment-by-age or race interaction for the primary efficacy endpoint Complete Response in the overall phase. The data are insufficient to perform a meaningful treatment by gender analysis.

7.4.1.4 Explorations for drug-disease interactions

Study 071 enrolled only patients with breast cancer who were scheduled to receive moderately emetogenic chemotherapy. Therefore, an analysis of treatment-by-disease interaction was not performed.

7.4.1.5 Explorations for drug-drug interactions

The current application did not include any new pharmacokinetic or drug interaction studies. Since the original approval, Merck has conducted Phase IV drug interaction studies which are summarized in Section 1.3.5 of this review.

7.4.2 Causality Determination

The safety data from this submission and the original NDA does not suggest that the use of aprepitant is associated with any specific adverse event.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimen is similar to the currently approved aprepitant regimen. The 125/80 mg aprepitant dosing, administered for three days, is the same as the currently approved dose. The differences in the proposed regimen ($5HT_3$ and Steroid) reflect the current "Standard of Care" for patients receiving moderately emetogenic chemotherapy.

Table 45
Dosing Regimen Comparison

Day 1	Days 2 to 3
Regimen used in Original NDA (Highly Emetogenic Chemotherapy)	
Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 32 mg IV	Aprepitant 80 mg PO Daily Dexamethasone 8 mg PO Daily (morning)
Proposed Regimen (Moderately Emetogenic Chemotherapy)	
Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 16mg PO	Aprepitant 80 mg PO Daily

8.2 Drug-Drug Interactions

There are no additional clinical issues regarding drug-drug interactions.

8.3 Special Populations

There are no additional clinical issues regarding Special Populations.

Data from the original NDA demonstrated the following:

> Aprepitant was well tolerated in patients with mild to moderate hepatic insufficiency and no dosage adjustment is necessary in these patients. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9).
>
> Aprepitant was well tolerated in patients with renal insufficiency. No dosage adjustment is necessary for patients with renal insufficiency or for patients with ESRD undergoing hemodialysis.
>
> Aprepitant was well tolerated in patients regardless of age. No dosage adjustment is necessary in elderly patients.

8.4 Pediatrics

On September 15, 2004 Merck submitted a Proposed Pediatric Study Request to qualify for pediatric exclusivity. This study request included two studies in pediatric patients >2 years of age. This submission is reviewed and signed off in DFS (October 19, 2004).

With this S-NDA Merck requested a partial *waiver* for performing studies in pediatric patients <2 years of age. To be consistent with recent pediatric study requests for other antiemetics used in the prevention of CINV, this request for waiver was denied (Review in DFS: May, 4, 2005). Merck was encouraged to evaluate pediatric patients 6 months of age or younger.

8.5 Advisory Committee Meeting

The initial aprepitant NDA was discussed during a GI Advisory Committee Meeting on March 6, 2003. Several of the post-marketing Phase IV commitments requested by the Agency were based on recommendations from the committee members. In this Reviewer's opinion, there are no outstanding issues that require GI Advisory Committee discussion.

8.6 Literature Review

Utilizing the Agency's on-line databases and resources, a search of the current literature did not identify any specific safety concerns.

8.7 Postmarketing Risk Management Plan

Not Applicable

9 OVERALL ASSESSMENT

9.1 Conclusions

The efficacy results from Study 071 are not sufficient to support approval for the proposed new indications: *the prevention of* (b) (4) *nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.*

Study 071 was only successful in demonstrating that the aprepitant regimen was superior to standard therapy for the "no vomiting" endpoint. The treatment group differences failed to reach statical significance for all of the nausea related endpoints. Furthermore, Study 071 failed to demonstrate that the aprepitant regimen offered any significant advantage over standard therapy for Complete Response in the acute and/or delayed phase time periods separately. (b) (4)

The analyses of the individual components of the primary endpoint (No Vomiting and No Rescue therapy), demonstrated the aprepitant regimen had no significant effect on the use of rescue therapy. In this Reviewer's opinion, the success of the "no vomiting" endpoint is not sufficient to grant approval of the proposed indications.

Additionally, the efficacy during the multiple cycle portion of the study is uncertain. Based on the protocol definition of Complete Response in the overall phase, Merck reports that the antiemetic effectiveness of the aprepitant regimen was maintained throughout the multiple cycles, as evidenced by the consistent ~10% difference between treatment groups. This Reviewer has already commented on the limitations of this endpoint as an independent indicator of efficacy. Based on the Applicant's own analysis, the aprepitant regimen did not offer significant improvement over the standard therapy for the symptoms of nausea during Cycles 1 through 4. Also, due to the defined data analysis plan, the statical significance of this 10% treatment group difference can not be ascertained.

This Reviewer is also concerned that the results of Study 071 may not necessarily be generalizable to all patients receiving moderately emetogenic chemotherapy. Greater than 99% of the patients were female. This is an important limitation in the efficacy data; during the original NDA approval for the highly emetogenic chemotherapy indication, a significant treatment-by-gender interaction was identified in one of the two pivotal trials. It is unknown whether this gender interaction would be more significant in patients receiving moderate emetogenic agents.

The study only evaluated the safety and efficacy of aprepitant when administered with moderately emetogenic chemotherapeutic regimens used to treat breast cancer. These results may not necessarily be generalizable to other moderate emetogenic chemotherapy regimens.

As a comparison to this application, the approval of palonosetron, the only other drug indicated for the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic chemotherapy, was based on *two* multicenter, double-blind, active controlled trials. Each study enrolled greater than 560 patients and included both male and female patients with several different types of cancer, including but not limited to: breast, lung, colon, rectal, gastric, prostate and ovarian.

It is not this Reviewer's intention to compare the results of the palonosetron trials with the aprepitant trial. The palonosetron application is being referenced for its study design, enrollment criteria and to emphasize that the approval was based on two well controlled trials.

9.2 Recommendation on Regulatory Action

The single trial, Protocol 071, is inadequate to support approval of the proposed new indication(s): "the prevention of (b) (4) *nausea* and *vomiting* associated with initial and repeated courses of moderately emetogenic cancer chemotherapy."

The study only succeeded in demonstrating that the aprepitant regimen was superior to standard therapy for the prevention of vomiting. The study failed to demonstrate that the aprepitant regimen offered any significant advantage over the standard therapy for control of nausea or the use of rescue therapy. In this Reviewer's opinion the regulatory action should be "Approvable"; the efficacy results are not sufficiently "robust" to support approval of the requested new indications.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Not Applicable

9.3.2 Required Phase 4 Commitments

No additional Phase IV commitments are requested at this time.

9.4 Labeling Review

A detailed labeling review is not required at this time if the regulatory action is "Approvable." No changes are necessary in the current label at this time.

9.5 Comments to Applicant

Merck should consider additional Phase III studies to further evaluate the safety and efficacy of the aprepitant regimen in the prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy. Future studies should enroll both male and female patients and should not be limited to breast cancer. Future studies should be designed to demonstrate that the aprepitant regimen is effective in the prevention of *both* nausea and vomiting in *both* the acute and delayed phase time periods.

APPENDICES

9.6 Review of Individual Study Reports

Appendix A (filed in DFS)

9.7 Line-by-Line Labeling Review

Not Applicable

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/s/

Gary DellaZanna
7/18/05 10:25:47 AM
MEDICAL OFFICER

Hugo Gallo Torres
7/18/05 07:03:30 PM
MEDICAL OFFICER
The MTL agrees with the MO's "Approvable" recommendation. Main deficiencies: only 1 study, no effect on Nausea, and effects evaluated almost exclusively in females. Needed for approval is an additional clinical trial, addressing these defiencies.

Protocol 071

Aprepitant

A Randomized, Double-Blind, Parallel-Group Study Conducted Under In-House Blinding Conditions to Determine the Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated With Moderately Emetogenic Chemotherapy

Clinical Phase III

Study Period: Start: October 10, 2002
End: February 11, 2004

Study Design:

Study 071 was a worldwide, multicenter, randomized, double-blind, parallel-group study that evaluated the safety and efficacy of aprepitant in the prevention of chemotherapy induced nausea and vomiting during initial and a multiple cycles of moderately emetogenic chemotherapy regimens used in the treatment of breast cancer.

Eligible patients were randomly allocated to one of the following two treatment arms using a computer generated random allocation schedule.

Table 1
Treatment Arms

Treatment Regimen	Day 1	Days 2 to 3
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 16mg PO	Aprepitant 80 mg PO Daily Ondansetron placebo PO Daily (BID)
Standard Therapy	Aprepitant Placebo PO Dexamethasone 20 mg PO Ondansetron 16mg PO	Aprepitant Placebo PO Daily Ondansetron 8 mg PO Daily (BID)

Medical Officer Comment:
The treatment regimens in each arm were acceptable. The protocol defined "Standard of Care" for moderate emetogenic chemotherapy was acceptable. The results of this single study may not be generalizable to both male and female patients since it was limited to patients with breast cancer.

Study Objectives:

The Applicant defined the following Study Objectives:

Primary Objectives

To compare the aprepitant regimen and the standard regimen with respect to efficacy and tolerability in the first cycle of chemotherapy.

Secondary Objective

To compare the aprepitant regimen and the standard regimen with respect to the Functional Living Index—Emesis (FLIE) questionnaire in the first cycle of chemotherapy.

Exploratory Objectives

To compare the aprepitant regimen and the standard regimen with respect to:

Efficacy and tolerability in multiple cycles of chemotherapy
Health Economics first cycle and multiple cycles of chemotherapy

Medical Officer Comment:
The study objectives and sample size were acceptable for a Phase III study. The Agency does not consider Health Economics during the review process.

Schedule of Clinical Observations:

Table 2
Schedule of Clinical Observations and Laboratory Measurements-Cycle 1

Visit Type:	Prestudy	Treatment							Posttreatment	Follow-Up
Study Day:	-28 to -1	1				2	3	4 to 6	6 to 8†	14 to 29†
Procedure		-2.5 hr	-1.0 hr	-0.5 hr	0 hr					
Medical history	X	X								
Reviewed inclusion/exclusion criteria	X	X								
Informed consent	X									
Physical examination	X									X‡
Vital signs and weight‡	X	X							X	X‡
12-lead ECG	X									X‡
Laboratory tests (L) and review of results (R)	L‖	R							L	L, R
Reviewed of Concomitant Medication	X	X				X	X	X	X	X
Aprepitant or placebo dosing			X			X	X			
Ondansetron or placebo dosing			X----------X¶			X	X			
Dexamethasone or placebo dosing				X						
Chemotherapy infusion#					X					
Daily telephone contact (scripted questions)						X	X	X††		
Diary completion		X			X	X	X	X		
FLIE questionnaire		X						X‡‡		
Pill count for study medications									X	
HEA instrument									X	X
Reviewed adverse experiences	X----------									----------X

† One visit occured during each designated period of study days.

‡ Weight, physical exam, and ECG were done at this visit if the patient was not entering the extension phase.

‖ Weight was collected during the Prestudy and Follow-Up visits only.

| Labs were completed within 7 days of initiation of study medication and included a pregnancy test in women of childbearing potential.

¶ The first capsule of ondansetron or placebo was administered 30 to 60 minutes prior to chemotherapy, according to established (clinic or office) practice. The second capsule of ondansetron or placebo was administered 8 hours after ingestion of the first dose.

Cyclophosphamide was administered over ≤2 hours. If doxorubicin or epirubicin was used, it was infused over ≤1 hour.

†† If the patient came into the office for the Posttreatment Visit on Day 6, the Telephone contact was not to be made.

‡‡ FLIE was completed on Day 6.

Ref: p071.pdf Table 5-2 Page 39, scanned.

Table 3
Schedule of Clinical Observations and Laboratory Measurements- Cycles 2 Through 4

Visit Type:		Treatment†							Follow-Up
Study Day:	Pretreatment‡	1				2	3	4 to 6	14 to 29‖
Procedure		-2.5 hr	-1.0 hr	-0.5 hr	0 hr				
Reviewed multiple cycle eligibility criteria	X								
Medical history	X								
Physical examination									X‖
Vital signs	X	X							X
12-lead ECG									X‖
Laboratory tests (L) and review of results (R)	L¶	R							L, R
Reviewed concomitant medication	X	X				X	X	X	X
Aprepitant or placebo dosing			X			X	X		
Ondansetron or placebo dosing			X----------X*			X	X		
Dexamethasone or placebo dosing				X					
Chemotherapy infusion††					X				
Telephone contact								X‡‡	
Diary completion		X			X	X	X	X	
Pill count for study medications									X
HEA instrument									X
Reviewed adverse experiences	X----------X								

† Subsequent cycles of chemotherapy should not have been administered within 14 days of the previous cycle.

‡ The evaluations done at the Follow-Up Visit on Day 14 to 29 in the previous cycle could serve as the pretreatment observations for entry into the next cycle of chemotherapy. Patients may have participated for a maximum of 4 cycles.

‖ One visit occured during this designated period of study days.

¦ Physical exam, including weight, and ECG were to be done at this visit if the patient discontinued or did not participate in the next study cycle of chemotherapy.

¶ Labs were completed within 7 days of initiation of study medication and included a pregnancy test in women of childbearing potential.

* The first capsule of ondansetron or placebo was administered 30 to 60 minutes prior to chemotherapy, according to established (clinic or office) practice. The second capsule of ondansetron or placebo was administered 8 hours after ingestion of the first dose.

†† Cyclophosphamide was administered over ≤2 hours. If doxorubicin or epirubicin was used, it was infused over ≤1 hour.

‡‡ Telephone call on Day 4 and Day 6 served only to remind the patient to complete the diary, check medication compliance, and record missing doses.

Ref: p071.pdf Table 5-3 Page 40, scanned.

Medical Officer Comment:
The scheduled safety and efficacy assessments were acceptable for this Phase III trial.

Financial Disclosure and Conflict of Interest:

Medical Officer Comment:
Merck certified that that they did not enter into any financial agreement with the clinical investigators whereby the value of their compensation could be affected by the outcome of the studies.

Ethics:

Medical Officer Comment:
Merck certified that the study was conducted in conformance with applicable country or local requirements regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Investigators:

Medical Officer Comment:
This was a multicenter, multinational study that included 109 centers located in the United States, Germany, Austria, Canada, Hong Kong, Hungary, Spain, United Kingdom, Italy, Australia, and Greece. The participating investigators were all qualified individuals.

Dose Selection:

Medical Officer Comment:
The dose selection for both treatment arms was acceptable for this Phase III study. The 125/80 mg aprepitant dosing regimen, administered for three days, is the currently approved dose. The Safety and Efficacy of this dosing regimen was demonstrated in several Phase II and III protocols.

Ondansetron is approved for the prevention of acute nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy. The protocol dose (8 mg BID for three days) is a recognized dose for the prevention of CINV due to moderately emetogenic cancer chemotherapy.

Dexamethasone is commonly used in the prevention of chemotherapy induced nausea and vomiting and is considered part of the "Standard of Care." Patients in the Standard Regimen group received a total daily dose of 20 mg oral dexamethasone, which is consistent with the published guidelines for the prevention of moderately emetogenic chemotherapy.

The aprepitant group received a reduced dose of oral dexamethasone (12 mg on Day 1). This dose adjustment is consistent with recommendations in the current aprepitant label.

Study Population Selection

Medical Officer Comment:
The protocol enrolled only patients with a diagnosis of breast cancer who were scheduled to receive moderately emetogenic chemotherapeutic agents. This enrollment criterion essentially limited the study to female patients. The Applicant states they selected this population because breast cancer is a common malignancy that often utilizes moderately emetogenic chemotherapeutic agents.

This Reviewer is concerned that the results of this single study, which enrolled greater than 99% female patients, may not be generalizable to both male and female patients scheduled to receive moderate emetogenic chemotherapy. During the original NDA approval a treatment-by-gender interaction was identified in one of the two pivotal trials. In Study 052, the efficacy of the aprepitant regimen was statistically superior to standard therapy in female patients only. It is unknown whether this gender interaction would be more significant in patients receiving moderate emetogenic chemotherapy.

Table 4
Original NDA
Treatment by Gender
Complete Response Endpoint

Female

	MK-0869 Regimen n/m (%)	Standard Therapy n/m (%)
Overall Phase	76/98 (78)**	38/98 (39)
Acute Phase	88/97 (91)**	66/98 (67)
Delayed Phase	77/98 (79)**	41/98 (42)

Male

	MK-0869 Regimen n/m (%)	Standard Therapy n/m (%)
Overall Phase	113/162 (70)	98/162 (61)
Acute Phase	143/162 (88)	137/162 (85)
Delayed Phase	119/162 (74)	104/162 (64)

**: $p<0.01$ when compared with Standard Therapy; †: Complete Response = No emesis with no rescue therapy; n/m = Number of patients with desired response/number of patients included in time point.

Ref: Original NDA, Statical Review, Table 2.2.2.1.1

Additionally, this enrollment criterion limited the chemotherapeutic agents to those used to treat breast cancer. There are no data on the safety and efficacy of aprepitant in other moderately emetogenic chemotherapeutic regimens.

Enrollment Criteria

Inclusion Criteria

Cycle 1

Male or Female ≥18 years of age
Diagnosed with breast cancer
Predicted life expectancy of ≥4 months
Karnofsky score ≥60
Females of Childbearing potential had to demonstrate a negative pregnancy test
Females of Childbearing potential had to agree to use contraception
Able to read, understand and complete study questionnaires
Completed written informed consent
Naïve to emetogenic chemotherapy Hesketh Level 3 or higher.
Scheduled to receive first course of moderately emetogenic chemotherapy.

Scheduled to receive the following agents either alone or in combination:

I.V. cyclophosphamide 750-1500 mg/m^2 (± 5%)
I.V. cyclophosphamide 500-1500 mg/m^2 (±5%)
and I.V. doxorubicin ≤60 mg/ m^2 (± 5%)
I.V. cyclophosphamide 500-1500 mg/ m^2 (±5%)
and I.V. epirubicin ≤100 mg/ m^2 (± 5%)

Multi-Cycle Extension Inclusion Criteria (Cycles 2, 3, and 4)

Satisfactory completion of the study procedures to date
Scheduled to continue to receive the same chemotherapy regimen

Exclusion Criteria

Cycle 1

Symptomatic primary or metastatic CNS malignancy
Scheduled to receive cisplatin or any other Hesketh Level ≥ 3 chemotherapy
Received or was to receive radiation therapy to the abdomen or pelvis in the week prior to treatment
Vomited in the 24 hours prior to treatment Day 1
History of Hesketh Level ≥3 emetogenic chemotherapy
Active infection
Any uncontrolled disease (e.g., diabetic ketoacidosis, gastrointestinal obstruction)
Current use of any illicit drugs or current evidence of alcohol abuse

Mentally incapacitated
Hypersensitivity to ondansetron or dexamethasone
Taking systemic corticosteroid therapy at any dose;
Use of a non-registered investigational drug within 28 days
Use of barbiturates, rifampicin or rifabutin, phenytoin or carbamazepine within 28 days
Use of any of the following in the 7 days prior to Treatment Day 1: terfenadine, cisapride, astemizole, clarithromycin (azithromycin, erythromycin and roxithromycin were permitted), ketoconazole or itraconazole (fluconazole was permitted), amifostine or pimozide.
Use of any of the following in the 48 hours prior to Treatment Day 1:
5-HT_3 antagonists (ondansetron, granisetron, dolasetron, or tropisetron), phenothiazines (e.g., prochlorperazine, fluphenazine, perphenazine, thiethylperazine, or chlorpromazine), butyrophenones (e.g., haloperidol or droperidol), benzamides (e.g., metoclopramide or alizapride), domperidone or cannabinoids, benzodiazepines or opiates, (except for single daily doses of lorazepam)

Abnormal laboratory values:
Absolute Neutrophil Count <1500/mm3 and WBC count <3000/mm3
Platelet count <100,000/mm3
AST (aspartate transaminase) >2.5 x upper limit of normal
ALT (alanine transaminase) >2.5 x upper limit of normal
Bilirubin >1.5 x upper limit of normal
Creatinine >1.5 x upper limit of normal
Positive pregnancy test

<u>Multi-Cycle Extension Exclusion Criteria</u> (Cycles 2, 3, and 4)

Scheduled to receive the next cycle of chemotherapy within 14 days of receiving the previous cycle.

Medical Officer Comment:
Although the enrollment criteria permitted male and female patients to be randomized, limiting the study to breast cancer essentially made this study a single gender study.

<u>Rescue Therapy</u>

Patients were instructed to take rescue therapy if needed for nausea or vomiting. Patients were provided with a prescription for rescue medications according to investigator selection.

Permitted rescue medications included: 5-HT_3 antagonists (granisetron, dolasetron, tropisetron or ondansetron), phenothiazines (e.g., prochlorperazine, fluphenazine, perphenazine) butyrophenones (e.g., haloperidol or droperidol), benzodiazepines benzamides (e.g., metoclopramide or alizapride), corticosteroids, domperidone.

Medical Officer Comment:
During Cycle 1, patients recorded the date, time, and type of rescue therapy in their diary. The protocol defined use of rescue medication was acceptable for this clinical trial.

Prior and Concomitant Therapy

All prescribed and over-the-counter drugs taken by the patient 28 days prior to Cycle 1 were recorded and reviewed prior to randomization. The patients were instructed that no drug therapy of any type was to be initiated without the knowledge of the investigator.

The following drugs with antiemetic properties were not permitted in the 48 hours prior to Treatment Day 1:

5-HT_3 antagonists (ondansetron, granisetron, dolasetron, or tropisetron)
phenothiazines (e.g., prochlorperazine, fluphenazine, perphenazine)
butyrophenones (e.g., haloperidol or droperidol)
benzamides (e.g., metoclopramide or alizapride)
domperidone, cannabinoids.

Systemic corticosteroids were excluded except as specified in the protocol. Additionally, benzodiazepines and/or opiate therapy were not permitted to be initiated within 48 hours of Treatment Day 1 (except a single daily dose of lorazepam).

Medical Officer Comment:
After the initiation of chemotherapy (0 to 120 hours), the above agents were permitted, as a therapy to treat nausea and vomiting as well as other conditions. The "other conditions" are important when considering the efficacy data. The protocol stipulated that only antiemetic medications that were administered in the context of "established nausea or emesis" were considered rescue medication. If these drugs were administered for other reasons, they were not recorded as "rescue therapy." The use of these drugs will be further discussed under the Results section of this review.

Discontinuation

A patient could be discontinued from the study for any of the following reasons:

The patient wished to withdraw.
The patient had an adverse experience and did not want to continue
The patient was advised by the investigator not to continue.
The patient failed to comply with the study requirements
The patient required medication not permitted by the protocol
Any other reason, in the opinion of the investigator that precluded further participation by the patient.

Definition of Study Completion

A patient was considered to have completed the study if he/she completed Cycle 1

Medical Officer Comment:
The protocol defined reasons for discontinuation from the study and definition for Study Completion were acceptable.

Study Medication Administration and Blinding

Medical Officer Comment:
Patients were assigned to either the aprepitant regimen or standard regimen according to a randomization schedule that used a blocking factor of 4. Patients who continued in to the multiple cycle extension portion of the study received the same blinded therapy that they had been administered in Cycle 1. The randomization process, blinding procedures, and medication administration were acceptable.

Treatment Compliance

Study medication dosing instructions were given to the patient prior to discharge.
During Cycle 1, patients were contacted by telephone each morning on Days 2 through 6 to assess the patient's status and ensure the patient's diary was completed. When the patients returned for their Day 6 to 8 Visit, study personnel reviewed the diary with the patient to ensure that it had been completed appropriately. Any errors, omissions, or ambiguities were then corrected by the patient. Rescue medications and vomiting episodes were transcribed by study site personnel into the case report form.

Medical Officer Comment:
The protocol included daily phone contact with each patient for the first week of Cycle 1. The quality control for maintaining patient compliance was acceptable. Compliance was defined as the ratio of the number of days the patient took all assigned therapy and the number of days between their first and last day of therapy.

Treatment compliance was balanced; more than 95% of patients in each treatment group were 100% compliant with the study regimen [aprepitant (95.4%) vs standard therapy (95.8%)].

Efficacy Assessments

Definitions:

Overall Phase:	0 to 120 hours post initiation of chemotherapy
Acute Phase:	0 to 24 hours post initiation of chemotherapy
Delayed Phase:	>24 to ≤120 hours post initiation of chemotherapy
Complete Response:	No emesis, no rescue therapy
No Emesis:	No vomiting or retching or dry heaves (includes patients who received rescue therapy).
No Nausea:	Maximum nausea VAS <5 mm
No Significant Nausea:	Maximum nausea VAS <25 mm
Complete Protection:	No emesis, no rescue therapy, no significant nausea (maximum nausea <25 mm on VAS)
Total Control:	No emesis, no rescue therapy, and no nausea (maximum nausea <5 mm on VAS).

Medical Officer Comment:
The protocol definitions are acceptable. The same definitions were used in the studies submitted with the original NDA. Nausea was self-assessed using a 100-mm horizontal visual analogue scale (VAS) in the patient diary.

Efficacy—Cycle 1

Efficacy assessments started just prior to chemotherapy infusion (0 hours) and were continued for 5 days, until the morning of Day 6 (~120 hours). During Cycle 1, patients recorded episodes of vomiting, use of rescue therapy, and daily nausea severity in their diary.

Nausea Assessment

During Cycle 1, nausea was self-assessed daily using a 100-mm horizontal visual analogue scale (VAS) in the patient diary. Patients responded to the following question: "How much nausea have you had over the last 24 hours?"

The left side of the scale (0 mm) was labeled "no nausea," and the right side (100 mm) was labeled "nausea as bad as it could be." The patient was instructed to record the assessment of nausea between 8:00 AM and 10:00 AM on Days 2 through 6. The recording was to coincide with the time patients took their study drug on Days 2 to 3.

Vomiting Assessment

A vomiting episode was defined as expulsion of stomach contents through the mouth. Retching, defined as a non-productive attempt to vomit was also recorded as vomiting. Vomiting episodes were considered distinct if separated by the absence of vomiting and retching for at least 1 minute. During Cycle 1, the patient recorded the time and date of each vomiting episode in the diary at the time of occurrence.

Medical Officer Comment:
The efficacy assessments during the Cycle 1 were acceptable. The protocol definitions for vomiting and retching, as well as the VAS to measure nausea severity were acceptable.

Efficacy—Multiple Cycles

The Applicant reports that during the multiple cycle extension portion of the study, efficacy data collection was "simplified." Only nausea severity was recorded daily for 5 days after the administration of chemotherapy for each cycle.

On Day 6, the patient answered two "yes/no" questions: whether they had experienced any vomiting episodes and whether they had used rescue therapy since the most recent administration of chemotherapy. Rescue medication and other concomitant treatment were not recorded in the diaries during multiple cycles.

Medical Officer Comment:
It is uncertain how "efficacy data collection was simplified" if patients were instructed to record their nausea severity daily. For this reason, this Reviewer questions why the Applicant chose not to record vomiting episodes and use of rescue therapy daily. The "Yes/No" question would not have significantly added to the patient's "work" if they were already completing a VAS for nausea. Regardless, the efficacy assessments during the multiple-cycle extension period were acceptable, but could have been more informative.

Patient-Reported Impact of CINV on Quality of Life

The effect of nausea and vomiting on quality of life was assessed using the Functional Living Index—Emesis (FLIE) questionnaire (Secondary Endpoint). The Applicant reports that this is a validated patient-reported measure of the impact of CINV on daily life. The questionnaire

consists of 9 items on nausea and 9 items on vomiting, each graded on a 7-point scale. Values are calculated and reported for total score, nausea score, and vomiting score.

Patients were given a practice questionnaire prior to chemotherapy administration in Cycle 1. The questionnaire was then administered on the morning of *Day 6*, after the patient had completed the diary. The questionnaire was not administered in Cycles 2 to 4.

For this study, Merck defined a patient's symptoms of CINV had "No Impact" on daily life if the patient's total score was >108.

Medical Officer Comment:
The Applicant submitted reference material to support that the Functional Living Index—Emesis (FLIE) questionnaire is a validated tool for assessment of CINV (Ref P071.pdf, page 55). In the submitted reference material, the FLIE questionnaire was administered three days after chemotherapy treatment. In Study 071, the questionnaire was administered on Day 6.

The Functional Living with Emesis (FLIE) questionnaire was reviewed in consultation with the Study Endpoints and Label Development (SEALD) Division to help interpret whether the data support the Applicant's proposed indication. Their comments are outlined in the Efficacy Results section of this review.

Endpoints:

There were three distinct time periods analyzed during Cycle 1: overall phase (0 to 120 hours post-initiation of chemotherapy), acute phase (0 to 24 hours), and delayed phase (25 to 120 hours).

Primary Endpoint:

Complete Response: Overall phase (0 to 120 hours)

Secondary Endpoints:

Functional Living Index Emesis (FLIE): Total Score

Medical Officer Comment:
A Responder for the primary endpoint, Complete Response in the overall phase of Cycle 1, was defined as a patient having no vomiting and did not require rescue therapy in the 120 hours following the initiation of chemotherapy (Cycle 1). This primary endpoint is similar to the endpoint that was used in the original NDA. It is important to note that the primary endpoint did not include an assessment of nausea. This will be discussed in the Efficacy Results section of this review.

The protocol defined one secondary endpoint; the proportion of patients reporting that their CINV had no impact on daily life, assessed by the FLIE questionnaire. The Applicant defined "no impact" as a FLIE total score > 108. This is an acceptable approach.

Exploratory Endpoints:

In addition to the primary and secondary endpoints the protocol defined the following exploratory endpoints:

Complete Response:	Acute phase (0 to 24 hours) Delayed phase (25 to 120 hours)
No Vomiting:	Overall, Acute, and Delayed phases
No Use of Rescue Therapy:	Overall, Acute, and Delayed phases

Table 5
Additional Exploratory Endpoint Analysis

Exploratory Endpoint Analyses Proportion of patients with:	Phase			
	Overall	Acute	Delayed	0 to 72 Hours
No significant nausea (peak VAS <25 mm)	x	x	x	x
No nausea (peak VAS <5 mm)	x	x	x	x
Time to first vomiting episode	x			
More than 3 vomiting episodes (Frequency of 1, 2, and 3 episodes as well as a display by day were provided)	x			
Relationship between acute and delayed phase vomiting		x	x	
Complete protection (no vomiting, no use of rescue therapy, and no significant nausea, i.e., peak VAS <25 mm)	x	x	x	
Total control (no vomiting, no use of rescue therapy, and no nausea, i.e., peak VAS <5 mm)	x	x	x	

Ref. P071.pdf, Page 111

Medical Officer Comment:
The primary endpoint did not include an assessment of nausea. Therefore, the exploratory endpoints, "Complete Protection" and "Total Control", which include an assessment of nausea and vomiting as well as rescue therapy, may be more clinically important.

Safety

During the data collection period covered by the patient diary, nausea and vomiting were not considered adverse events unless they resulted in a hospitalization. After the period covered by the patient diary (i.e., after the morning of Day 6), nausea and vomiting were then captured as adverse events.

All adverse events were graded by the investigator according to severity: mild, moderate, or severe and according to the National Cancer Institute (NCI) Common Toxicity Criteria.

If clinical or laboratory progression of a cancer was documented, the episode of progressive cancer was reported as a non-serious adverse event. Progression of a preexisting cancer was only considered "serious" if it met the usual criteria for serious adverse event.

The protocol included the following schedule for laboratory tests in each cycle.

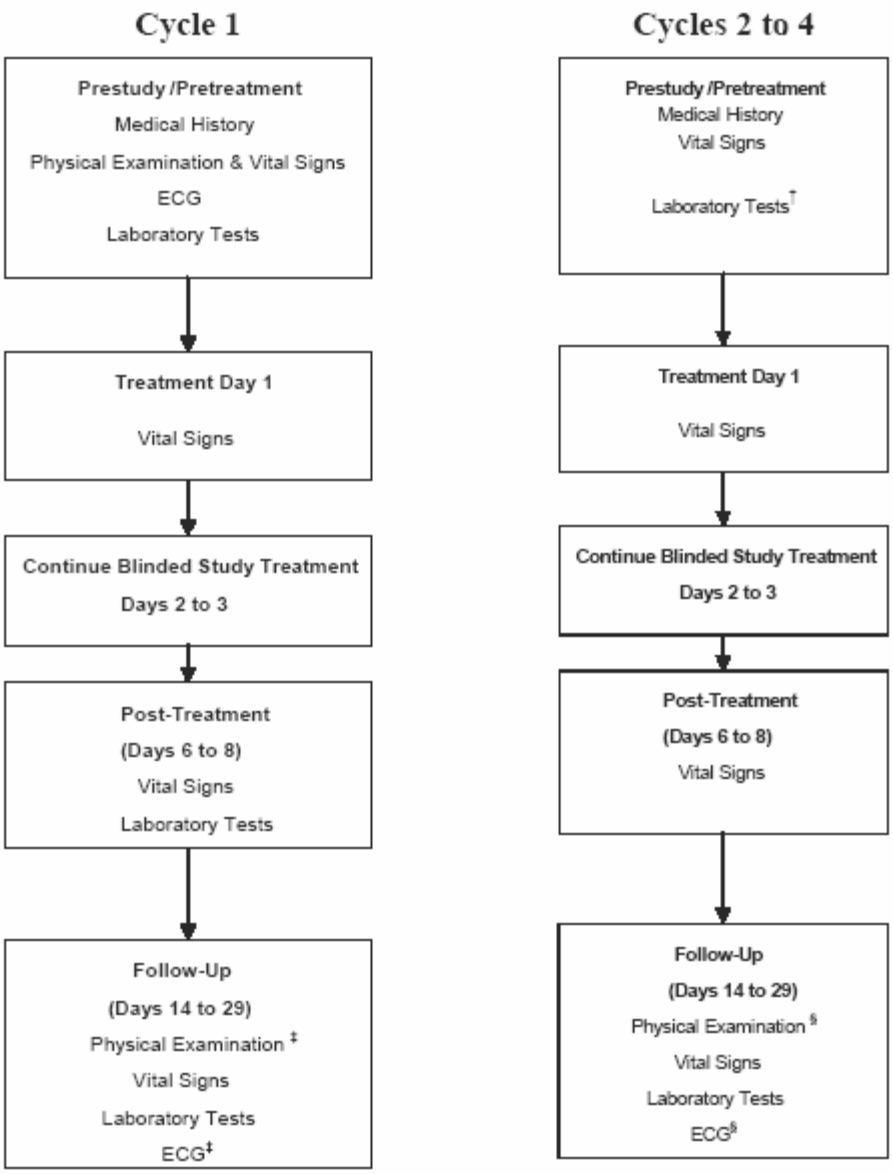
Table 6
Protocol-Specified Laboratory Tests

Hematology	Chemistry	Urinalysis
Hemoglobin	Bicarbonate	pH
Hematocrit	Creatinine	Protein
Total WBC	Total bilirubin	Glucose
Neutrophils	AST (SGOT)	
Lymphocytes	ALT (SGPT)	Microscopy:†
Monocytes	Alkaline phosphatase	WBCs
Eosinophils	Glucose (random)	RBCs
Basophils	Albumin	Epithelial cells
Platelet count	Sodium	Casts (specify)
	Potassium	
	Chloride	
	Urea/BUN (only 1 of the 2 must be done)	
	Calcium	
	Magnesium	
	Prothrombin Time‡ (PT)	
	FSH§	
	β-hCG‖	

† To have been performed only if preceding urinalysis values were abnormal.
‡ For patients on COUMADIN™, PT tests will be performed by a local laboratory.
§ Postmenopausal women only if needed.
‖ Females of childbearing potential.

Ref: P071.pdf , Table 5-5, Page 59

Figure 1
Scheduled Safety Assessments



† Laboratory evaluations performed at the follow-up visit of the previous cycle could have served as baseline for entry into the subsequent cycle.
‡ Only required when patient did not continue in the multiple-cycle extension.
§ Only required at study discontinuation or completion.
ECG = Electrocardiogram.
Data Source: [3.3]
Ref: P071.pdf , Fig 5-2, Page 57

The Applicant reports that because of the expected effects of chemotherapy in this patient population, out of range laboratory values were not necessarily considered adverse events, but were assessed as to whether or not they were clinically significant.

Medical Officer Comment:
The protocol defined safety monitoring and definitions for serious and non-serious adverse events were acceptable. Since nausea and vomiting are known side effects of moderately emetogenic chemotherapy, excluding them as adverse events, unless they resulted in hospitalization, is acceptable in this trial.

Interpreting abnormal laboratory values will be difficult in this patient population. As per the protocol, a laboratory value could have been considered clinically significant by the investigator, and still not reported as an adverse event if the change was a predictable outcome of chemotherapy, and it did not result in clinical intervention. Per protocol, only laboratory findings that were inconsistent with the predictable effects of the patient's chemotherapy regimen and that were considered to be clinically significant were reported as adverse events. This is an acceptable approach for this patient population.

Study Population:

Medical Officer Comment:
Two patient populations were defined for the efficacy analysis: modified-intention-to-treat (mITT) population and the per-protocol (PP) population. The primary efficacy analysis was performed on the modified-intention-to-treat (mITT) population. The PP population analysis was used as supportive evidence of efficacy.

The modified-intention-to-treat (MITT) population included all patients who received study medication and had at least one post-treatment assessment on Day 1 and Day 2. If a patient was a "failure" on any day in Cycle 1, that patient was included in the MITT population for analysis of the overall phase of Cycle 1.

The mITT population in Cycles 2 through 4 included all patients who entered each additional cycle, received chemotherapy, and had an assessment after receiving chemotherapy for that cycle.

Per-Protocol Population (Efficacy Analysis)

The per-protocol population excluded those patients who were excluded from the mITT population and those who were identified as having a protocol violation.

The definition of a protocol violation included:

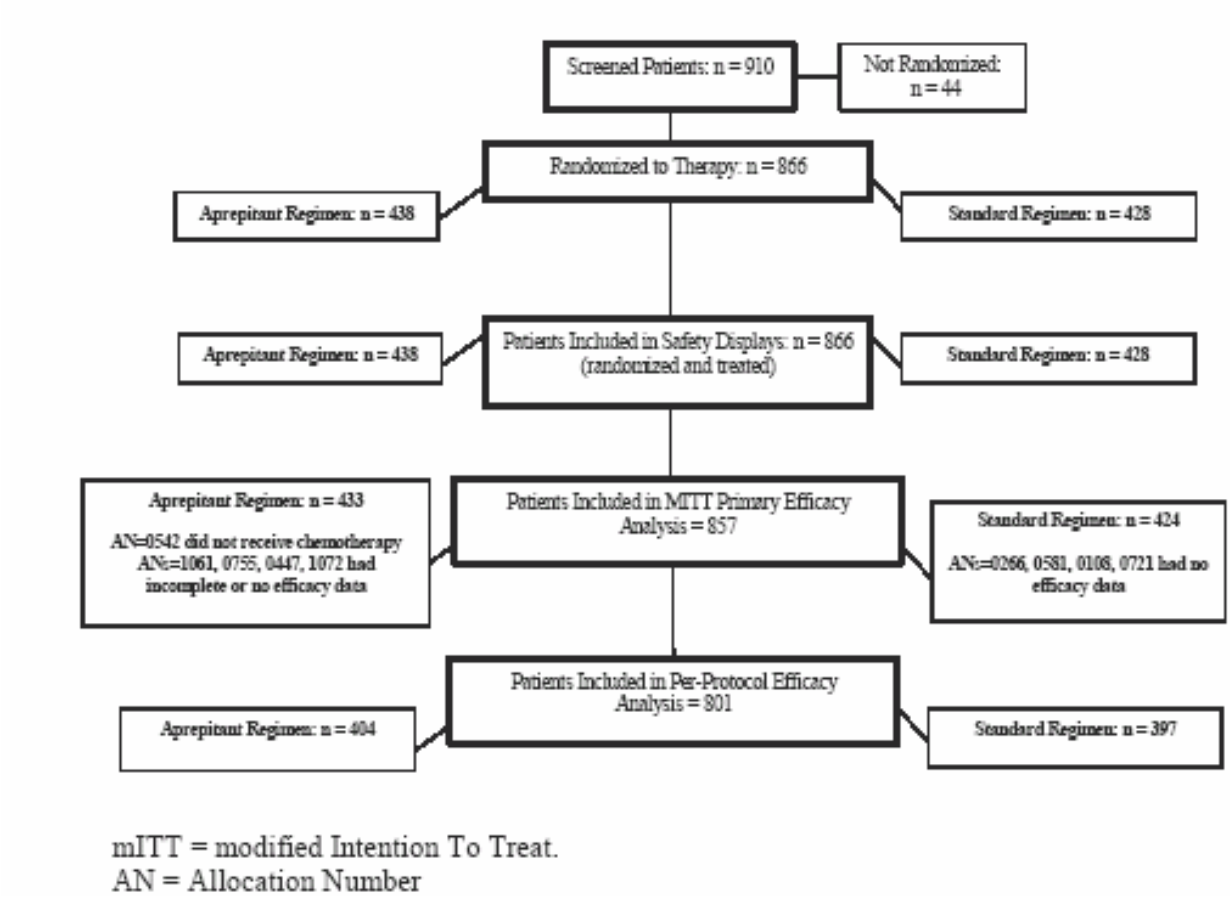
- Patients who received a non-protocol, clinically significant dose of corticosteroids within 48 hours of chemotherapy or during the 5 days following chemotherapy.
- Patients who did not take all protocol-required doses of the study drug
- Patients who took rescue medication without a vomiting episode or significant nausea (≥25 mm on the VAS Scale).

Medical Officer Comment:
The protocol defined mITT and PP populations are acceptable. As stated above, the primary efficacy analysis was performed on the mITT population, with the PP population analysis used as supportive evidence of efficacy. Protocol violators were identified prior to breaking the blinding of the study.

Patient Enrollment:

A total of 910 patients were screened with 866 randomized [aprepitant group (438), standard therapy (428)]. Forty-four patients screened were not randomized. The following are the most common reasons a patient was not randomized: scheduled to receive non-protocol chemotherapy regimen (7), benzodiazepines in past 48 hours (6), abnormal baseline laboratory values (4), mentally incapacitated (3).

Figure 2
Profile of Patient Enrollment



mITT = modified Intention To Treat.
AN = Allocation Number

Ref: P071.pdf, Fig. 6-1, pg. 78

Demographics and Characteristics

Table 7
Demographics
Cycle 1

Demographics	Treatment Group	
	Aprepitant Regimen (N=438)	Standard Regimen (N=428)
Sex		
Male	2	0
Female	436	428
Race		
Caucasian	349	332
Black	34	36
Asian	33	36
Hispanic	19	21
Other	3	3
Age		
Mean	53.1	52.1
Median	53.0	52.0
Min-Max	25 to 78	23 to 78
Age ≥ 65 years	58	53
Ref: P071.pdf, Fig. 6-8, pg. 92		

Medical Officer Comment:
Study 071 was essentially a single gender study. Of the 866 patients enrolled only two were male and both were in the aprepitant group.

At baseline, the aprepitant group had a lower incidence of patients reporting a history of motion sickness than the standard therapy group [aprepitant (17%) vs standard (21%)]. Since a history of motion sickness may be a risk factor for the development of CINV, this 4% difference in treatment groups may have resulted in a bias in favor of the aprepitant group.

The demographics of the patients who continued into Cycles 2 through 4 were similar to Cycle 1. However, incidence of patients with a history of motion sickness was more balanced in Cycles 2 through 4 [aprepitant (16.1) vs standard (17.2)].

Table 8
Demographics
Type of Malignancy and Stage
Cycle 1

Malignancy	Aprepitant Regimen (N=438)	Standard Regimen (N=428)
Ductal carcinoma	357	356
Ductal carcinoma in situ	24	22
Inflammatory carcinoma	1	0
Lobular carcinoma	38	30
Lobular carcinoma in situ	0	5
Medullary carcinoma	6	5
Mucinous carcinoma	8	4
Papillary carcinoma	1	2
Null	3	4
Stage		
I	21.5	22.2
II	57.5	57.9
IIIa	11.6	11.0
IIIb	5.5	4.7
IV	3.4	3.3
Null	0.5	0.9
Ref: P071.pdf, Fig. 6-8, pg. 92		

Table 9
Chemotherapy during Cycle 1

Chemotherapy	Treatment Group	
	Aprepitant Regimen (N=438)	Standard Regimen (N=428)
No I.V. Chemotherapy	**0.2%**	**0**
≥ 1 I.V. Chemotherapy	**99.8%**	**100%**
Cyclophosphamide	**99.8%**	**100%**
Docetaxel	0.5%	0.9%
Doxorubicin	69.6%	68.2%
Epirubicin	28.8%	30.8%
Fluorouracil	29.9%	30.4%
Methotrexate	1.4%	0.9%
Paclitaxel	0.5%	0.0%
Ref: P071.pdf, table 6-12, pg. 100		

Medical Officer Comment:
The study arms were balanced in terms of malignancy cell type, stage of cancer and type of chemotherapy. All but one patient (AN 0542) received concomitant study related I.V. chemotherapy. The most common chemotherapy regimen included cyclophosphamide + doxorubicin (60.6%). The second most common regimen was cyclophosphamide + epirubicin + fluorouracil (21.6%). The chemotherapies used during Cycles 2 through 4 were similar to those in Cycle 1.

Table 10
Days between Chemotherapy Cycles by Treatment Group

Chemotherapy Cycle	Cycle 1 to 2 (N=384)	Cycle 2 to 3 (N=364)	Cycle 3 to 4 (N=345)
Aprepitant Regimen			
Mean	**21.3**	**21.4**	**21.5**
Standard Deviation	**2.9**	**3.0**	**3.1**
Median	**21.0**	**21.0**	**21.0**
Range	**13.2 to 34.1**	**13.0 to 41.0**	**12.9 to 35.1**
Standard Regimen			
Mean	**21.3**	**21.5**	**21.2**
Standard Deviation	**3.4**	**3.8**	**3.3**
Median	**21.0**	**21.0**	**21.0**
Range	**13.0 to 49.1**	**13.1 to 48.0**	**13.9 to 35.0**

Ref: p071.pdf Page 102

Medical Officer Comment:
Study medications were administered for three days during each chemotherapy cycle. The median, mean and range of days between chemotherapy cycles were similar between treatment groups and should not have resulted in a bias.

Handling of Dropouts or Missing Data

Medical Officer Comment:
The efficacy analyses were based on responses in the patient diary. Missing data for vomiting episodes was imputed by carrying forward the preceding data not missing (LOCF). This carry forward approach was used in the delayed phase only (25 to 120 hours). No data in the acute phase (0 to 24 hours) were carried forward into the delayed phase. The acute phase represented only one efficacy measurement, so no carrying forward was possible. If efficacy data were missing on Day 2, no carrying forward was done. This approach to missing data is acceptable for this Phase III study and should not result is a study bias.

Safety Population

Medical Officer Comment:
The protocol defined safety population was acceptable; it included all patients who were randomized and received at least one dose of study therapy.

Protocol Amendments:

Table 11
Select Protocol Amendments

Amendment	Date	Description
01	7/08/2002	Genetic analysis during Cycle 1 (International study sites only)
03	1/08/2003	Increased number of US study sites from 60 to ~90 Modified Inclusion Criteria: • increased dose of I.V. epirubicin from ≤90 mg/m^2 to ≤100 mg/m^2 • Added Taxanes as permitted medication Modified Exclusion Criteria: • Minimum chemotherapy cycle time was reduced from 21 days to 14 days.
10	1/27/2004	Added an elective open-label multiple cycle extension (Cycles 5 to 7) for patients to complete a 7-cycle chemotherapy regimen if warranted
Ref: P071.pdf, Section 5.8, Pg. 75		

Medical Officer Comment:
The protocol amendments, as well as the final protocol, were reviewed to see if any of the revisions would have impacted the interpretation of the study results. The final protocol and amendments were acceptable.

Concomitant Medical Therapy

Medical Officer Comment:
Overall, the use of concomitant medical therapy was similar between treatment groups. The three most commonly reported concomitant medications were in the categories of immunostimulants (17.6%), antibacterial agents (16.4%) and analgesics (13.2%), which are not expected to influence the results.

Rescue Therapy

Medical Officer Comment:
The protocol defined any antiemetic medication that was administered in the context of established nausea or emesis as a rescue medication. Patients who required rescue therapy were recorded as treatment failures. In situations where the reason for administration of an antemetic was not clear in the patient diary, the antiemetic was also defined as rescue therapy.

The application included the following tables listing by "Drug Category" of specific medications that patients received during Cycle 1.

Table 12
Patient Medications by Drug Category
Cycle 1 (Day 1)
(Incidence >0%)

Chemotherapy	Treatment Group	
	Aprepitant Regimen (N=438)	Standard Regimen (N=428)
No Rescue Medication	87.2%	83.9%
≥1 Rescue Medication	12.8%	16.1%
Antiemetic and Antinauseant	**3.9**	**4.7**
Diphenhydramine (+) haloperidol (+) lorazepam	0.2%	0%
Dolasetron	1.1%	0.7%
Granisetron	0.2%	0.2%
Granisetron HCl	0.2%	0.2%
Ondansetron	0.7%	0%
Ondansetron HCl	1.6%	3.7%
Trimethobenzamide HCl	0%	0.2%
Not Administered as an Antiemetic or Antinauseant but may have anti-nausea and vomiting properties		
Metoclopramide	1.1	1.2
Metoclopramide HCl	0.7	0.5
Lorazepam	2.3	4.2
Prochlorperazine	2.5	4.4
Prochlorperazine maleate	3.7	4.9
Promethazine	0	0.5
Promethazine HCl	0.9	0.9
Dexamethasone	0.5	0.2

Ref: P071.pdf, Modified Table 6-16, pg. 105

Table 13
Patient Medications
Cycle 1 (Days 2 to 6)
(Incidence >0%)

Chemotherapy	Treatment Group	
	Aprepitant Regimen (N=438)	Standard Regimen (N=428)
No Rescue Medication	62.1	59.8
≥1 Rescue Medication	37.9	40.2
Antiemetic and Antinauseant	***11.9***	***12.6***
Diphenhydramine (+) haloperidol (+) lorazepam	0.5	0
Dolasetron	1.8	1.9
Granisetron	0.9	0.7
Granisetron HCl	1.1	1.2
Ondansetron	1.1	0.7
Ondansetron HCl	6.4	7.7
Trimethobenzamide HCl	0.2	0.5
Tropisetron	0.2	0.7
Tropisetron HCl	0.2	0
Not Administered as an Antiemetic or Antinauseant but may have anti-nausea and vomiting properties		
Metoclopramide	6.2	4.9
Metoclopramide HCl	2.1	3.0
Lorazepam	4.6	7.7
Prochlorperazine	7.3	8.2
Prochlorperazine maleate	9.4	12.9
Dimenhydrinate	0.2	0.7
Promethazine	2.3	0.7
Promethazine HCl	2.1	1.4
Dexamethasone	2.1	3.5
Methylprednisolone	0.2	0.2
Ref: P071.pdf, Modified Table 6-17, pg. 106		

Medical Officer Comment:
The Study summary states the following: "Only antiemetic medication that was administered in the context of established nausea or emesis was considered rescue medication" (Ref page 104, P071.pdf). Therefore patients could receive medications with known antiemetic properties and still not be recorded as treatment failures if the reason for the medication was something other than nausea and vomiting.

The preceding tables were generated from the Applicant's Tables 6-16 and 6-17. It is not clear how the Applicant determined the Drug Category. For example, Promethazine (Phenergan®) is listed as a Respiratory System therapy and Prochlorperazine maleate (Compazine®) is listed under the category Nervous System.

Even though the above lists of medications include drugs with antiemetic properties and some that have antiemetic indications, the use of these drugs should not have resulted in a bias in favor of the aprepitant regimen. Most of the questionable therapies were used more frequently in the standard therapy group. One must consider that the use of these drugs may have resulted in a bias in favor of the standard therapy.

Accounting of Patients:

Table 14
Patient Disposition

Chemotherapy Cycle	Aprepitant (N=438)	Standard (N=428)	Total (N=866)
	n (%)	n (%)	n (%)
Cycles 1 to 4			
Discontinued During a Cycle:	**5.7%**	**5.4%**	**5.5%**
Discontinued After a Cycle:	**16.4%**	**22.4%**	**19.3%**
Completed:	**77.9%**	**72.2%**	**75.1%**
Cycle 1			
Discontinued During a Cycle:	**1.8%**	**1.6%**	**1.7%**
Discontinued After a Cycle:	**10.3%**	**14.5%**	**12.4%**
Completed:	**87.9%**	**83.9%**	**85.9%**
Cycle 2			
Discontinued During a Cycle:	**0.9%**	**0.9%**	**0.9%**
Discontinued After a Cycle:	**3.9%**	**4.7%**	**4.3%**
Completed:	**83.1%**	**78.3%**	**80.7%**
Cycle 3			
Discontinued During a Cycle:	**0.9%**	**2.1%**	**1.5%**
Discontinued After a Cycle:	**2.3%**	**3.3%**	**2.8%**
Completed:	**79.9%**	**72.9%**	**76.4%**
Cycle 4			
Discontinued During a Cycle:	**2.1%**	**0.7%**	**1.4%**
Completed:	**77.9%**	**72.2%**	**75.1%**

Aprepitant Regimen: ondansetron 8 mg P.O. twice daily and dexamethasone 12 mg P.O. plus aprepitant 125 mg P.O. on Day 1 and aprepitant 80 mg P.O. once daily on Days 2 and 3.

Standard Regimen: ondansetron 8 mg P.O. twice daily plus dexamethasone 20 mg P.O. on Day 1 and ondansetron 8 mg P.O. twice daily on Days 2 to 3.

Ref: p071.pdf Page 81

Medical Officer Comment:
The proportion of patients who discontinued during a cycle and those who completed a given cycle were balanced between treatment arms. The data do not suggest that the aprepitant regimen adversely affected the tolerability of the chemotherapy regimen.

Discontinuation During a Cycle:

Table 15
Overall Disposition of Patients
Cycle 1

Chemotherapy Cycle 1	Aprepitant (N=438)	Standard (N=428)	Total (N=866)
Discontinued *prior* to Completion	**8**	**7**	**15**
Clinical Adverse Event	**2**	**1**	**3**
Lack efficacy	**3**	**2**	**5**
Withdrew consent	**1**	**4**	**5**
Protocol deviation	**1**	**0**	**1**
Discontinued *after* Completion	**45**	**62**	**107**
Clinical Adverse Event	**5**	**5**	**10**
Lab Adverse Event	**2**	**1**	**3**
Ineligible	**3**	**7**	**10**
Lack efficacy	**17**	**31**	**48**
Withdrew consent	**16**	**14**	**30**
Protocol deviation	**2**	**2**	**4**
Refused Chemotherapy	**0**	**1**	**1**
Completed Cycle 1 and Continued	**385**	**359**	**744**

Aprepitant Regimen: ondansetron 8 mg P.O. twice daily and dexamethasone 12 mg P.O. plus aprepitant 125 mg P.O. on Day 1 and aprepitant 80 mg P.O. once daily on Days 2 and 3.
Standard Regimen: ondansetron 8 mg P.O. twice daily plus dexamethasone 20 mg P.O. on Day 1 and ondansetron 8 mg P.O. twice daily on Days 2 to 3.
Ref: p071.pdf Page 83

Medical Officer Comment:
The number of patients who discontinued therapy prior to completion of a Cycle 1 was balanced between treatment groups [aprepitant (8) vs standard (7)]. The most common reason for discontinuing study therapy prior to completion of Cycle 1 was Lack of Efficacy [aprepitant (3) vs standard (2)] and Withdrew Consent [aprepitant (1) vs standard (4)].

The reported reasons for discontinuing therapy after completion of Cycle 1 did not suggest that aprepitant adversely affected the tolerability of the chemotherapy regimen [aprepitant (45) vs standard (62)]. Fewer patients in the aprepitant group than the standard therapy group discontinued therapy due to lack of efficacy [aprepitant (17) vs standard (31)].

The following table shows the overall disposition of patients for Cycles 1 through 4.

Table 16
Overall Disposition of Patients Cycles 1 through 4

Chemotherapy Cycle	Aprepitant (N=438)	Standard (N=428)	Total (N=866)
Discontinued *prior* to Completion	**25**	**23**	**48**
Clinical Adverse Event	**7**	**3**	**10**
Lab Adverse Event	**0**	**2**	**2**
Ineligible	**4**	**3**	**7**
Lack efficacy	**3**	**5**	**8**
Lost to follow-up	**1**	**1**	**2**
Withdrew consent	**5**	**6**	**11**
Protocol deviation	**2**	**2**	**4**
Other	**3**	**1**	**4**
Discontinued *after* Completion	**72**	**96**	**168**
Clinical Adverse Event	**8**	**8**	**16**
Lab Adverse Event	**3**	**1**	**4**
Ineligible	**4**	**9**	**13**
Lack efficacy	**33**	**47**	**80**
No Response to Chemotherapy	**1**	**1**	**2**
Withdrew consent	**20**	**22**	**42**
Protocol deviation	**2**	**3**	**5**
Refused Chemotherapy	**0**	**3**	**3**
Completed Cycles 1-4 Did not Continue into Cycles 5-7	**299**	**276**	**575**
Completed Cycles 1-4 Continued into Cycles 5-7	**42**	**33**	**75**

Aprepitant Regimen: ondansetron 8 mg P.O. twice daily and dexamethasone 12 mg P.O. plus aprepitant 125 mg P.O. on Day 1 and aprepitant 80 mg P.O. once daily on Days 2 and 3.

Standard Regimen: ondansetron 8 mg P.O. twice daily plus dexamethasone 20 mg P.O. on Day 1 and ondansetron 8 mg P.O. twice daily on Days 2 to 3.

Ref: p071.pdf Page 82

Medical Officer Comment:
The number of patients who discontinued therapy prior to completion of a cycle, during Cycles 1 through 4, was balanced between treatment groups [aprepitant (25) vs standard (23)]. During Cycles 1 through 4, the most common reason patients discontinued therapy prior to completion of a chemotherapy cycle was a Clinical Adverse Event [aprepitant (7) vs standard (3)]. This imbalance will be considered in the Safety section of this review. A review of these data by each cycle (1, 2, 3, and 4) did not generate any specific concerns.

Open Label Extension Study: (Amendment 10)

Following completion of Cycle 4, patients were eligible to continue into an open-label portion of the study (Cycles 5 to 7). Forty-two patients (9.6%) in the aprepitant group and 33 (7.7%) patients in the standard therapy group elected to enter the extension study.

Efficacy Results

Analysis Population:

A total of 866 patients where randomized; however, one patient did not receive chemotherapy and eight did not provide posttreatment efficacy data necessary to evaluate Complete Response in the overall phase. Therefore, 857 patients were included in the mITT efficacy analysis of Complete Response in the overall phase (primary endpoint).

Table 17
Excluded from the Modified Intention-to-Treat Population

Reason for Exclusion	Acute Phase n/m (%)	Delayed Phase n/m (%)	Overall Phase n/m (%)
Aprepitant Regimen			
Total excluded	**6/438 (1.4)**	**5/438 (1.1)**	**5/438 (1.1)**
Incomplete efficacy data	**2/438 (0.5)**	**1/438 (0.2)**	**2/438 (0.5)**
No chemotherapy	**1/438 (0.2)**	**1/438 (0.2)**	**1/438 (0.2)**
No efficacy data	**3/438 (0.7)**	**3/438 (0.7)**	**2/438 (0.5)**
Standard Regimen			
Total excluded	**5/428 (1.2)**	**4/428 (0.9)**	**4/428 (0.9)**
Incomplete efficacy data	**1/428 (0.2)**	**0/428 (0.0)**	**0/428 (0.0)**
No chemotherapy	**0/428 (0.0)**	**0/428 (0.0)**	**0/428 (0.0)**
No efficacy data	**4/428 (0.9)**	**4/428 (0.9)**	**4/428 (0.9)**

Acute Phase: 0 to 24 hours following initiation of chemotherapy.
Delayed Phase: 25 to 120 hours following initiation of chemotherapy.
Overall Phase: 0 to 120 hours following initiation of chemotherapy.
n/m = Number of patients excluded/number of patients randomized.
Ref: P071.pdf Table 6-6

Medical Officer Comment:
The number of patients excluded from the Modified Intention-to-Treat Population during Cycle 1 was small and was balanced between treatment groups. These exclusions are not expected to result in any unfair bias.

Primary Endpoint:

Complete Response Overall Phase: No Emesis, No Rescue Therapy (0 to 120 hours)

Medical Officer Comment:
The primary endpoint (Complete Response in the overall phase) is similar to the primary endpoint that was used in the original NDA.

Based on the Applicant's analysis and the Agency's Statical review, the aprepitant group had a statistically significantly more patients reporting Complete Response in the Overall Phase (primary endpoint) than the standard therapy group. During the 5 days post-chemotherapy administration (Overall Phase), 50.8% of patients in the aprepitant group compared to 42.5% of the patients receiving standard therapy reported Complete Response. The unadjusted absolute difference in Complete Response (8.3%) represents a 20% relative improvement over standard therapy.

Table 18
Complete Response by Treatment Group
MITT population
Applicant's Analysis

Phase	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	Delta	p-Value	Corrected p-Value*
Overall Phase (Primary Endpoint)	**220/433 (50.8)**	**180/424 (42.5)**	**8.3%**	**0.015***	
Acute Phase[Ŧ]	**327/432 (75.7)**	**292/423 (69.0)**	**6.7%**	**0.034**	**N.S**
Delayed Phase[Ŧ]	**240/433 (55.4)**	**208/424 (49.1)**	**6.3%**	**0.064**	**N.S.**

Ref: Table 3.1.2 , P071.pdf
Significant at the two-sided significance level of 0.05 when compared with Standard Therapy using logistic regression
N.S.= not significant
Ŧ exploratory endpoints
* after Hochberg multiplicity adjustment

Medical Officer Comment:
Interestingly, the Merck's analysis for Complete Response during the acute and delayed phase time periods individually (exploratory endpoints) demonstrated only a numerical improvement in the aprepitant group over the standard therapy group when corrected for multiplicity; statistical significance was not maintained in these two time periods.

This is a concerning finding, considering the proposed indication is "the prevention of (b) (4) *nausea and vomiting."* (b) (4)

Secondary and Related Exploratory Endpoints:

Medical Officer Comment:
The secondary endpoint was defined as the proportion of patients who reported that their chemotherapy induced nausea and vomiting had no impact on their activities of daily life. The effects of nausea and vomiting on a patient's quality of life was assessed using the Functional Living Index—Emesis (FLIE) questionnaire during Cycle 1. The protocol defined "no impact on daily life" as a total FLIE score >108 in the overall phase of Cycle 1. The total score was calculated as the sum of nine nausea specific and nine vomiting specific questions graded on a 7-point scale.

The Functional Living with Emesis (FLIE) questionnaire was reviewed in consultation with the Study Endpoints and Label Development (SEALD) Division to help interpret whether the data support the Applicant's proposed indications. Their comments will be summarized at the end of this section. The following table shows the results of the FLIE questionnaire, including the protocol defined secondary endpoint and related endpoints.

Table 19
Patients with no impact of CINV on daily life (total score >108)
mITT patient population

Phase	FLIE Domain or Item Number	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value*
Protocol Defined Secondary Endpoint				
Nausea and Vomiting Specific	**Total Score**	**271/427 63.5%**	**229/412 55.6%**	**0.019**
Related to Secondary Endpoint				
Vomiting Specific	**Vomiting Domain**	**366/427 85.6%**	**296/412 71.8%**	**<0.001**
"ability to enjoy daily meal"	**Item 13**	**392/427 91.8%**	**325/412 78.9%**	**<0.001**
"daily functioning"	**Item 16**	**394/427 92.3%**	**329/413 79.7**	**<0.001**
"hardship on other people"	**Item 18**	**395/427 92.5%**	**330/413 79.9**	**<0.001**
Nausea Specific	**Nausea Domain**	**229/428 53.5%**	**210/416 50.5%**	**0.339**
"ability to enjoy daily meal"	**Item 4**	**247/428 57.7%**	**228/416 54.9%**	**Not Tested**
"daily functioning"	**Item 7**	**261/428 61.0%**	**234/416 56.3%**	
"hardship on other people"	**Item 8**	**258/428 60.3%**	**233/416 56.0%**	

Ref: Table 3.1.2
n/m = Number of patients with "No Impact of CINV on Daily Life"/number of patients included in the analysis of the item.

Medical Officer Comments:
As assessed by the FLIE <u>total score</u>, significantly more patients in the aprepitant group than the standard therapy group reported that their CINV had "no impact on daily life" [aprepitant (63.5%) vs Standard (55.6%)] (p=0.019)].

Based on the Applicant's data analysis plan, since the FLIE total score revealed statistically significant treatment group differences, Merck performed the same logistic regression model on the vomiting specific and nausea specific domains of the questionnaire.

The results of the FLIE questionnaire paralleled the results of the primary and exploratory endpoints; the statistical significance of the "total score" is driven by the vomiting specific questions; the nausea-specific domain score did not reach statistical significance.

<u>Vomiting Domain:</u>

> *For the vomiting domain, significantly more patients in the aprepitant group than the standard group reported that vomiting had "no impact on daily life" [aprepitant (85.7%) vs Standard (71.8%)] (p<0.001).*
>
> *Since the FLIE vomiting-specific domain score revealed a statistically significant treatment group difference, the Applicant then analyzed FLIE vomiting-specific domain questions, adjusting for multiplicity via Hochberg's multiplicity procedure: "ability to enjoy a daily meal" (Item 13), "daily functioning" (Item 16), and "hardship on other people" (Item 18). The aprepitant regimen was significantly better than the standard regimen with respect to each of pre-specified FLIE vomiting-specific domain questions (p<0.001).*

<u>Nausea Domain:</u>

> *For the nausea-specific domain score, the treatment group difference (3%) failed reach statistical significance (p=0.339). Based on the data analysis plan, since the nausea-specific domain score did not reveal a significant treatment group difference, no further analysis was performed on the nausea-specific domain.*

<u>Study Endpoints and Label Development Comments regarding FLIE:</u>

The following is a limited summary of the Study Endpoints and Label Development (SEALD) Division consult.

1. *A single study is generally considered inadequate to meet regulatory requirements for substantial evidence to support statements in labeling or advertising.*

2. *Analysis of the FLIE vomiting scale demonstrated that patients receiving EMEND® were significantly more likely to report scores that could be described as "minimal or no impact of vomiting on daily life". However the FLIE nausea scale did not differ between treatment groups. In the SEALD division's opinion the statements proposed for the revised label would give the false impression that aprepitant significantly improves both nausea and vomiting outcomes.*

   Based on the results of Study 071, SEALD questions whether a total FLIE score >108 is appropriate to define symptoms as "minimal or no impact of nausea and vomiting on the patients life".

3. *The FLIE was originally developed to assess the impact of chemotherapy-induced nausea and vomiting (CINV) on patients' daily lives over the 3 days following chemotherapy. In this submission the questionnaire was administered at Day 6.*

   The SEALD division noted that the 5-day version of the FLIE may not be a valid assessment of what patients experienced over the 5-days post chemotherapy. Published validation of the 5-day recall version of the FLIE focused on discriminant validity and did not address construct validity, recall errors or other concerns raised by extending the recall. The validation study did not compare the original 3-day recall version of the FLIE to the 5-day recall version. SEALD's concerns regarding the validity of the 5-day FLIE were not about biased conclusions about treatment effectiveness because Study 071 was a randomized, active-control trial. The change in recall period applies equally to both groups and is not expected to differentially affect treatment groups responses in the study.

4. *SEALD discourages patient-reported outcome instruments that require patients to summarize long period of time as this would introduce recall errors and difficulty interpreting responses. They recommend that the Division request that Merck submit evidence that the 5-day recall version of the FLIE provides a valid and reliable measure of the impact of CINV on the daily lives of patients receiving chemotherapy.*

Additional Exploratory Endpoints:

Medical Officer Comment:
The proposed indication is for the prevention of both nausea and vomiting. Since the primary endpoint did not include a nausea specific assessment, it is this Reviewer's opinion that for approval, the nausea indication would need to be supported by the analyses of the exploratory nausea endpoints.

Table 20
Efficacy Outcomes in Overall Phase
Patients by Treatment Group—Cycle 1
(Modified-Intention-to-Treat)
Applicant's Analysis

Efficacy Outcome	Aprepitant Regimen %	Standard Regimen %	Treatment Difference	p-Value
Primary Endpoint				
Complete response	**50.8%**	**42.5%**	**8.3%**	**0.015**
Exploratory Endpoints				
No vomiting	**75.7%**	**58.7%**	**17%**	**<0.001**
No Rescue therapy	**58.7%**	**56.2%**	**2.5%**	**N.S.**
No nausea (VAS <5 mm)	**33%**	**33%**	**0**	**N.S.**
No significant nausea (VAS <25 mm)	**60.9%**	**55.7%**	**5.2**	**N.S.**

Ref: clinical-overview.pdf Table 2.5:3
N.S.=not significant

Medical Officer Comment:
Based on the Applicant's analyses, the aprepitant regimen was significantly better than standard therapy for Complete Response in the overall phase (No vomiting and No Rescue therapy) and the exploratory endpoint No Vomiting in the overall phase.

As previously stated, the Complete Response in the acute and delayed phase time periods (exploratory endpoints) demonstrated only a numerical improvement in the aprepitant group over the standard therapy group when corrected for multiplicity.

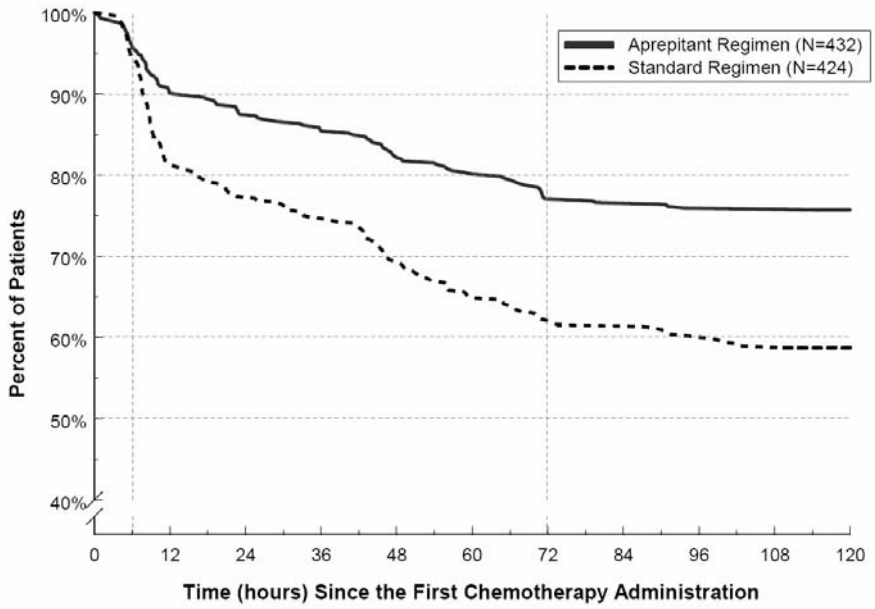
The aprepitant regimen had no significant effect on the exploratory endpoints of nausea or the use of rescue therapy. Based on the above results, the success of the primary endpoint, Complete Response (No Vomiting and No Rescue therapy), is being driven by the No Vomiting variable. In this Reviewer's opinion, the data do not support the proposed indication, "the prevention of (b) (4) *nausea and vomiting."*

Table 21
No Vomiting by Treatment Group
MITT population
Applicant's Analysis

Phase	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	Delta	p-Value
No Vomiting				
Overall Phase	**75.7%**	**58.7%**	**17%**	**<0.001**
Acute Phase	**87.5%**	**77.3%**	**10.2%**	**<0.001**
Delayed Phase	**80.8%**	**69.1%**	**11.7%**	**<0.001**
Ref: clinical-overview.pdf Page 15 exploratory endpoints				

The following graph shows that the aprepitant regimen had a statistically significant effect on the time to first vomiting episode in the overall phase of Cycle 1. Both treatment groups appear similar until ~6 hours post-chemotherapy and then diverge, maintaining a treatment effect over the 120 hours.

Figure 3
Kaplan-Meier Curves for Time to First Vomiting Episode From Start of Chemotherapy Administration in the Overall Phase—Cycle 1 (Modified Intention-to-Treat Analysis)



Note: The reference lines at 6 hours and 72 hours reflect the time at first separation and the time interval when most vomiting episodes occurred, respectively.
[Ref. 5.3.5.1; P071]

Medical Officer Comment:
In order to address multiplicity in the exploratory efficacy endpoints, Merck employed a closed testing procedure, grouping the exploratory endpoints and testing each group in a sequential fashion such that subsequent groups would not be tested unless the prior groups revealed at least one statistically significant finding. Hochberg's procedure was used to adjust for testing the multiple efficacy endpoints within the group to control the type I error at the 0.05 level.

Table 22
Exploratory Endpoints (Cycle 1)
mITT Patient Population
Applicant's Analysis

Exploratory Endpoints	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Complete Response			
Acute phase (0 to 24 hours)	327/432 (75.7)	292/423 (69.0)	0.034
Delayed phase (25 to 120 hours)	240/433 (55.4)	208/424 (49.1)	**N.S.**
No Vomiting			
Acute phase	378/432 (87.5)	327/423 (77.3)	<0.001
Delayed phase	349/432 (80.8)	293/424 (69.1)	<0.001
No Use of Rescue Therapy			
Acute phase	355/429 (82.8)	336/420 (80.0)	**N.S.**
Delayed phase	271/432 (62.7)	253/423 (59.8)	**N.S.**
No Significant Nausea (maximum VAS <25 mm)			
Overall phase	262/430 (60.9)	236/424 (55.7)	**N.S.**
Acute phase	342/430 (79.5)	331/423 (78.3)	**N.S.**
Delayed phase	281/430 (65.3)	260/423 (61.5)	**N.S.**
0 to 72 hours	274/430 (63.7)	254/424 (59.9)	**N.S.**
No Nausea (maximum VAS <5 mm)			
Overall phase	142/430 (33.0)	140/424 (33.0)	**N.S.**
Acute phase	261/430 (60.7)	250/423 (59.1)	**N.S.**
Delayed phase	159/430 (37.0)	154/423 (36.4)	**N.S.**
0 to 72 hours	167/430 (38.8%)	159/424 (37.5)	**N.S.**
Complete Protection (no vomiting, no rescue and maximum nausea VAS <25 mm)			
Overall phase	184/433 (42.5)	156/424 (36.8)	**N.S.**
Acute phase	296/431 (68.7)	272/423 (64.3)	**N.S.**
Delayed phase	203/433 (46.9)	180/424 (42.5)	**N.S.**
Total Control (no vomiting, no rescue and maximum nausea VAS <5 mm)			
Overall phase	125/433 (28.9)	115/424 (27.1)	**N.S.**
Acute phase	241/431 (55.9)	222/423 (52.5)	**N.S.**
Delayed phase	139/433 (32.1)	132/424 (31.1)	**N.S.**

Ref: Table 3.1.3, Statistical Review
†: Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group,
investigator group, and age category (<55 years, ≥55 years).
VAS = Visual analogue scale.

Medical Officer Comment:
Except for complete response in acute phase and no vomiting in both acute and delayed phases, the unadjusted p-values for the rest of the exploratory endpoint analyses were nonsignificant (greater than 0.05). Furthermore, after applying the protocol's defined multiplicity adjustments, none of the exploratory endpoints reached statical significance. The aprepitant regimen demonstrated no significant advantage over the standard therapy for any of the nausea endpoints or the use of rescue therapy.

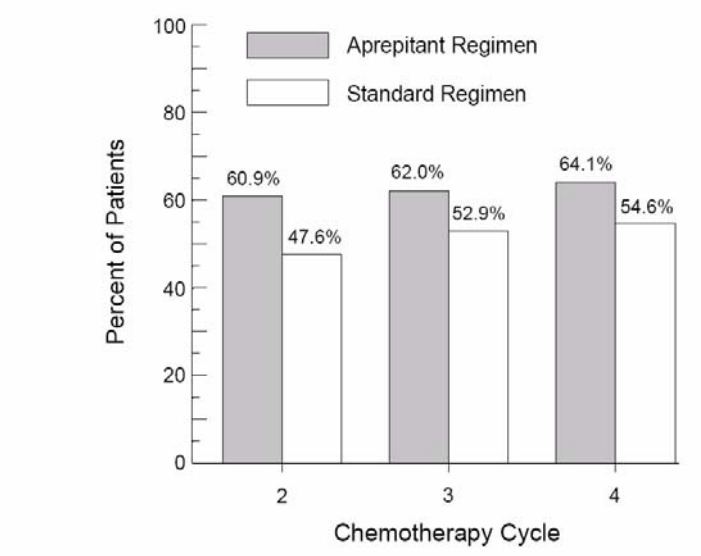
It is this Reviewer's opinion that the efficacy results are not sufficiently "robust" to support approval of the requested new indication. There is an incongruency between the effects of the aprepitant regimen on nausea and those effects on vomiting.

Efficacy in Multiple Cycles:

The data analysis of Cycles 2 through 4 was exploratory in nature. The purpose of these analyses was to compare the sustainability of efficacy across multiple cycles of chemotherapy.

Medical Officer Comment:
Based on the protocol definition of Complete Response in the overall phase, Merck reports that the antiemetic effectiveness of the aprepitant regimen was maintained throughout the multiple cycles, as evidenced by the consistent ~10% difference between treatment groups.

Figure 4
Percentage of Patients With a Complete Response in Cycles 2 through 4 (Modified Intention-to-Treat Population)
Applicant's Analysis



Aprepitant (N)	379	358	343
Standard (N)	355	325	304

N = Number of patients with evaluble data.
[Ref. 5.3.5.1; P071]

Ref: Figure 2.5:3 clinical-review.pdf

Medical Officer Comment:
Considering the limitations of the complete response endpoint as an independent indicator of efficacy, [redacted](b) (4)*. Also, due to the defined data analysis plan, the statical significance of this 10% treatment group difference can not be ascertained.*

Similar to Cycle 1, the aprepitant regimen had little effect on the nausea endpoints during the multiple cycle extension portion of Study 071.

In the summary of efficacy (clinical-overview.pdf, page 16), the Applicant states the following:

> "The key efficacy data collected during this optional portion of the study consisted of Day 6 patient self assessments of whether the patient had experienced vomiting or taken rescue therapy within the past 5 days since the initiation of chemotherapy in each respective cycle. Unlike Cycle 1, in which patients were asked to record each episode of vomiting or the use of rescue medication, during the multiple-cycle analysis, patients reported one response for the entire 5-day period after chemotherapy initiation."

This statement is misleading and not completely correct. During the multiple cycle extension portion of the study, the Applicant collected nausea severity. The Nausea VAS was the only efficacy assessment recorded daily during this period. It was assessed on Days 1 through 5 during each Cycle. This analysis was not included in the study summary or the summary of efficacy. This analysis was it obtained through an information request.

The following tables show the exploratory analysis of nausea over Cycles 1 through 4. Since these results were exploratory, Merck states the results should be considered "only as hypothesis generating and not for making any inference regarding nausea in the multiple cycles."

Table 23
Exploratory Endpoint
No Nausea (Peak VAS<5 mm)
(Cycle 1-4)
mITT Patient Population
Applicant's Analysis

Exploratory Endpoints	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Cycle 1			
Overall phase (0 to 120 hours)	142/430 (33.0)	140/424 (33.0)	N.S.
Acute phase (0 to 24 hours)	261/430 (60.7)	250/423 (59.1)	N.S.
Delayed phase (25 to 120 hours)	159/430 (37.0)	154/423 (36.4)	N.S.
Cycle 2			
Overall phase (0 to 120 hours)	137/380 (36.1)	125/357 (35.0)	N.S.
Acute phase (0 to 24 hours)	255/380 (67.1)	210/357 (58.8)	0.024.
Delayed phase (25 to 120 hours)	150/380 (39.5)	134/357 (37.5)	N.S.
Cycle 3			
Overall phase (0 to 120 hours)	134/360 (37.2)	136/328 (41.5)	N.S.
Acute phase (0 to 24 hours)	234/359 (65.2)	209/328 (63.7)	N.S.
Delayed phase (25 to 120 hours)	141/360 (39.2)	142/327 (43.4)	N.S.
Cycle 4			
Overall phase	155/344 (45.1)	131/307 (42.7)	N.S.
Acute phase	236/344 (68.6)	206/307 (67.1)	N.S.
Delayed phase	161/343 (46.9)	133/307 (43.3)	N.S.

Ref: Modified Tables 1, 3, 5, 7 Clinical Attachment.pdf
†: Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group,
investigator group, and age category (<55 years, ≥55 years).
VAS = Visual analogue scale.

Table 25
Exploratory Endpoint
No Significant Nausea (Peak VAS<25 mm)
(Cycle 1-4)
mITT Patient Population
Applicant's Analysis

Exploratory Endpoints	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Cycle 1			
Overall phase (0 to 120 hours)	262/430 (60.9)	236/424 (55.7)	N.S.
Acute phase (0 to 24 hours)	342/430 (79.5)	331/423 (78.3)	N.S.
Delayed phase (25 to 120 hours)	281/430 (65.3)	260/423 (61.5)	N.S.
Cycle 2			
Overall phase (0 to 120 hours)	249/380 (65.5)	203/357 (56.9)	0.020
Acute phase (0 to 24 hours)	324/380 (85.3)	277/357 (77.6)	0.010
Delayed phase (25 to 120 hours)	261/380 (68.7)	217/357 (60.8)	0.028
Cycle 3			
Overall phase (0 to 120 hours)	256/360 (71.1)	213/328 (64.9)	N.S.
Acute phase (0 to 24 hours)	315/359 (87.7)	276/328 (84.1)	N.S.
Delayed phase (25 to 120 hours)	258/360 (71.7)	219/327 (67.0)	N.S.
Cycle 4			
Overall phase	255/344 (74.1)	219/307 (71.3)	N.S.
Acute phase	301/344 (87.5)	263/307 (85.7)	N.S.
Delayed phase	262/343 (76.4)	225/307 (73.3)	N.S.

Ref: Modified Tables 2,4,6,8 Clinical Attachment.pdf
†: Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group,
investigator group, and age category (<55 years, ≥55 years).
VAS = Visual analogue scale.

Medical Officer Comment:
In this Reviewer's opinion, the multiple cycle efficacy data do not support the proposed indication, the prevention of (b) (4) *nausea and vomiting. Based on the Applicant's analysis, the aprepitant regimen did not offer significant improvement over the standard therapy for the symptoms of nausea during Cycles 1 through 4.*

The results of the exploratory "No Nausea" endpoint only reached statical significance in the Acute Phase of Cycle 2. The treatment group difference for the "No Nausea" endpoint failed to be statistically significant in the overall and delayed phase of Cycle 2 as well as all three phases during Cycles 1, 3 and 4. The results for the "No Significant Nausea" endpoint (Peak VAS<25 mm) demonstrated similar findings. The treatment group differences failed to be statistically significant in all three phases of Cycles 1, 3 and 4. These data are important since the proposed indication is the prevention of both nausea and vomiting.

Subgroup Analysis

Treatment by Gender Analysis:

Medical Officer Comment:
A meaningful treatment-by-gender analysis could not be performed; only two out of 857 patients in the mITT population were male. Considering a significant treatment-by-gender interaction was observed in one of the two pivotal trials submitted with the original NDA (Study P052), the results of Study 071 may not necessarily predict the efficacy in males.

The Applicant should perform a study evaluating the efficacy of the aprepitant regimen in both male and female patients receiving moderate emetogenic cancer chemotherapy.

Safety Evaluation and Results

Exposure:

Aprepitant Exposure (Cycle 1)

During Cycle 1, exposure was calculated as the difference between the number of days between first and last day of therapy and the "actual days on therapy."

Table 26
Exposure to Study Medication
Study 071 ITT Population

Exposure	Treatment Group	
	Aprepitant Regimen N=438	Standard Regimen N=428
Actual Days on Therapy		
Mean (SE)	2.99 ± 0.21	2.98 ± 0.17
Median	3	3
Range	1 to 4[T]	1 to 3
Days Off Therapy		
Mean (SE)	0.02 ± 0.19	0.02 ± 0.17
Median	0	0
Range	0 to 2	0 to 2

Ref: Modified Table 6-19 P071.pdf Page 109
Actual days on therapy: defined as the number of days the patient took a pill from an active bottle.
Days off therapy: defined as the difference between the number of days between first and last day on therapy and the "actual days on therapy" (number of days patient took a pill from the active bottle).

[T] Three patients (AN 25, AN 593 and AN 638) in the Aprepitant Regimen restarted their study medication regimen after Day 1 to account for at least a one day delay in their chemotherapy initiation due to problems with administering their chemotherapy.

Table 27
Number of Patients on Study Drug by Daily Dose
Aprepitant Exposure Cycle 1

	Days				Total	Range Days of Drug	Mean Days of Drug
	1	2	3	>3			
Aprepitant Regimen							
Any dose	4	0	432	2	438	1 to 4	3.0
80 mg	1	433	0	0	434	1 to 2	2.0
125 mg	435	3	0	0	438	1 to 2	1.0
Ref: Table 8-1 P071.pdf							

All 438 patients randomized to receive the aprepitant regimen received aprepitant. Of the 438 randomized, 434 completed the Cycle 1. Two patients received aprepitant for 4 days because their chemotherapy regimen was delayed for one day delay after receiving aprepitant. Four patients received aprepitant for only one day.

Aprepitant Exposure (Cycle 1 to 4)

The range of days on aprepitant (Cycles 1 to 4) was between 1 to 13 days. The mean number of days exposure to aprepitant was 10.4 days (any dose). Of the 438 patients randomized into the aprepitant group 343 received aprepitant for 11 to 12 days (any dose).

Dexamethasone (Cycle 1)

Of the 438 patients randomized to the aprepitant group, 4 patients did not receive the 12mg protocol dose of dexamethasone.

Table 28
Number of Patients on Study Drug by Daily Dose
Dexamethasone Exposure Cycle 1

	Days				Total	Range Days of Drug	Mean Days of Drug
	1	2	3	4			
Aprepitant Regimen							
Any dose	435	2	0	0	437	1 to 2	1.0
2.4 mg	1	0	0	0	1	1	1.0
12 mg	434	2	0	0	436	1 to 2	1.0
Standard Regimen							
Any dose	428	0	0	0	428	1	1.0
4 mg	1	0	0	0	1	1	1.0
20 mg	427	0	0	0	427	1	1.0
Ref: Table 8-2 P071.pdf							

Dexamethasone (Cycle 1 to 4)

Of the 865 randomized patients who received dexamethasone during Cycles 1 to 4, the majority of patients received dexamethasone for 4 days. The range of days was between 1 to 5 days. The mean number of days on dexamethasone (any dose) was 3.5 days in the aprepitant group and 3.3 days in the standard therapy group.

One patient never received dexamethasone, and 4 patients received a lower dose of dexamethasone than prescribed by the protocol.

Ondansetron Exposure (Cycle 1)

Of the 438 patients randomized to the aprepitant group, 12 patients did not receive the protocol 16-mg ondansetron dose on Day 1.

Table 29
Number of Patients on Study Drug by Daily Dose
Ondansetron Exposure Cycle 1

	Days				Total	Range Days of Drug	Mean Days of Drug
	1	2	3	>3			
Aprepitant Regimen							
Any dose	432	6	0	0	438	1 to 2	1.0
8 mg	6	5	0	0	11	1 to 2	1.5
16 mg	427	0	0	0	427	1	1.0
24 mg	1	0	0	0	1	1	1.0
Standard Regimen							
Any dose	2	4	422	0	428	1 to 3	3.0
8 mg	11	2	0	0	13	1 to 2	1.2
16 mg	7	9	411	0	427	1 to 3	2.9
24 mg	3	0	0	0	3	1	1.0
Ref: Table 8-3 P071.pdf							

Ondansetron Exposure (Cycles 1 to 4)

The range of days on ondansetron was between 1 to 13 days in the standard therapy group and 1 to 7 days in the aprepitant group. The mean number of days on ondansetron was 3.5 days in the aprepitant group versus 9.9 days in the standard therapy group.

One patient in the aprepitant group and 3 patients in the standard therapy group took a dose of ondansetron greater than the protocol specified daily dose. There were 63 patients [aprepitant (25) vs standard (38)] who took a dose of ondansetron <16 mg (specified daily dose) on one or more days during Cycles 1 to 4.

Medical Officer Comment:
The exposure to study drug was acceptable for this Phase III study. The exposure data does not suggest that a bias in favor of either treatment arm occurred.

Adverse Experiences (Cycle 1)

Table 30
Adverse Events Summary Cycle 1
Study 071

Adverse Experience	Treatment Group	
	Aprepitant (N=438) n (%)	Standard (N=428) n (%)
Patients with Adverse Event(s)	320 (73.1)	320 (74.8)
Patients with Serious Adverse Event(s)	15 (3.4)	18 (4.2)
Discontinued from Study due to AE	7 (1.6)	5 (1.2)
Discontinued from Study due to SAE	1 (0.2)	2 (0.5)
Ref: Modified Table 8-7 P071.pdf		

Medical Officer Comment:
One or more adverse events were reported by 73.9% of the 866 patients [aprepitant (320) and standard therapy (320)]. The incidence of serious adverse events and discontinuations from the study due to AEs were balanced between treatment groups.

Adverse Events by Body System

Table 31
Select Adverse Events by Body System
(Incidence ≥2%)
(Cycle 1)
Safety Population Study 071

Adverse Experience	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Adverse Event(s)	320 (73.1)	320 (74.8)
Blood and Lymphatic System	**53 (12.1)**	**57 (13.3)**
Anemia	12 (2.7)	11 (2.6)
Febrile neutropenia	9 (2.1)	9 (2.1)
Neutropenia	39 (8.9)	36 (8.4)
Gastrointestinal Disorders	**168 (38.4)**	**159 (37.1)**
Abdominal pain upper	9 (2.1)	6 (1.4)
Constipation	54 (12.3)	77 (18.0)
Diarrhea	24 (5.5)	27 (6.3)
Nausea	31 (7.1)	32 (7.5)
General Disorders		
Mucosal inflammation	11 (2.5)	15 (3.5)
Pyrexia	7 (1.6)	11 (2.6)
Anorexia	19 (4.3)	25 (5.8)
Headache	72 (16.4)	70 (16.4)
Alopecia	105 (24.0)	95 (22.2)
Rash	12 (2.7)	4 (0.9)
Infections and Infestations	**41 (9.4)**	**50 (11.7)**
Nasopharyngitis	3 (0.7)	10 (2.3)
REF: Modified Table 8-10 p071.pdf		

Medical Officer Comment:
Overall, the adverse event profile during Cycle 1 was similar between treatment groups. The most frequently reported adverse events were alopecia (24.0% vs. 22.2%), fatigue (21.9% vs.21.5%), headache (16.4% vs.16.4%), constipation (12.3% vs.18.0%), and neutropenia (8.9% vs.8.4%) in the aprepitant group and standard therapy group respectively. A review of the severity of these events, based on NCI criteria, did not identify any concerning trends or finding during Cycle 1

Adverse Experiences (Multiple Cycle)

Table 32
Adverse Events Summary Cycle 2 to 4
Study 071

Adverse Experience	Treatment Group	
	Aprepitant (N=385) n (%)	Standard (N=359) n (%)
Patients with Adverse Event(s)	308 (80.0)	260 (72.4)
Patients with Serious Adverse Event(s)	17 (4.4)	13 (3.6)
Discontinued from Study due to AE	7 (1.8)	4 (1.1)
Discontinued from Study due to SAE	5 (1.3)	0 (0.0)
Deaths	1 (0.3)	0 (0.0)
Ref: Modified Table 8-8 P071.pdf		

Medical Officer Comment:
An imbalance in chemotherapy exposure occurred during Cycles 2 to 4. The aprepitant group received 1099 patient-cycles of chemotherapy compared to 1006 patient cycles in the standard therapy group. To adjust for this imbalance, the Applicant also reported the adverse event profile for Cycles 2 to 4 based on a patient-cycle analysis (i.e., each patient-cycle is uniquely counted as opposed to only once per patient).

Table 33
Adverse Events Summary Cycle 2 to 4
Adjusted for Patient Exposure (Cycles on Chemotherapy)
Study 071

Adverse Experience	Treatment Group	
	Aprepitant Patient-Cycles (N=1099) n (%)	Standard Patient-Cycles (N=1006) n (%)
Patients with Adverse Event(s)	545 (49.6)	464 (46.1)
Patients with Serious Adverse Event(s)	17 (1.5)	15 (1.5)
Discontinued from Study due to AE	7 (0.6)	4 (0.4)
Discontinued from Study due to SAE	5 (0.5)	0 (0.0)
Ref: Modified Table 8-9 P071.pdf		

Medical Officer Comment:
The Applicant's proposal to evaluate AEs based on patient exposure to chemotherapy seems reasonable, considering a higher incidence of adverse events would be expected with a longer exposure to chemotherapy.

The treatment groups were similar with respect to the incidence of clinical adverse events after adjusting for patient exposure to chemotherapy. The aprepitant group had a higher incidence of AEs (49.6%) than the standard therapy group (46.1%), but this difference was not statistically significant. The two treatment groups were balanced in terms of serious adverse events (1.5%)

Adverse Events by Body System

Table 34
Select Adverse Events by Body System
(Incidence ≥2%)
Cycle 2 to 4
Safety Population Study 071

Adverse Experience	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Adverse Event(s)	308 (80.0)	260 (72.4)
Blood and Lymphatic System	**57 (14.8)**	**46 (12.8)**
Anemia	14 (3.6)	20 (5.6)
Febrile neutropenia	11 (2.9)	8 (2.2)
Neutropenia	35 (9.1)	21 (5.8)
Gastrointestinal Disorders	**161 (41.8)**	**135 (37.6)**
Constipation	38 (9.9)	49 (13.6)
Diarrhea	33 (8.6)	19 (5.3)
Nausea	46 (11.9)	41 (11.4)
Vomiting	6 (1.6)	9 (2.5)
General Disorders		
Mucosal inflammation	10 (2.6)	22 (6.1)
Pyrexia	11 (2.9)	12 (3.3)
Anorexia	13 (3.4)	14 (3.9)
Headache	36 (9.4)	33 (9.2)
Dizziness	19 (4.9)	10 (2.8)
Alopecia	49 (12.7)	53 (14.8)
Rash	9 (2.3)	8 (2.2)
Infections and Infestations	**66 (17.1)**	**60 (16.7)**
Nasopharyngitis	9 (2.3)	11 (3.1)
Upper Respiratory infection	13 (3.4)	14 (3.9)

REF: Modified Table 8-11 p071.pdf

Medical Officer Comment:
As previously noted, the magnitude of any treatment group difference in the safety analysis for Cycles 2 to 4 may have been influenced by the imbalance in chemotherapy exposure between treatment groups [aprepitant (1099 patient-cycles) versus standard (1006 patient-cycles].

For the most part, the treatment groups were similar with respect to the incidence of most adverse events in Cycles 2 to 4. There was a somewhat higher incidence of neutropenia (9.1% vs 5.8%), and diarrhea (8.6% vs 5.3%) in the aprepitant group than the standard therapy group, but these differences were not significant.

The most frequently reported adverse events during Cycles 2 to 4 were fatigue (20.8% vs. 17.5%), alopecia (12.7% vs. 14.8%), nausea (11.9% vs. 11.4%), constipation (9.9% and 13.6%), headache (9.4% vs. 9.2%), and dyspepsia (10.6% vs. 7.8%) in the aprepitant group and standard therapy group respectively.

The severity of adverse events was analyzed in terms of NCI criteria. With respect to the more severe NCI toxicity, Grade 3/4 neutropenia occurred more frequently in the aprepitant group [27 patients (7.0%)] than the standard therapy group [13 patients (3.6%)]. Additionally, grade 3/4 febrile neutropenia also occurred more frequently in the aprepitant group [11 patients (2.9%)] than the standard therapy group [7 patients (1.9%)].

The small treatment group differences in neutropenia and febrile neutropenia was even smaller after adjusting for the imbalance in chemotherapy patient-cycles. Adjusting for patient exposure, the percentage of patient-cycles with Grade 3/4 neutropenia in Cycles 2 to 4 was 2.5% (27/1099) in the aprepitant group versus 1.3% (13/1006) in the standard therapy group. Similarly, the incidence of febrile neutropenia was 1.0% (11/1099) in the aprepitant group versus 0.7% (7/1006) in the standard therapy group.

Serious Adverse Events:

(Cycle1)

Table 35
Select Serious Adverse Events by Body System
(Incidence 0%)
Cycle 1
Safety Population Study 071

Adverse Experience	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Serious Adverse Event(s)	15 (3.4)	18 (4.2)
Blood and Lymphatic System	**9 (2.1)**	**10 (2.3)**
Febrile neutropenia	7 (1.6)	8 (1.9)
Neutropenia	2 (0.5)	3 (0.7)
Gastrointestinal Disorders	**3 (0.7)**	**2 (0.5)**
Abdominal Pain	1 (0.2)	2 (0.5)
Enterocolitis	1 (0.2)	0
Vomiting	2 (0.5)	0
General Disorders		
Chest pain	0	1 (0.2)
Pyrexia	0	1 (0.2)
Cardiac Disorders	**1 (0.2)**	0
Sinus tachycardia	1 (0.2)	0
Infections and Infestations	**2 (0.5)**	**4 (0.9)**
Catheter site infection	0	1 (0.2)
Neutropenic sepsis	1 (0.2)	1 (0.2)
Peritonsillar abscess	0	1 (0.2)
Pneumonia	1 (0.2)	
Sinusitis	0	1 (0.2)
Vascular Disorders	**1 (0.2)**	**2 (0.5)**
Deep vein thrombosis	0	2 (0.5)
Hypertension	1 (0.2)	0
REF: Modified Table 8-17 p071.pdf		

Medical Officer Comment:
The treatment groups were similar with respect to the incidence of serious adverse events. The most frequently occurring serious adverse experience was febrile neutropenia which occurred in 1.6% of the patients in the aprepitant group compared to 1.9% of patients receiving standard therapy.

(Cycles 2 to 4)

Table 37
Select Serious Adverse Events by Body System
(Incidence 0%)
Cycle 2 to 4
Safety Population Study 071

Adverse Experience	Treatment Group	
	Aprepitant N=385 n (%)	Standard N=359 n (%)
Serious Adverse Event(s)	17 (4.4)	13 (3.6)
Blood and Lymphatic System	**8 (2.1)**	**5 (1.4)**
Febrile neutropenia	7 (1.8)	5 (1.4)
Neutropenia	1 (0.3)	2 (0.6)
Gastrointestinal Disorders	**2 (0.5)**	**2 (0.6)**
Constipation	0	1 (0.3)
Dyspepsia	1 (0.3)	0
Nausea	1 (0.3)	1 (0.3)
Vomiting	0	1 (0.3)
General Disorders		
Chest pain	1 (0.3)	0
Pyrexia	1 (0.3)	0
Impaired healing	0	1 (0.3)
Skin Disorders	1 (0.3)	0
Rash erythematous	1 (0.3)	0
Cardiac Disorders	1 (0.3)	0
Myocardial infarction	1 (0.3)	0
Infections and Infestations	**4 (1.0)**	**3 (0.8)**
Bursitis infective	1 (0.3)	0
Cellulitis	0	1 (0.3)
Infection	1 (0.3)	0
Perineal abscess	0	1 (0.3)
Pneumonia	1 (0.3)	1 (0.3)
Sepsis	1 (0.3)	0
Vascular Disorders	1 (0.3)	1 (0.3)
Deep vein thrombosis	1 (0.3)	1 (0.3)
REF: Modified Table 8-19 p071.pdf		

Medical Officer Comment:
As previously noted, there was an imbalance in patient-cycles of chemotherapy in Cycles 2 to 4 [aprepitant (1099 patient-cycles) versus standard (1006 patient-cycles]. The incidence and type of serious adverse events in Cycles 2 to 4 were similar between treatment groups. The most frequently occurring serious adverse event in Cycles 2 to 4 was febrile neutropenia [aprepitant (1.8%) versus standard (1.4%). A review of the CRF for the serious adverse events did not identify any specific safety concerns.

Discontinued Due to Adverse Experiences

(Cycle 1)

Table 38
Select Adverse Events
Resulting in Discontinuation (Incidence 0%)
Cycle 1
Safety Population Study 071

Adverse Experience	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Adverse Event(s)	7 (1.6)	5 (1.2)
Gastrointestinal Disorders	2 (0.5)	1 (0.2)
Diarrhea	0	1 (0.2)
Enterocolitis	1 (0.2)	0
Hematochezia	0	1 (0.2)
Nausea	1 (0.2)	0
Investigations		
Weight decreased	1 (0.2)	0
Metabolism and Nutrition		
Dehydration	1 (0.2)	1 (0.2)
Nervous System Disorders		
Headache	1 (0.2)	1 (0.2)
Migraine	1 (0.2)	0
Respiratory System Disorders		
Dyspnea	0	1 (0.2)
Skin Disorders		
Rash	1 (0.2)	0
Pruritus	1 (0.2)	0
Vascular Disorders		
Deep vein thrombosis	0	1 (0.2)
Flushing	1 (0.2)	0
REF: Modified Table 8-21 p071.pdf		

Medical Officer Comment:
A total of 12 patients discontinued from the study due to an adverse event during Cycle 1 [aprepitant (7), standard (5)]. Overall, the treatment groups were similar with respect to adverse events resulting in discontinuation.

(Cycle 2 to 4)

Table 39
Select Adverse Events
Resulting in Discontinuation (Incidence 0%)
Cycle 2 to 4
Safety Population Study 071

Adverse Experience	Treatment Group	
	Aprepitant N=385 n (%)	Standard N=359 n (%)
Serious Adverse Event(s)	7 (1.8)	4 (1.1)
Blood and Lymphatic System	2 (0.5)	0
Febrile neutropenia	2 (0.5)	0
Gastrointestinal Disorders	0	1 (0.3)
Nausea	0	1 (0.3)
General Disorders		
Weight decreased	1 (0.3)	0
Anorexia	1 (0.3)	0
Confusional state	1 (0.3)	0
Asthma	0	1 (0.3)
Dyspnea	1 (0.3)	0
Skin Disorders	1 (0.3)	1 (0.3)
Alopecia	0	1 (0.3)
Rash erythematous	1 (0.3)	0
Cardiac Disorders		
Myocardial infarction	1 (0.3)	0
Immune System Disorders		
Hypersensitivity	0	1 (0.3)
Infections and Infestations	2 (0.5)	0
Infection	1 (0.3)	0
Sepsis	1 (0.3)	0
Vascular Disorders		
Deep vein thrombosis	1 (0.3)	0
REF: Modified Table 8-19 p071.pdf		

Medical Officer Comment:
The number of patients that discontinued from the study due to an adverse event during Cycles 2 to 4 was small. A total of 11 patients discontinued from the study due to an adverse event during Cycles 2 to 4 [aprepitant (7), standard (4)]. Two patients (0.5%) in the aprepitant group discontinued from the study due to febrile neutropenia. One patient discontinued due to sepsis, this case will be discussed in detail in the reported Deaths section of this review.

Summary of Laboratory Adverse Experiences

(Cycle 1)

Table 40
Laboratory Adverse Events
Cycle 1
Safety Population Study 071

Event Category	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Post baseline labs	436	426
Laboratory Adverse Event	77 (17.7)	75 (17.6)
Serious Lab Adverse Events	0	0
Reported as Drug Related	4 (0.9)	8 (1.9)
Discontinued due to Lab AE	0	0
REF: Modified Table 8-25 p071.pdf		

Table 41
Specific Laboratory Adverse Events
(Incidence >= 2%)
Cycle 1
Safety Population Study 071

Event Category	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Laboratory Adverse Event	77 (17.7)	75 (17.6)
Blood Chemistry Test	**18/436 (4.1)**	**22/425 (5.2)**
ALT increased	9/436 (2.1)	7/423 (1.7)
Blood glucose increased	7/436 (1.6)	9/425 (2.1)
Blood urea increased	1/3 (33.3)	0/1 (0.0)
Hematology Laboratory Test	**63/436 (14.4)**	**68/426 (16.0)**
Granulocyte count decreased	0/15 (0.0)	2/9 (22.2)
Hemoglobin decreased	10/432 (2.3)	20/422 (4.7)
Neutrophil count decreased	38/436 (8.7)	41/426 (9.6)
White blood cell count decreased	40/432 (9.3)	38/422 (9.0)
REF: Modified Table 8-27 p071.pdf		

Medical Officer Comment:
It is important to reiterate that the data presented as laboratory adverse experiences were dependent on the investigator's judgment that the abnormality fulfilled the criteria of an adverse experience. Therefore, not all of the out of range laboratory values were reported as adverse events.

Overall, the incidence of laboratory adverse events during Cycle 1 was similar between the two treatment groups. There were more adverse events reported as Drug Related in the standard therapy group than in the aprepitant group. There were no laboratory adverse events reported as serious or that resulted in discontinuation from the study.

Table 42
Patients with Clinically Significant Laboratory Abnormalities
Cycle 1
Days 6 to 29

Lab Test	CSLA Criteria	Number (%) with CSLA		p-Value*
		Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	
Blood Chemistry				
Serum glucose	>250 mg/dL	9/415 (2.2)	9/407 (2.2)	N.S.
Serum albumin	<2 gm/dL	0/420 (0.0)	0/411 (0.0)	*N.S.*
Serum sodium	<130 mEq/L	1/422 (0.2)	1/416 (0.2)	N.S.
	>155 mEq/L	0/422 (0.0)	0/416 (0.0)	*N.S.*
Serum potassium	<3 mEq/L	2/401 (0.5)	0/403 (0.0)	N.S.
	>6 mEq/L	0/401 (0.0)	1/403 (0.2)	N.S.
Serum bicarbonate	<10 mEq/dL	0/416 (0.0)	0/409 (0.0)	*N.S.*
Hematology				
Hemoglobin	<8.0 gm/dL	1/417 (0.2)	0/413 (0.0)	N.S.
WBC count	<2 x 10^3/microL	56/423 (13.2)	55/418 (13.2)	N.S.
Neutrophil count	*<1 x 10^3/microL*	110/418 (26.3)	93/416 (22.4)	N.S.
Platelet count	*<50 x 10^3/microL*	0/418 (0.0)	0/411 (0.0)	*N.S.*
Hepatic Function				
Total serum bilirubin	>3 x ULN	0/426 (0.0)	0/417 (0.0)	*N.S.*
AST	>5 x ULN	1/398 (0.3)	2/393 (0.5)	N.S.
ALT	>5 x ULN	3/411 (0.7)	4/407 (1.0)	N.S.
Alkaline phosphatase	*>5 x ULN*	0/415 (0.0)	0/414 (0.0)	*N.S.*
Renal Function				
Serum creatinine	*>3 x ULN*	0/429 (0.0)	0/418 (0.0)	*N.S.*

Ref: Table 8-32 P071.pdf
* Based on Fisher's Exact 2-tailed Test.
CSLA= protocol defined Clinically Significant Laboratory Abnormalities

Medical Officer Comment:
The above analysis was performed using protocol defined clinically significant laboratory values. This analysis did not identify any specific concerns. However, there were a higher percentage of patients with a neutrophil count <1x10^3/microL in the aprepitant group (26.3%) compared to the standard therapy group (22.2%). The clinical significance of this is unknown.

(Cycle 2 to 4)

Table 43
Laboratory Adverse Events
Cycle 2 to 4
Safety Population Study 071

Event Category	Treatment Group	
	Aprepitant N=385 n (%)	Standard N=359 n (%)
Post baseline labs	385	359
Laboratory Adverse Event	74 (19.2)	65 (18.1)
Serious Lab Adverse Events	0	1 (0.3)
Reported as Drug Related	4 (1.0)	7 (1.9)
Discontinued due to Lab AE	0	0
REF: Modified Table 8-26 p071.pdf		

Table 44
Specific Laboratory Adverse Events
(Incidence >= 2%)
Cycles 2 to 4
Safety Population Study 071

Event Category	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Laboratory Adverse Event	74 (19.2)	65 (18.1)
Blood Chemistry Test	**26/385 (6.8)**	**23/359 (6.4)**
ALT increased	10/385 (2.6)	8/358 (2.2)
AST increase	5/383 (1.3)	8/358 (2.2)
Blood glucose increased	12/385 (3.1)	7/359 (1.9)
Hematology Laboratory Test	**60/385 (15.6)**	**58/359 (16.2)**
Granulocyte count decreased	0/13 (0.0)	1/9 (11.1)
Hematocrit decreased	7/382 (1.8)	7/355 (2.0)
Hemoglobin decreased	28/382 (7.3)	26/355 (7.3)
Neutrophil count decreased	27/385 (7.0)	23/359 (6.4)
White blood cell count decreased	23/382 (6.0)	23/355 (6.5)
White blood cell count increased	2/382 (0.5)	3/355 (0.8)
REF: Modified Table 8-28 p071.pdf		

Medical Officer Comment:
As previously noted, there was imbalance in patient-cycles of chemotherapy between the treatment groups [aprepitant (1099 patient-cycles) versus standard (1006 patient-cycles].

The incidence of laboratory adverse events during Cycles 2 to 4 was similar between the two treatment groups and did not suggest a safety signal. There was only one report of a serious laboratory adverse event during Cycles 2 to 4. Patient AN 722, receiving standard therapy, experienced a decrease in platelets that was reported as a serious laboratory adverse event. There were no patients discontinued from the study due to a laboratory adverse event during Cycles 2 to 4.

Table 45
Patients with Clinically Significant Laboratory Abnormalities
Days 6 to 29
Cycles 2 to 4

Lab Test	CSLA Criteria	Number (%) with CSLA	
		Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)
Blood Chemistry			
Serum glucose	>250 mg/dL	15/369 (4.1)	10/342 (2.9)
Serum albumin	<2 gm/dL	0/371 (0.0)	0/344 (0.0)
Serum sodium	<130 mEq/L	1/373 (0.3)	0/350 (0.0)
	>155 mEq/L	1/373 (0.3)	0/350 (0.0)
Serum potassium	<3 mEq/L	4/356 (1.1)	0/337 (0.0)
	>6 mEq/L	1/356 (0.3)	1/337 (0.3)
Serum bicarbonate	<10 mEq/dL	0/369 (0.0)	0/342 (0.0)
Hematology			
Hemoglobin	<8.0 gm/dL	2/369 (0.5)	1/342 (0.3)
WBC count	<2 x 10^3/microL	49/375 (13.1)	44/350 (12.6)
Neutrophil count	*<1 x 10^3/microL*	98/372 (26.3)	78/351 (22.2)
Platelet count	*<50 x 10^3/microL*	2/371 (0.5)	1/345 (0.3)
Hepatic Function			
Total serum bilirubin	>3 x ULN	0/378 (0.0)	0/350 (0.0)
AST	>5 x ULN	0/352 (0.0)	2/331 (0.6)
ALT	>5 x ULN	0/366 (0.0)	2/344 (0.6)
Alkaline phosphatase	*>5 x ULN*	0/367 (0.0)	0/347 (0.0)
Renal Function			
Serum creatinine	*>3 x ULN*	0/379 (0.0)	0/354 (0.0)

Ref: Table 8-33 P071.pdf
* Based on Fisher's Exact 2-tailed Test.
CSLA= protocol defined Clinically Significant Laboratory Abnormalities

Medical Officer Comment:
Analysis using protocol definition for clinically significant laboratory changes did not identify any specific concerns or trends. The aprepitant group experienced a slightly higher percentage of patients with a neutrophil count <1x10^3 /microL (26.3%) compared to the Standard therapy (22.2%). Adjusting for patient exposure, the difference was much smaller (13.6% versus 12.4%) and did not suggest a safety signal. Hepatic function abnormalities occurred in <1% of patients during Cycles 2 to 4. There were no patients in the aprepitant group who developed protocol defined clinically significant changes.

Vital Signs, Physical Observations

Table 46
Clinically Significant Vital Sign Abnormality
Cycle 1
Safety Population Study 071

Vital Sign	Treatment Group	
	Aprepitant n (%)	Standard n (%)
Systolic Blood Pressure		
≥180 mmHg and ≥20 mmHg Inc.	1/421 (0.2)	1/408 (0.2)
≤90 mmHg and ≥20 mmHg Dec.	2/421 (0.5)	7/408 (1.7)
Diastolic Blood Pressure		
≥105 mmHg and ≥15 mmHg Inc.	1/421 (0.2)	1/408 (0.2)
≤50 mmHg and ≥15 mmHg Dec.	3/421 (0.7)	0/408 (0.0)
Pulse Rate (bpm)		
≥120 bpm and ≥15 bpm Inc.	2/418 (0.5)	3/406 (0.7)
≤50 bpm and ≥15 bpm Dec.	0/418 (0.0)	1/406 (0.2)
Respiratory Rate (rpm)		
>18 rpm	157/388 (40.5)	141/376 (37.5)
>8 rpm	0/388 (0.0)	0/376 (0.0)

REF: Modified Table 8-28 p071.pdf

CSVA= Protocol defined Clinically Significant Vital Sign Abnormality
Inc.=Increase
Dec.=Decrease
n/m = Number of randomized Cycle 1 patients in each treatment group with a CSVA/number of randomized Cycle 1 patients in each treatment group with vital sign data.

Medical Officer Comment:
The incidence of Clinically Significant Vital Sign Abnormalities (CSVA) was similar between treatment groups. The most frequently occurring CSVA was a respiratory rate >18 rpm [aprepitant (40.5%) versus standard (37.5%)] in Cycle 1. The significance of this small difference is unknown.

Merck also performed an analysis of summary statistics for changes from baseline in vital signs (blood pressure, pulse rate, and respiratory rate) for patients in Cycle 1. The mean and standard deviation for each variable was analyzed and no concerning findings was identified.

Electrocardiogram (ECG)

Cycle 1

Summary statistics (mean and standard deviation) were calculated for the PR interval and QTc interval pre-chemotherapy and at the patient discontinuation visit.

Table 47
Summary Statistics for 12-Lead Electrocardiogram (ECG)

Visit	Treatment	N	Mean	SD
PR Interval (msec)				
Pre-Chemotherapy	Aprepitant Regimen	406	154.53	22.32
	Standard Regimen	385	154.76	25.50
Discontinuation	Aprepitant Regimen	341	154.03	23.18
	Standard Regimen	344	153.21	22.40
QTc Interval (msec)				
Pre-Chemotherapy	Aprepitant Regimen	408	405.22	33.73
	Standard Regimen	380	407.41	33.48
Discontinuation	Aprepitant Regimen	342	416.32	39.88
	Standard Regimen	347	413.93	39.47

Ref: Modified Table 8-39 P071.pdf

Medical Officer Comment:
The analysis of the ECG summary statistics did not identify any specific safety concerns.

Deaths

(Cycle 1)

There were no deaths reported in Cycle 1.

(Multiple Cycle)

There was one death reported in Cycles 2 to 4. The patient (AN 179) died as a result of a serious infection/sepsis during Cycle 3.

Case Summary:

The patient was 58-year-old white female with a past medical history of breast cancer, and a series of co-morbidities that include: asthma, hypertension, depression, hyperlipidemia, insomnia, seasonal allergies, obstructive sleep apnea, arthritis, hard of hearing, decreased hemoglobin, and diabetes, myocardial infarction, constipation, anemia and neutropenia.

The patient was randomized to the aprepitant group and was started on study drug on 13-Jan-2003 (Relative Day 1 of Cycle 1) in conjunction with cyclophosphamide 600 mg/m^2, and doxorubicin hydrochloride 60 mg/m^2 for 1 day.

The patient completed study drug for Cycle 1 on Relative Day 3. On Relative Day 17, the patient experienced a mild infection which is documented as resolved during Cycle 3, (Relative Day 53). On Relative Day 53, the patient experienced a non-serious adverse experience of febrile neutropenia which is reported as resolved on (b) (6)

The case summary also reports the patient presented to the emergency room with fever, chills, and shortness of breath, hypotension, pneumonia and an infected right breast implant on (b) (6)

The patient was admitted to intensive care on (b) (6) with a diagnosis of sepsis and was treated with broad spectrum antibiotics. The patient's laboratory studies demonstrated: white blood cell count of 4.3 X 109/L (normal range = 3.7 to 11.8 X 109/L) and neutrophil count of 2.9 X 109/L (normal range = 2.0 to 9.0 X 109/L).

The patient status deteriorated into cardiovascular collapse with pulmonary failure. Laboratory results on (b) (6) revealed: white blood cell count of 25.3 X 109/L (normal range = 3.7 to 11.8 X 109/L). Attempts to withdraw vasopressor medications and to wean the patient off of the ventilator were unsuccessful. Comfort measures were provided and the vasopressor support was withdrawn at the family's request on (b) (6) The patient expired on (b) (6).

Medical Officer Comment:
The adverse event was reported as "definitely not" related to study drug (aprepitant regimen) by the investigator. Based on my review of the case report form and the overall safety data submitted with this application, this event is not in itself suggestive of a safety signal. However, the case summary has several conflicting statements, which are mentioned here for accuracy (P071.pdf, page 181).

The patient is reported as developing a "mild infection" on Day 17 of Cycle 1, which "resolved on Relative Day 53." The following day (b) (6), the patient was admitted to the ICU with a diagnosis of infected right breast implant, pneumonia and hypotension. The patient was diagnosed with sepsis which progressed into multisystem failure that did not respond to aggressive therapy. This Reviewer does not attribute these events as Drug Related; however I am concerned about the quality of the reporting of the event in the summary.

Discussion:

Efficacy:

The efficacy results from Study 071 are not sufficient to support approval for the proposed new indications: the prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

Study 071 was only successful in demonstrating that the aprepitant regimen was superior to standard therapy for the "no vomiting" endpoint. The treatment group differences failed to reach statical significance for all of the nausea related endpoints. Furthermore, Study 071 failed to demonstrate that the aprepitant regimen offered any significant advantage over standard therapy for Complete Response in the acute and/or delayed phase time periods separately. (b) (4)

Multiple Cycles

Based on the protocol definition of Complete Response in the overall phase, Merck reports that the antiemetic effectiveness of the aprepitant regimen was maintained throughout the multiple cycles, as evidenced by the consistent ~10% difference between treatment groups. This Reviewer does not agree that this endpoint is acceptable as an independent indicator of efficacy. Based on the Applicant's own analysis, the aprepitant regimen did not offer significant improvement over the standard therapy for the symptoms of nausea during Cycles 1 through 4.

In the original NDA application, for the highly emetogenic chemotherapy indication, the results for the exploratory endpoints were more supportive of efficacy. It is this Reviewer's opinion that the efficacy results from Study 071 are not sufficiently "robust" to support approval of the requested new indication based on a single study.

The following tables are from the Original NDA.

Table 52
Original NDA
Summary of Efficacy

	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)**	136/260 (52.3)
Acute Phase	231/259 (89.2)**	203/260 (78.1)
Delayed Phase	196 / 260 (75.4)**	145/260 (55.8)
Study 054		
Overall Phase	163 / 260 (62.7)**	114/263 (43.3)
Acute Phase	216 / 261 (82.8)**	180/263 (68.4)
Delayed Phase	176 / 260 (67.7)**	123/263 (46.8)
Complete Protection (no emetic episodes, no rescue therapy, maximum nausea VAS<25)		
Study 052		
Overall Phase	163 / 257 (63.4)**	128 / 260 (49.2)
Acute Phase	217 / 256 (84.8)**	194 / 260 (74.6)
Delayed Phase	172 / 259 (66.4)**	134 / 260 (51.5)
Study 054		
Overall Phase	145 / 261 (55.6)**	107 / 263 (40.7)
Acute Phase	208 / 260 (80.0)**	170 / 263 (64.6)
Delayed Phase	159 / 261 (60.9)**	116 / 263 (44.1)
Total Control (no emetic episodes, no rescue therapy, maximum nausea VAS<5)		
Study 052		
Overall Phase	117/257 (45.5)	104/260 (40.0)
Acute Phase	181/256 (70.7)	167/260 (64.2)
Delayed Phase	127/259 (49.0)	111/260 (42.7)
Study 054		
Overall Phase	116/261 (44.4)**	84/263 (31.9)
Acute Phase	166/261 (63.6)	149/263 (56.7)
Delayed Phase	130/261 (49.8)**	89/263 (33.8)
Ref: Original NDA Review Modified Tables 2 and 3		

** p<0.01 when compared with Standard Therapy
*p<0.05 when compared with Standard Therapy

Table 53
Original NDA
Summary of Efficacy

	Aprepitant Regimen n/m (%)	Standard Therapy n/m (%)
No Use of Rescue Medication		
Study 052		
Overall Phase	210/260 (80.8)**	184/260 (70.8)
Acute Phase	244/259 (94.2)*	231/260 (88.8)
Delayed Phase	211/260 (81.2)*	191/260 (73.5)
Study 054		
Overall Phase	214/260 (82.3)**	191/263 (72.6)
Acute Phase	251/261 (96.2)**	236/263 (89.7)
Delayed Phase	216/260 (83.1)*	195/263 (74.1)
No Significant Nausea (maximum nausea VAS<25)		
Study 052		
Overall Phase	188/257 (73.2)	171/259 (66.0)
Delayed Phase	195/259 (75.3)	178/260 (68.5)
Study 054		
Overall Phase	185/260 (71.2)	168/263 (63.9)
Delayed Phase	189/260 (72.7)	172/263 (65.4)
No Nausea (maximum nausea VAS<5)		
Study 052		
Overall Phase	122 / 257 (47.5)	115 / 260 (44.2)
Delayed Phase	132 / 259 (51.0)	124 / 260 (47.7)
Study 054		
Overall Phase	**127 / 260 (48.8)***	**102 / 263 (38.8)**
Delayed Phase	**137 / 260 (52.7)****	**105 / 263 (39.9)**
Ref: Original NDA Review Modified Table 3		

** p<0.01 when compared with Standard Therapy
*p<0.05 when compared with Standard Therapy

Safety

Study 071 did not identify any concerning safety signals or concerns during Cycles 1 through 4. The safety profile of the aprepitant regimen appears acceptable for use in *female* patients receiving moderate emetogenic chemotherapy regimens used to treat *breast cancer*. There are currently no data on the safety of the aprepitant regimen in other moderately emetogenic chemotherapeutic regimens.

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/s/

Gary DellaZanna
7/18/05 10:35:39 AM
MEDICAL OFFICER

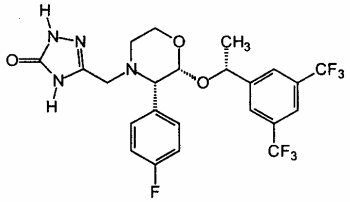
Hugo Gallo Torres
7/18/05 06:27:17 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-549/S-008

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW # 1	1. Organization: HFD-180	2. NDA number: 21-549	
3. Name and Address of Applicant (City & State): Merck & Co., Inc. Sumneytown Pike, P. O. Box 4, BLA-20 West Point, PA 19486		4. AF Number: 5. Supplement(s)	
6. Name of Drug: Emend®	7. Nonproprietary Name: Aprepitant	Numbers	Dates
		SE1-008	9/29/2004
8. Supplement Provides for: Prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.		9. Amendments & Other (Reports, etc.) Dates: None	
10. Pharmacological Category: Antiemetic	11.How Dispensed: RX _X_ OTC	12. Related IND/NDA/DMF(s):	
13.Dosage Form: Capsule	14. Potency: 80 mg, 125 mg		
15. Chemical Name and Structure: 5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one 		16. Records and Reports:	
		Current Yes __ No	
		Reviewed Yes __ No	

17. Comments:

CC: NDA 21-549
HFD-180/Div File/NDA 21-549
HFD-181/BScroggs
HFD-180/RFrankewich
R/D init: LZhou

18. Conclusions and Recommendations:
Recommend that the Regulatory Health Project Manager issue an Approval letter for this supplement.

19.Reviewer

Name:	Signature	Date Completed:
Raymond P. Frankewich, Ph.D.		December 22, 2004

REVIEW NOTES

This supplement contains:

- Efficacy data to support the proposed change;
- Changes to labeling.

The changes to labeling have been reviewed. None of the changes involve CMC information.

However, since the proposed supplement is submitted to qualify a new indication (which may result in more extensive use of this drug), an Environmental Assessment (EA), or a claim for a categorical exclusion from having to submit an EA, may be required. In order to address this, the applicant has submitted the following statement:

Merck is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 C.F.R. §25.31(b). The production of aprepitant meets the requirements of a categorical exclusion under 21 C.F.R. §25.31(b) because the estimated concentration of drug substance at the point of entry, referred to as the Expected Introduction Concentration (EIC) into the aquatic environment will be below 1 part per billion (ppb). The EIC calculation includes all forms and strengths of the drug substance. To Merck's best knowledge no extraordinary circumstances exist in regards to this action.

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/s/

Ray Frankewich
12/22/04 12:44:46 PM
CHEMIST

Liang Zhou
12/22/04 01:26:57 PM
CHEMIST
Betsy: Ray's recommnedation is just from a CMC point of view. So that AP letter should be pending clinical review and recommnedation.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-549/S-008

STATISTICAL REVIEW(S)

NDA#: 21-549/SE1-008

SPONSOR: Merck

NAME OF DRUG: Emend (Aprepitant) Capsules 80 mg/125 mg

INDICATION: Prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy

DOCUMENT REVIEWED: Electronic submission received 7/27/2005.

REVIEWER: Wen-Jen Chen, Ph.D., Statistician

MEDICAL DIVISION: Gastrointestinal and Coagulation Drug Products

STATISTICAL KEYWORDS: Clinical studies; NDA review; Non-inferiority.

Introduction

The purpose of this submission is to respond to the issue of robustness provided by the data from Study 071 raised from the teleconference on July 12, 2005. In this submission, the applicant provides justifications regarding the robustness of the data as well as the post-hoc non-inferiority analysis for the Protocol 071 nausea endpoints (no significant nausea and no nausea). In this review, this reviewer focuses on the justification of the post-hoc non-inferiority analysis.

The applicant applied the logistic regression model, with treatment, investigator, and age group as explanatory variables, to calculate the odds ratios of aprepitant regimen versus standard therapy with respect to the two nausea endpoints (no significant nausea and no nausea). The applicant also calculated the associated confidence intervals. However, instead of calculating 95% two-sided confidence interval as deduced by two one-sided tests with significance level of 2.5% each set for clinical equivalence analysis, the applicant calculated 90% two-sided confidence intervals for odds ratios. The two-sided 90% confidence interval is narrower than that of the two-sided 95% confidence interval and the non-inferiority analysis based upon the 90% two-sided confidence interval calculated by the applicant is therefore not acceptable.

More critically, after superiority of the study drug (aprepitant) to the active-controlled drug (standard) failed for the two nausea endpoints, the non-inferiority margin selected in the post-hoc non-inferiority analysis presented by the applicant in this submission has at least the following statistical issues.

Comments on post-hoc non-inferiority analysis

1.) Loss of credibility on the selection of non-inferiority margin

ICH E10, "Guidance for Industry, E10 choice of Control Group and Related Issues in Clinical Trials", states that 'prior to the trial, an equivalence or non-inferiority margin, sometimes called *delta*, is selected'. This margin is the degree of inferiority of the test treatments to the control that the trial will attempt to exclude statistically. In addition, theoretically, it is always possible to choose a non-inferiority margin leading to a conclusion of non-inferiority if it is chosen after the data have been inspected. Accordingly, the non-inferiority analysis along with its margin should be pre-specified at the protocol stage before conducting the study, to preserve its credibility.

However, noted by this reviewer, only the superiority analyses of aprepitant regimen to standard regimen for the primary, secondary, and exploratory endpoints were planned in the protocol; the non-inferiority analysis along with the associated margin for aprepitant versus standard were not pre-specified in the protocol. Then, after superiority of aprepitant regimen to standard regimen failed for nausea as indicated by the clinical study report, the applicant tries to apply a post-hoc non-inferiority analysis to support the nausea claim in the proposed indication. Since the applicant had already inspected the efficacy data for aprepitant regimen versus standard regimen on nausea, the margin selected is influenced by the efficacy results of the current study (Study# P071). Accordingly, the selected non-inferiority margin is biased in favor of the study drug (aprepitant regimen) and thus, can not be used in assessing the non-inferiority of aprepitant regimen to standard regimen.

2.) Loss of position as confirmatory hypothesis

As indicated by the applicant's submission, NDA 21-549/S-008 was a phase III study to support aprepitant regimen in the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy. It is well known that a phase III study is a confirmatory clinical trial. It means that a phase III study is designed to confirm that aprepitant regimen has efficacy for the proposed indication by testing a pre-specified null hypothesis formulated based upon superiority or non-inferiority setting to answer whether or not the study drug aprepitent is effective to prevent chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy. Therefore, if the applicant decided on applying non-inferiority analysis to confirm that aprepitant regimen is effective for the proposed indication, the inferiority null hypothesis along with its delta margin should have been pre-specified during the protocol stage. In contrast, if the non-inferiority margin is selected after data is examined, not only is the inferiority null hypothesis not formulated before conducting the trial, but also the selected margin is data dependent and is biased. Thus, the inferiority null hypothesis including a margin influenced by data of the current study (Study P071) is a post-hoc hypothesis and can not be considered a confirmatory hypothesis.

3.) Significance level of the non-inferiority analysis inflated

As stated in the above two sections, after un-blinding data codes, the post-hoc non-inferiority margin selected may be directly or indirectly influenced by the examination of the current trial data. As a result, the significance level for testing the null hypothesis of

aprepitant regimen inferior to standard regimen is inflated. For detailed discussion on the issue of the inflation of the significance level, refer to Hung HMJ, and Wang SJ, "Multiple testing of non-inferiority hypotheses in active controlled trials", Journal of Biopharmaceutical Statistics 14(2), 327-335, 2004.

4.) Lack of comparison to historical data in margin selection

ICH E10 emphasized that the margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active drug would be reliably expected to have as compared with placebo in the setting of the planned trial. Identification of the smallest effect size that the active drug would be reliably expected to have is only possible when there is historical evidence of sensitivity to drug effects and, indeed, identification of the margin is based upon that evidence. In addition, the margin should also be identified based on past experience in placebo-controlled trials with adequate design under conditions similar to those planned for the new trial.

However, the applicant selected the post-hoc margin of 0.65 on the odds ratio scale (Aprepitant vs. Standard) based on an approximate 10 percent difference between treatment groups (ie. 45% vs. 55% for aprepitant vs. standard). The 10 percent difference between the two treatment groups determined for the post-hoc non-inferiority margin is chosen without comparing the efficacy of reference drug standard regimen to placebo using historical placebo-controlled trials adequately designed under conditions similar to those planned for the current study (Study P071) as E10 recommended. Accordingly, the post-hoc margin selected in this manner is not acceptable.

Conclusion

In conclusion, from a statistical perspective, since the non-inferiority analysis along with its margin were not pre-specified in the protocol but specified only after examining the current trial data, the validity of the non-inferiority analysis is lost. Accordingly, the results from the post-hoc non-inferiority analysis should not be used to support the proposed indication in any way.

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/s/

Wen-Jen Chen
10/4/2005 12:08:02 PM
BIOMETRICS

Stella Grosser
10/6/2005 04:49:02 PM
BIOMETRICS

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number:	21-549/SE1-008
Drug Name:	Emend (Aprepitant) Capsules 80 mg/125 mg
Indication(s):	Prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy
Applicant:	Merck
Date(s):	Electronic submission received 9/29/2004.
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Wen-Jen Chen, Ph.D. (HFD-715)
Concurring Reviewers:	Stella Grosser, Ph.D. (HFD-715)
Medical Division:	Gastrointestinal and Coagulation Drug Products
Medical Reviewer:	Gary Della'Zanna, MD (HFD-180)
Project Manager:	Betsy Scroggs, Pharm.D. (HFD-180)

Statistical Keywords: Clinical studies; NDA review.

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1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

- ✓ From the statistical perspective, based upon the primary, secondary, and exploratory endpoint analyses, if the medical reviewer does not deem that the two studies (P052 and P054) submitted by the original NDA for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic cancer chemotherapy can be used to support the indication proposed by this NDA supplement then, the single Study P071 does not provide substantial evidence to demonstrate that the aprepitant regimen is superior to the standard therapy in prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy.

  Even if the medical division considers the two previous Studies (P052 and P054) can be used to support the proposed indication of this supplemental NDA, due to lack of enrollment of men, the conclusion of superiority of the aprepitant regimen to the standard therapy shown in women may not be concluded for men.

1.2 Brief Overview of Clinical Studies

- ✓ A single phase III Study P071 is submitted to support the use of aprepitant regimen in the prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. This study was conducted in patients receiving moderately emetogenic chemotherapy. The primary purpose for the study was to confirm that the aprepitant regimen provided superior prevention of moderately emetogenic chemotherapy induced nausea and vomiting compared with a 3 day standard therapy as measured by the proportion of patients with complete response in the 120 hours following the first cycle of chemotherapy (primary endpoint defined in section 3.1).

  This was a worldwide, multi-center, randomized, double-blind, parallel-group study with in-house blinding. Of total 910 patients screened, eight hundred and sixty six (866) patients were randomized to either aprepitant regimen or standard regimen.

1.3 Statistical Issues and Findings

- ✓ The analysis performed by this reviewer using Mantel-Haenszel method with investigator group as stratum indicates that the success rate of complete response in the overall phase for patients treated with the aprepitant regimen is significantly higher than that of the standard therapy.
- ✓ The result from the secondary endpoint (no impact of CINV on daily life) shows that the percentage of patients with total Functional Living Index-Emesis score > 108 for the aprepitant regimen is significantly higher than that of the standard therapy. In addition, the percents of patients with "no impact of CINV on daily life" assessed by three specific

items as well as the overall score in the vomiting domain are significantly higher for the aprepitant regimen than the standard therapy [This is in contrast to the same measures in the nausea domain, where there were no significant differences between aprepitant regimen and standard therapy]. Although the result for the secondary endpoint and its related hypotheses analyzed from this reviewer's multiplicity adjustment is the same as that of the applicant, the multiplicity adjustment schemes between this reviewer and the applicant are different.

- ✓ For the five groups of exploratory endpoints in the classification on page 8 of this review, based upon the multiplicity adjustment strategy proposed by the applicant, the aprepitant regimen is not superior to the standard therapy.
- ✓ It is noted that only two (0.2%) out of 857 patients in the mITT population enrolled in this trial are males. Due to lack of information for men, the conclusion of superiority of the aprepitant regimen to the standard therapy shown in women may not be applied to men. This concern is supported by the efficacy result of males shown by Study P052 submitted by the applicant under original NDA submission dated September 27, 2002 to support the use for prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic cancer chemotherapy. For that study, the complete response rate in the overall phase of the aprepitant regimen was not significantly higher than that of the standard therapy.
- ✓ This reviewer's analysis indicates that none of the investigator group has an unusually high complete response rate in the overall phase for patients treated with apreppitant regimen compare to that of patients treated with standard regimen. Accordingly, one may conclude that the superiority of the aprepitant regimen to the standard therapy assessed by complete response in the overall phase is not dominated by any investigator group.
- ✓ Finally, to conclude that a single study is adequate in support of an effectiveness claim, the guidance for industry (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998) recommends that the efficacy result should be statistically very persuasive. The Guidance emphasizes that in one single study, a very low p-value (for example, 0.00125) indicates the result is highly inconsistent with the null hypothesis of no treatment effect. However, the applicant's two-sided p-value ($p = 0.015$) for the treatment comparison on the complete response in the overall phase is not very low. In addition, from results of the secondary and exploratory endpoint analysis, the efficacy of aprepitant regimen is not better than that of standard therapy assessed by the nausea-specific domain of the secondary endpoint and by the exploratory endpoints.

2.0 INTRODUCTION

2.1 Overview

In the introduction of the clinical study report, the sponsor made the following observations with regard to Aprepitant:

> Many cancer chemotherapeutic agents have the tendency to induce the syndrome of chemotherapy induced nausea and vomiting, especially when administered in combination.

Cisplatin is particularly emetogenic and has been the benchmark agent used for the evaluation of novel antiemetic therapies. In published classification schemes of chemotherapy emetogenicity, a cisplatin dose of >50 mg/m^2 is consistently defined as being representative of highly emetogenic chemotherapy, along with less commonly used agents such as melphalan and dacarbazine.

Aprepitant (also known as L-000754030) is a potent and selective nonpeptide NK1-receptor antagonist with a long duration of action in preclinical models. Aprepitant is metabolized by CYP3A4 and is also an inducer and dose-dependent inhibitor of this enzyme. Aprepitant as administered for chemotherapy induced nausea and vomiting produces moderate CYP3A4 inhibition of orally administered CYP3A4 substrates including midazolam and corticosteroids. Aprepitant is also an inducer of CYP2

A single phase III Study P071 is submitted to support the use of aprepitant regimen in the prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. This study was conducted in patients receiving moderately emetogenic chemotherapy. The primary purpose for the study was to confirm that the aprepitant regimen provided superior prevention of moderately emetogenic chemotherapy induced nausea and vomiting compared with a 3 day standard therapy as measured by the proportion of patients with complete response (primary endpoint defined in section 3.1) in the 120 hours following the first cycle of chemotherapy.

2.2 Data Sources

To assess the clinical efficacy of aprepitant regimen in the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy, this reviewer reviewed electronic NDA supplement (SNDA) submission, dated September 27, 2005. In addition, data used by this reviewer's statistical analysis was submitted by the applicant on December 17, 2004 and located at "\\CDSESUB1\N21549\S 008\2004-12-17".

3.0 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study Design and Endpoints

The primary objectives of the study were to compare the aprepitant regimen and the standard regimen with respect to efficacy and tolerability in the first cycle of chemotherapy.

This was a worldwide, multi-center, randomized, double-blind, parallel-group study with in-house blinding to assess the efficacy and tolerability of aprepitant in the prevention of chemotherapy induced nausea and vomiting during an initial chemotherapy cycle and a multiple cycle extension (maximum of 4 cycles of chemotherapy).

Eligible patients who met the inclusion but not exclusion criteria were randomized to 1 of 2 treatment groups (Table 3.1.1) according to a randomization schedule generated by the applicant. A blocking factor of 4 was used to generate the allocation schedule. Of total 910 patients screened, eight hundred and sixty six (866) patients were randomized to receive either aprepitant regimen or standard regimen.

Table 3.1.1 (Applicant's) Treatment Regimen

Treatment Regimen	Day 1	Days 2 to 3
Aprepitant	Aprepitant 125 mg P.O. Ondansetron 16 mg P.O. Dexamethasone 12 mg P.O. Dexamethasone placebo P.O.	Aprepitant 80 mg P.O. daily Ondansetron placebo P.O. daily (every 12 hours)
Standard	Aprepitant placebo P.O. Ondansetron 16 mg P.O. Dexamethasone 20 mg P.O.	Aprepitant placebo P.O. daily Ondansetron 8 mg P.O. daily (every 12 hours)
P.O. = By mouth.		

During chemotherapy Cycle 1, patients reported episodes of vomiting, use of rescue therapy, and daily nausea assessments in a diary from the initiation of chemotherapy infusion (0 hours) until the morning of Day 6 (~120 hours). After completion of Cycle 1, patients had the option to participate in a multiple-cycle extension for a maximum of 4 cycles if they fulfilled the multiple-cycle enrollment criteria.

During the multiple-cycle phase, the patient diary was used to capture the daily nausea severity assessments for 5 days after the administration of chemotherapy for each cycle that the patient entered. In addition, on Day 6, the patient recorded whether or not any vomiting episodes or nausea occurred since the start of chemotherapy as well as any use of rescue therapy.

The effect of nausea and vomiting on quality of life was assessed using the Functional Living Index-Emesis (FLIE) questionnaire. The FLIE questionnaire is a validated patient-reported measure of the impact of chemotherapy induced nausea and vomiting on daily life. There are 9 items on nausea and 9 items on vomiting on a 7-point scale that are reported as a total score, nausea score, and vomiting score. For the purposes of this study, "No Impact" of chemotherapy induced nausea and vomiting (CINV) on daily life is defined as an average item score of >6 on the 7-point scale (>108 total score).

There were three phases in Cycle 1: overall phase - 0 to 120 hours post-initiation of chemotherapy, acute phase - 0 to 24 hours post-initiation of chemotherapy, and delayed phase - 25 to 120 hours post-initiation of chemotherapy.

The primary efficacy endpoint was the complete response in the overall phase in Cycle 1. Complete response was defined as no vomiting and no use of rescue therapy in the 120 hours following the initiation of chemotherapy in Cycle 1. Then, the secondary endpoint was the proportion of patients with no impact on daily life assessed by FLIE (Functional Living Index –

Emesis) total score > 108 in the overall phase in Cycle 1. The total FLIE score was calculated from at least 12 of the 18 FLIE items (i.e., ≥66% overall item response rate) and both the vomiting and nausea domains must be present to calculate a FLIE total score while the total FLIE domain (vomiting or nausea) score was calculated based upon at least 5 of the 9 FLIE domain items (i.e., >50% overall item response rate).
Finally, the exploratory endpoints analyzed in support of the primary and secondary endpoints were as follows:

- Complete Response in acute and delayed phases;
- No Nausea (peak visual analog scale [VAS] < 5mm) during acute, delayed, and overall phases;
- No Significant Nausea (peak VAS < 25 mm) during acute, delayed, and overall phases;
- Time to first vomiting episode in the overall phase.
- Complete Protection (no vomiting, no rescue therapy, and no significant nausea, i.e., peak VAS < 25 mm) in overall, acute, and delayed phases;
- Total Control (no vomiting, no rescue therapy, and no nausea, i.e., peak VAS < 5 mm) in acute, delayed, and overall phases;
- No Nausea (peak VAS < 5mm) during the 0 to 72 hours time frame;
- No Significant Nausea (peak VAS < 25 mm) during the 0 to 72 hours time frame;
- The frequency of vomiting events during the overall time frame, as assessed by the proportion of patients with more than 3 vomiting episodes during the overall phase.

Statistical Methodologies

Two patient populations were considered for the efficacy analysis: the modified-intention-to-treat (mITT) population and the per-protocol (PP) population. The efficacy analysis using the mITT approach was the primary approach. All patients treated were used for the analysis of safety.

In the overall phase, the mITT population included all patients who had at least a post-treatment assessment on Day 1 and Day 2 after receiving chemotherapy and taking at least 1 dose of study therapy. However, if a patient was a “failure” on any day in Cycle 1, that patient was included in the mITT population for analysis of the overall phase of Cycle 1.

In the acute phase, the mITT population included all patients who had a post-treatment assessment on Day 1 after receiving chemotherapy and taking at least 1 dose of double-blind therapy.

In the delayed phase, the mITT population included all patients who had at least a post-treatment assessment on Day 2 after receiving chemotherapy and taking at least 1 dose of double-blind therapy. However, if a patient was a “failure” on any day in the delayed phase of Cycle 1, that patient was included in the mITT population for analysis.

The per-protocol population excluded those patients who were excluded from the mITT population and those who were identified as protocol violators at baseline or at specific visits.

The applicant emphasized that this population was used to support the primary efficacy analysis only and was considered a secondary approach.
In the primary efficacy analysis of complete response, the treatment comparison was made using a logistic regression model with terms for treatment, investigator group (grouped by region in the U.S., East versus Middle/West, and by country for International), and age category (<55 years, ≥55 years). A two-sided p-value ≤0.05 was considered statistically significant and was used to establish a treatment-related effect in favor of the aprepitant regimen versus the standard regimen.

The comparisons of treatments with respect to the secondary and exploratory binary efficacy variables were made in the same fashion as that described for the primary efficacy analysis using a logistic regression model. For the time to first vomiting (time to failure), Kaplan-Meier curves, depicting the percentage of patients who are free of vomiting since the initiation of chemotherapy, were presented. The Log-Rank test stratifying on investigator group and age category was used for treatment comparison. The time interval for this display was 0 to 120 hours. Patients who discontinued the study before 120 hours prior to a vomiting episode were censored at their time of discontinuation.

For the sample size calculation, the applicant indicated that a total of 820 patients (410 patients per treatment group) were planned to be enrolled in the study to yield a total of 750 evaluable patients with at least one post-treatment evaluation. With 375 evaluable patients per regimen and assuming a true response rate with the standard regimen of 52%, this study would have 80% power to detect the superiority of the aprepitant regimen, if the true aprepitant regimen effect was 10 percentage points (ie., 62%) higher than the standard regimen. If the true difference was 12 percentage points, the power would be 90%.

As for the handling of missing data, the applicant indicated that the patient diary was used during Cycle 1 to collect the data for all vomiting episodes, all use of rescue medication, and a daily nausea assessment during the 5-day period following the initiation of chemotherapy. Then, efficacy endpoints based on the patient diary used only the available data with no imputation of missing data with the exception of the frequency of vomiting episodes.

For the mITT approach for analysis of vomiting frequency by day within Cycle 1, the missing data was imputed by carrying forward the preceding data that are not missing in the delayed phase only. No data in the acute phase was carried forward into the delayed phase. The acute phase represents only one efficacy measurement, so no carrying forward was possible. Within the delayed phase (25 to 120 hours post chemotherapy), carrying forward was done from the preceding non-missing data. If efficacy data were missing on Day 2, no carrying forward was done.

For the multiplicity adjustment, the applicant indicated that there was only one primary hypothesis: the aprepitant regimen would be superior to the standard regimen, as measured by the proportion of patients with complete response in the 120 hours following the first cycle of chemotherapy. Accordingly, no multiplicity adjustment was required.

The primary hypothesis for the secondary endpoint is that the aprepitant regimen would be superior to the standard regimen measured by proportion of patients with no impact on daily life (FLIE total scores > 108) in the overall phase in Cycle 1. Since the primary hypothesis for the secondary endpoint was only tested provided the hypothesis for the primary endpoint was satisfied, this secondary endpoint hypothesis was tested at significance level of 0.05. Following the primary hypothesis for the secondary endpoint, for each of the vomiting and nausea domains, the applicant also tests the domain hypothesis comparing the proportions of patients between aprepitant regimen and standard therapy with FLIE domain total score > 54 (calculated from questions 10 to 18 for vomiting domain and questions 1 to 9 for nausea domain).

If the primary hypothesis for the secondary endpoint was found to be significant ($p<0.05$), treatment differences were evaluated separately for each domain (Nausea, Vomiting) hypothesis. If a domain hypothesis was significant at significance level of 0.05, then three individual items (ability to enjoy a meal, daily functioning, personal hardship) associated with that domain were to be evaluated. Hochberg's procedure was used as a multiplicity adjustment when testing individual items.

Finally, to address multiplicity raised by the exploratory endpoints, a closed testing procedure was employed by grouping the exploratory efficacy endpoints and testing each group of endpoints in a sequential fashion such that subsequent groups of efficacy endpoints would not be tested unless the prior groups each revealed at least one statistically significant finding. Hochberg's procedure was used to adjust for testing the multiple efficacy endpoints within the group to control the type I error at the 0.05 level. The groups of efficacy endpoints are listed below in the order in which they were to be tested:

Group 1

- Complete Response in acute and delayed phases;

Group 2

- No Significant Nausea in the overall phase;
- Time to first vomiting episode in the overall phase;
- Complete Protection (no vomiting, no rescue therapy, and no significant nausea) in overall phase.

Group 3

- No vomiting in the delayed phase;
- No Significant Nausea in the delayed phase;
- Complete Protection in the delayed phase.

Group 4

- No vomiting in the acute phase;
- No Significant Nausea in the acute phase;
- Complete Protection in the acute phase.

Group 5

- Total Control (no vomiting, no rescue therapy, and no nausea, i.e., peak VAS < 5 mm) in acute, delayed, and overall phases;
- No Use of Rescue Therapy in the acute and delayed Phases;
- No Nausea in the 0 to 72 hours time frame;
- No Significant Nausea in the 0 to 72 hours time frame; and
- ≥3 vomiting episodes in the Overall phase.

The exploratory endpoints were only considered for statistical significance provided the primary and secondary hypotheses were satisfied.

Patient Disposition

The applicant indicated that of the total 910 patients screened, 866 patients were randomized: 438 and 428 patients respectively, received aprepitant and standard regimens. The safety population included 866 randomized patients while mITT and PP populations respectively, included 857 (433 in aprepitant and 424 in standard) and 801 patients (404 in aprepitant and 397 in standard).

Table 3.1.1 presents the disposition of Cycle 1 patients.

Table 3.1.1† (Applicant) Overall disposition of patients for Cycle 1

Time Frame	Aprepitant Regimen N=438	Standard Regimen N=428	Total N=866
Cycle 1	**n=438**	**n=428**	**n=866**
Patient discontinued prior to completion of cycle; reason provided below:	8	7	15
Clinical AE	2	1	3
Lack efficacy	3	2	5
Pt. discont. for other	1	0	1
Pt. withdrew consent	1	4	5
Protocol dev.	1	0	1
Patient discontinued after completion of cycle; reason provided below:	45	62	107
Clinical AE	5	5	10
Ineligible	3	7	10
Laboratory AE	2	1	3
Lack efficacy	17	31	48
Noncompliance with Rx	0	1	1
Pt. withdrew consent	16	14	30
Protocol dev.	2	2	4
Refused chemo.	0	1	1
Patient completed and entered next cycle	385	359	744

†: Extracted from the applicant's Table 6-3 at sub-section 6.1.2. of the electronic study report.

Table 3.1.1 indicated that of the 866 patients randomized, 744 (85.9%) patients completed Cycle 1 and continued into Cycle 2. The most common reason for not continuing into Cycle 2 after completion of Cycle 1 of the study was due to lack of efficacy: 17 (3.9%) and 31 (7.2%) of the patients on the aprepitant regimen and standard regimen, respectively. The second most common reason for not continuing into Cycle 2 of the study was withdrawal of consent: 16 (3.7%) and 14 (3.3%) patients on the aprepitant regimen and standard regimen, respectively. There were 8 (1.8%) and 7 (1.6%) patients in the aprepitant regimen and standard regimen, respectively, who discontinued therapy prior to the completion of Cycle 1 with the most common reasons due to withdrawal of consent (5 patients) and due to lack of efficacy (5 patients).

Demographics and Baseline Characteristics

For patients in Cycle 1, the demographic and baseline characteristics (Table 6-8 at sub-section 6.5.1 of the electronic study report) were gender, age, race, type of malignancy, stage of malignancy, history of morning sickness, history of motion sickness, and history of vomiting associated with pregnancy. The applicant indicated that the two treatment groups were generally similar with respect to baseline demographics and characteristics.

Patient age ranged from 23 to 78 years with a mean age of 52.6 years. There were 864 (99.8%) female and 2 (0.2%) male patients. The majority of patients were White (78.6%). Most patients had ductal carcinoma as their type of malignancy (82.3%). In terms of stage of malignancy, a majority of patients were Stage II (57.7%) followed by Stage I (21.8%), Stage IIIa (11.3%), Stage IIIb (5.1%), and Stage IV (3.3%). Most patients had no history of motion sickness (80.9%). There were 30.5% of patients with a history of vomiting associated with pregnancy.

Applicant's Efficacy Analysis Results and Conclusions

The sponsor indicated that of the 438 patients randomized to aprepitant regimen, one did not receive chemotherapy and four had incomplete or no efficacy data while for the 428 patients randomized to standard regimen, 4 had no efficacy data. Therefore, 857 patients were included in the Modified-Intent-to-Treat (mITT) efficacy analyses.

The main focus for the evaluation of efficacy in this clinical study report is Cycle 1 data, for which all mITT efficacy analyses are presented. In addition, a per-protocol analysis is presented for the primary endpoint only.

Primary endpoint analysis

For the primary endpoint analysis, Table 3.1.2 presents the number of patients with complete response by treatment group and phase using mITT patient population. The three phases in Table 3.1.2 were defined as follows: overall phase - 0 to 120 hours post initiation of chemotherapy, acute phase - 0 to 24 hours post initiation of chemotherapy, and delayed phase - 25 to 120 hours post initiation of chemotherapy. The applicant indicated that complete response assessed in acute and delayed phases is deemed as exploratory endpoint. The p-values in Table 3.1.2 are for the efficacy comparisons between aprepitant regimen and standard therapy.

Table 3.1.2 (Applicant's) Complete response† by treatment group and phase using mITT patient population

	Aprepitant Regimen n/m (%)	Standard Therapy n/m (%)	p-Value
Overall Phase	220/433 (50.8)	180/424 (42.5)	0.015*
Acute Phase	327/432 (75.7)	292/423 (69.0)	0.034
Delayed Phase	240/433 (55.4)	208/424 (49.1)	0.064

*: Significant at the two-sided significance level of 0.05 when compared with Standard Therapy using logistic regression model with treatment group, investigator group and age category [<55 year, ≥55 years] as model parameters.
†: Complete Response = No vomiting with no use of rescue therapy;
n/m = Number of patients with desired response/number of patients included in time point.

As seen in Table 3.1.2, the applicant indicated that in the overall phase (the primary endpoint), during the 5 days post-chemotherapy administration, 50.8% of patients in the aprepitant regimen group and 42.5% of the patients in the standard regimen group reported Complete Response. The aprepitant regimen group had statistically significantly higher percentage than the standard regimen group (p=0.015). Note that the unadjusted absolute difference in Complete Response (8.3%) represents a 20% relative improvement. There was no evidence of a treatment by investigator group or treatment by age category interaction.

For the exploratory endpoints of the complete response in the acute and delayed phases, the applicant indicated that after Hochberg multiplicity adjustment, in the acute phase (first 24 hours following chemotherapy administration), the Complete Response rate for the aprepitant regimen (75.7%) was numerically higher (p=0.034; adjusted p= 0.064) than that of the standard regimen (69.0%). A similar result was found in the delayed phase (>24 hours to 120 hours post-

chemotherapy administration): the Complete Response rate for the aprepitant regimen was also numerically higher than that of the standard regimen (55.4% versus 49.1%; p=0.064; adjusted p=0.064).

In addition, the applicant also indicated that at significance level of 0.05, the results from per protocol population analysis on the Complete Response rates were similar to those of the mITT analysis.

Secondary endpoint analysis

Table 3.1.3 presents the results of the secondary endpoint analysis (proportion of patients with total FLIE score > 108) to assess the impact of CINV on daily life. As in the primary endpoint analysis, the logistic regression analysis, adjusted for treatment group, investigator group, and age category (<55 year, ≥55 years), was used to compare the proportions of patients with no impact of CINV on daily life between the two treatment groups.

Table 3.1.2 (Applicant's) Number of patients with no impact of CINV on daily life † by treatment group using mITT patient population

	FLIE Domain or Item Number	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value‡
Primary				
Nausea- and vomiting-specific	Total Score	271/427 (63.5)	229/412 (55.6)	0.019
Secondary				
Vomiting-specific	Vomiting domain	366/427 (85.7)	296/412 (71.8)	<0.001
Vomiting-specific "ability to enjoy daily meal"	Item 13	392/427 (91.8)	325/412 (78.9)	<0.001
Vomiting-specific "daily functioning"	Item 16	394/427 (92.3)	329/413 (79.7)	<0.001
Vomiting-specific "hardship on other people"	Item 18	395/427 (92.5)	330/413 (79.9)	<0.001
Nausea-specific	Nausea domain	229/428 (53.5)	210/416 (50.5)	0.339
Nausea-specific "ability to enjoy daily meal"	Item 4	247/428 (57.7)	228/415 (54.9)	No test performed
Nausea-specific "daily functioning"	Item 7	261/428 (61.0)	234/416 (56.3)	
Nausea-specific "personal hardship"	Item 8	258/428 (60.3)	233/416 (56.0)	

† "No Impact of CINV on Daily Life" is defined as an average item score of >6 on the 7 point scale.
‡ Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group, investigator group, and age category (<55 years, ≥55 years). Shaded cells represent items not tested since the domain score was not statistically significant.
CINV = Chemotherapy-induced nausea and vomiting.
FLIE = Functional Living Index-Emesis.
n/m = Number of patients with "No Impact of CINV on Daily Life"/number of patients included in the analysis of the item.

Table 3.1.2 that as assessed by the FLIE total score, 63.5% of the patients in the aprepitant regimen group reported "no impact on daily life" compared to 55.6% of the patients in the

standard regimen group. The treatment difference was significant (p=0.019). The applicant indicated that since the FLIE total score analysis revealed significant treatment group differences, analyses (proportion of patients with FLIE domain total score > 54) on the vomiting and nausea domains were performed using the same logistic regression model as previously described for the total score.

For the vomiting domain, there were 85.7% of patients in the aprepitant regimen group compared to 71.8% of patients in the standard regimen group with "no impact on daily life" as assessed by the FLIE vomiting-specific domain score. This treatment group difference favoring the aprepitant regimen was statistically significant (p<0.001).

Since the FLIE vomiting-specific domain score revealed a significant treatment group difference, an analysis of the following FLIE vomiting-specific domain questions was performed with adjusting for multiplicity via Hochberg's multiplicity procedure: "ability to enjoy a daily meal" (Item 13), "daily functioning" (Item 16), and "hardship on other people" (Item 18). As with the vomiting-specific domain score, the aprepitant regimen was significantly better than the standard regimen with respect to each of pre-specified FLIE vomiting-specific domain questions (p<0.001): 91.8% versus 78.9% for "ability to enjoy a daily meal", 92.3% versus 79.7% for "daily functioning," and 92.5% versus 79.9% for "hardship on other people," in the aprepitant regimen versus the standard regimen, respectively.

For the nausea domain, there were 53.5% of patients in the aprepitant regimen group compared to 50.5% of patients in the standard regimen group with "no impact on daily life" as assessed by the FLIE nausea-specific domain score. This treatment group difference, numerically favoring the aprepitant regimen, was not statistically significant (p=0.339).

Since the FLIE nausea-specific domain score did not reveal a significant treatment group difference, no test of treatment group differences was performed with respect to the FLIE nausea-specific domain questions.

Exploratory endpoint analysis

The applicant indicated that since the primary and secondary efficacy hypotheses were satisfied, exploratory efficacy endpoints were additionally tested. In order to address multiplicity, a closed testing procedure was employed by grouping the exploratory efficacy endpoints and testing each group in a sequential fashion such that subsequent groups of efficacy endpoints would not be tested unless the prior groups each revealed at least one statistically significant finding. Hochberg's procedure was used to adjust for testing the multiple efficacy endpoints within the group to control the type I error at the 0.05 level. Refer to page 8 of this review for the groups of efficacy endpoints listed in the order in which they were tested.

As indicated in the sub-section for the primary endpoint analysis result, the complete response rates in the acute and delayed phases (exploratory endpoints stated in Group 1) for the aprepitant regimen were not statistically significantly higher than that of the standard regimen. According

to the closed test procedure with the hierarchy structure on the groups of exploratory endpoints, no further testing of the groups of endpoints was done. It followed that for all tested exploratory endpoints, the event rates in aprepitant regimen were not significantly higher than that of standard regimen. In addition, since time to first vomiting episode was categorized in Group 2 and using the multiplicity adjustment technique proposed by the applicant, time to first vomiting episode of aprepitant regimen was not significantly longer than that of standard regimen. All p-values for the analyses of key exploratory endpoints presented by Table 3.1.3 were for summary purposes only.

Table 3.1.3 (Applicant's) Exploratory endpoint event rates in Cycle 1 by treatment group and phase using mITT patient population

	Aprepitant Regimen	Standard Regimen	
	n/m (%)	n/m (%)	p-Value†
Complete Response			
Acute phase (0 to 24 hours)	327/432 (75.7)	292/423 (69.0)	0.034
Delayed phase (25 to 120 hours)	240/433 (55.4)	208/424 (49.1)	0.064
No Vomiting			
Acute phase	378/432 (87.5)	327/423 (77.3)	<0.001
Delayed phase	349/432 (80.8)	293/424 (69.1)	<0.001
No Use of Rescue Therapy			
Acute phase	355/429 (82.8)	336/420 (80.0)	0.366
Delayed phase	271/432 (62.7)	253/423 (59.8)	0.407
No Significant Nausea (maximum VAS <25 mm)			
Overall phase	262/430 (60.9)	236/424 (55.7)	0.116
Acute phase	342/430 (79.5)	331/423 (78.3)	0.699
Delayed phase	281/430 (65.3)	260/423 (61.5)	0.219
0 to 72 hours	274/430 (63.7)	254/424 (59.9)	0.247
No Nausea (maximum VAS <5 mm)			
Overall phase	142/430 (33.0)	140/424 (33.0)	0.903
Acute phase	261/430 (60.7)	250/423 (59.1)	0.730
Delayed phase	159/430 (37.0)	154/423 (36.4)	0.944
0 to 72 hours	167/430 (38.8%)	159/424 (37.5)	0.777
Complete Protection (no vomiting, no rescue and maximum nausea VAS <25 mm)			
Overall phase	184/433 (42.5)	156/424 (36.8)	0.094
Acute phase	296/431 (68.7)	272/423 (64.3)	0.202
Delayed phase	203/433 (46.9)	180/424 (42.5)	0.198
Total Control (no vomiting, no rescue and maximum nausea VAS <5 mm)			
Overall phase	125/433 (28.9)	115/424 (27.1)	0.664
Acute phase	241/431 (55.9)	222/423 (52.5)	0.372
Delayed phase	139/433 (32.1)	132/424 (31.1)	0.862

†: Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group, investigator group, and age category (<55 years, ≥55 years).
n/m = Number of patients with desired response/number of patients included in time point.
VAS = Visual analogue scale.

For the exploratory endpoint event rates, Table 3.1.3 indicated that except for complete response in acute phase and no vomiting in both acute and delayed phases, the p-values for the exploratory endpoint analyses were greater than 0.05. Although after multiplicity adjustments, the aprepitant regimen was not shown to have significantly higher event rates than that of the standard regimen for any of the tested exploratory endpoints, the applicant indicated that the

efficacy of the aprepitant regimen might be supported by the reduction in vomiting when compared to that of the standard regimen.

Statistical Reviewer's Comments and Analysis

In order to validate the sponsor's efficacy claim, this reviewer first performs the efficacy analysis to compare the complete response rates in the overall phase (primary endpoint) between aprepitant regimen and standard therapy by investigator group, using mITT patient population. Then, this reviewer will make comments on the multiplicity adjustment method the applicant applied to the secondary endpoint and on the efficacy of the aprepitant regimen shown by the primary, secondary and exploratory endpoints, declared by the applicant.

Primary endpoint analysis by investigator group

In order to explore whether superiority of the aprepitant regimen to the standard regimen shown by the applicant's primary endpoint (complete response in the overall phase) analysis was dominated by certain investigators, this reviewer first calculates the success rates for the complete response in the overall phase by the investigator group. Then, the reviewer applies Breslow-Day statistic to test the interaction between treatment and investigator group. If the interaction does not show significance, Mantel-Haenszel tests with and without investigator group as the stratum are applied to compare the efficacy between the two drug regimens.

Table 3.1.4 presents the rate of the complete response in the overall phase (primary endpoint) by treatment and investigator group using mITT patient population.

Table 3.1.4 (Reviewer's) Complete response in overall phase by treatment and investigator group using mITT patient population

INVGRP†	TREATMENT	COMP_RSP‡	SUCCESS COUNT	TOTAL ENROLLED	PERCENT
Australia	APREPITANT	SUCCESS	3	8	38.0
	STANDARD	SUCCESS	3	7	43.0
Cannada	APREPITANT	SUCCESS	7	17	41.0
	STANDARD	SUCCESS	9	22	41.0
United Kingdom	APREPITANT	SUCCESS	3	7	43.0
	STANDARD	SUCCESS	2	5	40.0
Germany	APREPITANT	SUCCESS	17	25	68.0
	STANDARD	SUCCESS	11	26	42.0
Spain	APREPITANT	SUCCESS	12	25	48.0
	STANDARD	SUCCESS	11	23	48.0
Italy	APREPITANT	SUCCESS	29	40	73.0
	STANDARD	SUCCESS	22	39	56.0
Hungary	APREPITANT	SUCCESS	12	20	60.0
	STANDARD	SUCCESS	14	20	70.0
Austria	APREPITANT	SUCCESS	6	7	86.0
	STANDARD	SUCCESS	4	7	57.0
Hong Kong	APREPITANT	SUCCESS	8	22	36.0
	STANDARD	SUCCESS	10	22	45.0
Greece	APREPITANT	SUCCESS	3	6	50.0
	STANDARD	SUCCESS	1	3	33.0
US: East	APREPITANT	SUCCESS	56	103	54.0
	STANDARD	SUCCESS	47	103	46.0
US: Middle/West	APREPITANT	SUCCESS	64	153	42.0
	STANDARD	SUCCESS	46	147	31.0

†: Investigator group. ‡: Complete Response.

Table 3.1.4 shows that the for the three investigator groups Australia, Hungary, and Hong Kong , the success rates of complete response for patients treated with aprepitant regimen were numerically lower than that of patients treated with standard therapy. However, Breslow-Day test for heterogeneity across investigato group does not show significance (p=0.81), indicating that the impact of investigator-group effect on treatment efficacy comparison may be ignored. In addition, Table 3.1.4 demonstrates that none of the investigator group has abnormally higher complete response rate in patients treated with apreppitant regimen than that of patients treated with standard regimen. Accordingly, one may conclude that the superiority of the aprepitant regimen to the standard therapy is not dominated by any investigator group.

Since Breslow-Day test does not show that the interaction between treatment and investigator group is significant, in order to explore whether the efficacy result performed by the applicant is sensitive to the analysis methods, Mantel-Haenszel tests with and without investigator group as the stratum are applied to compare the efficacy between aprepitant and standard regimens.

Table 3.1.5 presents the results of efficacy comparisons on the primary endpoint between the aprepitant regimen and standard therapy with and without stratum.

Table 3.1.5 (Reviewer's) Efficacy comparisons on complete response† using mITT patient population

	Aprepitant Regimen n/m (%)	Standard Therapy n/m (%)	p-Value for Mantel-Haneszel Test	
			With Stratum‡	Without Stratum
Overall Phase	220/433 (50.8)	180/424 (42.5)	0.012*	0.014*

*: Significant at the two-sided significance level of 0.05 when compared with Standard Therapy;
†: Complete Response = No vomiting with no use of rescue therapy; ‡: using investigator group as stratum;
n/m = Number of patients with desired response/number of patients included in time point.

Table 3.1.5 indicates that at significance level of 0.05, the success rate of complete response in overall phase for patients treated with aprepitant regimen is significantly lower than that of standard therapy tested by Mantel-Haenszel method (p=0.012 and p=0.014, respectively for using and without using investigator group as stratum). In addition, the three p-values 0.015 (performed by the applicant presented by Table 3.1.2), 0.012, and 0.014 are close to one another, indicating that the superiority of the aprepitant regimen to standard therapy is not affected by different analysis methods.

Comment on the multiplicity adjustment method

Noted by this reviewer, the primary hypothesis for the secondary endpoint (daily quality of life) was that the proportion of patients with no impact on daily life (FLIE total scores > 108) between aprepitant regimen and standard therapy was the same. Then, after the primary hypothesis was rejected, the proportions of patients with total FLIE domain score greater than 54 were compared for the nausea domain and the vomiting domain. Although the proportions of patients with total FLIE score greater than 108 may have some relationships with each of the proportions of patients with the total FLIE domain scores greater than 54, the primary hypothesis that compares the proportions of patients between aprepitant regimen and standard therapy with total FLIE score greater than 108 can not be written as the intersection of the two domain hypotheses that the proportions of patients with the total FLIE domain score greater than 54 between the aprepitant regimen and the standard therapy are the same. Accordingly, the primary hypothesis for the secondary endpoint and the two domain hypotheses do not form a closed family. It follows that the applicant's multiplicity adjustment scheme using 0.05 for testing each domain (Nausea, Vomiting) hypothesis after the primary hypothesis for the secondary endpoint was found to be significant may inflate the overall significance level of 0.05 set for testing the hypotheses associated with secondary endpoint:: the primary hypothesis for the secondary endpoint, two hypotheses formed by the two domains (nausea, vomiting), and the six hypotheses formed by the six items (three items from each domain).

After rejecting the primary hypothesis of the secondary endpoint, in order to preserve the significance level of 0.05 for testing the hypothesis for the intersection of the two domain hypotheses formed by nausea and vomiting domains, Hochberg's procedure is recommended for use as a multiplicity adjustment when testing the two individual domain hypothesis. After multiplicity adjustment, if a domain hypothesis is significant at a level given by Hochberg's procedure, then, the three hypotheses formed by the three individual items (ability to enjoy a meal, daily functioning, and personal hardship) associated with that domain are to be evaluated by Hochberg's multiplicity adjustment procedure at the same significance level used for the

domain hypothesis. Conversely, if a domain hypothesis is not significant at a level given by Hochberg's procedure, then, the three individual items associated with that domain are not to be evaluated.

Based upon the multiplicity scheme recommended by this reviewer, after the primary hypothesis for the secondary endpoint being rejected, the nausea domain hypothesis is not rejected since the p-value ($p=0.339$) for testing the null hypothesis of nausea domain greater than .05. Therefore, the hypotheses related to the three items associated with nausea domain are not to be tested. Then, a significance level of 0.025 is used for testing the null hypothesis of vomiting domain. Since the p-value ($p<0.001$) for testing the null hypothesis of vomiting domain smaller than .025, the vomiting null hypothesis is rejected. Accordingly, the hypotheses for the three items associated with vomiting domain are evaluated at significant level of 0.025 and Hochberg's procedure is employed to adjust the multiplicity induced by testing three hypotheses. Since the p-values of the three item hypotheses associated with the vomiting domain are all less than 0.025, for the three items associated with the vomiting domain, the aprepitant regimen is significantly better than the standard regimen. Although the result for the secondary endpoint and its related hypotheses analyzed using this reviewer's multiplicity adjustment is the same as the result obtained by the applicant, the multiplicity adjustment schemes are different.

For the exploratory endpoint analysis, the applicant first prioritized the groups formed by associated exploratory endpoints. Then, each group of exploratory endpoints was tested in a sequential fashion such that subsequent groups of efficacy endpoints would not be tested unless the prior groups each revealed at least one statistically significant finding. Hochberg's procedure was used to adjust for testing the multiple efficacy endpoints within the group to control the type I error at the 0.05 level. This reviewer agrees with the applicant's multiplicity adjustment technique applied to the exploratory endpoints. However, as the applicant's results showed, no exploratory endpoint was shown significant in favor of aprepitant regimen.

Comment on the issue of Gender

Noted by this reviewer, only two (0.2%) out of 857 patients in the mITT population enrolled in this trial are males. Due to no information provided by males, the superiority of the aprepitant regimen to the standard therapy shown by females may not be applied to males.

In addition, a significant interaction between treatment and gender on the treatment efficacy comparison was shown in Study P052 submitted by applicant under original NDA submission dated September 27, 2002 to support the use for prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic cancer chemotherapy. For that study, the interaction between treatment regimen and gender is significant and the complete response rate for males in the overall phase of the aprepitant regimen was not significantly higher than that of standard therapy.

Since only two males were included in the study, it was not possible to test the interaction between treatment and gender in Study P071. Thus, the concern of interaction between treatment

and gender can not be ruled out. In addition, in light of the result for males shown by Study P052, the complete response rate in the overall phase for males in the aprepitant regimen in study P071 may be shown not significantly higher than that of the standard therapy, had sufficient males enrolled in the study.

Overall comments on the efficacy of Aprepitant Regimen

To conclude that a single study is adequate in support of an effectiveness claim, the guidance for industry (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998) recommends that the efficacy result should be statistically very persuasive. The Guidance emphasizes that in one single study, a very low p-value (for example, 0.00125) indicates the result is highly inconsistent with the null hypothesis of no treatment effect. However, the applicant's two-sided p-value ($p = 0.015$) for the treatment comparison on the complete response in the overall phase is not very low. In addition, from results of the secondary and exploratory endpoint analysis, the efficacy of aprepitant regimen is not better than that of standard therapy assessed by the nausea-specific domain pertaining to the secondary endpoint and by the exploratory endpoints.

Accordingly, based upon the results on the primary, secondary, and exploratory endpoint analyses demonstrated in the single Study P071, if the medical reviewer does not deem that the two studies (P052 and P054) submitted by the original NDA for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic cancer chemotherapy can be used to support the indication proposed by this NDA supplement then, the single Study P071 does not provide substantial evidence to demonstrate that the aprepitant regimen superior to the standard therapy in prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy.

Even if the medical division considers the two previous Studies (P052 and P054) can be used to support the proposed indication by this NDA supplement submission, due to lack of enrollment of men, the conclusion of superiority of the aprepitant regimen to the standard therapy shown in women may not be concluded for men.

3.2 Evaluation of Safety

In cycle 1, clinical adverse experiences were reported by 640 of 866 patients (73.9%) who received study drug or control. Of the 640 patients, three hundred twenty (320) patients (73.1%) in the aprepitant regimen and 320 patients (74.8%) in the standard regimen reported one or more clinical adverse experiences. The overall incidence of clinical adverse experiences was similar between two treatment groups. The most commonly reported clinical adverse experiences in both treatment groups included alopecia, fatigue, and headache. In addition, drug-related clinical adverse experiences (determined by the investigator to be possibly, probably, or definitely study drug related) occurred in 20.6% of patients who received study drug: 21.5% and 19.6% of patients in the aprepitant regimen group and standard regimen group, respectively.

Serious clinical adverse experiences occurred in 3.8% of patients who received study drug: 3.4% and 4.2% of patients in the aprepitant regimen group and the standard regimen group, respectively. Drug-related serious clinical adverse experiences (determined by the investigator to be study drug related) occurred in 2 patients who received study drug: both patients were in the aprepitant regimen group.

Twelve patients (7 patients in the aprepitant regimen group and 5 in the standard regimen group) discontinued study drug therapy due to clinical adverse experiences. Seven patients (0.8%) who received study drug discontinued study drug therapy due to a drug-related clinical adverse experience: 5 patients (1.1%) in the aprepitant regimen group and 2 patients (0.5%) in the standard regimen group. There were 3 patients (0.8%) who were discontinued from study drug therapy due to serious clinical adverse experiences: 1 patient (0.2%) in the aprepitant regimen group and 2 patients (0.5%) in the standard regimen group. One patient in the aprepitant regimen discontinued study drug therapy due to a serious drug related adverse experience. Table 3.2.1 summarizes clinical adverse experience in Cycle 1.

Table 3.2.1 (Applicant's) Summary of clinical adverse experience in Cycle 1

Event Category	Aprepitant Regimen N=438 n (%)	Standard Regimen N=428 n (%)	Difference (95% CI‡)	p-Value§
With one or more adverse experience	320 (73.1)	320 (74.8)	-1.7 (-7.5, 4.1)	0.589
With no adverse experience	118 (26.9)	108 (25.2)		
With drug-related adverse experiences†	94 (21.5)	84 (19.6)	1.8 (-3.6, 7.2)	0.556
With serious adverse experiences	15 (3.4)	18 (4.2)	-0.8 (-3.5, 1.9)	0.597
With serious drug-related adverse experiences	2 (0.5)	0 (0.0)	0.5 (-0.5, 1.6)	
Who died	0 (0.0)	0 (0.0)	0.0 (-0.9, 0.9)	
Discontinued due to adverse experiences	7 (1.6)	5 (1.2)	0.4 (-1.3, 2.2)	0.773
Discontinued due to drug-related adverse experiences	5 (1.1)	2 (0.5)	0.7 (-0.7, 2.2)	
Discontinued due to serious adverse experiences	1 (0.2)	2 (0.5)	-0.2 (-1.5, 0.9)	
Discontinued due to serious drug-related adverse experiences	1 (0.2)	0 (0.0)	0.2 (-0.7, 1.3)	

† Determined by the investigator to be possibly, probably or definitely drug related. ‡ CI = Confidence intervals.
§ p-Values are from Fisher's Exact test. Only shown for prespecified categories.
Aprepitant Regimen = ondansetron 8 mg P.O. twice daily and dexamethasone 12 mg P.O. plus aprepitant 125 mg P.O. on Day 1 and aprepitant 80 mg P.O. once daily on Days 2 to 3.
Standard Regimen = ondansetron 8 mg P.O. twice daily plus dexamethasone 20 mg P.O. on Day 1 and ondansetron 8 mg P.O. twice daily on Days 2 to 3.
P.O. = By mouth.
N = Number of randomized Cycle 1 patients in each treatment group.

4.0 SUBGROUP ANALYSIS

4.1 Gender, Race, and Age

In order to assess the consistency of the treatment effect of the aprepitant regimen relative to the standard therapy across subgroups, this reviewer performs subgroup analysis on the primary endpoint of the complete response in the overall phase based upon mITT patient population. Since more than 87% of mITT patients were under age 65 and over 99% of mITT patients were

females in study P071, the subgroup analyzed is only for Race group (Caucasian vs. Non-Caucasian).

Since the results of Mantel-Haenszel test and the applicant's logistic regression analysis on the primary endpoint analysis are similar, to avoid adjusting for the age group (< 55 versus ≥ 55) used by the applicant as a model parameter in the logistic regression analysis, this reviewer apply Mantel-Haenszel test to compare the treatment effect in the sub-group analysis for Caucasian and Non-Caucasian.

Race group (Caucasian versus Non-Caucasian)

Table 4.1.1 presents the results of treatment efficacy comparisons by Race group (Caucasian versus Non-Caucasian).

Table 4.1.1 (Reviewer's) Complete response in the overall phase using mITT population, by race

	APREPITANT REGIMEN m/n (%)	STANDARD THERAPY m/n (%)	P-VALUE†
Caucasian	179/345 (51.2)	148/328 (45.1)	0.08
Non-Caucasian	41/88 (46.6)	32/96 (33.3)	0.07

†: P-value for Mantel-Haenszel test comparing treatments.

Table 4.1.1 shows that for both Caucasian and Non-Caucasian sub-groups, the percentages of complete response for the aprepitant regimen and standard therapy are only numerically higher than that of the standard therapy (p=0.08 for Caucasian and p=0.07 for Non-Caucasian).

4.2 Other Special/Subgroup Populations- Not applicable

5.0 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

- The analysis performed by this reviewer using Mantel-Haenszel method with investigator group as stratum indicates that the success rate of complete response in the overall phase for patients treated with the aprepitant regimen is significantly higher than that of the standard therapy.
- The result from the secondary endpoint (no impact of CINV on daily life) shows that the percentage of patients with total Functional Living Index-Emesis score > 108 for the aprepitant regimen is significantly higher than that of the standard therapy. In addition, the percents of patients with "no impact of CINV on daily life" assessed by three specific items as well as the overall score in the vomiting domain are significantly higher for the aprepitant regimen than the standard therapy [This is in contrast to the same measures in the nausea domain, where there were no significant differences between aprepitant regimen and standard therapy]. Although the result for the secondary endpoint and its related hypotheses analyzed from this reviewer's multiplicity adjustment is the same as that of the applicant, the multiplicity adjustment schemes between this reviewer and the

applicant are different.

- For the five groups of exploratory endpoints in the classification on page 8 of this review, based upon the multiplicity adjustment strategy proposed by the applicant, the aprepitant regimen is not superior to the standard therapy.
- It is noted that only two (0.2%) out of 857 patients in the mITT population enrolled in this trial are males. Due to lack of information for men, the conclusion of superiority of the aprepitant regimen to the standard therapy shown in women may not be applied to men. This concern is supported by the efficacy result of males shown by Study P052 submitted by the applicant under original NDA submission dated September 27, 2002 to support the use for prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic cancer chemotherapy. For that study, the complete response rate in the overall phase of the aprepitant regimen was not significantly higher than that of the standard therapy.
- This reviewer's analysis indicates that none of the investigator group has an unusually high complete response rate in the overall phase for patients treated with apreppitant regimen compare to that of patients treated with standard regimen. Accordingly, one may conclude that the superiority of the aprepitant regimen to the standard therapy assessed by complete response in the overall phase is not dominated by any investigator group.
- Finally, to conclude that a single study is adequate in support of an effectiveness claim, the guidance for industry (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998) recommends that the efficacy result should be statistically very persuasive. The Guidance emphasizes that in one single study, a very low p-value (for example, 0.00125) indicates the result is highly inconsistent with the null hypothesis of no treatment effect. However, the applicant's two-sided p-value ($p = 0.015$) for the treatment comparison on the complete response in the overall phase is not very low. In addition, from results of the secondary and exploratory endpoint analysis, the efficacy of aprepitant regimen is not better than that of standard therapy assessed by the nausea-specific domain of the secondary endpoint and by the exploratory endpoints.

5.2 Conclusions and Recommendations

- From the statistical perspective, based upon the primary, secondary, and exploratory endpoint analyses, if the medical reviewer does not deem that the two studies (P052 and P054) submitted by the original NDA for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic cancer chemotherapy can be used to support the indication proposed by this NDA supplement then, the single Study P071 does not provide substantial evidence to demonstrate that the aprepitant regimen is superior to the standard therapy in prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy.

  Even if the medical division considers the two previous Studies (P052 and P054) can be used to support the proposed indication of this supplemental NDA, due to lack of enrollment of men, the conclusion of superiority of the aprepitant regimen to the standard therapy shown in women may not be concluded for men.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-549/S-008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-549 S008	Submission Date(s): 9/29/2004
Brand Name	Emend
Generic Name	Aprepitant capsules
Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Gastrointestinal and Coagulation Drug Products
Sponsor	Merck & Co., Inc., West Point, PA 19486
Relevant IND(s)	50,283
Submission Type; Code	Efficacy Supplement ; 505b(1)
Formulation; Strength(s)	Oral capsules; Aprepitant 80 mg and 120 mg
Indication	Prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy

Executive Summary and Recommendation:

The biopharmaceutics submission comprises of a single bioequivalence study conducted to bridge Zofran manufactured in UK, used in the clinical efficacy study #071, with Zofran manufactured in US. The bioequivalence study report and conclusions are acceptable from a Clinical Pharmacology perspective.

Background

The sponsor submitted a single clinical efficacy study # 071 and bioequivalence study #095 in support of proposed indication "Treatment of CINV associated with moderately emetogenic chemotherapy" for Emend. Study # 071 is "A randomized, double-blind, parallel-group study conducted under in-house blinding conditions to determine the efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy". This study was conducted to compare the Aprepitant Regimen and the Standard Regimen with respect to efficacy and tolerability in the first cycle of chemotherapy. Aprepitant Regimen comprised of ondansetron 8 mg P.O. twice daily and dexamethasone 12 mg P.O. plus aprepitant 125 mg P.O. on Day 1 and aprepitant 80 mg P.O. once daily on Days 2 and 3. Standard Regimen comprised of ondansetron 8 mg P.O. twice daily plus dexamethasone 20 mg P.O. on Day 1 and ondansetron 8 mg P.O. twice daily on Days 2 to 3. In order to conduct the study # 071 in double-blind fashion, the active 8-mg U.K. ZOFRAN™ (ondansetron) tablets were over-encapsulated and placebo ondansetron capsules were

made available for the study. Study # 095 was conducted to show bioequivalence between Zofran manufactured in US and over-encapsulated Zofran manufactured in UK.

BE Study Results:

Study # 095 was an open-labeled, single-dose, randomized, 3-period crossover study at a single center to determine the bioequivalence of a clinical trial formulation of ondansetron (an over-encapsulated 8-mg tablet of U.K. ZOFRAN™), a non-U.S. marketed formulation of ondansetron (an 8-mg tablet of U.K. ZOFRAN™), and a U.S. marketed formulation of ondansetron (an 8-mg tablet of U.S. ZOFRAN™) in 12 normal healthy adult male and female subjects 18 to 55 years of age. All subjects participated in all 3 treatment periods. The synopsis of study # 095 is attached to this review. Blood samples were collected over 24 hours following each dose and analyzed employing a validated LC/MS/MS method for plasma ondansetron concentrations at the following time points: 0 (predose); 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, and 24 hours postdose. The tables below indicates the calculated area under the plasma concentration-time curve (AUC0-∞), maximum plasma concentration (Cmax), time to maximum plasma concentration (T_{max}), and terminal half-life ($t_{½}$).

PK Variable	Geometric Mean † For Treatment			Geometric Mean Ratio			90% Confidence Interval for Geometric Mean Ratio			P-Value for Geometric Mean Ratio		
	A	B	**C**	A/B	**A/C**	B/C	A/B	**A/C**	B/C	A/B	**A/C**	B/C
$AUC_{0-\infty}$ (nM•hr)	**644**	712	**649**	0.904	**0.99**	1.096	(0.796, 1.028)	**(0.873, 1.126)**	(0.965, 1.245)	0.19	**>0.25**	0.229
C_{max} (nM)	**82**	93	**86**	0.886	**0.95**	1.073	(0.813, 0.966)	**(0.872, 1.037)**	(0.984, 1.170)	0.026	**>0.25**	0.175

† Least squares estimate for geometric means of AUC and Cmax are based on an ANOVA performed on the natural-log transformed values. Treatments:
A = an over-encapsulated single 8-mg tablet of U.K. ZOFRAN™ (ondansetron) taken P.O.
B = a single 8-mg tablet of ZOFRAN™ (ondansetron) which is marketed in the United Kingdom (U.K.) taken P.O.
C = a single 8-mg tablet of ZOFRAN™ (ondansetron) which is marketed in the United States (U.S.) taken P.O.

From a regulatory perspective, only statistical comparison of treatment groups A and C (in bold) are pertinent to this application. As indicated in the table, both AUC and Cmax of Zofran tablet manufactured in US and Zofran tablet manufactured in UK and over-encapsulated are bioequivalent. The median T_{max} for both the groups A and C was 2 hours.

Drug-Drug interaction potential with moderately emetogenic chemotherapeutic agents

Aprepitant is a moderate CYP3A4 inhibitor *in vivo*. The potential for drug interactions between aprepitant and chemotherapeutic agents metabolized by CYP3A4 was a discussion at the Gastrointestinal Drugs Advisory Committee Meeting on March 6, 2003. As a condition for approval, the sponsor agreed to conduct (Post-Marketing Commitment (PMC) # 1) drug interaction study with docetaxel, a CYP3A4 substrate. The results of the PMC #1 study were previously reviewed (see review attached). Briefly, administration of aprepitant regiment did not alter the pharmacokinetics of docetaxel administered intravenously. Merck submitted a protocol to fulfill PMC#2 "Merck will conduct a drug interaction study to evaluate the effect of aprepitant on either vinorelbine or irinotecan". The sponsor chose to study drug interaction between aprepitant and

vinorelbine. The protocol was reviewed and the study is currently in progress with the report anticipated in the 3rd quarter of 2006. It is noteworthy that both docetaxel and vinorelbine do not qualify as moderate or highly emetogenic chemotherapy according to the Hesketh classification (J Clin Oncol 15:103-109, 1997).

In addition, in a September 4, 2003 pre-NDA meeting the Agency expressed its concern with the potential for drug interaction between cyclophosphamide and aprepitant. In response, the sponsor referred to the data submitted in the original NDA and human clinical data indicating role of CYP2B6 not CYP3A4 in the activation of cyclophosphamide. Previously, data was submitted from *in vitro* drug interaction studies conducted to fulfill PMC # 5 "Merck will submit to FDA a report on the assessment of the inhibitory properties of aprepitant on CYP2C8 and CYP2B6 *in vitro* in human liver microsomes". Following review of this data, it was concluded that aprepitant may not cause CYP2B6 or CYP2C8-inhibition related drug interactions. The sponsor's explanation is adequate to alleviate the above mentioned Agency's concern.

Attachment 1: Synopsis of Study # 095

MERCK RESEARCH LABORATORIES

CLINICAL STUDY REPORT
I. SYNOPSIS

MK-0869
Ondansetron, Over-Encapsulated Tablet/Tablet
Chemotherapy-Induced Nausea and Vomiting (CINV)

PROTOCOL TITLE/NO.: An Open-Label, Randomized, Single-Dose, 3-Period Crossover Study to Determine the Bioequivalence of 3 Formulations of Ondansetron in Healthy Young Adult Male and Female Subjects #095

INVESTIGATOR(S)/STUDY CENTER(S): Howard E. Greenberg, M.D., Thomas Jefferson University Clinical Research Unit - Clinical Pharmacology, Philadelphia, PA

PRIMARY THERAPY PERIOD: 03-Nov-2003 to 17-Nov-2003. The study is complete. The frozen file date was 10-Mar-2004

CLINICAL PHASE: I

DURATION OF TREATMENT: Each subject received each of 3 treatments which consisted of single-dose oral administration of: an 8-mg over-encapsulated U.K. ZOFRAN™ tablet (ondansetron which is marketed in the United Kingdom, GlaxoSmithKline) designated as Treatment A, an 8-mg U.K. ZOFRAN™ (ondansetron) tablet designated as Treatment B, and an 8-mg U.S. ZOFRAN™ tablet (ondansetron which is marketed in the United States) designated as Treatment C. Between each treatment period there was a washout of a minimum of 7 days. The study duration was ~6 weeks.

OBJECTIVE(S): (1) To assess the bioequivalence of a Merck clinical trial formulation of ondansetron (an over-encapsulated 8-mg U.K. ZOFRAN™ tablet) compared to a U.S. marketed formulation of ondansetron (an 8-mg U.S. ZOFRAN™ tablet) as assessed by $AUC_{0-\infty}$ and C_{max}. (2) To assess the bioequivalence of a Merck clinical trial formulation of ondansetron (an over-encapsulated 8-mg U.K. ZOFRAN™ tablet) compared to a non-U.S. marketed formulation of ondansetron (an 8-mg U.K. ZOFRAN™ tablet) as assessed by $AUC_{0-\infty}$ and C_{max}. (3) To compare the plasma concentration profiles of ondansetron following administration of a Merck clinical trial formulation of ondansetron (an over-encapsulated 8-mg U.K. ZOFRAN™ tablet), a non-U.S marketed formulation of ondansetron (an 8-mg U.K. ZOFRAN™ tablet), and a U.S. marketed formulation of ondansetron (an 8-mg U.S. ZOFRAN™ tablet).

STUDY DESIGN: Open-labeled, single-dose, randomized, 3-period crossover study with a washout of at least 7 days between treatment periods.

SUBJECT DISPOSITION:

ENTERED: Total	12
Male (age range)	7 (27 to 41 yrs)
Female (age range)	5 (25 to 33 yrs)
COMPLETED:	12
DISCONTINUED:	0
Clinical adverse experience	0
Laboratory adverse experience	0
Other	0

DOSAGE/FORMULATION NOS.: Treatment A consisted of an over-encapsulated single 8-mg tablet of U.K. ZOFRAN™ (ondansetron) taken P.O.; Treatment B consisted of a single 8-mg tablet of ZOFRAN™ (ondansetron) which is marketed in the United Kingdom (U.K.) taken P.O.; and Treatment C consisted of a single 8-mg tablet of ZOFRAN™ (ondansetron) which is marketed in the United States (U.S.) taken P.O. The order in which the subject received Treatments A, B, and C was determined by a randomized allocation schedule. All subjects participated in all 3 treatment periods.

Study Treatment/Drug Product	PR&D Number	Stock Number./ Lot Number	Clinical Batch (Control) Number	Formulation Number
Treatment A				
Over-encapsulated U.K. ZOFRAN™ (ondansetron) 8-mg tablet	56517	BC-1615	CA-B365	MR-4959
Lactose (b) (4)	56517	BC-1587	NA	NA
(b) (4)	56517	BC-1614	NA	NA
Treatment B				
U.K. ZOFRAN™ (ondansetron) 8-mg tablet	56517	BC-1615	CA-B365	MR-4989
Treatment C				
U.S. ZOFRAN™ (ondansetron) 8-mg tablet (NDC No. 0173-0447-00)	56517	3ZP1267	CA-B365	MR-4986

PR&D = Pharmaceutical Research & Development.
NDC = National Drug Code.
NA = Not Applicable.

DIAGNOSIS/INCLUSION CRITERIA: Healthy, nonsmoking adult males and females between 18 and 55 years of age, within 30% of ideal weight, and who weighed at least 45 kg. Female subjects could not be pregnant or breast-feeding, and female subjects of childbearing potential were required to use specified birth control measures.

EVALUATION CRITERIA: Pharmacokinetic: Blood samples were collected over 24 hours following each dose and analyzed for plasma ondansetron concentrations at the following time points: 0 (predose); 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, and 24 hours postdose Area under the plasma concentration-time curve ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and terminal half-life ($t_{½}$) were calculated. Safety: Physical examinations (including vital signs), laboratory safety tests, and ECG measurements were obtained at prestudy and poststudy. Vital signs (blood pressure and heart rate) were measured at predose, 4, and 24 hours postdose in each period. Pregnancy tests (serum β-hCG) were done in female subjects of childbearing potential at prestudy and poststudy, and a urine pregnancy test was done prior to dosing within each treatment period. Subjects were monitored for adverse experiences throughout the study.

STATISTICAL PLANNING AND ANALYSIS: Power: Assuming a true within-subject variance of 0.0225 for ln-$AUC_{(0-\infty)}$, with n=12 subjects, alpha=.05, and 20 degrees of freedom for error, then there would be 0.93 probability that the 90% confidence interval for the true geometric mean AUC ratio (U.K. over-encapsulated tablet/U.S. tablet) would lie within the bounds (0.80 to 1.25), given that the true geometric mean ratio is 1.0. The probability would be the same for the secondary hypothesis regarding the U.K. over-encapsulated tablet versus the U.K. tablet. Assuming a true within-subject variance of 0.0207 for ln-C_{max}, with n=12 subjects, alpha=.05, and 20 degrees of freedom for error, then there would be 0.94 probability that the 90% confidence interval for the true geometric mean C_{max} ratio (U.K. over-encapsulated tablet/U.S. tablet) would lie within the bounds (0.80 to 1.25), given that the true geometric mean ratio is 1.0. The probability would be the same for the secondary hypothesis regarding the U.K. over-encapsulated tablet versus the U.K. tablet. Methods: Separate analyses were performed for $AUC_{0-\infty}$ and C_{max}. The individual values for each of the 3 treatments (A – U.K. over-encapsulated tablet, B – U.K. tablet, C – U.S. tablet) were natural log-transformed and evaluated in an analysis of variance (ANOVA) model appropriate for a 3-period crossover design. The model contained period and treatment as fixed effects, with subject included as a random effect. A similar model, now with an added factor for carryover, was used to test for the presence of a first-order carryover effect at the α=.05 level. To address the primary hypothesis of bioequivalence of the U.S. tablet and the U.K. over-encapsulated tablet, a two-sided 90% confidence interval for the true mean difference (U.K. over-encapsulated tablet – U.S. tablet) in log-AUC was calculated using the least squares means and the mean square error from the ANOVA and referencing a t-distribution with 20 d.f. These limits were exponentiated to obtain the corresponding 90% confidence interval for the true geometric mean ratio (U.K. over-encapsulated tablet /U.S. tablet). Using similar methods, a two-sided 90% confidence interval was also constructed for the geometric mean ratio of C_{max}. Bioequivalence of the U.S. tablet and the U.K. over-encapsulated tablet was declared if both of these confidence intervals fell within the bounds (0.80, 1.25). To address the secondary hypothesis of bioequivalence of the U.K. tablet and the U.K. over-encapsulated tablet, methodology similar to that used in the testing of the primary hypothesis was employed. Bioequivalence was declared if the 90% confidence intervals for the geometric mean ratios (U.K. over-encapsulated tablet/U.K. tablet) of both $AUC_{0-\infty}$ and C_{max} fell within the bounds (0.80, 1.25). As an exploratory analysis, using methodology similar to that used in the testing of the primary and secondary hypotheses, two-sided 90% confidence intervals were also constructed for the geometric mean ratios (U.K. tablet/U.S. tablet) of $AUC_{0-\infty}$ and C_{max}. Descriptive statistics were provided by treatment for $AUC_{0-\infty}$, C_{max}, T_{max}, and half-life.

RESULTS: Pharmacokinetic: The following is a summary of the plasma pharmacokinetic parameters for ondansetron following single-dose oral administration of an 8-mg over-encapsulated U.K. ZOFRAN™ tablet (Treatment A), an 8-mg U.K. ZOFRAN™ tablet (Treatment B), and an 8-mg U.S. ZOFRAN™ tablet (Treatment C).

Summary of Plasma Pharmacokinetic Parameters of Ondansetron Following Single-Dose Administration of an Over-Encapsulated 8-mg U.K. ZOFRAN™ Tablet, an 8-mg U.K. ZOFRAN™ Tablet, and an 8-mg U.S. ZOFRAN™ Tablet

	Geometric Mean † For Treatment			Geometric Mean Ratio			90% Confidence Interval for Geometric Mean Ratio			P-Value‡ for Geometric Mean Ratio			
PK Variable	A	B	C	A/B	A/C	B/C	A/B	A/C	B/C	A/B	A/C	B/C	MSE§
AUC0-∞ (nM•hr)	644	712	649	0.904	0.991	1.096	(0.796, 1.028)	(0.873, 1.126)	(0.965, 1.245)	0.190	> 0.250	0.229	0.0328
Cmax (nM)	82	93	86	0.886	0.951	1.073	(0.813, 0.966)	(0.872, 1.037)	(0.984, 1.170)	0.026	> 0.250	0.175	0.0150
Tmax (hr)	2.0	1.5	2.0										
Half-life (hr)	5.3	5.4	5.0										

† Least squares estimate for geometric means of AUC and Cmax are based on an ANOVA performed on the natural-log transformed values. Median used in lieu of geometric mean for T_{max} and harmonic mean used in lieu of geometric mean for half-life.

‡ Corresponds to null hypothesis of zero between treatment difference (on the log scale), versus a two-sided alternative.

§ Mean Square Error (MSE) on the natural-log scale.

Treatments

A = an over-encapsulated single 8-mg tablet of U.K. ZOFRAN™ (ondansetron) taken P.O.

B = a single 8-mg tablet of ZOFRAN™ (ondansetron) which is marketed in the United Kingdom (U.K.) taken P.O.

C = a single 8-mg tablet of ZOFRAN™ (ondansetron) which is marketed in the United States (U.S.) taken P.O.

Safety: There were no serious clinical, laboratory, or other adverse experiences and no subjects died during the study. No subject discontinued from the study. Only two (17%) of the 12 subjects reported clinical adverse experiences. One female subject (Alloc. No. 0005) reported a nonserious clinical adverse experience of pruritis rated by the investigator as mild and possibly drug related after administration of the over-encapsulated 8-mg U.K. ZOFRAN™ tablet (Treatment A). One male subject (Alloc. No. 0007) reported a nonserious clinical adverse experience of nasopharyngitis rated by the investigator as mild and probably not drug related during the poststudy period following administration of the over-encapsulated 8-mg U.K. ZOFRAN™ tablet (Treatment A) in Period 3. There were no laboratory adverse experiences.

CONCLUSIONS: (1) The over-encapsulated 8-mg U.K. ZOFRAN™ tablet is bioequivalent to the 8-mg U.S. ZOFRAN™ tablet. (2) Comparison of the over-encapsulated 8-mg U.K ZOFRAN™ tablet to the 8-mg U.K ZOFRAN™ tablet met the established bioequivalence criteria for C_{max}, but failed to meet the established bioequivalence criteria for $AUC_{0-\infty}$.

AUTHORS:

Sabrina Marsilio, B.S. Assoc. Med. Prog. Coord. Clinical Pharmacology	Laura B. Rosen, M.D., Ph.D. Associate Director Clinical Pharmacology	James Kost, Ph.D. Biometrician CBARDS	Xiujiang Li, Ph.D. Sr. Res. Pharmacokineticist Drug Metabolism

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/s/

Srikanth Nallani
6/6/05 09:20:33 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
6/6/05 09:41:40 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-549/S-008

OTHER REVIEW(S)

MEDICAL OFFICER INTER-DIVISION CONSULTATION
DIVISION OF DRUG ONCOLOGY PRODUCTS

NDA #: 21-549/S-008
Letter Date: September 29, 2004
CDER Stamp Date: September 29, 2004
Priority Designation: Standard review
Drug Name: Emend (Aprepitant)
Applicant: Merck & Co., Inc.
Therapeutic Class: NK_1 receptor antagonist
Drug Formulation: Capsule 125/80 mg
Referring Division: Gastroenterology Drug Products (GI), HFD-180
Medical Officer: Gary Della'Zanna, D.O., M.Sc.
Medical Team Leader: Hugo Gallo-Torres, M.D., Ph.D., P.N.S.
Project Manager: Betsey Scroggs, Pharm.D
Consultant: Nancy S. Scher, M.D.
Oncology Medical Team Leader: Ann T. Farrell, M.D.
Consult Log-In Date: August 24, 2005
Consult Completion Date: September 22, 2005
Reason for Consultation: Although the pivotal trial for this NDA met its primary endpoint, the review division was concerned if the results from a single study were sufficiently robust to support approval for the *moderately* emetogenic indication. After internal discussion, the GI division has determined that the efficacy for *highly* emetogenic chemotherapy from the original NDA could be considered supportive to the current application. GI division requests Oncology comment on Questions 1-4 below before taking action on the application.

Proposed Indication: Prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of *moderately* emetogenic cancer (MEC) chemotherapy.

Brief Regulatory History: Aprepitant was approved in March 2003 as a component of a three day, three drug regimen for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) associated with initial and repeat courses of *highly* emetogenic chemotherapy regimens. On September 29, 2004, Merck submitted supplemental NDA 21-549/S-008 for the current proposed indication (see above).

The submission contained a single Phase 3, multicenter, worldwide, randomized, double-blind, parallel-group trial that enrolled patients diagnosed with breast cancer who were scheduled to receive moderately emetogenic chemotherapy. The trial is entitled, "A Randomized, Double-Blind, Parallel-Group Study Conducted Under In-House Blinding Conditions to Determine the Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated with Moderately Emetogenic Chemotherapy (Protocol 071).

Synopsis of Randomized Trial #071

Hypothesis

Primary

- The Aprepitant Regimen will be superior to the Standard Regimen, as measured by the proportion of patients with Complete Response in the 120 hours following the first cycle of chemotherapy (no vomiting and no use of rescue)
- The Aprepitant Regimen and the Standard Regimen will be well tolerated in the first cycle of chemotherapy

Secondary

- The Aprepitant Regimen will be superior to the Standard Regimen, as measured by the proportion of patients with no impact on daily life on the Functional Living Index-Emesis (FLIE) questionnaire in the first cycle of chemotherapy

Treatment Arms

Patients were randomized to receive one of two antiemetic treatment arms, each regimen containing dexamethasone and ondansetron plus either aprepitant or aprepitant placebo.

Treatment Arms

	Day 1	Days 2 to 3
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 8mg PO BID	Aprepitant 80 mg PO Daily Ondansetron placebo PO Daily BID
Standard Therapy	Aprepitant Placebo PO Dexamethasone 20 mg PO Ondansetron 8mg PO BID	Aprepitant Placebo PO Daily Ondansetron 8 mg PO Daily BID

Reviewer comment: The dose of dexamethasone on day one is 40% lower in the aprepitant arm compared with the standard therapy arm. In the "Precautions" Section of the current drug label, it states that aprepitant is "a substrate, a moderate inhibitor, and an inducer of CYP3A4. It is recommended that "oral dexamethasone doses should be reduced by approximately 50% when coadministered with Emend, to achieve exposures of dexamethasone similar to those obtained when it is given without Emed."

Patient population

The patient population included 866 breast cancer patients (438 aprepitant, 428 standard; overall 99.8% female) who were scheduled to have their first course of moderately emetogenic chemotherapy (MEC) which included IV

cyclophosphamide. The patients were required to be naïve to emetogenic chemotherapy (>= Hesketh Level 3). Patients could be treated with one of the following non-cisplatin MEC regimens:

- IV cyclophosphamide (750-1500mg/m2± 5%)
- IV cyclophosphamide (500-1500mg/m2± 5%) and IV doxorubicin (≤60mg/m2± 5%)
- IV cyclophosphamide (500-1500mg/m2± 5%) and IV epirubicin (≤90mg/m2± 5%)

In addition, other chemotherapeutic agents Hesketh Level 2 or lower may be added to the above chemotherapeutic regimens. The study arms were balanced for type of chemotherapy.

Efficacy Measurements

Episodes of vomiting, daily nausea and use of rescue therapy were to be recorded in a patient diary from the start of chemotherapy infusion until the morning of day 6 (hours 0-120). The primary efficacy measure is Complete Response in the overall period, the proportion of patients with No Vomiting and No Rescue Therapy. The FLIE was to be completed for cycle 1.

Results

The following efficacy tables were provided by the primary medical reviewer, Dr. Della'Zanna.

Complete Response
Cycle 1

Phase	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Overall Phase (0 to 120 hours)*	220/433 (50.8)	180/424 (42.5)	0.015
Acute phase (0 to 24 hours)ǂ	327/432 (75.7)	292/423 (69.0)	0.034¥
Delayed phase (25 to 120 hours) ǂ	240/433 (55.4)	208/424 (49.1)	N.S.

Ref: Table 3.1.2 , P071.pdf
* Primary Endpoint
ǂ Exploratory Endpoint
¥ Not Significant after applying the Applicant's multiplicity adjustment
(Confirmed by Agency Statistician, Dr. Wen-Jen Chen, Ph.D.)

Efficacy Outcomes in Overall Phase
Cycle 1

Efficacy Outcome	Aprepitant Regimen %	Standard Regimen %	Treatment Difference	p-Value
Primary Endpoint				
Complete response	**50.8%**	**42.5%**	**8.3%**	**0.015**
Exploratory Endpoints				
No vomiting	**75.7%**	**58.7%**	**17%**	**<0.001**
No rescue therapy	**58.7%**	**56.2%**	**2.5%**	**N.S.**
No nausea (VAS <5 mm)	**33%**	**33%**	**0**	**N.S.**
No significant nausea (VAS <25 mm)	**60.9%**	**55.7%**	**5.2**	**N.S.**

Ref: clinical-overview.pdf Table 2.5:3
N.S.=not significant after applying the Applicant's multiplicity adjustment
(Confirmed by Agency Statistician, Dr. Wen-Jen Chen, Ph.D.)

The applicant met the primary efficacy endpoint, with a significant difference in the proportion of patients with Complete Response, defined as no vomiting and no rescue therapy during the overall phase of 0-120 hours during cycle one of therapy. The FDA analysis also showed that the applicant met the protocol defined secondary endpoint.

The FDA did additional exploratory analyses. When the acute (0-24 hours) and delayed phases (24-120 hours) were evaluated separately, there was no statistically significant difference in Complete Response for either the Acute phase or for the Delayed phase. For the overall phase, the difference in the regimens was statistically significant in favor of aprepitant for no vomiting, but not for other parameters (no rescue, no nausea, no significant nausea).

Questions from GI Division and Responses from Oncology Division

1) Is the active comparator recognized as being effective in the prevention CINV associated with moderately emetogenic chemotherapy?

DDOP Response: Yes.

2) Study 071 succeeded for both the primary and secondary endpoints. Is the Oncology Division concerned that the *exploratory endpoints* for nausea, rescue therapy and complete response in the acute and delayed phase separately failed to differentiate aprepitant from the active comparator?

DDOP Response: No. The trial succeeded in its primary and secondary endpoints. It succeeded dramatically ($p<0.001$) in the important exploratory

endpoint of “no vomiting” in the overall phase. The trial also showed numerical superiority for aprepitant in Complete Response during the Acute phase and for “no significant nausea” overall. The “no nausea” and “no rescue” exploratory endpoints seem less clinically significant than the “no vomiting” endpoint.

3) The results of the exploratory endpoints were not statically significant, but were numerically in favor of aprepitant. Do these results demonstrate a Clinically Meaningful effect, considering the effectiveness of the active comparator?

DDOP Response: Yes. Complete Response and “no vomiting” results were clinically meaningful. The other endpoints were not.

4) Can the results from Study 071 which enrolled >99% female patients, and only evaluated the safety and efficacy of aprepitant in moderately emetogenic chemotherapeutic regimens used to treat breast cancer, be generalizable to all patients receiving moderately emetogenic chemotherapy? If not, can studies in male patients be performed as a Phase IV commitment?

DDOP Response: We do not believe that the results from Study 071 are generalizable. You mention that there is evidence of gender influence in other antiemetic trials. Furthermore, one would expect differences might be observed in outcome with other combinations of chemotherapy and other underlying malignancies. Consider an approval limited to MEC in patients with breast cancer. Future trials should be well-designed, not only as regards gender, but to include a variety of solid tumors and chemotherapy regimens. In view of the potential for drug-drug interactions (with chemotherapy drugs) with aprepitant, its use should not be further generalized without additional trials and PK studies.

Additional Comments

Was the data persuasive regarding efficacy in subsequent cycles since the indication is proposed for initial and repeat courses of MEC chemotherapy?

Nancy S. Scher, M.D.
Medical Reviewer DDOP

Ann T. Farrell, M.D.
Medical Team Leader DDOP

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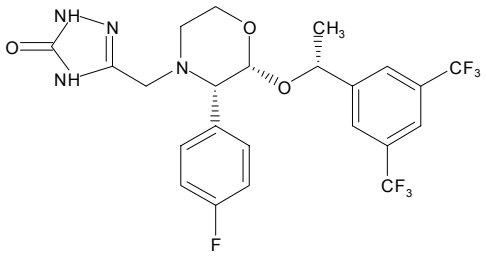
/s/

Nancy Scher
9/23/2005 02:10:09 PM
MEDICAL OFFICER

Ann Farrell
9/23/2005 04:00:51 PM
MEDICAL OFFICER

Oncology Consult

S-NDA 21-549
Aprepitant



S-NDA: 21-549

Chemical Name: Aprepitant

Indication: Prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of *moderately* emetogenic cancer (MEC) chemotherapy.

Medical Officer: Gary Della'Zanna D.O. M.Sc.

Medical Team Leader: Hugo Gallo-Torres M.D., Ph.D., P.N.S.

Project Manager: Betsey Scroggs, Pharm. D.

Background:

Aprepitant was first approved in March 2003 as part of a three day, three drug regimen for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) associated with initial and repeat courses of *highly* emetogenic chemotherapy regimens.

On September 29, 2004, Merck submitted S-NDA 21549/S008 seeking approval for the prevention of (b) (4) nausea and vomiting associated with initial and repeated courses of *moderately* emetogenic chemotherapy. The submission consisted of a single Phase III multicenter, randomized, double-blind, parallel-group trial that enrolled patients diagnosed with breast cancer who were scheduled to receive moderately emetogenic chemotherapy.

Patients were randomly assigned to one of the following two treatment arms: Aprepitant regimen or Standard Therapy regimen.

Table 1
Treatment Arms

	Day 1	Days 2 to 3
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 8mg PO (BID)	Aprepitant 80 mg PO Daily Ondansetron placebo PO Daily (BID)
Standard Therapy	Aprepitant Placebo PO Dexamethasone 20 mg PO Ondansetron 8mg PO (BID)	Aprepitant Placebo PO Daily Ondansetron 8 mg PO Daily (BID)

It was *originally* the Medical Officer's opinion that, although Study 071 succeeded for its primary endpoint, the efficacy results from the *single* study were not sufficiently robust to support approval of the proposed new indication(s), the prevention of (b) (4) *nausea* and *vomiting* associated with initial and repeated courses of moderate emetogenic chemotherapy.

After several internal discussion, regarding whether the Moderate emetogenic indication is related to the Highly emetogenic indication, the Review team agreed that the results from the original NDA could be considered supportive for the current application.

The Division expressed the following concerns regarding the efficacy data.

1. (b) (4) Drugs that were found to be safe and effective for acute phase nausea and vomiting were not necessarily effective during the delayed phase. Study 071 failed to demonstrate that the aprepitant regimen offered any significant advantage over Standard Therapy for Complete Response in the Acute and/or Delayed phase time periods separately.

2. Analyses of all nausea related endpoints failed to differentiate aprepitant from the active comparator.

3. Analyses of the use of rescue therapy endpoints (exploratory endpoints) failed to differentiate aprepitant from the active comparator.

4. Study 071 may not be generalizable to all patients receiving moderately emetogenic chemotherapy. Greater than 99% of the patients enrolled in Study 071 were female. This is an important limitation in the efficacy data. During the original NDA approval for the highly emetogenic indication, a significant treatment-by-gender interaction was identified in one of the two pivotal trials.

The Review team determined that, with the supporting evidence from the original NDA, the S-NDA (Moderately Emetogenic) may be approved, based on the submitted efficacy data. Prior to the regulatory action, the GI Division would like your comments on the following questions.

1) Is the active comparator recognized as being effective in the prevention CINV associated with moderately emetogenic chemotherapy?

2) Study 071 succeeded for both the primary and secondary endpoints. Is the Oncology Division concerned that the *exploratory endpoints* for nausea, rescue therapy and complete response in the acute and delayed phase separately failed to differentiate aprepitant from the active comparator?

3) The results of the exploratory endpoints were not statically significant, but were numerically in favor of aprepitant. Do these results demonstrate a Clinically Meaningful effect, considering the effectiveness of the active comparator?

4) Can the results from Study 071 which enrolled >99% female patients, and only evaluated the safety and efficacy of aprepitant in moderately emetogenic chemotherapeutic regimens used to treat breast cancer, be generalizable to all patients receiving moderately emetogenic chemotherapy? If not, can studies in male patients be performed as a Phase IV commitment?

Consult Aids:

Location of S-NDA:

\\Cdsesub1\n21549\S_008\2004-09-29

Efficacy Assessments Definitions:

Overall Phase:	0 to 120 hours post initiation of chemotherapy
Acute Phase:	0 to 24 hours post initiation of chemotherapy
Delayed Phase:	>24 to ≤120 hours post initiation of chemotherapy
Complete Response:	No emesis, no rescue therapy
No Emesis:	No vomiting or retching or dry heaves (includes patients who received rescue therapy).
No Nausea:	Maximum nausea VAS <5 mm
No Significant Nausea:	Maximum nausea VAS <25 mm
Complete Protection:	No emesis, no rescue therapy, no significant nausea (maximum nausea <25 mm on VAS)
Total Control:	No emesis, no rescue therapy, and no nausea (maximum nausea <5 mm on VAS).

Efficacy Tables from Study 071

Complete Response
Cycle 1

Phase	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Overall Phase (0 to 120 hours)*	220/433 (50.8)	180/424 (42.5)	0.015
Acute phase (0 to 24 hours)[ŧ]	327/432 (75.7)	292/423 (69.0)	0.034[¥]
Delayed phase (25 to 120 hours) [ŧ]	240/433 (55.4)	208/424 (49.1)	N.S.

Ref: Table 3.1.2 , P071.pdf
* Primary Endpoint
ŧ Exploratory Endpoint
¥ Not Significant after applying the Applicant's multiplicity adjustment
(Confirmed by Agency Statistician, Dr. Wen-Jen Chen, Ph.D.)

Efficacy Outcomes in Overall Phase
Cycle 1

Efficacy Outcome	Aprepitant Regimen %	Standard Regimen %	Treatment Difference	p-Value
Primary Endpoint				
Complete response	**50.8%**	**42.5%**	**8.3%**	**0.015**
Exploratory Endpoints				
No vomiting	**75.7%**	**58.7%**	**17%**	**<0.001**
No rescue therapy	**58.7%**	**56.2%**	**2.5%**	**N.S.**
No nausea (VAS <5 mm)	**33%**	**33%**	**0**	**N.S.**
No significant nausea (VAS <25 mm)	**60.9%**	**55.7%**	**5.2**	**N.S.**

Ref: clinical-overview.pdf Table 2.5:3
N.S.=not significant after applying the Applicant's multiplicity adjustment
(Confirmed by Agency Statistician, Dr. Wen-Jen Chen, Ph.D.)

Patients with No Impact of CINV on Daily Life

Phase	FLIE Domain or Item Number	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value*
Protocol Defined Secondary Endpoint				
Nausea and Vomiting Specific	**Total Score > 108**	**271/427 63.5%**	**229/412 55.6%**	**0.019**
Related to Secondary Endpoint				
Vomiting Specific	**Vomiting Domain**	**366/427 85.6%**	**296/412 71.8%**	**<0.001**
"ability to enjoy daily meal"	**Item 13**	**392/427 91.8%**	**325/412 78.9%**	**<0.001**
"daily functioning"	**Item 16**	**394/427 92.3%**	**329/413 79.7**	**<0.001**
"hardship on other people"	**Item 18**	**395/427 92.5%**	**330/413 79.9**	**<0.001**
Nausea Specific	**Nausea Domain**	**229/428 53.5%**	**210/416 50.5%**	**N.S.**
"ability to enjoy daily meal"	**Item 4**	**247/428 57.7%**	**228/416 54.9%**	**Not Tested**
"daily functioning"	**Item 7**	**261/428 61.0%**	**234/416 56.3%**	
"hardship on other people"	**Item 8**	**258/428 60.3%**	**233/416 56.0%**	

Ref: Table 3.1.2
Based on a logistic regression model with terms for treatment group, investigator group, and age category (<55 years, ≥55 years).
Shaded cells items not tested since the domain score was not statistically significant.
CINV = Chemotherapy-induced nausea and vomiting.
FLIE = Functional Living Index-Emesis.
n/m = Number of patients with "No Impact of CINV on Daily Life"/number of patients included in the analysis of the item.

Exploratory Endpoints (Cycle 1)

Exploratory Endpoints	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value
Complete Response			
Acute phase (0 to 24 hours)	327/432 (75.7)	292/423 (69.0)	0.034**
Delayed phase (25 to 120 hours)	240/433 (55.4)	208/424 (49.1)	N.S.
No Vomiting			
Acute phase	378/432 (87.5)	327/423 (77.3)	<0.001**
Delayed phase	349/432 (80.8)	293/424 (69.1)	<0.001**
No Use of Rescue Therapy			
Acute phase	355/429 (82.8)	336/420 (80.0)	N.S.
Delayed phase	271/432 (62.7)	253/423 (59.8)	N.S.
No Significant Nausea (maximum VAS <25 mm)			
Overall phase	262/430 (60.9)	236/424 (55.7)	N.S.
Acute phase	342/430 (79.5)	331/423 (78.3)	N.S.
Delayed phase	281/430 (65.3)	260/423 (61.5)	N.S.
0 to 72 hours	274/430 (63.7)	254/424 (59.9)	N.S.
No Nausea (maximum VAS <5 mm)			
Overall phase	142/430 (33.0)	140/424 (33.0)	N.S.
Acute phase	261/430 (60.7)	250/423 (59.1)	N.S.
Delayed phase	159/430 (37.0)	154/423 (36.4)	N.S.
0 to 72 hours	167/430 (38.8%)	159/424 (37.5)	N.S.
Complete Protection (no vomiting, no rescue and maximum nausea VAS <25 mm)			
Overall phase	184/433 (42.5)	156/424 (36.8)	N.S.
Acute phase	296/431 (68.7)	272/423 (64.3)	N.S.
Delayed phase	203/433 (46.9)	180/424 (42.5)	N.S.
Total Control (no vomiting, no rescue and maximum nausea VAS <5 mm)			
Overall phase	125/433 (28.9)	115/424 (27.1)	N.S.
Acute phase	241/431 (55.9)	222/423 (52.5)	N.S.
Delayed phase	139/433 (32.1)	132/424 (31.1)	N.S.

Ref: Table 3.1.3, Statistical Review
†: Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group
** Not statically significant after adjusting for multiplicity
VAS = Visual analogue scale.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gary DellaZanna
8/17/2005 03:13:07 PM
MEDICAL OFFICER

Hugo Gallo Torres
8/17/2005 04:24:50 PM
MEDICAL OFFICER

STUDY ENDPOINT REVIEW

ACTION TRACKING NUMBER	2005.002.A.00092
APPLICATION TYPE	NDA
SUBMISSION NUMBER	21-549
SUBMISSION CODE	Serial Submission SEI 008
SUBMISSION EPOCH	NDA
LETTER DATE	June 14, 2005
STAMP DATE	Not available
PDUFA GOAL DATE	
DATE OF CONSULT REQUEST	April 1, 2005
REVIEW DIVISION	HFD 180
MEDICAL TEAM LEADER	Gary Della'Zanna
REVIEW DIVISION PM	Betsy Scroggs
SEALD REVIEWER	Laurie Burke
REVIEW COMPLETION DATE	July 21, 2005
ESTABLISHED NAME	aprepitant
TRADE NAME	EMEND®
THERAPEUTIC CLASS	Antiemetic
APPLICANT	Merck
PRIORITY DESIGNATION	S
ENDPOINT(S) CONCEPT(S)	Impact of chemotherapy-induced nausea and vomiting (CINV) on daily functioning
INSTRUMENT(S)	Functional Living with Emesis (FLIE)
FORMULATION	Oral
DOSING REGIMEN	**Day 1 post-chemotx:** Aprepitant 125 mg; ondansetron 8 mg x 2 doses; dexamethasone 12 mg **Days 2 to 3 post-chemotx:** Aprepitant 80 mg QD
INDICATION	Prevention of (b) (4) nausea and vomiting associated with initial and repeated courses of moderately emetogenic cancer chemotherapy
INTENDED POPULATION(S)	Patients receiving moderately emetogenic chemotherapy

STUDY ENDPOINT REVIEW

Table of Contents

1 EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Gastrointestinal and Anti-coagulation Drug Products (HFD-180) regarding the adequacy of the Functional Living with Emesis (FLIE) questionnaire with 5-day recall as a secondary endpoint measure of the impact of EMEND® (aprepitant) treatment on chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately emetogenic chemotherapy. Based on a review of the validation documentation, study report and data analysis plan for the 071 protocol submitted in NDA 21-549 /SEI0008 [1] and other documents, (b) (4) The presentation of FLIE-vomiting domain scores in labeling may be considered.

2 RECOMMENDATIONS ON REGULATORY ACTION

Section 2 provides responses to the Review Division's questions and recommendations for advice to provide to the Sponsor regarding the adequacy of the endpoints the Sponsor proposes to use to support the desired indication.

1. Is the FLIE QOL considered validated to the Agency's Standards? Merck used the FLIE in the original NDA as "supportive" for the primary and secondary endpoints, therefore it does not appear in the label.

   SEALD Response:

   The FLIE was used to support statements in the approved EMEND label. The Clinical Studies section of the approved labeling is quoted below:

   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%).*

   For the study design and indication referenced here, the FLIE was found to be a valid and reliable measure of nausea and vomiting for studies in patients undergoing highly emetogenic chemotherapy.

2. In the current submission (**moderately** emetogenic chemotherapy), Merck intends to use it as the only secondary endpoint. Is the quality of the questionnaire sufficient to be the basis of an approval and appear in the label?

SEALD Response: Even though the FLIE is the "only secondary endpoint," it is important to note that the FLIE is a composite measure with several scores that could represent multiple

endpoint possibilities. (b) (4) We would not object to the presentation of FLIE-vomiting domain scores in labeling. These positions are based on the following observations:

a. In general, we do not recommend that patient-reported outcome instruments require patients to summarize their experience over long periods of time as this introduces recall errors and difficulty interpreting responses. The preferred approach for episodic events like nausea and vomiting is to have patients report in real time or daily as was done in the survey study by O'Brien et al. Merck's published validation of the 5-day recall version of the FLIE presents evidence of construct and convergent validity and reliability comparing FLIE results to the number of vomiting episodes and nausea ratings in a 5-day daily diary. (See Martin et al.) We are less inclined to challenge a 5-day recall period for "memorable" events like vomiting than we would be for less succinct symptoms like nausea.
b. (b) (4)
c. Presentation of the FLIE vomiting domain results in labeling may be supported but only if presented in the context of "no effect" on the nausea domain. If the Division decides to include FLIE results in labeling, we recommend that the labeling explains the results in terms of the concept measured ("the impact vomiting on daily living") rather than to present results in the context of the measurement instrument (i.e., reporting FLIE scores only).
d. (b) (4)

3. Merck included Reference material to show the questionnaire is validated. In the Reference, it appears the FLIE was administered/evaluated on Day 3 (not sure). In this submission the questionnaire was administered at Day 6. If this is a validated tool..... is it acceptable that the questionnaire was administered on Day 6. What effect will that have on the results?

SEALD Response: See response to question #2.

4. In the submission Merck defined a value of 108 as representing "No Impact" on life. Is there evidence to support this statement? Is this validated?

SEALD Response: Current labeling for EMEND describes a FLIE score of 108 as evidence of "minimal or no impact of nausea and vomiting on the patients life". Data supporting the 108 FLIE is based on baseline scores. However, results from the 071 study raise questions about the appropriateness of this cut-point because no significant differences were observed between treatments for the nausea subscale of the FLIE. This suggests that the total scores reflect differences between treatments that are due to emesis only.

5. Against the Division's recommendations, Merck submitted only one Study to support this new indication.

SEALD Response: The fact that only one study is available to support these findings raises questions about whether substantial evidence has been provided to support the desired labeling language. Statements based on a PRO (primary or secondary endpoints) require substantial evidence to support labeling or advertising claims. The substantial evidence requirements apply equally to the primary and secondary endpoints. However, the studies that supported the original approval may be considered confirmatory evidence.

6. There is only one primary endpoint and one secondary endpoint.

SEALD Response: Please elaborate on your concern. It is not clear how the number of endpoints affects the adequacy of the FLIE data.

3 APPENDICES

3.1 Functional Living with Emesis (5-day recall version used in Protocol 071)

An example of the FLIE proposed for Protocol 071 as a measure of the impact of CINV on daily functioning is provided on the following pages.

CYCLE 1 - TREATMENT (DAY 6)

FLIE2-5

Compound	Protocol	Study Site	IIN	VISIT	Patient's/Subject's ID	Baseline No.	Allocation No.
MK-0869	071-00			3			

Investigator's name:	Staff's initials:	Date:

CYCLE 1 - TREATMENT (DAY 6)

FLIE3-5

Compound	Protocol	Study Site	IIN	VISIT	Patient's/Subject's ID	Baseline No.	Allocation No.
MK-0869	071-00			3			

CYCLE 1 - TREATMENT (DAY 6)

FLIE4-5

Compound	Protocol	Study Site	IIN	VISIT	Patient's/Subject's ID	Baseline No.	Allocation No.
MK-0869	071-00			3			

CYCLE 1 - TREATMENT (DAY 6)

FLIE5-5

Compound	Protocol	Study Site	IIN	VISIT	Patient's/Subject's ID	Baseline No.	Allocation No.
MK-0869	071-00			3			

4 REFERENCES

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/s/

Laurie Burke
7/22/05 10:37:49 AM
INTERDISCIPLINARY

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-549 Supplement # 008 Efficacy Supplement Type SE- 1

Trade Name: Emend
Established Name: aprepitant
Strengths: Capsule, 80 mg and 125 mg

Applicant: Merck and Company
Agent for Applicant: N/A

Date of Application: 9/29/2004
Date of Receipt: 9/29/2004
Date clock started after UN: N/A
Date of Filing Meeting: 11/03/2004
Filing Date: 11/28/2004
Action Goal Date (optional): 7/28/2005 User Fee Goal Date: 7/29/2005

Indication(s) requested: The prevention of chemotherapy induced nausea and vomiting (CINV) associated with moderately emetogenic chemotherapy (MEC).

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 6
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the*

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: Emend was approved 3/26/2003 at 80 mg and 125 mg as NCE with an Exclusivity Expiry of 3/26/2008

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☒

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? All parts except the paper certifications.

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 3 Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☐ NO ☒

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 50283

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 9/04/2003 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☐ YES ☐ NO ☒

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☒

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☐ YES ☒ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☒

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☒
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/03/2004

BACKGROUND: NDA 21-549 for Emend (aprepitant) Capsules, 80 mg and 125 mg was approved as an NME on 3/26/2003. Emend is approved for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy, including high dose cisplatin.

The link is provided below.
Application: N021549 Document: 2620698 Location: \\CDSESUB1\N21549\S_008\2004-09-29

This application, SE1-008 provides to expand the indication to include the prevention of chemotherapy induced nausea and vomiting (CINV) associated with moderately emetogenic chemotherapy (MEC). A pre-sNDA meeting was held 9/04/2003. Studies were conducted under IND 50,283. The firm seeks approval with the submission of 1 large multicenter study Protocol # 071: "A Randomized, Double-Blind, Parallel-Group Study Conducted Under In-House Blinding Conditions to Determine the Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated With Moderately Emetogenic Chemotherapy (Protocol 071).

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Joyce Korvick, Hugo Gallo-Torres, Gary Della'Zanna, Stella Grosser, Wen Jen Chen, Jasti Choudary, Sushanta Chakder, Ray Frankewich, Srikanth Nallani

ASSIGNED REVIEWERS (including those not present at filing meeting) : Jasti Choudary, Supervisory Pharmacologist, Liang Zhou, Chemistry Team leader, Suresh Doddapaneni, Biopharmaceutics Team leader.

Discipline	**Reviewer**
Medical:	Gary Della'Zanna
Secondary Medical:	Hugo Gallo-Torres, MOTL
Statistical:	Wen Jen Chen
Pharmacology:	Sushanta Chakder
Statistical Pharmacology:	NA
Chemistry:	Ray Frankewich
Environmental Assessment (if needed):	NA
Biopharmaceutical:	Srikanth Nallani
Microbiology, sterility:	NA
Microbiology, clinical (for antimicrobial products only):	NA
DSI:	NA
Regulatory Project Management:	Betsy Scroggs
Other Consults:	DDMAC, DSRCS

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO ☒

- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A ☒	FILE ☐	REFUSE TO FILE ☐
STATISTICS	N/A ☐	FILE ☒	REFUSE TO FILE ☐
BIOPHARMACEUTICS		FILE ☒	REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY	N/A ☐	FILE ☒	REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☒

CHEMISTRY		FILE ☒	REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Microbiology YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: Supplements involving labeling will be acted on before this action. After S-009 action taken, firm will submit a final updated draft label with all previously approved changes.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Betsy Scroggs, Pharm.D.
Regulatory Project Manager, HFD-180

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   ***NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

    - Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

      YES ☐ NO ☐

    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

      YES ☐ NO ☐

    - EITHER

      The number of the applicant's IND under which the studies essential to approval were conducted.

      IND# _____ NO ☐

      OR

      A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

      YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

    YES ☐ NO ☐

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Betsy Scroggs
6/22/05 02:24:22 PM
CSO

STUDY ENDPOINT REVIEW

ACTION TRACKING NUMBER	2005.002.A.00049
APPLICATION TYPE	NDA
SUBMISSION NUMBER	21-549
SUBMISSION CODE	Serial Submission SEI 008
SUBMISSION EPOCH	NDA
LETTER DATE	September 29, 2004
STAMP DATE	Not available
PDUFA GOAL DATE	Not stated
DATE OF CONSULT REQUEST	April 1, 2005
REVIEW DIVISION	HFD 180
MEDICAL TEAM LEADER	Gary Della'Zanna
REVIEW DIVISION PM	Betsy Scroggs
SEALD REVIEWER	Jane Scott
REVIEW COMPLETION DATE	April 29, 2005
ESTABLISHED NAME	aprepitant
TRADE NAME	EMEND®
THERAPEUTIC CLASS	Antiemetic
APPLICANT	Merck
PRIORITY DESIGNATION	S
ENDPOINT(S) CONCEPT(S)	Impact of chemotherapy-induced nausea and vomiting (CINV) on daily functioning
INSTRUMENT(S)	Functional Living with Emesis (FLIE)
FORMULATION	oral
DOSING REGIMEN	**Day 1 post-chemotx:** Aprepitant 125 mg; ondansetron 8 mg x 2 doses; dexamethasone 12 mg **Days 2 to 3 post-chemotx:** Aprepitant 80 mg QD
INDICATION	Prevention of (b) (4) nausea and vomiting associated with initial and repeated courses of moderately emetogenic cancer chemotherapy
INTENDED POPULATION(S)	Patients receiving moderately emetogenic chemotherapy

STUDY ENDPOINT REVIEW

Table of Contents

1 EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Gastrointestinal and Anti-coagulation Drug Products (HFD-180) regarding the adequacy of the Functional Living with Emesis (FLIE) questionnaire as a measure of the impact of chemotherapy-induced nausea and vomiting (CINV) on daily functioning in patients receiving moderately emetogenic chemotherapy and antiemetic regimens containing EMEND® (aprepitant). The review of the study report and data analysis plan for the 071 protocol submitted in NDA 21-549 /SEI0008 [1] and other documents noted the following concerns:

1. Merck submitted data from a single well-controlled study to support claims based on the FLIE. A single study is generally considered inadequate to meet regulatory requirements for substantial evidence to support statements in labeling or advertising. However, we would support the Division if it considers that the studies in the original approval for use of Emend with highly emetogenic chemotherapy provides confirmatory evidence of the current study under review.

2. The proposed revisions to the EMEND® product label based on the 071 protocol for the indication in moderately emetogenic chemotherapy states that there was a higher proportion of patients with "minimal or no impact of nausea or vomiting on daily life." Analysis of the FLIE vomiting scale found that patients receiving EMEND® were significantly more likely to report scores that could be described as "minimal or no impact of vomiting on daily life". However the FLIE *nausea* scale did not differ between treatments in the 071 study. The statements proposed for the revised label would give the false impression that aprepitant significantly improves both nausea and vomiting outcomes. There are several options to address this concern:

    a. To support the proposed language ("minimal or no impact of nausea or vomiting on daily life") the sponsor would need to provide data confirming that significantly more patients receiving EMEND®-containing regimens had a score of 6 or more for all items in the nausea scale AND the vomiting scale of the FLIE.

    b. Labeling statements could be revised to "minimal or no impact of vomiting on daily life" based on analyses presented and (b) (4)

    c. Labeling statements could be revised to describe impact of vomiting and nausea separately being careful to not imply that nausea went away completely.

Throughout this document, hypertext references to documents reviewed are noted in brackets [ ].

Conclusions and recommendations are based on the sources available for review. The Sponsor provided limited information for review. Additional information readily retrieved from PubMed also was reviewed, when available, to better understand the development and validation of the proposed endpoint measures.

2 RECOMMENDATIONS ON REGULATORY ACTION

Section 2 provides responses to the Review Division's questions and recommendations for advice to provide to the Sponsor regarding the adequacy of the endpoints the Sponsor proposes to use to support the desired indication.

1. Is the FLIE QOL considered validated to the Agency's Standards? Merck used the FLIE in the original NDA as "supportive" for the primary and secondary endpoints, therefore it does not appear in the label.

SEALD Response:

The FLIE has been used to support statements in the approved EMEND label as noted below.

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%). (from page 7 of the approved EMEND label in Clinical Studies section]*

For the study design and indication referenced here, the FLIE was found to be a valid and reliable measure of nausea and vomiting for studies in patients undergoing highly emetogenic chemotherapy.

2. In the current submission, Merck intends to use it as the only secondary endpoint. Is the quality of the questionnaire sufficient to be the basis of an approval and appear in the label?

SEALD Response: FLIE is an adequate PRO assessment to support statements regarding the impact of nausea/vomiting on the daily lives of patients on chemotherapy if properly implemented in the protocol. The implementation of the FLIE in the 071 protocol follows recommended standards for adequate and well controlled studies, including pre-specification of study endpoints and adequate control for multiple comparisons.

3. Merck included Reference material to show the questionnaire is validated. In the Reference, it appears the FLIE was administered/evaluated on Day 3 (not sure). In this submission the questionnaire was administered at Day 6. If this is a validated tool..... is it acceptable that the questionnaire was administered on Day 6. What effect will that have on the results?

SEALD Response: The FLIE was originally developed to assess the impact of chemotherapy-induced nausea and vomiting (CINV) on patients' daily lives over the 3 days following

chemotherapy. More recent studies of CINV include assessments covering the 5 days following chemotherapy in an effort to capture information during both the acute (within 24 h) and delayed (up to 5-7 days) phases of CINV.[2,3] The published validation of the 5-day recall version of the FLIE examines discriminant validity and does not address construct validity, recall errors or other concerns raised by extending the recall.[2] This study did not compare the original 3-day recall version of the FLIE to the 5-day recall version nor did it confirm that patients summarized experiences over a time period that spans days 1 through 5 post chemotherapy.

In general, we would not recommend that patient-reported outcome instruments require patients to require and summarize long period of time as this would introduce recall errors and difficulty interpreting responses. The preferred approach would have been to have patients report daily as was done in the survey study by O'Brien et al. [4]

The developer of the FLIE indicated in a telephone conversation that Merck has conducted studies to document that validity of the 5-day recall for the FLIE. The one published validation study on the validity of the 5-day recall version does not address the issues of recall directly. We recommend that the Division request that Merck submit evidence that the 5-day recall version of the FLIE provides a valid and reliable measure of the impact of CINV on the daily lives of patients receiving chemotherapy.

4. In the submission Merck defined a value of 108 as representing "No Impact" on life. Is there evidence to support this statement? Is this validated?

SEALD Response: Current labeling for EMEND describes a FLIE score of 108 as evidence of "minimal or no impact of nausea and vomiting on the patients life". Data supporting the 108 FLIE is based on baseline scores patients have reported prior to initiating chemotherapy and supportive antiemetic treatment. However, results from the 071 study raise questions about the appropriateness of this cut-point based on the total score. No significant differences were observed between treatments for the nausea subscale of the FLIE. This suggests that the total score reflect differences between treatments that are due to emesis only. It would be misleading to state that there was "minimal or no impact of nausea and vomiting on daily life" if there was no corresponding difference between treatments for the FLIE nausea scale. The sponsor may choose to remove references to nausea from the statements in the label or provide analysis demonstrating that a significantly greater proportion of patients receiving EMEND® had item scores of ≥ 6 for all items in both the nausea and the vomiting scale to confirm a "minimal effect of nausea and vomiting on daily life".

5. Against the Division's recommendations, Merck submitted only one Study to support this new indication.

SEALD Response: The fact that only one study is available to support these findings raises questions about whether substantial evidence has been provided to support the desired labeling language. Statements based on a PRO (primary or secondary endpoints) require substantial evidence to support labeling or advertising claims. The substantial evidence requirements apply equally to the primary and secondary endpoints. However, the studies that supported the original approval may be considered confirmatory evidence.

6. There is only one primary endpoint and one secondary endpoint.

SEALD Response: Please elaborate on your concern. It is not clear how the number of endpoints affects the adequacy of the FLIE data.

3 BACKGROUND

3.1 Proposed Indication and Supporting Endpoints

"EMEND, in combination with other antiemetic agents, is indicated for the prevention of (b) (4) nausea and vomiting associated with initial and repeat courses of

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

3.2 Related Products

Ondansetron, granisetron

3.3 Pre-submission Endpoint Activity

SEALD provided consultation on earlier submissions for EMEND regarding adequacy of the FLIE to support labeling statements about the impact of aprepitant on the daily functioning of patients receiving highly emetogenic chemotherapy. The approved product label for EMEND states:

> *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%).

4 ENDPOINT-RELATED DOCUMENTATION REVIEWED

This section describes the methods used for the SEALD review of the FLIE and review notes for each instrument based on documents reviewed.

4.1 Endpoint Review Methodology

The methodology used to review and respond to the Division's questions regarding the adequacy of the FLIE for evaluating the impact of antiemetic therapy on daily functioning of patients on chemotherapy involved the following five steps:

1) review submitted questions from the Review Division
2) review NDA submitted by the Sponsor
    a. identify the desired claim or indication associated with each proposed endpoint

   b. review past research the Sponsor proposes as evidence of the appropriateness of the proposed endpoint instruments
3) review medical officer's review of protocols
4) review key articles to evaluate the adequacy of the endpoint's
   a. development
   b. measurement properties (reliability, validity, ability to detect change, how to interpret scores)
   c. translations and adaptations
   d. how the instrument has performed in other studies

4.2 Endpoint Review Notes: Functional Living with Emesis (FLIE) Questionnaire as a measure of the impact of CINV on daily functioning of chemotherapy patients

A description of the Functional Living Index-Emesis (FLIE), and the SEALD review notes follow. The FLIE, a patient-reported outcome measure, was originally developed to assess the impact of chemotherapy-induced nausea and vomiting (CINV) on patients' daily lives over the 3 days following chemotherapy. More recent studies of CINV include assessments covering the 5 days following chemotherapy in an effort to capture information during both the acute (within 24 h) and delayed (up to 5-7 days) phases of CINV.[2,3] Some evidence of the validity of a 5 day recall has been published [2]. Other trials also have used the 5-day recall version of the FLIE [3]

Dimensions covered by the questionnaire: Nausea (9 items); Vomiting (9 items)
Time for completion: 10 min
Age range: Adults
Scoring:
Response options: Visual Analog Scale (VAS) graduated from 1 to 7
Available scores:
Total score: Minimum score: 18; Maximum score: 126;
Scores by dimension: Minimum score: 9; Maximum score: 63
Score direction: Higher score = better QoL
Minimal Important Difference (MID): Not evaluated
A scoring and interpretation manual is available from the developer (Celeste Lindley)

4.2.1 Endpoint Development and Validation

Prior SEALD consults found adequate evidence to support the use of the FLIE as a measure of the impact of nausea and vomiting the daily lives of patients receiving highly emetogenic chemotherapy.

Among the studies available to document the validity of the FLIE, a particularly interesting one is a 5-day prospective survey of patients receiving chemotherapy for cancer in five centers in Canada collected data with the FLIE as a daily diary.[4] On the day of chemotherapy 38 of the 92 patients (41%) experienced emesis with or without nausea, and over the 5 days of the survey 72 patients (78%) reported at least one episode of nausea or emesis. The absolute risk of either problem decreased over time, but the risk of nausea relative to emesis increased over time. The FLIE scores indicated significant worsening of functional status after chemotherapy. On the day

after treatment the main impact was from emesis, particularly with regard to leisure activities, household tasks and hardship to the family. As seen in other studies of health-related quality of life, nausea was found to have a significantly greater impact than emesis on overall functioning. This study provides some further evidence of the value of the FLIE for understanding the impact of CINV and demonstrates that daily assessments with the FLIE using a 24 hour recall provide more detailed understanding of the impact of antiemetic treatment for CINV.

A substudy of the 017 trial evaluating the validity of the FLIE using a 5-day recall period was published in the European Journal of Cancer in 2003.[2] Using daily dairies the study collected number of vomiting episodes per day, a daily VAS for nausea severity, and rescue medications. Prior to initiating chemotherapy and on day 6 after chemotherapy, patients completed the FLIE (5-day recall version). For each item in the FLIE, item scores > 6 were classified as evidence of "no impact on daily life" (NIDL). Sum of the 9 nausea items (nausea scale) and the 9 vomiting items (vomiting scale) are added to create a total score. For the scales and total score, NIDL was defined as an average item score of > 6 (> 56 for the scales; > 118 for the total score). Analyses compared the proportion of patients with NIDL two treatment groups receiving aprepitant containing regimens at two dosing levels and a third group receiving standard therapy without aprepitant. Results reported for the nausea scale, the vomiting scale, the total score, and for each item of the FLIE. Patients receiving the higher dose regimen of aprepitant (identical to the 071 study dose) were more likely to be classified as NIDL than standard therapy without aprepitant for all FLIE items, for both the nausea and the vomiting scale scores and for the total score.

Comments:

1. The 5-day version of the FLIE may not be a valid assessment of what patients experienced over the 5-days post chemotherapy. Published validation of the 5-day recall version of the FLIE focuses on discriminant validity and does not address construct validity, recall errors or other concerns raised by extending the recall. [2] The validation study did not compare the original 3-day recall version of the FLIE to the 5-day recall version.
2. Concerns regarding the validity of the 5-day FLIE [2] are not about biased conclusions about treatment effectiveness because the 071 study was a randomized, active-control trial. The change in recall period applies equally to both groups and is not expected to differentially affect treatment groups in the study.
3. A 3-day recall focuses on the period when the majority of patients are most likely to experience vomiting and severe nausea whereas the 5-day recall asks patients to summarize experiences that span high nausea and vomiting risk immediately post chemotherapy with lower risk of both symptoms occurring 5 days after chemo. Compared with the 3-dau FLIE, the 5-day FLIE is more likely to reflect the patient's **current** experience than to summarize experience over the five day period. Studies have shown that people tend to respond based on their current status even when asked to summarize over the past several days. Part of this is a cognitive bias associated with blurry memory and part is because it is hard to summarize highly disparate experiences. A daily diary would be the best way to capture the variability in CINV and its impact on patients' functioning. that is A validation study to confirm that the 5-day FLIE provides a valid summary of both acute and longer-term CINV would need to have patients complete a daily diary version of the FLIE, then administer the 3-day recall and

5-day recall version of the FLIE to see how those responses compare with the trajectory of daily FLIE scores.

4. The daily diary version of the FLIE with its 24-hour recall [4] would have been preferable, if there was evidence to confirm the modifications to the 3-day recall FLIE did not alter the validity of the daily FLIE.

4.2.2 Endpoint Translation and Adaptation

An adapted version of the FLIE that permits 5-day recall was used in the current submission for EMEND. A study by

Comments:

- Evidence for the validity of the 5-day recall version of the FLIE focuses on construct validity. [2]

4.2.3 Endpoint Interpretation

The Division questions the proposed cut-point of 108 as evidence of minimal or no impact of emesis on daily functioning.

Research in 43 patients undergoing bone marrow transplantation who were randomized to receive either i.v. granisetron or oral granisetron were asked to complete the FLIC and the FLIE concurrently upon admission to the hospital and post chemotherapy. This study provides some additional confirmation of the interpretation of scores of ≥ 108 as evidence of minimal or no impact of CINV in that mean scores prior to chemotherapy were at 108 and went down following chemotherapy (as would be expected based on the scoring of the FLIE). However, the article did not explain the recall period referenced in the version of the FLIE used (3-day or 5-day). See table 1 below

Table 1. Descriptive Statistics of the FLIC and FLIE Scores: HRQoL Scores and Distributions for the Evaluable Patients

In an earlier study of 115 patients receiving either ondansetron and granisetron for the treatment of CINV, there was evidence based on the 3 day recall version of the FLIE that a score of 108 may reflect limited impact of CINV on patients' lives.[5]

Immediately before and 72 hours after chemotherapy, each patient rated his or her reaction to the FLIE. The occurrence of nausea in the granisetron group was 40.0% compared with 43.2% in the ondansetron group; the occurrence of vomiting was 18.8% in the granisetron group and 11.1% in the ondansetron group. Patients who received highly emetogenic chemotherapy had significantly lower scores on the FLIE after chemotherapy than before. Patients with both nausea and vomiting reported a much higher negative impact on functional status after chemotherapy than those with nausea only. The mean pre-chemotherapy and post-chemotherapy FLIE scores were 124.2 and 110.4 for granisetron and 124.9 and 111.9 for ondansetron. Both the pre and post chemotherapies scores exceeded 108, on average, in this population treated with approved antiemitic therapies.

Comments:
These findings suggest a higher score for "no impact" would be needed but the caveat of "minimal impact" may be adequately covered and already was approved in a more toxic regimen.

4.2.4 Endpoint Implementation in the 071 Protocol

Protocol 017 was a multicenter, randomized, double-blind, parallel-group, controlled trial with in-house blinding to assess the safety and efficacy of the Aprepitant Regimen in the prevention of CINV in patients diagnosed with breast cancer who will be treated with a non-cisplatin MEC regimen. Both male and female patients with breast cancer and no history of emetogenic chemotherapy use are eligible for this study. Patients in each treatment group were instructed to take a daily dose of study drug for the 3-day period according to the following blinded treatment regimens:

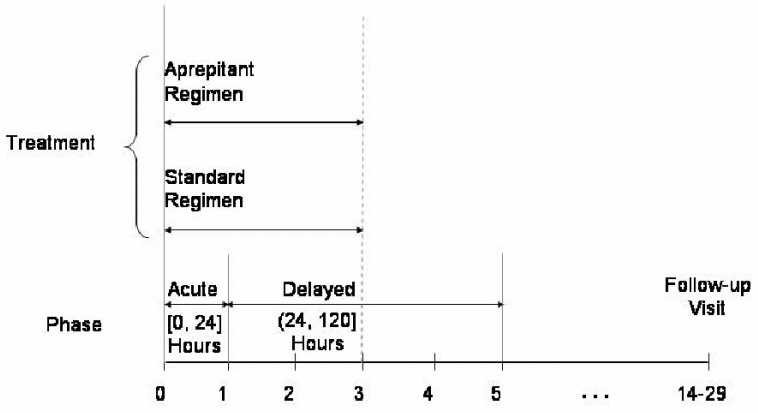
Table 1

Study Medication Schedule

Regimen (N)	Study Medication	Day 1		Day 2		Day 3	
		Bottle	Dose	Bottle	Dose	Bottle	Dose
Aprepitant (375)	Aprepitant	A	125 mg capsule	D	80 mg capsule	D	80 mg capsule
	Ondansetron 8 mg	B	1 capsule 30 to 60 minutes prior to chemotherapy; 1 capsule 8 hours after first dose	E	1 placebo capsule every 12 hours	E	1 placebo capsule every 12 hours
	Dexamethasone 4 mg	C	3 tablets + 2 placebo tablets				
Standard (375)	Aprepitant	A	125 mg placebo capsule	D	80 mg placebo capsule	D	80 mg placebo capsule
	Ondansetron 8 mg	B	1 capsule 30 to 60 minutes prior to chemotherapy; 1 capsule 8 hours after first dose	E	1 capsule every 12 hours	E	1 capsule every 12 hours
	Dexamethasone 4 mg	C	5 tablets				

Figure 1

Treatment and Phase Within a Cycle



On Days 4 and 5, measurements were taken, but no treatment given. The treatment was administered to the patients in a double-blinded manner during Cycles 1 through 4.

Patients were treated with IV cyclophosphamide and many also received other I.V. chemotherapies, most commonly, doxorubicin (68.9%), fluorouracil (30.1%), or epirubicin (29.8%).

The effect of nausea and vomiting on quality of life was assessed using the FLIE questionnaire in protocol 071. The 9 items regarding the effects of nausea and 9 items about the impact of vomiting, each of which are rated on a 7-point scale for severity over the past five days, are reported as a total score, nausea score, and vomiting score. Page 19 of the study report for 071 describes the interpretation of the FLIE in this protocol:

> *"For the purposes of the 071 study, "No Impact" of chemotherapy induced nausea and vomiting on daily life is defined as an average item score of >6 on the 7-point scale (>108 total score)."*

The data analysis plan further describes the scoring and hypotheses regarding the FLIE in this protocol as follows:

> *Each domain score and total score are calculated using an algorithm defined in detail in Section VI.D of this DAP. For this study, "No Impact of CINV on Daily Life" is defined as an average score >6 on the 7-point scale (i.e., >108 total score or >54 domain score). The following variables will be used for analysis:*
>
> - *FLIE total score >108 (Questions 1 to 18),*
> - *FLIE vomiting total score >54 (Questions 10 to 18),*
> - *Daily functioning score >6 (Question 16)*
> - *Ability to enjoy a meal score >6 (Question 13)*
> - *Personal hardship score>6 (Question 17)*
> - *FLIE nausea total score >54 (Questions 1 to 9),*
> - *Daily functioning score >6 (Question 7)*
> - *Ability to enjoy a meal score >6 (Question 4)*
> - *Personal hardship score >6 (Question 8)*

A modified ITT population was prespecified in the DAP as all patients who had at least a post-treatment assessment on Day 1 and Day 2 after receiving chemotherapy and took at least 1 dose of double-blind therapy. Patients were counted in the treatment group to which they were randomized. However, if a patient was a "failure" on any day in Cycle 1, that patient was included in the MITT population for analysis of the overall phase of Cycle 1.
A closed testing procedure was employed to control for multiplicity. The data analysis plan specified this as follows:

> *As the secondary hypothesis will only be tested provided the primary efficacy hypothesis is satisfied (i.e., closed testing), the FLIE total score will be tested at the α=0.05 level. If the total score is found to be significant at the α =0.05 level, further analyses will be done to determine the exact nature of the significant*

difference. The following approach will be taken to ensure that the overall α =0.05 level is maintained for the secondary hypothesis:

If the FLIE total score is significant ($p \leq 0.05$), treatment differences will be evaluated separately for each domain (Nausea, Vomiting) total score, and (if significant, $p \leq 0.05$, for a domain) for 3 individual items for each domain (ability to enjoy a meal, daily functioning, personal hardship). Hochberg's [3] procedure will be used as a multiplicity adjustment when testing individual items. The procedure requires ranking the p-values from largest to smallest, and, if the largest p-value $p \leq 0.05$, all comparisons for the individual items will be considered statistically significant. Otherwise, if the second largest p-value $\leq$ 0.025, all comparisons with smaller p-values will be considered statistically significant. This process continues until the i_{th} largest p-value $\leq 0.05/i$ is met or all p-values are determined to be not statistically significant.

The following text and table from pages 23-25 of the 071 clinical study report summarizes the results of the analysis of the post chemotherapy day 6 assessment of the FLIE as well as data from the daily diary assessments for nausea, vomiting, and rescue therapy use.

Table 7-6

Number (%) of Patients With "No Impact of CINV on Daily Life[†]"
by Treatment Group—Cycle 1
(Modified Intention-to-Treat Population)

	FLIE Domain or Item Number	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value[‡]
Primary				
Nausea- and vomiting-specific	Total Score	271/427 (63.5)	229/412 (55.6)	0.019
Secondary				
Vomiting-specific	Vomiting domain	366/427 (85.7)	296/412 (71.8)	<0.001
Vomiting-specific "ability to enjoy daily meal"	Item 13	392/427 (91.8)	325/412 (78.9)	<0.001
Vomiting-specific "daily functioning"	Item 16	394/427 (92.3)	329/413 (79.7)	<0.001
Vomiting-specific "hardship on other people"	Item 18	395/427 (92.5)	330/413 (79.9)	<0.001
Nausea-specific	Nausea domain	229/428 (53.5)	210/416 (50.5)	0.339
Nausea-specific "ability to enjoy daily meal"	Item 4	247/428 (57.7)	228/415 (54.9)	No test performed
Nausea-specific "daily functioning"	Item 7	261/428 (61.0)	234/416 (56.3)	
Nausea-specific "personal hardship"	Item 8	258/428 (60.3)	233/416 (56.0)	

Table 7-6 shows the proportion of patients with no impact of CINV on daily life by treatment group for the Cycle 1 mITT population. Logistic regression analysis, adjusted for treatment group, investigator group, and age category (<55 year, ≥ 55 years), was used to determine statistical significance of the treatment difference. As assessed by the FLIE total score, 63.5% of the patients in the Aprepitant Regimen group reported "no impact on daily life" compared to 55.6% of the patients in the Standard Regimen group. The treatment difference was significant (p=0.019) [4.1; 4.3]. Since the FLIE total score analysis revealed significant treatment group differences, an analysis of the FLIE Domains was performed using the same logistic regression model as previously described for the total score.

Table 7-17 summarizes the primary and secondary efficacy findings (including exploratory results) from protocol 071. Section 7.4 of the study report summarizes the findings as follows:

Table 7-17 displays a summary of key efficacy results for the Cycle 1 mITT population. The Aprepitant Regimen was shown to be significantly superior to the Standard Regimen with respect to the primary and secondary endpoints of patient reported Complete Response 0 to 120 hours post-chemotherapy and "no impact on daily life" as assessed by the FLIE questionnaire, respectively. The vomiting component of the primary and secondary endpoints showed the greatest treatment difference between the Aprepitant Regimen and the Standard Regimen. It is noteworthy that the Aprepitant Regimen yielded numerically greater efficacy in every endpoint measured in the study.

Table 7-17

Number (%) of Patients With Favorable Response in Cycle 1
by Treatment Group and Phase (Modified-Intention-to-Treat Analysis)

	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value[†]
Primary Efficacy Endpoint to Address Primary Hypothesis			
Complete response (no vomiting and no use of rescue therapy) in the 0 to 120 hours following chemotherapy	220/433 (50.8)	180/424 (42.5)	0.015
Components of Primary Efficacy Endpoint			
No vomiting	327/432 (75.7)	249/424 (58.7)	<0.001
No use of rescue therapy	253/431 (58.7)	237/422 (56.2)	0.480
Secondary Efficacy Endpoint to Address Secondary Hypothesis			
No impact on daily life (FLIE Total)	271/427 (63.5)	229/412 (55.6)	0.019
Components of Secondary Efficacy Endpoint			
Vomiting domain	366/427 (85.7)	296/412 (71.8)	<0.001
"ability to enjoy daily meal"	392/427 (91.8)	325/412 (78.9)	<0.001
"daily functioning"	394/427 (92.3)	329/413 (79.7)	<0.001
"hardship on other people"	395/427 (92.5)	330/413 (79.9)	<0.001
Nausea domain	229/428 (53.5)	210/416 (50.5)	0.339
Exploratory Endpoints			
Complete Response			
Acute phase (0 to 24 hours)	327/432 (75.7)	292/423 (69.0)	0.034
Delayed phase (25 to 120 hours)	240/433 (55.4)	208/424 (49.1)	0.064
No Vomiting			
Acute phase	378/432 (87.5)	327/423 (77.3)	<0.001
Delayed phase	349/432 (80.8)	293/424 (69.1)	<0.001
No Use of Rescue Therapy			
Acute phase	355/429 (82.8)	336/420 (80.0)	0.366
Delayed phase	271/432 (62.7)	253/423 (59.8)	0.407
No Significant Nausea (maximum VAS <25 mm)			
Overall phase	262/430 (60.9)	236/424 (55.7)	0.116
Acute phase	342/430 (79.5)	331/423 (78.3)	0.699
Delayed phase	281/430 (65.3)	260/423 (61.5)	0.219
0 to 72 hours	274/430 (63.7)	254/424 (59.9)	0.247
No Nausea (maximum VAS <5 mm)			
Overall phase	142/430 (33.0)	140/424 (33.0)	0.903
Acute phase	261/430 (60.7)	250/423 (59.1)	0.730
Delayed phase	159/430 (37.0)	154/423 (36.4)	0.944
0 to 72 hours	167/430 (38.8%)	159/424 (37.5%)	0.777
Complete Protection (no vomiting, no rescue and maximum nausea VAS <25 mm)			
Overall phase	184/433 (42.5)	156/424 (36.8)	0.094
Acute phase	296/431 (68.7)	272/423 (64.3)	0.202
Delayed phase	203/433 (46.9)	180/424 (42.5)	0.198

MK-0869 Prot. No. 071
Aprepitant to Prevent Nausea and Vomiting in Patients Receiving Moderately Emetogenic Chemotherapy
-25-

Table 7-17 (Cont.)

Number (%) of Patients With Favorable Response in Cycle 1 by Treatment Group and Phase (Modified-Intention-to-Treat Analysis)

	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value†
Total Control (no vomiting, no rescue and maximum nausea VAS <5 mm)			
Overall phase	125/433 (28.9)	115/424 (27.1)	0.664
Acute phase	241/431 (55.9)	222/423 (52.5)	0.372
Delayed phase	139/433 (32.1)	132/424 (31.1)	0.862

† Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group, investigator group, and age category (<55 years, ≥55 years). The p-values reported for exploratory endpoints are for summary purposes only.
Aprepitant Regimen = ondansetron 8 mg P.O. twice daily and dexamethasone 12 mg P.O. plus aprepitant 125 mg P.O. on Day 1 and aprepitant 80 mg P.O. once daily on Days 2 and 3.
Standard Regimen = ondansetron 8 mg P.O. twice daily plus dexamethasone 20 mg P.O. on Day 1 and ondansetron 8 mg P.O. twice daily on Days 2 to 3.
n/m = Number of patients with desired response/number of patients included in time point.
VAS = Visual analogue scale.

Data Source: [4.1; 4.3]

4.2.5 Endpoint Conclusions

1. Merck has conducted studies to document that validity of the 5-day recall for the FLIE. The information on the validity of a 5-day recall for the FLIE should be submitted so we can confirm it. The one published validation study does not address the issues of recall. We should ask Merck to provide reports from their internal studies conducted to confirm the adequacy of the 5-day recall version of the FLIE.

2. The implementation of the FLIE in the 071 protocol follows recommended standards for adequate and well controlled studies, including pre-specification of study endpoints and adequate control for multiple comparisons.

3. Reliance on the (b) (4) may be misleading if both nausea and vomiting do not improve significantly with treatment. It appears that nausea did not improve significantly with aprepitant therapy (no significant difference between groups) in the 071. Although FLIE vomiting scores and total scores improved, the nausea scores did not improve significantly. This raises questions about claims that minimal or no impact of CINV was demonstrated in the 071 protocol. If significant nausea remains for many patients (as appears to be the case), the statements proposed for the revised label would be misleading; they would give the false impression that aprepitant improves both nausea and vomiting outcomes.

4. In general, we are not recommending sponsors to extend recall periods more than a couple of days. The preferred approach would have been to have patients report daily as was done in the survey study by O'Brien et al. [4]

5. The fact that only one study is available to support these findings raises questions about whether substantial evidence has been provided to support the desired labeling language. But this concern may be eliminated if the studies in the original approval are considered confirmatory evidence of a treatment benefit.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

CYCLE 1 - TREATMENT (DAY 6)

FLIE2-5

Compound	Protocol	Study Site	IIN	VISIT	Patient's/Subject's ID	Baseline No.	Allocation No.
MK-0869	071-00			3			

Investigator's name:	Staff's initials:	Date:

CYCLE 1 - TREATMENT (DAY 6)

FLIE3-5

Compound	Protocol	Study Site	IIN	VISIT	Patient's/Subject's ID	Baseline No.	Allocation No.
MK-0869	071-00			3			

CYCLE 1 - TREATMENT (DAY 6)

FLIE4-5

Compound	Protocol	Study Site	IIN	VISIT	Patient's/Subject's ID	Baseline No.	Allocation No.
MK-0869	071-00			3			

CYCLE 1 - TREATMENT (DAY 6)

FLIE5-5

Compound	Protocol	Study Site	IIN	VISIT	Patient's/Subject's ID	Baseline No.	Allocation No.
MK-0869	071-00			3			

6 REFERENCES

[1] \\Cdsesub1\n21549\S_008\2004-09-29\clinstat\studies

[2] Martin AR, Pearson JD, Cai B, Elmer M, Horgan K, Lindley C. Assessing the impact of chemotherapy-induced nausea and vomiting on patients' daily lives: a modified version of the Functional Living Index-Emesis (FLIE) with 5-day recall. Support Care Cancer. 2003 Aug;11(8):522-7. Epub 2003 Jun 25

[3] Glaus A, Knipping C, Morant R, Bohme C, Lebert B, Beldermann F, Glawogger B, Ortega PF, Husler A, Deuson R. Chemotherapy-induced nausea and vomiting in routine practice: a European perspective. Support Care Cancer. 2004 Oct;12(10):708-15.

[4] O'Brien BJ, Rusthoven J, Rocchi A, Latreille J, Fine S, Vandenberg T, Laberge F. Impact of chemotherapy-associated nausea and vomiting on patients' functional status and on costs: survey of five Canadian centres. CMAJ. 1993 Aug 1;149(3):296-302.

[5] Farley PA, Dempsey CL, Shillington AA, Kulis-Robitaille C, Colgan K, Bernstein G.Patients' self-reported functional status after granisetron or ondansetron therapy to prevent chemotherapy-induced nausea and vomiting at six cancer centers. Am J Health Syst Pharm. 1997 Nov 1;54(21):2478-82.

drafted	4/28/05 js
concur	4/29/05 lb

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/s/

Jane A. Scott
4/29/05 05:38:38 PM
UNKNOWN

Laurie Burke
5/2/05 03:19:40 PM
INTERDISCIPLINARY

Sandra L. Kweder
5/12/05 09:46:45 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: February 2, 2005

TO: Joyce Korvick, M.D., Acting Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

VIA: Betsy Scroggs, Pharm. D., Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Emend® (aprepitant) Capsules, NDA 21-549/S-008

Summary

The sponsor submitted and Efficacy Supplement September 29, 2004 to expand the INDICATION to include:

"EMEND, in combination with other antiemetic agents, is indicated for the prevention of (b) (4)

The product has a currently approved PPI and the only proposed revision to the PPI is the following:

"What are the possible side effects with EMEND?"

- Added headache and hair loss

Comments and Recommendations

1. The proposed revision to the PPI is acceptable. The current approved PPI has consumer-friendly language that allows for the added INDICATION.

2. Do not use all uppercase letters to emphasize a word or statement (the exception in the tradename). All uppercase letters are difficult to read. Bold, underline, or increase the font size for emphasis.

Please call us if you have any questions.

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/s/

Jeanine Best
2/2/05 03:29:04 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
2/3/05 10:20:33 AM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-549/S-008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-549 SUPPL # 008 HFD # 180

Trade Name Emend

Generic Name aprepitant

Applicant Name Merck & Company, Inc.

Approval Date, If Known October 28, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-549 Emend (aprepitant)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

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

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☒ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA 21-549: MRL Clinical Study Report, Multicenter Study: A Randomized, Double-Blind, Parallel-Group Study Conducted Under In-House Blinding Conditions to Determine the Efficacy and Tolerability of
Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated With Moderately Emetogenic Chemotherapy
(Protocol 071)

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 50,283 YES ☒ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Betsy Scroggs, Pharm.D.
Title: Regulatory Health Project Manager
Date: October 26, 2005

Name of Office/Division Director signing form: Joyce Korvick, M.D., M.P.H.
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Joyce Korvick

10/28/2005 01:27:31 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # 21-549 Supplement Type (e.g. SE5): SE1 Supplement Number: 008

Stamp Date: September 29, 2004 Action Date: October 28, 2005

HFD: 180 Trade and generic names/dosage form: Emend (aprepitant) Capsules, 80 mg and 125 mg

Applicant: Merck and Company, Inc. Therapeutic Class: 6S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **X N Please check all that apply: X Partial Waiver X Deferred Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min kg mo. 0 yr. Tanner Stage
Max kg mo. 6 yr. Tanner Stage

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

X Other: Formulation (capsule) for this age group is not appropriate.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo.__6____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__17___ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **X Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _12-31-2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: Betsy Scroggs, Pharm.D., RPM

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-549/S-008
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Betsy Scroggs
10/28/2005 12:52:09 PM

October 31, 2005

This Pediatric Page dated October 27, 2005 has been revised and updated as of Friday, October 28, 2005. Please refer to pediatric page dated October 28, 2005.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # 21-549 Supplement Type (e.g. SE5): SE1 Supplement Number: 008

Stamp Date: September 29, 2004 Action Date: October 28, 2005

HFD: 180 Trade and generic names/dosage form: Emend (aprepitant) Capsules, 80 mg and 125 mg

Applicant: Merck and Company, Inc. Therapeutic Class: 6S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **X N Please check all that apply: X Partial Waiver X Deferred Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min kg mo. 0 yr. Tanner Stage
Max kg mo. 1 yr. Tanner Stage

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **X Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo.__1____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__17___ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **X Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): 12-31-2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: Betsy Scroggs, Pharm.D., RPM

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-549/S-008
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Betsy Scroggs
10/27/2005 04:04:58 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Attention: Shannon Benedetto

FROM:
Betsy Scroggs, Pharm.D.
Project Managers: HFD-180
(301) 827-1250
scroggsb@cder.fda.gov

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/09/2004	N/A	**21-549**	Package Insert	**9/29/2004**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Emend (aprepitant)	**Medium**	Anti-emetic	**6/22/2005**

NAME OF FIRM: **Merck**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Review of PI

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: Please review the package insert (PI). Please note that the patient package insert (PPI) has been consulted to DSRCS.

Background: NDA 21-549/SE1/008 was submitted 9/29/2004 and received 9/29/2004. This 505(b)(1) standard review application proposes the following indication "for the Prevention of CINV associated with MEC" in addition to the approved "for prevention of acute and delayed nausea and vomiting associate with initial and repeat courses of Highly emetogenic chemotherapy, including high dose Cisplatin."
The original NDA was approved March 26, 2003. The User Fee Goal Date is 7/29/2005.
The EDR link follows below.

Application: N021549 Drug Trade Name: EMEND (APREPITANT) 80MG/125MG
Sponsor Name: MERCK
29-SEP-2004 SE1 008 Application: N021549 Emend® (aprepitant) Capsules, 80 mg and 125 mg
Document: 2620698 Location: \\CDSESUB1\N21549\S_008\2004-09-29
Goal Date: 7/29/2005

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Betsy Scroggs, Pharm.D., CSO HFD-180	☑DFS MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Betsy Scroggs
12/10/04 04:44:17 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-549	Efficacy Supplement Type SE-1	Supplement Number: 008	
Drug: Emend® (aprepitant) Capsules, 80 mg and 125 mg		Applicant: Merck & Co., Inc.	
RPM: Betsy Scroggs, Pharm.D.		HFD-180	Phone # 301.796-0991

Application Type: **(X)** 505(b)(1) **( )** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **( )** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): N/A

❖ Application Classifications:	
• Review priority	**(X)** Standard **( )** Priority
• Chem class (NDAs only)	6
• Other (e.g., orphan, OTC)	NA
❖ User Fee Goal Dates	The User Fee Goal Date was originally July 29, 2005. The date was extended in a letter dated July 26, 2005 to October 29, 2005. Action taken October 28, 2005.
❖ Special programs (indicate all that apply)	**(X)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X)** Paid UF ID number 4831_____
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify) _____
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions)

	( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	**( )** Yes **(X)** No
• This application is on the AIP	**( )** Yes **(X)** No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	**(X)** Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	**(X)** Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) **( )** Verified 21 CFR 314.50(i)(1) **( )** (ii) **( )** (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	**( )** N/A (no paragraph IV certification) **( )** Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next*	**( )** Yes **( )** No **( )** Yes **( )** No

paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity). *If "**No**," continue with question (3).*	
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).	**( )** Yes **( )** No
*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?	**( )** Yes **( )** No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).	**( )** Yes **( )** No
*If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	

❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	October 28, 2005 NME – 5 year exclusivity remains until March 26, 2008
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	**( )** Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	June 22, 2005
General Information	
❖ Actions	
• Proposed action	**(X)** AP **( )** TA **(X)** AE **( )** NA October 28, 2005
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter **( )** Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes **( )** Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X)** None **( )** Press Release **( )** Talk Paper **( )** Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	None
• Most recent applicant-proposed labeling	October 25, 2005 and includes all approved changes made since September 29, 2005 submission.
• Original applicant-proposed labeling	September 29, 2004
• Labeling reviews (including DDMAC, DMETS, DSRCS)	DSCRCS (PPI) February 3, 2005 DMETS – N/A DDMAC- June 22, 2005
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NDA 20-103 Zofran Tablets NDA 20-305 Kytril Tablets NDA 21-273 Aloxi Injection
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	October 27, 2005 sent to FDA via email. No changes since original 2003 approval.
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	#1 PREA – see action letter #2 PMC – see action letter

• Documentation of discussions and/or agreements relating to post-marketing commitments	October 27, 2005
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Stats IR /November 16, 2004 Filing letter /December 10, 2004 Ack letter / December 30, 2004 Clinical IR/ June 3, 2005 Clinical IR/ June 9, 2005 Clinical IR/ June 9, 2005 Clinical IR/ June 10, 2005 UFGD Extension letter/ July 26, 2005
❖ Memoranda and Telecons	Labeling TCONs October 14, 2005 in DFS October 27, 2005 October 21, 2005 in DFS October 27, 2005
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	September 4, 2003
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	MOTL #1/September 21, 2005 MOTL #2/September 27, 2005 Deputy Director/Pending -drafted
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	-MOR (PREA) /May 4, 2005 -SEALD #1/May 12, 2005 -MOR #1/July 18, 2005 with July 18, 2005appendix -SEALD #2/July 22, 2005 -MO Memo for Oncology Consult/August 17, 2005 -MOR #2/September 19, 2005 -Oncology Review/ September 23, 2005 -SEALD #2/July 22, 2005
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	MOR #1/July 18, 2005, page #64
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Drafted

❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	Review #1/July 6, 2005 Review #2/October 6, 2005
❖ Biopharmaceutical review(s) *(indicate date for each review)*	June 6, 2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	December 22, 2004
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	December 22, 2004 (see CMC review above)
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: N/A **( )** Acceptable **( )** Withhold recommendation
❖ Methods validation	**N/A** **( )** Completed **( )** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	NAI/October 11, 2005
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/s/

Betsy Scroggs
12/8/2005 01:39:35 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 14, 2005

To: Vijay Tammara	**From:** Betsy Scroggs, Pharm.D. Consumer Safety Officer
Company Merck & Company, Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: 484-344-2516	**Fax number:** (301) – 796-9905
Phone number: 484-344-3180	**Phone number:** 301-796-0991

NDA 21-549/S-008 Emend FDA labeling 10-14-1005

Subject: *Please find our draft labeling recommendations. Please note that the changes were made to your proposed labeling submitted June 22, 2005 in PDF format and on September 16, 2005 in Word as annotated format via email..*
We look forward to discussing the attached document with you.

Total no. of pages including cover: 34

DOCUMENT TO BE MAILED? NO

33 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

Betsy Scroggs
10/27/2005 09:46:28 PM
CSO

From: Scroggs, Betsy
Sent: Friday, October 21, 2005 4:35 PM
To: 'Tammara, Vijay'
Subject: NDA 21-549/S-008 MEC FDA 10-21-2005 labeling comment: see Table 3

Dear Vijay:

Thank you for your emailed 10-18-2005 reply containing your labeling agreements (attached labeling with accepted changes) after our 10-18-2005 labeling teleconference. As I just described to you via telephone, please review the additional comments regarding Table 3 and as pasted below.

Table 3

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

ENDPOINTS	Aprepitant Regimen (N = 433)† %	Standard Therapy (N = 424)† %	p-Value
PRIMARY ENDPOINT			
Complete Response‡	51	42	0.015
OTHER PRESPECIFIED ENDPOINTS			
No Emesis	76	59	(b) (4)
No Nausea	33	33	NS
No Significant Nausea	61	56	NS
No Rescue Therapy	59	56	NS
Complete Protection	43	37	NS

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

Regards,

Betsy

Betsy Scroggs, Pharm.D.
Regulatory Health Project Manager
Division of Gastroenterology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Telephone: (301) 796-0991
Fax: (301) 796-9894
email: ruth.scroggs@fda.hhs.gov

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/s/

Betsy Scroggs
10/27/2005 09:14:34 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 24, 2005

To: Vijay Tammara	**From:** Betsy Scroggs, Pharm.D. Consumer Safety Officer
Company Merck & Company, Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: 484-344-2516	**Fax number:** (301) – 796-9905
Phone number: 484-344-3180	**Phone number:** 301-796-0991

Subject: NDA 21-549/S-008 Emend Postmarketing commitment

Total number of pages including cover: 1

DOCUMENT TO BE MAILED? NO

We refer to your NDA 21/549/S-008 for Emend (aprepitant) submitted September 29, 2004. We also refer to our conversation this morning between you and Dr. Bob Silverman representing Merck & Company, Inc. and Dr. Joyce Korvick, DGP Division Director and myself to discuss and come to agreement on your conducting a postmarketing commitment as a condition of approval of this application.

As discussed following is our agreed upon Postmarketing Commitment:

POSTMARKETING COMMITMENT #1

Conduct a randomized controlled trial in patients receiving moderately emetogenic chemotherapy addressing the following issues:

> Your study must demonstrate generalizability among various chemotherapies including an evaluation of the efficacy in male patients. If the distinction of "acute" and delayed" is sought then efficacy must be demonstrated in each time frame. The study analysis and design should be such that these endpoints reach statistical significance.
>
> The results of this study are due by _____, XXXX.

Please respond to this fax with a letter of agreement noting any changes or comments as soon as possible. You may email the letter ahead to facilitate the process.
BHS

-----Original Message-----
From: Tammara, Vijay [mailto:vijay_tammara@merck.com]
Sent: Tuesday, October 25, 2005 12:18 PM
To: 'Scroggs, Betsy'
Subject: RE: NDA 21-549/S-008 MEC FDA 10-21-2005 labeling comment: see Tab le 3

Dear Betsy: Please, find the responses from MercK & Co., Inc for the two issues -
1) EMEND-MEC - Label: Table -3: statistical issue
2) Phase IV commitment

1) EMEND-MEC Label: Table -3: Statistical issue

It is recognized that No Vomiting endpoint would not have been declared statistically significant on the basis of the prospectively planned approach to address multiplicity for exploratory endpoints. However, irrespective of the multiplicity issue, the No Vomiting endpoint, as a principal component of the primary endpoint should have been classified as a secondary endpoint . This conceptual error was addressed in the CSR for the study which was included in the application(Section 5.8.4: Changes in Planned Analysis). When the prospectively planned approach to addressing multiplicity was applied to the No Vomiting endpoint as a secondary endpoint it was statistically significant. This would also be true if we applied the conservative Bonferroni approach as applied in HEC studies. In light of the importance of the No Vomiting endpoint as a clinical meaningful outcome for prescribers and as major driver of the difference in the primary endpoint (Complete Response), (b) (4)

Based on the above rationale, Merck proposes the presentation of Table 3 as follows:

Merck's Proposal

Table 3

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

ENDPOINTS	Aprepitant Regimen (N = 433)† %	Standard Therapy (N = 424)† %	p-Value
PRIMARY ENDPOINT			
Complete Response‡	51	42	0.015
OTHER PRESPECIFIED ENDPOINTS			
No Emesis	76	59	(b) (4)
No Nausea	33	33	NS
No Significant Nausea	61	56	NS
No Rescue Therapy	59	56	NS
Complete Protection	43	37	NS

†N: Number of patients included in the primary analysis of complete response.
‡Overall: 0 to 120 hours post-chemotherapy treatment.

(b) (4)

2: Phase IV commitment

Merck proposes a revision to FDA's proposal to simplify the language and to exclude the information related to [redacted] (b) (4) which is a guidance and not a requirement. Merck appreciates Agency's recommendation but feels that it should not be as part of the phase IV commitment. Therefore, Merck proposes to delete the text related to this and include information related to actual phase IV commitment i.e., to conduct a study for generalizability of the indication including evaluation of efficacy in men. Merck believes that the revised text reflects FDA's requirement and also includes the timelines for protocol preparation and study report submission. The details can be discussed further this afternoon during our teleconference.

FDA's Proposal:

The study must demonstrate generalizability among various chemotherapies including an evaluation of the efficacy in male patients. If the distinction of acute and delayed is sought then efficacy must be demonstrated in each time frame. The study analysis and design should be such that these endpoints reach statistical significance.

The results of the study are due by …… XXXXX.

Merck's Revision:

Conduct an appropriately powered randomized controlled clinical trial, in patients receiving MEC, designed to document generalizability among various chemotherapies and an evaluation of efficacy in male patients.

The sponsor will provide a protocol for Agency review and comments by 1Q06.

The study will be completed and results submitted by 4Q08.

Please, let me know if you have any questions further.

Thanks

Vijay

-----Original Message-----
From: Scroggs, Betsy [mailto:ScroggsB@cder.fda.gov]
Sent: Friday, October 21, 2005 4:35 PM
To: Tammara, Vijay
Subject: NDA 21-549/S-008 MEC FDA 10-21-2005 labeling comment: see Table 3

Dear Vijay:

Thank you for your emailed 10-18-2005 reply containing your labeling agreements (attached labeling with accepted changes) after our 10-18-2005 labeling teleconference. As I just described to you via telephone, please review the additional comments regarding Table 3 and as pasted below.

Table 3

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

ENDPOINTS

Aprepitant Regimen

(N = 433)†

%

	Standard Therapy (N = 424)[†] %	p-Value
PRIMARY ENDPOINT		
Complete Response[‡]	51	42	0.015
OTHER PRESPECIFIED ENDPOINTS		
No Emesis	76	59	(b) (4)
No Nausea	33	33	NS
No Significant Nausea	61	56	NS
No Rescue Therapy	59	56	NS
Complete Protection	43	37	NS

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

Regards,

Betsy

Betsy Scroggs, Pharm.D.
Regulatory Health Project Manager
Division of Gastroenterology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Telephone: (301) 796-0991
Fax: (301) 796-9894
email: ruth.scroggs@fda.hhs.gov

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/s/

Betsy Scroggs
10/27/2005 09:03:14 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Dorothy Pease, CPMS Oncology
WOC2 RM2095
HFD-150
1451 Rockville Pike
Rockville, MD 20852

FROM:
Betsy Scroggs, Pharm.D., RHPM
GI & Coagulation Drug Products
PKLN RM6B-17, HFD-180
5600 Fisher's Lane
Rockville, MD 20857

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
8/20/2005	N/A	21-549/S-008	Efficacy Supplement	9/29/2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Emend (aprepitant)	High	Antiemetic	9/20/2005 or earlier if possible.

NAME OF FIRM: Merck & Co., Inc.

REASON FOR REQUEST I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- X SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

COMMENTS/SPECIAL INSTRUCTIONS:

Background: Please see attachment.

Contacts: Dr. Gary Della'Zanna (301) 827-7452.

Thank you very much for your assistance. .
Betsy Scroggs, Pharm.D., RHPM (301) 827-1250

Attachment:

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Betsy Scroggs, Pharm.D.	☐ MAIL X DFS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

C:\Data\My Documents\Consults\IND 70268 Emend - HFD-150 consult req 08-05-2004.doc

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PDUFA GOAL DATE EXTENSION

NDA 21-549/S-008

Merck & Co., Inc.
Attention: Vijay Tammara, Ph.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tammara:

Please refer to your September 29, 2004 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Emend® (aprepitant) Capsules, 80 mg and 125 mg.

On July 22, 2005, we received (via email) your July 22, 2005, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 29, 2005.

If you have questions, call me at, 301-827-1250.

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm.D.
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Betsy Scroggs
7/26/05 12:03:54 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:

Raquel Peat
Study Endpoints and Label Development Team
Rockwall 2, Room 7217
HFD-020

FROM:

Betsy Scroggs, Pharm. D. HFD-180
Parklawn Building 6B-45

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 20, 2005		21-549	Quality of life questionnaire	June 14, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Emend	High	Antiemetic	July 14, 2005

NAME OF FIRM: Merck Pharmaceuticals, Inc..

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:
- ☐ See comments below

COMMENTS/SPECIAL INSTRUCTIONS:

Application: N021549
Document: 2717462
Location: \\CDSESUB1\N21549\S_008\2005-06-14

Please refer to our consult request dated April 1, 2005 and your review (thanks) dated May 12, 2005.

The sponsor has responded (see above link). Please review the the sponsor's June 14, 2005 response to our June 3, 2005 request for further clarification based on the May 12, 2005 review.

I would like comments back in 4 weeks if possible and we can have a meeting if necessary.

The medical officer is Gary Della'Zanna at (301) 827-7452

Thanks.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Betsy Scroggs	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Betsy Scroggs
6/20/05 11:57:52 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: June 10, 2005

To: Dr. Vijay Tammara	**From: Betsy Scroggs, Pharm.D. RPM**
Company: Merck and Co., Inc.	FDA/CDER/OND/ODEIII/DGCDP
Fax number: 484.344.2516	**Fax number: 301.443.9285**
Phone number: 484.344.3180	**Phone number:** 301.827.1250

Subject: Emend S-008 information request/ Assistance needed to locate data

Total no. of pages including cover: 2

Comments: We refer to your supplemental drug application for Emend [NDA 21-549/SE1-008] submitted September 29, 2004. This application consists of results from a single study protocol [071], in female patients and provides for the prevention of (b) (4) CINV associated with moderately emetogenic chemotherapy.

During further review of your NDA Executive Summary, we have have the following comment and request for information.
Comment: The current NDA Executive Summary template includes the following sections:

1.1.1 Assessment of Effect on Growth

1.1.2 Overdose Experience

1.1.3 Withdrawal Phenomena and/or Abuse Potential

1.1.4 Postmarketing Experience

Request: Please assist in locating this data in your overall development program.

In you post marketing experience section, can you comment on the number of prescriptions to date and the most commonly reported AEs?

Betsy Sc/roggs, Pharm.D., RPM

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/s/

Betsy Scroggs
6/10/05 01:04:42 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: June 9, 2005

To: Dr. Vijay Tammara	**From: Betsy Scroggs, Pharm.D. RPM**
Company: Merck and Co., Inc.	FDA/CDER/OND/ODEIII/DGCDP
Fax number: 484.344.2516	**Fax number: 301.443.9285**
Phone number: 484.344.3180	**Phone number:** 301.827.1250

Subject: Emend S-008 information request

Total no. of pages including cover: 4

Comments:

We refer to your supplemental drug application for Emend [NDA 21-549/SE1-008] submitted September 29, 2004. This application consists of results from a single study protocol [071], in female patients and provides for the prevention of (b) (4) CINV associated with moderately emetogenic chemotherapy.

We have the following comment and requests for information.

During review of #071, we note that Tables 8-7 and 8-8 show the number of patients that were discontinued from the study due to an AE/SAE and Table 8-21 shows a breakdown of the AEs leading to study termination.

Request for Information:

We request that you provide a breakdown of SAEs that resulted in study termination. Please construct a table or provide direction as to where this information is located in your application. We request that you provide your responses in writing by June 15, 2005. You may wish to have a teleconference if necessary.

Betsy Scroggs, Pharm.D., RPM

Table XX
Discontinued from Study due to Adverse Event

Adverse Experience	Treatment Group	
	Aprepitant (N=438) n (%)	Standard (N=428) n (%)
CYCLE 1		
Discontinued from Study due to AE	7 (1.6)	5 (1.2)
Discontinued from Study due to SAE	1 (0.2)	2 (0.5)
CYCLES 2 through 4 (Not Adjusted for Exposure)		
Discontinued from Study due to AE	7 (1.8)	4 (1.1)
Discontinued from Study due to SAE	5 (1.3)	0 (0.0)
Deaths	1 (0.3)	0 (0.0)
Ref: Modified Tables 8-7 and 8-8 P071.pdf		

Table XX
Select Adverse Events
Resulting in Discontinuation (Incidence 0%)
Cycle 1
Safety Population Study 071

Adverse Experience	Treatment Group	
	Aprepitant N=438 n (%)	Standard N=428 n (%)
Adverse Event(s)	7 (1.6)	5 (1.2)
Gastrointestinal Disorders	2 (0.5)	1 (0.2)
Diarrhea	0	1 (0.2)
Enterocolitis	1 (0.2)	0
Hematochezia	0	1 (0.2)
Nausea	1 (0.2)	0
Investigations		
Weight decreased	1 (0.2)	0
Metabolism and Nutrition		
Dehydration	1 (0.2)	1 (0.2)
Nervous System Disorders		
Headache	1 (0.2)	1 (0.2)
Migraine	1 (0.2)	0
Respiratory System Disorders		
Dyspnea	0	1 (0.2)
Skin Disorders		
Rash	1 (0.2)	0
Pruritus	1 (0.2)	0
Vascular Disorders		
Deep vein thrombosis	0	1 (0.2)
Flushing	1 (0.2)	0

REF: Modified Table 8-21 p071.pdf

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/s/

Betsy Scroggs
6/9/05 05:37:32 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: June 9, 2005

To: Dr. Vijay Tammara	**From: Betsy Scroggs, Pharm.D. RPM**
Company: Merck and Co., Inc.	FDA/CDER/OND/ODEIII/DGCDP
Fax number: 484.344.2516	**Fax number: 301.443.9285**
Phone number: 484.344.3180	**Phone number:** 301.827.1250

Subject: Emend S-008 information request

Total no. of pages including cover:

Comments:

We refer to your supplemental drug application for Emend [NDA 21-549/SE1-008] submitted September 29, 2004. This application consists of results from a single study protocol [071], in female patients and provides for the prevention of (b) (4) CINV associated with moderately emetogenic chemotherapy.

We have the following comment and requests for information.

During review of results of study #071, we note that neither Emend nor the standard of care comparator are performing as in previous clinical trials. Specifically, although there seems to be an effect on Vomiting, the aprepitant regimen demonstrated no significant advantage over standard therapy for any of the ***nausea*** endpoints or on the individual analysis of Complete Response in both the Acute as well as the Delayed Phase.

We request that you provide a plausible explanation for these findings.

We request that you provide your responses in writing by June 15, 2005.

You may wish to have a teleconference if necessary.

Betsy Scroggs, Pharm.D., RPM

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/s/

Betsy Scroggs
6/9/05 04:59:24 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: June 3, 2005

To: Vijay Tammara	Betsy Scroggs, Pharm.D. **From:** Consumer Safety Officer
Company Merck & Company, Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: 484-344-2516	**Fax number:** (301) – 827-1305
Phone number: 484-344-3180	**Phone number:** 301-827-1250
Subject: NDA 21-549/S-008 Emend	Information Request
Total no. of pages including cover: 2	

DOCUMENT TO BE MAILED? NO

Please refer to your NDA 21-549/S-008 for Emend submitted September 29, 2004 and our telephone conversation yesterday to let you know that that an information request would be faxed to you. As described yesterday, our request for information is a follows:

> Submit evidence that the 5-day recall version of the Functional Living with Emesis (FLIE) used in Protocol 071 provides a valid and reliable measure of the impact of chemotherapy induced nausea and vomiting (CINV) on the daily lives of patients receiving chemotherapy.

Call me if you have further questions. Additionally, if you need further clarification, you may submit your questions in writing and/or you may request an informal teleconference if necessary.

Betsy Scroggs, Pharm.D., R.P.M.

Attachment:

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/s/

Betsy Scroggs
6/3/05 03:28:57 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:

Raquel Peat
Study Endpoints and Label Development Team
Rockwall 2, Room 7217
HFD-020

FROM:

Betsy Scroggs, Pharm. D. HFD-180
Parklawn Building 6B-45

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 1, 2005		21-549	Quality of life questionnaire	September 29, 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Emend	Standard		May 1, 2005

NAME OF FIRM: Merck Pharmaceuticals, Inc..

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:
- ☐ See comments below

COMMENTS/SPECIAL INSTRUCTIONS: Here is a link to the EDR submission for the subject of this consult: *\\Cdsesub1\n21549\S_008\2004-09-29\clinstat\studies* .

Please see the following pages: Page 55 (Protocol definition for CINV having "No Impact") and Page: 418 (Reference).

Dr. Della'Zanna (the MO) has the following questions:

Is the FLIE QOL considered validated to the Agency's Standards?

Merck used the FLIE in the original NDA as "supportive" for the primary and secondary endpoints, therefore it does not appear in the label.

In the current submission, Merck intends to use it as the only secondary endpoint. Is the quality of the questionnaire sufficient to be the basis of an approval and appear in the label?

Merck included Reference material to show the questionnaire is validated. In the Reference, it appears the FLIE was administered/evaluated on Day 3 (not sure). In this submission the questionnaire was administered at Day 6. If this is a validated tool..... is it acceptable that the questionnaire was administered on Day 6. What effect will that have on the results?

In the submission Merck defined a value (b) (4) **as representing "No Impact" on life. Is there evidence to support this statement? Is this validated?**

Additional Information:

Against the Division's recommendations, Merck submitted only one Study to support this new indication. There is only one primary endpoint and one secondary endpoint.

Many clinically important endpoints were only exploratory in nature and were not statistically significant (preliminary Stat review)

I would like comments back in 4 weeks if possible and we can have a meeting if necessary.

Thanks.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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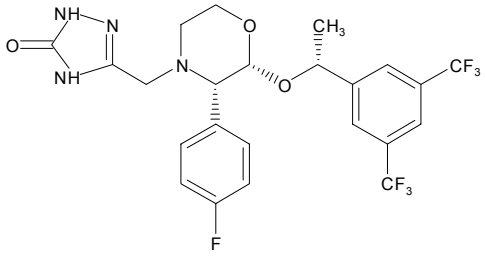
/s/

Brian Strongin
4/1/05 02:35:34 PM
Signing for Betsy Scroggs

NDA 21-549
Aprepitant



NDA:: 21-549/ S-008

Chemical Name: Aprepitant

Date Received: January 6, 2005

Route of Administration: Oral

Formulation: Capsule

Category: neurokinin 1 (NK_1) receptor antagonist

Sponsor: Merck

Documents Reviewed: Request for Waiver of Pediatric Studies <2 years of age
Proposed Pediatric Study Request, September 15, 2004
Kytril Written Request
Zofran Written Request September 3, 2004

Medical Officer: Gary Della'Zanna, D.O. M.Sc.

Medical Team Leader: Hugo Gallo-Torres M.D., Ph.D., P.N.S.

Project Manager: Betsy Scroggs, Pharm. D.

Background:

Aprepitant was approved in March 2003 as part of a three drug, three-day regimen for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) associated with initial and repeat courses of highly emetogenic chemotherapy regimens. The approved regimen includes aprepitant, a 5-HT3 antagonist and a corticosteroid.

Aprepitant (Emend®, MK-869, L-754030) is a highly selective substance P neurokinin-1 (NK1) receptor antagonist. Aprepitant crosses the blood-brain barrier and occupies brain NK1 receptors. It is theorized that the NK1 receptor antagonists exert their main antiemetic action by depressing the neural activity of the nucleus tractus solitarius lying ventrally to the area postrema.

Drug interaction studies submitted with the original NDA demonstrated that aprepitant is an inhibitor of CYP 3A4 on short-term administration and an inducer on longer administration. In one study, when aprepitant was administered as part of a 5 day regimen (125 mg on Day 1, 80 mg/day from Day 2 to 5) it acted as a moderate inhibitor of CYP 3A4, with a 2 to 3 fold mean increase in the AUC of midazolam (highly specific 3A4 substrate). Aprepitant also resulted in a two-fold increase in AUC of dexamethasone and diltiazem.

Aprepitant can also act as an inducer of CYP 3A4 with chronic administration. In one study it resulted in a 40% reduction in levels of ethinyl estradiol (CYP 3A4 substrate). Aprepitant was also shown to be an inducer of CYP 2C9. Patients on warfarin had a decrease of their International Normalized Ratio (INR) by 11% on Day 8 following a three day treatment regimen of aprepitant. The S-warfarin trough plasma concentration decreased by as much as 34% by Day 8.

In this submission, the Applicant is requesting a partial waiver for performing studies of Aprepitant for the prevention of moderate emetogenic chemotherapy induced nausea and vomiting in pediatric patients <2 years of age. To support this request, the Applicant states that the necessary studies would be impossible or highly impractical and sites the following:

> "As per PREA Section 505B (b)(2)(B)(i) (for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed). Additionally, as per CFR 314.55 (c) (3) (ii): 1) cancer is extremely rare in this age group (approximately 1500 diagnoses annually in the US), 2) these are geographically dispersed such that few eligible patients are seen in large regional cancer treatment centers per year, and 3) per PREA Section 505B (b)(2)(B)(iii) (I), the drug or biological product -(aa) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and (bb) is not likely to be used in a substantial number of pediatric patients in that age group because of the relatively infrequent use of emetogenic chemotherapy in these patients and in the general effectiveness of 5-HT3 receptor antagonists as monotherapy in those that do receive it.

Pediatric Labeling in Drug Class included in the Aprepitant Regimen:

Aprepitant (Emend®) was the first NK_1 receptor antagonists approved for the prevention of highly emetogenic CINV in adults. Aprepitant (Emend®) has no approved pediatric indications.

Presently, three 5-HT_3 receptor antagonists have been approved for the prevention of CINV in pediatric patients. A fourth drug in this class, Palonosetron, does not have any approved *pediatric* indications.

5-HT3 Receptor Antagonists
Approved Pediatric Indications

Drug	Mode	Indication	Age (years)	Approval Date
Kytril	Injection	CINV Moderate/High Emetogenic Chemotherapy	2-16 Adult	12/93
		PONV	Adult Only	8/02
Kytril	Tablet	CINV	Adult Only	3/00
Kytril	Tablet	RINV	Adult Only	7/00
Kytril	Solution	CINV and RINV	Adult Only	6/01
Zofran	Injection	CINV Moderate/High Emetogenic Chemotherapy	4-Adult	1/91
		PONV	2-12 Adult	5/96
Zofran	Tablet	CINV Moderate Emetogenic Chemotherapy	4-Adult	12/92
		RINV	Adult	
Zofran	Solution	CINV Moderate Emetogenic Chemotherapy	4-Adult	1/97
		RINV	Adult	
Zofran	Disintegrating Tablet	CINV Moderate Emetogenic Chemotherapy	4-Adult	1/99
		RINV	Adult	
Anzemet	Injection	CINV Moderate/High Emetogenic Chemotherapy	2-Adult	9/97
		PONV	2-Adult	9/97
Anzemet	Tablet	CINV Moderate Emetogenic Chemotherapy	2-Adult	9/97
		PONV	2-Adult	9/97
* Palonosetron (5-HT3 receptor antagonist) does not have pediatric approval				

Even though Corticosteroids are considered a "Standard of Care" for the prevention of CINV, they are not labeled or specifically approved for the prevention of CINV. There are no pediatric dosing recommendations for corticosteroid use in the prevention of CINV.

Conclusions/Recommendations:

1. The Sponsor is requesting a partial waiver for performing studies of Aprepitant for the prevention of *moderate* emetogenic chemotherapy induced nausea and vomiting in pediatric patients <2 years of age, sighting that the necessary studies are impossible or highly impractical, as per PREA Section 505B (b)(2)(B)(i).

   In this Reviewer's opinion, this partial waiver should be denied. To be consistent with recent study requests for other antiemetics used in the prevention of CINV, Merck should be asked to evaluate pediatric patients 6 months of age or younger.

   It is worth noting that in September 2004, Merck requested and was denied a deferral for pediatric studies in patients <2 years of age for the use of Aprepitant in the prevention of highly emetogenic chemotherapy induced nausea and vomiting.

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/s/

Gary DellaZanna
5/4/05 08:31:37 AM
MEDICAL OFFICER

Hugo Gallo Torres
5/4/05 09:31:47 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
DSRCS: Mary Dempsey/Tara Turner

FROM:
Betsy Scroggs, Pharm.D.
Project Managers: HFD-180
(301) 827-1250
scroggsb@cder.fda.gov

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
01-25-2005	N/A	**21-549**	PPI	**9/29/2004**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Emend (aprepitant)	**Medium**	Anti-emetic	**6/22/2005**

NAME OF FIRM: Merck

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Review of PPI

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: Please review the patient package insert (PPI). Please note that the package insert (PI) has been consulted to DMETS.

Background: NDA 21-549/SE1/008 was submitted 9/29/2004 and received 9/29/2004. This 505(b)(1) standard review application proposes the following indication "for the Prevention of CINV associated with MEC" in addition to the approved "for prevention of acute and delayed nausea and vomiting associate with initial and repeat courses of Highly emetogenic chemotherapy, including high dose Cisplatin."
The original NDA was approved March 26, 2003. The User Fee Goal Date is 7/29/2005.
The EDR link follows below.

Application: N021549 Drug Trade Name: EMEND (APREPITANT) 80MG/125MG
Sponsor Name: MERCK
29-SEP-2004 SE1 008 Application: N021549 Emend® (aprepitant) Capsules, 80 mg and 125 mg
Document: 2620698 Location: \\CDSESUB1\N21549\S_008\2004-09-29
Goal Date: 7/29/2005

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Betsy Scroggs, Pharm.D., CSO HFD-180	☑DFS MAIL ☐ HAND
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/s/

Betsy Scroggs
1/25/05 05:20:25 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-549/S-008

PRIOR APPROVAL SUPPLEMENT

Merck & Co., Inc.
Attention: Vijay Tammara, Ph.D.
Director, Regulatory Affairs-Domestic
770 Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486-0004

Dear Dr. Tammara

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: EMEND™ (aprepitant) Capsules.

NDA Number: 21-549

Supplement Number: 008

Review Priority Classification: Standard (S)

Date of Supplement: September 29, 2004

Date of Receipt: September 29, 2004

This supplemental application, submitted as an "Efficacy Supplement", provides for the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy.

This application has been filed in accordance with 21 CFR 314.101(a) and the 10-month user fee goal date will be July 29, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for patients less than 2 years of age and a deferral of pediatric studies for patients from 2 to 17 years of age for this application. We will notify you whether we have granted the requested waiver and deferral of the pediatric study requirement for this application.

Food and Drug
Administration
Rockville MD 20857

Please cite the application numbers listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm. D.
Regulatory Health Project Manager
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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/s/

Brian Strongin
12/30/04 02:04:56 PM
Signing for Betsy Scroggs.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Attention: Shannon Benedetto

FROM:
Betsy Scroggs, Pharm.D.
Project Managers: HFD-180
(301) 827-1250
scroggsb@cder.fda.gov

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/09/2004	N/A	**21-549**	Package Insert	**9/29/2004**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Emend (aprepitant)	**Medium**	Anti-emetic	**6/22/2005**

NAME OF FIRM: **Merck**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Review of PI

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: Please review the package insert (PI). Please note that the patient package insert (PPI) has been consulted to DSRCS.

Background: NDA 21-549/SE1/008 was submitted 9/29/2004 and received 9/29/2004. This 505(b)(1) standard review application proposes the following indication "for the Prevention of CINV associated with MEC" in addition to the approved "for prevention of acute and delayed nausea and vomiting associate with initial and repeat courses of Highly emetogenic chemotherapy, including high dose Cisplatin."
The original NDA was approved March 26, 2003. The User Fee Goal Date is 7/29/2005.
The EDR link follows below.

Application: N021549 Drug Trade Name: EMEND (APREPITANT) 80MG/125MG
Sponsor Name: MERCK
29-SEP-2004 SE1 008 Application: N021549 Emend® (aprepitant) Capsules, 80 mg and 125 mg
Document: 2620698 Location: \\CDSESUB1\N21549\S_008\2004-09-29
Goal Date: 7/29/2005

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Betsy Scroggs, Pharm.D., CSO HFD-180	☑DFS MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Betsy Scroggs
12/10/04 04:44:17 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-549/S-008

Merck & Co., Inc.
Attention: Vijay Tammara, Ph.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4
BLA-20
West Point, PA 19486

Dear Dr. Tammara:

Please refer to your September 29, 2004 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Emend (aprepitant) Capsules, 80 mg and 125 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 28, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

> A single study was submitted. On preliminary review there are concerns that the results may not be sufficiently robust to support approval based on a single study. More than one study is usually required for approval. Please refer to the guidance titled, "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May, 1998)."

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

If you have any questions, call Dr. Betsy Scroggs, Consumer Safety Officer at (301)-827-1250.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin

12/10/04 10:25:47 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 16, 2004

To: Vijay Tammara	**From:** Betsy Scroggs, Pharm.D. Consumer Safety Officer
Company Merck	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: 484-344-2516	**Fax number:** (301) – 827-1305
Phone number: 484-344-3180	**Phone number:** 301-827-1250
Subject:	NDA 21-549/S-008 Letter Date 9/29/2004
Total no. of pages including cover:	3

DOCUMENT TO BE MAILED? NO

Drug: **Emend (Aprepitant) Capsules 80 mg/125 mg**

Proposed Indication: **Prevention of** (b) (4) **nausea and vomiting associated with initial and repeated courses of moderately emetogenic cancer chemotherapy.**

In order to complete the review for Emend (Aprepitant) Capsules 80 mg/125 mg, we have the following information requests for Study PO71.

I. Provide data (of Cycle 1) of Study P071 for both modified-intent-to-treat and per-protocol populations in electronic format consistent with the guidance, *Regulatory Submissions in Electronic Format; General Considerations.* We recommend that you include the following variables:

a. Study number;
b. Investigator or Center code;
c. Region;
d. Patient number/name;
e. Treatment name;
f. Modified-intent-to-treat (Y for yes; N for no);
g. Use of concomitant chemotherapy (Y for yes; N for no);
h. Gender;
i. Age;
j. Race;

k. Complete Response in overall phase (success or failure);
l. Complete Response in acute phase (success or failure);
m. Complete Response in delayed phase (success or failure);
n. No Vomiting in overall phase (success or failure);
o. No Vomiting in acute phase (success or failure);
p. No Vomiting in delayed phase (success or failure);
q. No use of Rescue Therapy in overall phase (success or failure);
r. No use of Rescue Therapy in acute phase (success or failure);
s. No use of Rescue Therapy in delayed phase (success or failure);
t. No Impact of CINV on Daily Life assessed by total score/average item score (yes or no);
u. No Significant Nausea in overall phase (success or failure);
v. No Significant Nausea in acute phase (success or failure);
w. No Significant Nausea in delayed phase (success or failure);
x. No Nausea in overall phase (success or failure);
y. No Nausea in acute phase (success or failure);
z. No Nausea in delayed phase (success or failure);
aa. Time to first vomiting episode;
bb. Complete Protection in overall phase (success or failure);
cc. Complete Protection in acute phase (success or failure);
dd. Complete Protection in delayed phase (success or failure);
ee. Total Control in overall phase (success or failure);
ff. Total Control in acute phase (success or failure);
gg. Total Control in delayed phase (success or failure);

II. For the efficacy variables listed in I, submit the programs used to perform the analyses stated from section 7.1 to section 7.3 of the Clinical Study Report.

To the data set described by I, add additional variables needed (but not included in the above data set) for the above analyses. Please modify the programs to be able to input data from the data set described by I.

If you have any questions regarding this information request, please call me at the telephone number listed above.

Betsy Scroggs, Pharm.D., CSO

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/s/

Betsy Scroggs
11/16/04 02:31:59 PM