CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21549Orig1s010

Trade Name:	EMEND
Generic or Proper Name:	aprepitant
Sponsor:	MERCK & CO., Inc.
Approval Date:	June 30, 2006
Indication:	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. EMEND is indicated for the prevention of postoperative nausea and vomiting

CENTER FOR DRUG EVALUATION AND RESEARCH

21549Orig1s010

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21549Orig1s010

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-549/S-010

Vijay Tammara, Ph.D.
Director, Global Strategic Regulatory Development
Merck & Co., Inc.
P.O. Box 1000, UG2CD-48
North Wales, PA 19454

Dear Dr. Tammara:

Please refer to your supplemental new drug application dated August 29, 2005, received August 30, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMEND™ (aprepitant) Capsules, 40 mg.

We acknowledge receipt of your submissions dated December 28, 2005, January 30, February 3, March 1, March 9, April 11, May 4, June 8, June 20, June 23, June 28, June 29, and June 30, 2006.

This supplemental new drug application provides for the use of Emend™ (aprepitant) Capsules for the prevention of post-operative nausea and vomiting (PONV) utilizing a new 40 mg strength.

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 (PI) submitted June 23, 2006, Patient Package Insert submitted June 21, 2006, and the container and carton labels submitted January 30, 2006 with the inclusion of the following changes agreed to during our June 27, 2006 teleconference and your June 30, 2006 submission. In your June 30, 2006 submission, you agreed to make changes A, B, and C at your next printing of your carton, blister, and tri-fold labeling.

A. CARTON LABELING

- Change the color schemes used for the carton for each strength (40 mg, 80 mg, and 125 mg) in order to differentiate each strength.
- Relocate the net quantity so that it is not presented in close proximity to the product strength.
- Relocate the word “capsules” from directly under the text box containing the product strength to immediately following the established name.
- Increase the prominence of the word “capsules” so that it is the same size font as the active ingredient, aprepitant.

B. BLISTER LABELING

- Increase the font size of the strength of each blister label, and retain the current black/white color.
- For consistency, will change the physician sample package to read as follows: “Sample–Not for Sale”

C. TRI-FOLD LABEL

- Relocate the word “capsules” from directly under the text box containing the product strength to immediately following the established name.
- Increase the prominence of the word “capsules” so that it is the same size font as the active ingredient, aprepitant.
- Label each tri-fold section so that the strength contained in each blister is clearly delineated.

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as stated, in the product’s labeling may render the product misbranded and an unapproved new drug. Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 these submissions "**FPL for approved supplement NDA 21-549/S-010**." 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 deferring submission of your pediatric studies for ages 0 to less than 17 years of age until December 31, 2009.

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

1. Deferred pediatric study under PREA for the treatment of post-operative nausea and vomiting pediatric patients ages 0 to less than 17 years of age.

   Final Report Submission: December 31, 2009.

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

In addition, we remind you of your postmarketing study commitment in your submission dated June 29, 2006. This commitment is listed below.

> Title: *An open label study to evaluate the effect of a single 40-mg dose of aprepitant on the activity of Cytochrome P-450 2C9 in healthy young adult subjects*.
>
> | | |
> |---|---|
> | Protocol Submission: | October 31, 2006 |
> | Study Start: | February 28, 2007 |
> | Final report Submission: | December 31, 2007 |

Please note that we recommend that you submit your proposed protocol for review and comment in order for us to craft a mutually agreed-upon study to fulfill this 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:

> Food and Drug Administration
> Center for Drug Evaluation and Research
> Division of Drug Marketing, Advertising, and Communications
> 5901-B Ammendale Road
> Beltsville, MD 20705-1266

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
> Food and Drug Administration
> WO 22, Room 4447
> 10903 New Hampshire Avenue
> Silver Spring, MD 20993-0002

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 Health Project Manager, at (301) 796-0991.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy 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
6/30/2006 03:16:19 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21549Orig1s010

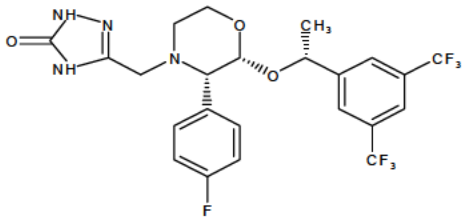
LABELING

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 40 mg, 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 40-mg capsule shell also contains yellow ferric oxide, and 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) and postoperative nausea and vomiting (PONV).

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

Following oral administration of a single 40 mg dose of EMEND in the fasted state, mean area under the plasma concentration-time curve ($AUC_{0-\infty}$) was 7.8 mcg•hr/mL and mean peak plasma concentration (C_{max}) was 0.7 mcg/mL, occurring at approximately 3 hours postdose (T_{max}). The absolute bioavailability at the 40-mg dose has not been determined.

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. At the dose range of 80-125 mg, the mean absolute oral

* Registered trademark of MERCK & CO., Inc., Whitehouse Station, New Jersey, 08889 USA

bioavailability of aprepitant is approximately 60 to 65%. Oral administration of the capsule with a standard high-fat 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 $AUC_{0-\infty}$ was 26% greater than dose proportional between 80-mg and 125-mg single doses administered in the fed state.

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_{0-24hr} 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_{0-24hr} 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_{0-24hr} 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) (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 $AUC_{0-\infty}$ 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.

Clinical Studies

Prevention of Chemotherapy Induced Nausea and Vomiting

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) Dexamethasone 8 mg PO Daily (morning)
Standard Therapy	Dexamethasone 20 mg PO Ondansetron 32 mg IV	Dexamethasone 8 mg PO Daily (morning) Dexamethasone 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			

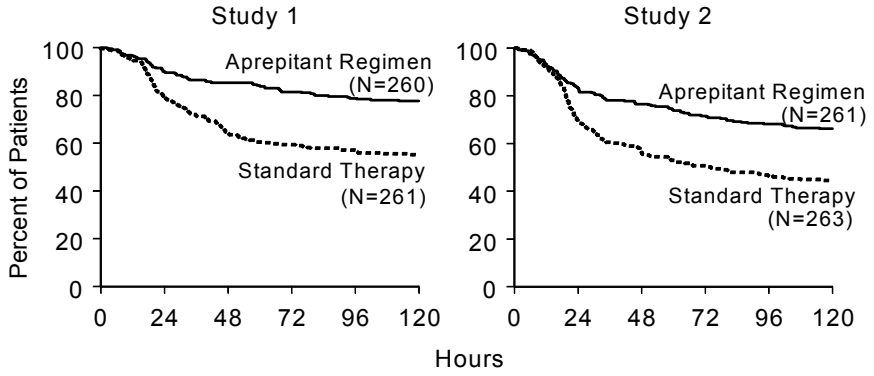
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
No Nausea			
Overall	49	39	NS*
Delayed phase	53	40	NS*
No Significant Nausea			
Overall	71	64	NS**
Delayed phase	73	65	NS**

†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

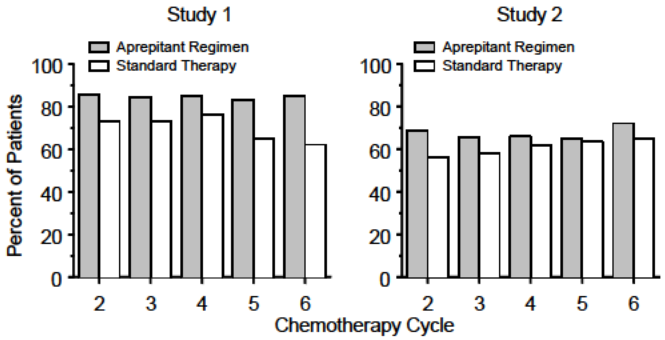


p-Value <0.001 based on a log rank test for Study 1 and Study 2; nominal p-values not adjusted for multiplicity.

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 chemo herapy 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.

Prevention of Postoperative Nausea and Vomiting (PONV)

In two multicenter, randomized, double-blind, active comparator-controlled, parallel-group clinical studies (PONV Studies 1 and 2), aprepitant was compared with ondansetron for the prevention of postoperative nausea and vomiting in 1658 patients undergoing open abdominal surgery. Patients were randomized to receive 40 mg aprepitant, 125 mg aprepitant, or 4 mg ondansetron. Aprepitant was given orally with 50 mL of water 1 to 3 hours before anesthesia. Ondansetron was given intravenously immediately before induction of anesthesia. A comparison between the 125 mg dose and the 40 mg dose did not demonstrate any additional clinical benefit. The remainder of this section will focus on the results in the 40 mg aprepitant dose recommended for PONV.

Of the 564 patients who received 40 mg aprepitant, 92% were women and 8% were men; of these, 58% were White, 13% Hispanic American, 7% Multi-Racial, 14% Black, 6% Asian, and 2% Other. The age of patients treated with 40 mg aprepitant ranged from 19 to 84 years, with a mean age of 46.1 years. 46 patients were 65 years or older, with 13 patients being 75 years or older.

The antiemetic activity of EMEND was evaluated during the 0 to 48 hour period following the end of surgery. The two pivotal studies were of similar design; however, they differed in terms of study hypothesis, efficacy analyses and geographic location. PONV Study 1 was a multinational study including the U.S., whereas, PONV Study 2 was conducted entirely in the U.S.

Efficacy measures in PONV Study 1 included:

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

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

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

The results of the primary and secondary endpoints for 40 mg aprepitant and 4 mg ondansetron are described in Table 4:

Table 4

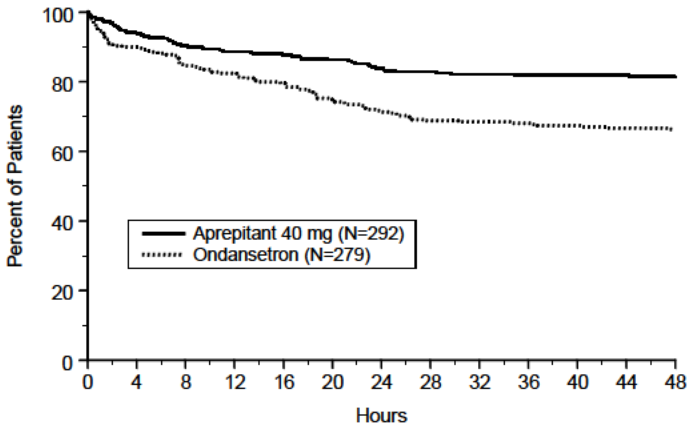
PONV Study 1
Response Rates for Select Efficacy Endpoints
(Modified-Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant Vs Ondansetron		
		Δ	Odds ratio†	Analysis
Primary Endpoints				
No Vomiting 0 to 24 hours (Superiority) (no emetic episodes)				
Aprepitant 40 mg	246/293 (84.0)	12.6%	2.1	P<0.001*
Ondansetron	200/280 (71.4)			
Complete Response (Non-inferiority: If LB‡ >0.65) (no emesis and no rescue therapy, 0 to 24 hours)				
Aprepitant 40 mg	187/293 (63.8)	8.8%	1.4	LB=1.02
Ondansetron	154/280 (55.0)			
Complete Response (Superiority: If LB >1.0) (no emesis and no rescue therapy, 0 to 24 hours)				
Aprepitant 40 mg	187/293 (63.8)	8.8%	1.4	LB=1.02+
Ondansetron	154/280 (55.0)			
Secondary Endpoint				
No Vomiting 0 to 48 (Superiority) (no emetic episodes)				
Aprepitant 40 mg	238/292 (81.5)	15.2%	2.3	P<0.001*
Ondansetron	185/279 (66.3)			

n/m = Number of responders/number of patients in analysis.
Δ Difference (%): Aprepitant 40 mg minus Ondansetron.
‡ LB= lower bound of 1-sided 97.5% confidence interval for the odds ratio.
* P-value of two-sided test <0.05.
+ Based on the prespecified fixed sequence multiplicity strategy, Aprepitant 40 mg was not superior to Ondansetron.
† Estimated odds ratio for Aprepitant versus Ondansetron. A value of >1 favors Aprepitant over Ondansetron.

The use of aprepitant did not affect the time to first use of rescue medication when compared to ondansetron. However, compared to the ondansetron group, use of aprepitant delayed the time to first vomiting , as depicted in Figure 3.

Figure 3
Percent of Patients Who Remain Emesis Free
During the 48 Hours Following End of Surgery



Efficacy measures in PONV Study 2 included:

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

PONV Study 2 failed to satisfy its primary hypothesis that aprepitant is superior to ondansetron in the prevention of PONV as measured by the proportion of patients with complete response in the 24 hours following end of surgery.

The study demonstrated that both dose levels of aprepitant had a clinically meaningful effect with respect to the secondary endpoint "no vomiting" during the first 24 hours after surgery and showed that the use of 40 mg aprepitant was associated with a 16% improvement over ondansetron for the no vomiting endpoint.

Table 5

PONV Study 2
(Modified-Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant Vs Ondansetron		
		Δ	Odds ratio†	p-Value
Primary Endpoint				
Complete Response (no emesis and no rescue therapy, 0 to 24 hours)				
Aprepitant 40 mg	111/248 (44.8)	2.5%	1.1	0.61
Ondansetron	104/246 (42.3)			
Secondary Endpoints				
No Vomiting (no emetic episodes, 0 to 24 hours)				
Aprepitant 40 mg	223/248 (89.9)	16.3%	3.2	<0.001*
Ondansetron	181/246 (73.6)			
No Use of Rescue Medication (for established emesis or nausea, 0 to 24 hours)				
Aprepitant 40 mg	112/248 (45.2)	-0.7%	1.0	0.83
Ondansetron	113/246 (45.9)			
No Vomiting 0 to 48 (Superiority) (no emetic episodes, 0 to 48 hours)				
Aprepitant 40 mg	209/247 (84.6)	17.7%	2.7	<0.001*

Ondansetron	164/245 (66.9)	

n/m = Number of responders/number of patients in analysis.
Δ Difference (%): Aprepitant 40 mg minus Ondansetron.
† Estimated odds ratio: Aprepitant 40 mg versus Ondansetron.
* Not statistically significant after pre-specified multiplicity adjustment.

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).

EMEND is indicated for the prevention of postoperative nausea and vomiting (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

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

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

PRECAUTIONS

General

EMEND, a dose-dependent inhibitor of CYP3A4, should be used with caution in patients receiving concomitant orally administered medicinal products, including chemotherapy agents that are primarily metabolized through CYP3A4. Moderate inhibition of CYP3A4 by aprepitant, 125 mg/80 mg regimen, could result in elevated plasma concentrations of these concomitant medicinal products.

Weak inhibition of CYP3A4 by a single 40 mg dose of aprepitant is not expected to alter the plasma concentrations of concomitant medicinal products that are primarily metabolized through CYP3A4 to a clinically significant degree.

The effect of EMEND on the pharmacokinetics of orally administered CYP3A4 substrates is greater than the effect of EMEND on the pharmacokinetics of intravenously administered CYP3A4 substrates (see 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 (125 mg/80 mg regimen) 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 (125 mg/80 mg regimen) 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, or following administration of a single 40 mg dose of

EMEND for the prevention of postoperative nausea and vomiting (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. For the prevention of chemotherapy induced nausea and vomiting, patients should be advised to take their first dose (125 mg) of EMEND 1 hour prior to chemotherapy treatment. For the prevention of postoperative nausea and vomiting, patients should receive their medication (40 mg capsule of EMEND) within 3 hours prior to induction of anesthesia.

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 125 mg/80 mg with each chemotherapy cycle, or following administration of a single 40 mg dose of EMEND for the prevention of postoperative nausea and vomiting.

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 weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

Effect of aprepitant on the pharmacokinetics of other agents

Weak inhibition of CYP3A4 by a single 40 mg dose of aprepitant is not expected to alter the plasma concentrations of concomitant medicinal products that are primarily metabolized through CYP3A4 to a clinically significant degree. However, higher aprepitant doses or repeated dosing at any aprepitant dose may have a clinically significant effect.

As a moderate inhibitor of CYP3A4 at a dose of 125 mg/80 mg, aprepitant can increase plasma concentrations of concomitantly administered oral medicinal products that are metabolized through CYP3A4 (see CONTRAINDICATIONS). For a given drug of CYP3A4 substrate, aprepitant 125 mg/80 mg may increase its plasma concentrations to a lesser extent when it is given intravenously rather than orally.

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 (125 mg/80 mg regimen), to achieve exposures of dexamethasone similar to those obtained when it is given without EMEND. The daily dose of dexamethasone

administered in clinical chemotherapy induced nausea and vomiting studies with EMEND reflects an approximate 50% reduction of the dose of dexamethasone (see DOSAGE AND ADMINISTRATION). A single dose of EMEND (40 mg) when coadministered with a single oral dose of dexamethasone 20 mg, increased the AUC of dexamethasone by 1.45-fold. Therefore, no dose adjustment is recommended.

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 (125 mg/80 mg regimen) to achieve exposures of methylprednisolone similar to those obtained when it is given without EMEND. Although the concomitant administration of methylprednisolone with the single 40 mg dose of aprepitant has not been studied, a single 40 mg dose of EMEND produces a weak inhibition of CYP3A4 (based on midazolam interaction study) and it is not expected to alter the plasma concentrations of methylprednisolone to a clinically significant degree. Therefore, no dose adjustment is recommended.

Chemotherapeutic agents: See PRECAUTIONS, *General*.

Docetaxel: In a pharmacokinetic study, EMEND (125 mg/80 mg regimen) 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, or following administration of a single 40 mg dose of EMEND for the prevention of postoperative nausea and vomiting.

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.

While studies have not been done with the 40 mg single PONV dose, the timing of EMEND administration relative to ovulation could cause contraceptive failure. Thus, patients should be instructed to use alternative or back-up methods of contraception 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 (125 mg/80 mg). A single dose of EMEND (40 mg) increased the AUC of midazolam by 1.2-fold on

Day 1, when a single oral dose of midazolam 2 mg was coadministered on Day 1 with EMEND 40 mg; this effect was not considered clinically important.

In another study with intravenous administration of midazolam, EMEND was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, and midazolam 2 mg IV was given prior to the administration of the 3-day regimen of EMEND and on Days 4, 8, and 15. EMEND increased the AUC of midazolam by 25% on Day 4 and decreased the AUC of midazolam by 19% on Day 8 relative to the dosing of EMEND on Days 1 through 3. These effects were not considered clinically important. The AUC of midazolam on Day 15 was similar to that observed at baseline.

An additional study was completed with intravenous administration of midazolam and EMEND. Intravenous midazolam 2 mg was given 1 hour after oral administration of a single dose of EMEND 125 mg. The plasma AUC of midazolam was increased by 1.5-fold. Depending on clinical situations (e.g., elderly patients) and degree of monitoring available, dosage adjustment for intravenous midazolam may be necessary when it is coadministered with EMEND for the chemotherapy induced nausea and vomiting indication (125 mg Day 1 followed by 80 mg on Days 2 and 3).

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

Carcinogenicity studies were conducted in Sprague-Dawley rats and in CD-1 mice for 2 years. In the rat carcinogenicity studies, animals were treated with oral doses ranging from 0.05 to 1000 mg/kg twice daily. The highest dose produced a systemic exposure to aprepitant (plasma $AUC_{0\text{-}24hr}$) of 0.7 to 1.6 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 1000 mg/kg twice daily caused an increase in the incidences of thyroid follicular cell adenomas and carcinomas in male rats. In female rats, it produced hepatocellular adenomas at 5 to 1000 mg/kg twice daily and hepatocellular carcinomas and thyroid follicular cell adenomas at 125 to 1000 mg/kg twice daily. In the mouse carcinogenicity studies, the animals were treated with oral doses ranging from 2.5 to 2000 mg/kg/day. The highest dose produced a systemic exposure of about 2.8 to 3.6 times the human exposure at the recommended dose. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice.

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 chemotherapy-induced nausea and vomiting clinical studies, of the total number of patients (N=544) treated with EMEND, 31% were 65 and over, while 5% were 75 and over. In well-controlled postoperative nausea and vomiting clinical studies, of the total number of patients (N=1120) treated with EMEND, 7% were 65 and over, while 2% 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 4400 individuals.

Chemotherapy Induced Nausea and Vomiting

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

Table 6

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/Fa igue	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 7 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3%.

Table 7

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

Table 8

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 that observed in Cycle 1.

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

Postoperative Nausea and Vomiting

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

Clinical adverse experiences were reported in approximately 60% of patients treated with 40 mg aprepitant compared with approximately 64% of patients treated with 4 mg ondansetron IV. Table 9 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3% of the combined studies.

Table 9

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

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

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

Infections and infestations: postoperative infection

Metabolism and nutrition disorders: hypokalemia, hypovolemia.

Nervous system disorders: dizziness, hypoesthesia, syncope.

Vascular disorders: hematoma

Respiratory, thoracic and mediastinal disorders: dyspnea, hypoxia, respiratory depression.

Gastrointestinal disorders: abdominal pain, abdominal pain upper, dry mouth, dyspepsia.

Skin and subcutaneous tissue disorders: urticaria

General disorders and administrative site conditions: hypothermia, pain.

Investigations: blood pressure decreased

Injury, poisoning and procedural complications: operative hemorrhage, wound dehiscence.

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

Nervous system disorders: dysarthria, sensory disturbance.

Eye disorders: miosis, visual acuity reduced.

Respiratory, thoracic and mediastinal disorders: wheezing

Gastrointestinal disorders: bowel sounds abnormal, stomach discomfort.

There were no serious adverse drug-related experiences reported in the postoperative nausea and vomiting clinical studies in patients taking 40 mg aprepitant.

Laboratory Adverse Experiences

One laboratory adverse experience, hemoglobin decreased (40 mg aprepitant 3.8%, ondansetron 4.2%), was reported at an incidence ≥3% in a patient receiving general anesthesia.

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

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

Other Studies

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

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

- ***Prevention of Chemotherapy Induced Nausea and Vomiting***

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.

- ***Prevention of Postoperative Nausea and Vomiting***

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

General Information

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 0006-0461-06 unit-dose packages of 6.

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 0006-0462-06 unit-dose packages of 6.

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

NDC 0006-3862-03.

No. 6741 – 40 mg capsules: Opaque, hard gelatin capsule with white body and mustard yellow cap with “464” and “40 mg” printed radially in black ink on the body. They are supplied as follows:

NDC 0006-0464-10 unit-of-use package of 1.

NDC 0006-0464-05 unit-dose packages of 5.

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 ~~December 2005~~

~~9565103~~

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

You should read this information before you take 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 nausea and vomiting.

- EMEND is used to prevent nausea and vomiting caused by chemotherapy treatment. When used for this purpose, EMEND is always used WITH OTHER MEDICINES.
- EMEND is used to prevent nausea and vomiting caused by surgery.
- 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.

*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.

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

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.

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

If you are a surgical patient, your doctor will give you a 40-mg capsule of EMEND before surgery.

- EMEND may be taken with or without food. Follow your doctor's instructions about eating before surgery.
- 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?

In patients taking the 125 mg/80 mg regimen of EMEND to prevent nausea and vomiting caused by chemotherapy, the most common side effects are:

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

In patients taking a single 40 mg dose of EMEND to prevent nausea and vomiting caused by surgery, the most common side effects are:

- constipation
- nausea
- itch
- fever
- low blood pressure
- headache

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. The 40-mg capsule shell also contains yellow ferric oxide.

Issued ~~October 2005~~

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21549Orig1s010

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	S-NDA
Submission Number	21-549
Submission Code	S-010
Letter Date	August 30, 2005
Stamp Date	August 30, 2005
PDUFA Goal Date	June 30, 2006
Reviewer Name	Gary Della'Zanna D.O., M.Sc.
Review Completion Date	May 31, 2006
Established Name	Aprepitant
Trade Name	Emend®
Therapeutic Class	NK_1 receptor antagonists
Applicant	Merck
Priority Designation	Standard Review
Formulation	Capsule
Dosing Regimen	40mg capsules (new)
Indication	Prevention of Postoperative Nausea and Vomiting
Intended Population	Surgery Patients

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The submitted data from Studies 090 and 091 are sufficient to support the approval of aprepitant for the prevention of Post-Operative Nausea and Vomiting (PONV). This recommendation is based on the studies demonstrating clinically meaningful results that are supported *in part* by statistically significant findings in Study 091.

The safety analysis did not identify any new safety concerns. The incidence and type of adverse and serious adverse events was similar among the three treatment groups. The safety analyses did not suggest that the use of aprepitant adversely affected the safety profile of the anesthesia or surgical procedure.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are currently no active risk management programs active or requested at this time.

1.2.2 Required Phase 4 Commitments

The review of S-NDA 21-549 demonstrated the aprepitant is safe and effective in the prevention of PONV and should be approved. However, this Reviewer identified the following issues which could not be answered with the submitted data. The Sponsor should be required to address these outstanding issues as Phase IV commitments.

1) A significant treatment-by-gender interaction was identified in one of the two pivotal trials submitted with the original aprepitant NDA (Highly Emetogenic CINV). This issue was not resolved in S-NDA 21-549 /008 (Moderately Emetogenic CINV), which enrolled greater than 99% female patients. There is currently an outstanding Phase IV commitment requested to evaluate the safety and efficacy of aprepitant in a patient population which includes more male patients for the prevention of CINV in patients receiving MEC.

   In this submission, 92% of the patients enrolled in the PONV trials were female. There are insufficient data available to perform a meaningful treatment by gender analysis. Although the limited number of male patients precludes any meaningful statistical interpretation, the analyses suggest that for the Complete Response endpoint, aprepitant may not be as efficacious as ondansetron in male patients. Since this remains an

unanswered question, it is this Reviewer's opinion that approval of the PONV indication should be contingent on Merck agreeing to perform a study to further evaluate the safety and efficacy of aprepitant in male patients undergoing surgery.

2. Aprepitant has a complex metabolism. Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. Data submitted with the original application demonstrated that following a *three* day regimen of aprepitant, patients on warfarin had an 11% decrease in their International Normalized Ratio (INR) on Day 8 and their S-warfarin trough plasma concentration decreased by as much as 34%.

   This information is currently included in the PRECAUTIONS section of the label. With this new indication (Prevention of PONV), the Sponsor proposes the following revisions to this section of the label (underlined portion)

   > 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, or following administration of a single 40 mg dose of EMEND for the prevention of postoperative nausea and vomiting (see PRECAUTIONS, *Drug Interaction*
   > (Ref: Proposed Label)

   It is this Reviewer's opinion that there are insufficient data to support that a single 40mg dose of aprepitant will affect the efficacy of warfarin.

   Although the proposed wording in the PRECAUTIONS section is safe and acceptable, it may result in requiring post operative patients to present to the hospital or lab numerous times during the post operative period to have their INR "monitored closely for 2 weeks". Since it is unknown whether this is necessary, this Reviewer/Clinician is concerned that the label require patients with recent major surgery (i.e. abdominal surgery or joint replacement) be transported to have lab work performed which may not be necessary. It is this Reviewer's opinion that approval of the PONV indication should be contingent on Merck agreeing to perform a study to evaluate whether a single 40mg dose of aprepitant will have a clinically important effect on warfarin.

3. Similarly, data from the original NDA has shown that coadministration of aprepitant and hormonal contraceptives may effect the efficacy of the birth control. The following information is currently included in the PRECAUTIONS section of the label.

   > *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.

This Reviewer/Clinician is concerned for the following reasons; for scheduled elective surgeries, patients will most likely be prescribed aprepitant by the anesthesia department during their preoperative screening visit, with instructions to take the medication just prior to going to the hospital, since the drug must be given "within 3 hours prior to induction of anesthesia." The treating surgeon may not know the patient was premedicated with aprepitant, therefore his discharge instructions will not include the recommendation that "back-up methods of contraception" be used for a month after surgery. Even if this information is conveyed to the patient during their preoperative screening visit (as much as 2 weeks before surgery), the patient may not remember after surgery.

Although the proposed wording in the PRECAUTIONS section is safe and acceptable, it may not apply to a single 40mg dose of aprepitant. There are insufficient data to support that a single 40mg dose of aprepitant will have a clinically important effect on hormonal contraceptives. To aid treating physicians in the safe use of this drug, approval of the PONV indication should be contingent on Merck agreeing to perform a study to evaluate whether a single 40mg dose of aprepitant will have a clinically important effect on the efficacy of the birth control.

The following is a summary and the status of requested Phase IV studies to date.

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 SDS media in the capsule formulation dissolution method, including studies on the (b) (4) for the nanoparticle capsule formulation."

Status: Commitment fulfilled.

1.2.3 Other Phase 4 Requests

On October 24, 2005, Emend was approved for "the prevention of nausea and vomiting associated with initial and repeat course of *moderately* emetogenic cancer chemotherapy." This approval was contingent on Merck agreeing to the following Phase IV commitments:

"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 (b) (4) 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."

(Ref: Approval Letter, October 24, 2005)

On April 4, 2006, Merck submitted Protocol 130, titled "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" to satisfy this Phase IV commitment. The review of this protocol is filed in DFS.

APPEARS THIS WAY ON ORIGINAL

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Merck submitted results from Protocols 090 and 091 to support the approval of the aprepitant for the prevention of PONV. The two protocols were identical with respect to study design, study population, treatments, and efficacy assessments. Both were multicenter, double-blind, randomized, active comparator-controlled, parallel-group studies that evaluated the safety and efficacy of aprepitant in the prevention of PONV in surgical patients. Although the studies were of similar design, they differed in terms of study hypotheses, efficacy analyses and geographic location. These issues will be discussed in more detail in the Efficacy Section of this review.

The study populations consisted of patients scheduled to receive general anesthesia for an open abdominal surgery requiring overnight hospital. Eligible patients were assigned to one of the following three treatment arms using a computer generated randomization schedule. Patients were treated with study medications only on Day 1, preoperatively.

Table 1
Treatment Arms

Treatment Group	*Bottle A (PO)*	*Vial B (I.V.)*
I	Aprepitant 125 mg PO Placebo Aprepitant 40mg PO	Placebo Ondansetron 4mg
II	Aprepitant 40mg PO Placebo Aprepitant 125 mg PO	*Placebo Ondansetron 4mg*
III	Placebo Aprepitant 125 mg PO *Placebo Aprepitant 40mg PO*	*Ondansetron 4mg*

1.3.2 Efficacy

Merck is seeking the following new indication and revisions to the dosage section of the current label:

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

In this Reviewer's opinion, both studies (Protocols 090, 091) successfully demonstrate that aprepitant provided effective protection against PONV. Since the two protocols had different study hypotheses, the results of each study will be discussed separately.

The interpretation of these results requires some clinical judgment since Study 090 failed to satisfy its primary hypothesis. However, Study 090 did demonstrate that both dose levels of aprepitant (40mg and 125mg) were clinically superior to ondansetron with respect to the secondary endpoint "No Vomiting" during the first 24 hours after surgery.

Study 091 succeeded in demonstrating that aprepitant was superior to ondansetron for the prespecified "No Vomiting" primary endpoint. It also succeeded for the prespecified second primary endpoint that aprepitant was "non inferior" to ondansetron for the Complete Response endpoint, an approved indication for ondansetron.

Protocol 090

The primary endpoint in Study 090 was Complete Response for 24-hours after surgery. The Complete Response endpoint is a composite end-point that includes two measured variables: "No Vomiting" and "No Rescue therapy". For Study 090 to succeed for its primary endpoint both variables would need to be statistically significantly better than ondansetron.

Study 090 failed to satisfy its primary hypothesis that aprepitant (125 mg, 40 mg) is superior to ondansetron in the prevention of PONV as measured by the proportion of patients with Complete Response (no Vomiting and No Rescue Therapy) in the 24 hours following end of surgery. The reason the study was unsuccessful was that the treatment group difference between the aprepitant groups and the ondansetron group were not statistically significant for *one* of the two composite variables that defined the primary endpoint. The results for the "No Rescue therapy" endpoint failed to reach statistical significance. Study 090, however, did demonstrate that both dose levels of aprepitant were clinically significantly superior to ondansetron with respect to the secondary endpoint "No Vomiting" during the first 24 hours after surgery. However, statistical significance can not be claimed due to the data analysis plan proposed by the sponsor.

From a clinical perspective, Study 090 demonstrated that the use of 40 mg aprepitant (proposed dose) was associated with a 16% improvement over ondansetron for the No Vomiting endpoint. Even more impressive, the treatment group difference for the No Vomiting variable was sustained for 48 hours after surgery (18%). In this Reviewer's opinion, these results are clinically meaningful and should be considered when assessing the efficacy of aprepitant.

Furthermore, even in the patients who did vomit (treatment failures), the aprepitant patients clinically did better. In both aprepitant groups, a greater proportion of patients who vomited experienced only one emetic episode (76% in the aprepitant 40 mg group, and 83% in the aprepitant 125 mg group). In contrast, only 52% of the ondansetron-treated patients who vomited suffered a single emetic event. In this Reviewer's opinion, even in the patients who failed, the results are clinically meaningful.

Table 2
Response Rates for Primary and Secondary Endpoints
Study 090
(Modified- Intention-to-Treat Population)

Treatment	n/N (%)	Aprepitant vs Ondansetron	
		Δ	p-Value
Complete Response (Primary Endpoint) (no emesis and no rescue therapy, 0 to 24 hours)			
Aprepitant 40 mg	111/248 (44.8)	2.5	N.S.
Aprepitant 125 mg	103/239 (43.1)	0.8	N.S.
Ondansetron	104/246 (42.3)		
No Vomiting (Secondary Endpoint) (no emetic episodes, 0 to 24 hours)			
Aprepitant 40 mg	223/248 (89.9)	16.3	<0.001*
Aprepitant 125 mg	227/239 (95.0)	21.4	<0.001*
Ondansetron	181/246 (73.6)		
No Rescue Therapy (Secondary Endpoint) (for established emesis or nausea, 0 to 24 hours)			
Aprepitant 40 mg	112/248 (45.2)	-0.7	N.S.
Aprepitant 125 mg	106/239 (44.4)	-1.5	N.S.
Ondansetron	113/246 (45.9)		
No Vomiting (Secondary Endpoint) (no emetic episodes, 0 to 48 hours)			
Aprepitant 40 mg	209/247 (84.6)	17.7	<0.001*
Aprepitant 125 mg	220/236 (93.2)	26.3	<0.001*
Ondansetron	164/245 (66.9)		

Ref: Study 090.pdf Page 21 of 1851
N.S.= Not Significant
Δ Treatment Group Difference Aprepitant vs. Ondansetron.
* Not statistically significant based on Sponsor's data analysis plan
n/N= Number of patients responder/number of patients in analysis.

Unlike Chemotherapy Induced Nausea and Vomiting (CINV), which is associated with repeat cycles of "Acute and Delayed" nausea and vomiting lasting 5 days or longer, in this Reviewer's opinion, the success of the No Vomiting endpoint is the most clinically important measure of efficacy in surgical patients. The most serious complications associated with PONV are directly related to the vomiting process (i.e. wound disruption, increased intraabdominal, intraocular and intracranial pressures, esophageal tears, electrolyte imbalance, and pulmonary aspiration. Whether of not a patient required rescue therapy is not clinically important.

This is in contrast to CINV, where the control of both nausea and vomiting is critical. Due to the repeat cycles of chemotherapy that can result in prolonged nausea and vomiting (5 days), control

of nausea as well as vomiting is critical in preventing malnutrition as well as the complications of vomiting outlined above.

Protocol 091

Based on the findings in Study 090, and after Study 091 was initiated, protocol 091 was amended and the Data Analysis Plan revised. The Primary Efficacy Hypothesis was changed from superiority of aprepitant over ondansetron for the Complete Response endpoint to the superiority of aprepitant over ondansetron for the No Vomiting endpoint. The revisions were made prior to breaking the blind and were found to be acceptable.

The revised protocol included six statistical null/alternative hypotheses that comprised the primary efficacy analyses. These were evaluated in a step-wise fashion, employing a closed testing procedure designed to control the overall Type I error rate at the 0.05 level.

The first primary efficacy endpoint was a superiority analysis for "No Vomiting in the 24-hours following the end of surgery". The results for the "No Vomiting" endpoint were statistically significantly higher in both of the aprepitant groups compared to the ondansetron group. These data and analyses were confirmed by the Agency.

The second *primary* efficacy endpoint included two efficacy hypotheses. The first hypothesis was that aprepitant was non-inferior to ondansetron for the Complete Response endpoint (No Vomiting and No Rescue Therapy). Based on the protocol defined non-inferiority margin, both aprepitant doses were non-inferior to ondansetron for the endpoint Complete Response. These data and analyses were also confirmed by the Agency.

Since the first hypothesis of the second *primary* efficacy endpoint was successful, the second hypothesis was tested: the superiority of aprepitant over ondansetron with respect to the Complete Response endpoint.

The Sponsor reported that, based on the protocol defined data analysis plan, both aprepitant doses were also superior to ondansetron for the Complete Response endpoint. However, the Agency's Statistical team does not agree with their analysis. The team agrees that Study 091 succeeded in demonstrating non-inferiority for the Complete Response endpoint; however, for the superiority analyses, statistical significance was not maintained based upon one-sided test, using a more appropriate 2.5% significance level and using the multiplicity adjustment method proposed by the sponsor.

The following table shows the *Agency's* analysis using the lower bound of the 1-sided 97.5% confidence interval.

Table 3
Study 091
Response Rates for Select Efficacy Endpoints
(Modified- Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant vs Ondansetron	
		Odds ratio	Analysis
Primary Endpoints			
No Vomiting (Superiority) (no emetic episodes, 0 to 24 hours)			
Aprepitant 40 mg	246/293 (84.0)	2.1	p<0.001*
Aprepitant 125 mg	253/293 (86.3)	2.5	p<0.001*
Ondansetron	200/280 (71.4)		
Complete Response (Non-inferiority: If LB‡ > 0.65) (no emesis and no rescue therapy, 0 to 24 hours)			
Aprepitant 40 mg	187/293 (63.8)	1.4	LB = 1.02
Aprepitant 125 mg	184/293 (62.8)	1.4	LB = 0.99
Ondansetron	154/280 (55.0)		
Complete Response (Superiority: If LB > 1.0) (no emesis and no rescue therapy, 0 to 24 hours)			
Aprepitant 40 mg	187/293 (63.8)	1.4	LB = 1.02+
Aprepitant 125 mg	184/293 (62.8)	1.4	LB = 0.99
Ondansetron	154/280 (55.0)		
Secondary Endpoint			
No Vomiting (Superiority) (no emetic episodes, 0 to 48 hours)		Δ	Odds Ratio∓
Aprepitant 40 mg	238/292 (81.5)	15.2%	2.3
Aprepitant 125 mg	246/290 (84.8)	18.5%	2.9
Ondansetron	185/279 (66.3)		

Ref: Study 091.pdf Modified Table 7-1 and 7-9 Agency's Analysis
Δ Treatment Group Difference Aprepitant vs. Ondansetron.
‡: LB = lower bound of the 1-sided 97.5% confidence interval.
*: P value for two-sided test < 0.05.
+: Since Aprepitant 125 mg was not superior to Ondansetron at significance level of 2.5%, by the applicant's proposed multiplicity adjustment method, Aprepitant 40 mg was not superior to Ondansetron either.
∓: Estimated odds ratio for Aprepitant versus Ondansetron. A value of >1 favors Aprepitant over Ondansetron.
n/m= Number of patients responder/number of patients in analysis.

Although it did not impact this Reviewer's interpretation of the efficacy results, it is necessary to note that this Reviewer questioned whether the studies used to calculate the non-inferiority margin were acceptable. None of the studies used in the calculation of the non-inferiority margin evaluated an appropriate combination of drug formulation and surgical procedure.

Table 4
Studies Used in Non-Inferiority Calculation
Ondansetron PONV Prevention Trials

Study Population	Drug	Complete Response		Odds Ratio
		Placebo	Active	
Women Out-patients	Ondansetron I.V.	64/139 46%	103/136 76%	3.66
Thoi	Ondansetron I.V.	63/143 44%	86/136 63%	2.18
Women In-patients	Ondansetron PO	105/327 32%	179/343 52%	2.31
Women In-patients	Ondansetron PO	54/204 26%	112/207 54%	3.27
Ref. Modified Table 5-5 Protocol 091				

The comparative *intravenous* ondansetron studies were performed on patients who had an *out-patient surgery*. It is unlikely that an outpatient surgery would have the same emetogenic potential as a more complicated surgery that required an over-night hospitalization. The comparative studies that were performed on patients who required an over-night hospitalization evaluated the only the oral formulation of ondansetron.

Although this reviewer questioned whether the studies used to calculate the non-inferiority margin were acceptable for the *second* primary efficacy endpoint; the success of the first primary endpoint (No Vomiting), in conjunction with the results of the non inferiority analysis and the other efficacy variables, support that both dose levels of aprepitant were effective in the prevention of PONV.

Study 091 demonstrated that the use of aprepitant was associated with a 13% improvement over ondansetron for the No Vomiting endpoint. As in Study 090, this represents a clinically significant improvement over a drug many consider a standard of care. The non-inferiority analyses do support that aprepitant is non-inferior to ondansetron for the Complete Response endpoint.

1.3.3 Safety

The safety and tolerability of aprepitant compared to ondansetron were assessed by statistical and clinical review of the proportions of patients reporting adverse experiences, reasons for discontinuation due to adverse experiences, laboratory values, physical examinations, and vital signs.

Since it was unknown whether aprepitant would affect the metabolism of the anesthetics used during surgical procedures, in addition to the standard safety evaluations, the Division requested the studies evaluate additional safety parameters: awakening time, duration of recovery, Serious Adverse Events (SAE) of excessive sedation and respiratory depression.

Overall, Studies 090 and 091 successfully demonstrated that aprepitant is as safe and as well tolerated as ondansetron when used to prevent PONV. The safety analysis did not identify any new safety concerns. The incidence and type of adverse and serious adverse events was similar among the three treatment groups. The safety analyses did not suggest that the use of aprepitant adversely affected the safety profile of the anesthesia or surgical procedure.

Demographics:

Table 5
Demographics
Studies 090 and 091

Demographics	Treatment Group		
	Aprepitant 40 mg (N=564) n/%	Aprepitant 125 mg (N=556) n/%	Ondansetron (N=538) n/%
Sex			
Female	519 (92.0)	510 (91.7)	503 (93.5)
Male	45 (8.0)	46 (8.3)	35 (6.5)
Race			
Caucasian	329 (58.3)	305 (54.9)	311 (57.8)
Black	78 (13.8)	101 (18.2)	75 (13.9)
Asian	32 (5.7)	35 (6.3)	36 (6.7)
Hispanic	76 (13.5)	73 (13.1)	76 (14.1)
Other	11 (2.0)	2 (0.4)	3 (0.6)
Age			
Mean	46.1	45.1	45.0
Median	45.0	45.0	44.0
SD	11.35	10.26	11.18
Age ≥ 65 years	46 (8.2)	34 (6.1)	37 (6.8)
Ref: Modified Table 2.7.4:3 Integrated Summary of Safety			

The PONV development program (Protocols 090 and 091) randomized a total of 1727 patients, of whom 1658 patients received active study drug [40mg group (564), 125mg group (556), ondansetron group (538). The three treatment groups were similar with respect to baseline demographics. Overall, 92% of the patients were females and the mean age was 45.4 ± 10.95 years.

Adverse Events:

The incidence and type of adverse and serious adverse events were similar among the three treatment groups.

Table 6
Adverse Events Summary
Studies 090 and 091

Adverse Experience	Treatment Group		
	Aprepitant 40mg (N=564) n/(%)	Aprepitant 125mg (N=556) n/(%)	Ondansetron (N=539) n/(%)
No Adverse Event(s)	228 (40.4)	202 (36.3)	194 (36.1)
≥ 1 Adverse Event(s)	336 (59.6)	354 (63.7)	344 (63.9)
≥ 1 Serious Adverse Event(s)	49 (8.7)	43 (7.7)	50 (9.3)
Death	1 (0.2)	1 (0.2)	1 (0.2)
Discontinued from Study due to AE	0 (0.0)	1 (0.2)	0 (0.0)
Discontinued from Study due to SAE	0 (0.0)	1 (0.2)	1 (0.2)
Ref: Modified Table 2.7.4:10 Integrated Summary of Safety			

Adverse Events by System Organ Class

Table 7
Select Adverse Events by Body System
(Incidence ≥ 2%)
Safety Population Study 090 and 091

Adverse Experience	Treatment Group		
	Aprepitant 40mg (N=564) n/(%)	Aprepitant 125mg (N=556) n/(%)	Ondansetron (N=538) n/(%)
Patients with No Adverse Event(s)	**228 (40.4)**	**202 (36.3)**	**194 (36.1)**
Patients with Adverse Event(s)	**336 (59.6)**	**354 (63.7)**	**344 (63.9)**
Blood and Lymphatic System	**18 (3.2)**	**23 (4.1)**	**24 (4.5)**
Anemia	17 (3.0)	23 (4.1)	23 (4.3)
Cardiac Disorders	**34 (6.0)**	**41 (7.4)**	**41 (7.6)**
Bradycardia	25 (4.4)	22 (4.0)	21 (3.9)
Sinus Tachycardia/ Tachycardia	4 (0.7)	11 (2.0)	9 (1.7)
Gastrointestinal Disorders	**148 (26.2)**	**145 (26.1)**	**145 (27.0)**
Abdominal distension	9 (1.6)	13 (2.3)	9 (1.7)
Constipation	48 (8.5)	34 (6.1)	41 (7.6)
Nausea	48 (8.5)	46 (8.3)	46 (8.6)
Vomiting	14 (2.5)	10 (1.8)	21 (3.9)
Infections, Infestations	**55 (9.8)**	**54 (9.7)**	**58 (10.8)**
Urinary tract Infection	13 (2.3)	17 (3.1)	17 (3.2)
Wound Infection	10 (1.8)	7 (1.3)	11 (2.0)
Nervous System Disorders	**54 (9.6)**	**72 (12.9)**	**58 (10.8)**
Headache	28 (5.0)	45 (8.1)	35 (6.5)
Respiratory, and Thoracic Disorders	**55 (9.8)**	**43 (7.7)**	**56 (10.4)**
Vascular Disorders	**56 (9.9)**	**58 (10.4)**	**49 (9.1)**
Hypotension	32 (5.7)	36 (6.5)	25 (4.6)
Hypertension	12 (2.1)	10 (1.8)	17 (3.2)

Ref: Modified Table 2.7.4:12 Integrated Summary of Safety
a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

Examination of the incidence and type of adverse events by Body System did not suggest that the use of aprepitant adversely affected the safety profile of the anesthesia or surgical procedure. For example, the incidence of "wound infection" and "anemia" were slightly higher in the ondansetron group. On examination of adverse events reported as drug related, the incidences of specific, drug-related adverse events were comparable across treatment groups.
These findings suggest that aprepitant is as safe as ondansetron in patients undergoing a surgical procedure.

1.3.4 Dosing Regimen and Administration

Eligible patients were assigned to one of the following three treatment arms using a computer generated randomization schedule. Patients were treated with study medications only on Day 1, preoperatively.

Table 8
Treatment Arms

Treatment Group	*Bottle A (PO)*	*Vial B (I.V.)*
I	Aprepitant 125 mg PO Placebo Aprepitant 40mg PO	Placebo Ondansetron 4mg I.V.
II	Aprepitant 40mg PO Placebo Aprepitant 125 mg PO	*Placebo Ondansetron 4mg* I.V.
III	Placebo Aprepitant 125 mg PO *Placebo Aprepitant 40mg PO*	*Ondansetron 4mg* I.V.

The oral study medication (aprepitant or placebo) was administered 1 to 3 hours prior to induction of anesthesia. The intravenous study medication (ondansetron or placebo) was given immediately before induction of anesthesia. The two dose levels of aprepitant (125mg and 40mg) were acceptable for these Phase III studies. They were based on dose ranging data from the CINV development program.

1.3.5 Drug-Drug Interactions

Aprepitant has a complex metabolism. Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. 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.

This current application included Study 108, a new drug interaction study with IV midazolam. It also referenced two previous studies submitted with the original NDA which are not included in the currently approved label. A brief summary of this data is outlined in Section 5 of this review. A detailed review of these studies was performed by the Agency's Biopharmaceutics division (Review in DFS).

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

Based on the specific eligibility criteria, the majority of patients in the PONV development program were expected to consist of women undergoing a gynecological surgery. Greater than 92% of the patients enrolled in the PONV studies were female, with the mean age being 45.4 ± 10.95 years.

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_{0-24hr} 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 (Cr Cl<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."

APPEARS THIS WAY ON ORIGINAL

2 INTRODUCTION AND BACKGROUND

In September1995, Merck Research Laboratories (Merck) submitted IND 48-924 to evaluate a water soluble injectable formulation of aprepitant (L-758298). 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.

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. Based on a formal review of the submitted data, the moderately emetogenic indication was approved with a slight modification to the indication:

- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy

Merck submitted the current application, S-NDA 21-549/010 on August 30, 2005, seeking approval for the prevention of Post Operative Nausea and Vomiting.

Aprepitant has also been studied as a treatment for major depression, schizophrenia, migraine headaches, dental pain, postherpetic neuralgia, as well as a treatment for motion-induced nausea.

2.1 Product Information

The approved formulation of aprepitant is an oral nanoparticle, substance P, neurokinin 1 (NK_1) receptor antagonist. It is currently marketed in two dose strengths (125mg and 80mg). With this application, Merck is proposing a third dose strength (40mg).

Aprepitant is currently 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 for the prevention of both moderately and highly emetogenic chemotherapy induced nausea and vomiting is 125 mg orally 1 hour prior to chemotherapy (Day 1) and 80 mg once daily in the morning on Days 2 and 3. With this application, Merck is seeking an indication for the prevention of PONV, using aprepitant as a mono-therapy.

2.2 Currently Available Treatment for Indications

There are several approved therapies for the prevention of PONV. Currently, the most effective and widely used therapies are in the class 5-HT_3 receptor antagonists. Other drugs with approved indications for nausea and vomiting include promethazine (Phenergan®), prochlorperazine (Compazine®), metoclopramide (Reglan®), and trimethobenzamide (Tigan®)

There are currently three 5-HT_3 antagonists approved for the PONV indication.

Table 9
5-HT_3 Antagonists
Approved for PONV

Drug	Mode	Age (years)	Approval Date
granisetron	Injection	Adult Only	8/02
ondansetron	Injection	2-12 Adult	5/96
dolasetron	Injection/ Tablet	2-Adult	9/97
* Palonosetron (5-HT_3 receptor antagonist) not approved for PONV			

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 December 2, 2004, Merck submitted a formal meeting request for a Type B (Pre-SNDA) meeting to discuss their plans for submitting a supplemental New Drug Application for a PONV indication for Emend. The Division met with Merck on February 24, 2005. During this meeting the Division discussed the change in the primary endpoint of Study 091 from Complete Response to two primary endpoints (No Vomiting and a non inferiority analysis for Complete Response). The Division accepted the revised endpoints, but noted that the success of the trial was "dependent on satisfying both primary endpoints". The Sponsor was informed they would need to provide a statistical justification for the overall significance level of the stepdown testing procedure proposed, taking into particular account the overlap in endpoints (no vomiting is part of a complete response).

The Division emphasized that two *successful* adequate and well-controlled studies were recommended to support any new indication and that we had serious concerns about the strength of the efficacy results on a preliminary review of Study 090.

The Division also agreed to defer submission of data on pediatric patients in the initial sNDA submission. The Sponsor was instructed to request deferral at the time of the sNDA submission and to include a deferral date and the rationale for requesting the deferral. (Ref: Meeting Minutes DFS 03/25/05)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The Chemistry review of S-NDA 21-549 /010 was not finalized at the time this review was completed. Any pertinent CMC issues will be addressed in the Team Leader supplemental review (See Hugo Gallo-Torres M.D., Ph.D., P.N.S Review).

3.2 Animal Pharmacology/Toxicology

Supplemental NDA 21-549/010 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 21-549/010
Original NDA 21-549 Review
S-NDA 21-549/008
Periodic Adverse Experience Report (April 25, 2006)
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 10
PONV Clinical Trials

Patients Randomized	Treatment Group		
	Aprepitant 40mg Oral	Aprepitant 125mg Oral	Ondansetron 4mg Intravenous
Study 090			
Randomized	**272**	**263**	**270**
completed	258	240	254
discontinued	14	23	16
Study 091			
Randomized	**307**	**313**	**302**
completed	301	298	285
discontinued	6	15	17

4.3 Review Strategy

A multi-specialty review of the Supplemental New Drug Application (S-NDA) 21-549 / 010 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 two pivotal trials were reviewed independently 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 reported that one of their study sites in Study 090 and two in Study 091 were identified as being non-compliant with some/all requirements of Good Clinical Practice. These data were not included in the primary efficacy analyses. These data were reviewed. Excluding these dat from the efficacy analyses did not affect my interpretation of the results.

Dr. Paul White – Dallas, Texas, 090-0024
Dr. John Moodie – Hamilton, New Zealand, 091-0002
Dr. Hector Alfaro – Mexico D.F., Mexico, 091-0029

With the exception of the above investigators, Merck certified that the studies were conducted in conformance with Good Clinical Practice standards and/or local statutes and regulations regarding informed consent, and 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

SNDA 21-549/010 included two clinical pharmacology studies: Protocols 107 and 108. Study 107 investigated the bioavailability and food effect on Emend 40 mg capsules while Study 108 was a drug interaction study with I.V. midazolam. The Sponsor also referenced two drug interaction studies, which were provided in the original NDA.

As a background, 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.

The Clinical Pharmacology review of S-NDA 21-549 /010 was not finalized at the time this review was completed. Any pertinent pharmacology issues will be addressed in the Team Leader supplemental review (See Hugo Gallo-Torres M.D., Ph.D., P.N.S Review).

The following is this Reviewer's brief summary of the new clinical pharmacology data submitted with SNDA 21-549 /010 (Protocols 107 and 108). A detailed formal review of these studies will be performed by the Agency's Biopharmaceutics division and will be filed in DFS.

5.1 Pharmacokinetics

Study 107:

Following single oral administration of Emend 40 mg under fasting conditions, mean AUC was 7997 ng. hr/mL and mean C_{max} was 712.8 ng/mL occurring at approximately 3 hours post dose.

At the 40 mg dose, a high fat breakfast delayed T_{max} for 2 hours and decreased C_{max} by 18% but did not alter the extent of absorption Note: Food effect is not critical for the proposed indication since patients are supposed to be fasted before surgery.
Multiple dose PK was not provided. Note: the 40 mg capsules will be administered for PONV as a single dose only.

5.2 Pharmacodynamics

The following pharmacodynamic information is summarized from the original NDA.

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).

This current application included Study 108, a drug interaction study with IV midazolam. It also referenced two previous studies submitted with the original NDA which are not included in the currently approved label.

Midazolam Interaction Studies:

Study 108:

Concomitant administration of oral aprepitant 125 mg increased the bioavailability of midazolam IV 2.0 mg (C_{max}: increased 20.3%; AUC: increased 47.1%).

Study 041:

Oral aprepitant 125 mg (on Day 1 of a 5 day regimen) produced a 2.27-fold increase in the oral midazolam AUC. Therefore, aprepitant 125 mg is considered a moderate inhibitor.

Conclusion of Midazolam Interaction Studies:

The effect of oral aprepitant 125 mg is greater on oral midazolam 2 mg (2.27 fold increase; Study 041) compared to IV midazolam 2 mg (1.47 fold increase; Study 108) most likely due to first pass effect for oral midazolam.

Oral Aprepitant given at a 40-mg dose (on Day 1 of a 5 day regimen) produced a 1.22-fold increase in the AUC of midazolam 2 mg PO. Therefore, aprepitant 40 mg is considered a weak inhibitor and is not expected to have a clinically important effect on IV midazolam.

No dosage adjustment is necessary when 2 mg midazolam IV is co-administered with either 40 mg or 125 mg of oral aprepitant.

Dexamethasone Interaction Studies:

The effect of oral aprepitant 40 mg on oral dexamethasone 20 mg (on Day 1 of a 5 day regimen) was evaluated in a study submitted to the original NDA. Aprepitant 40 mg orally increased the dexamethasone AUC to 1.45 fold (90% CI of 1.31, 1.61) and C_{max} to 1.20 fold.

Conclusion of Dexamethasone Interaction Studies

The effect of oral aprepitant 40 mg on oral dexamethasone 20 mg is not considered clinically important.

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 results from Protocols 090 and 091 to support the approval of the aprepitant for the prevention of PONV.

6.1.1 Methods

A multi-specialty review of the S-NDA 21-549 / 010 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:

Complete Response:	No Emesis, No Rescue therapy
No Vomiting:	No vomiting, retching or dry heaves Vomiting episodes were considered distinct if separated by the absence of symptoms for at least 1 minute. (includes patients who received rescue therapy).
Nausea:	assessed using 11 point Verbal Rating Score (VRS)
Rescue Therapy:	Any medication used to treat established nausea and vomiting

6.1.3 Study Design

Merck submitted results from Protocols 091 and 090 to support the approval of 40mg aprepitant for the prevention of PONV. The two protocols were identical with respect to study design, study population, study treatments, and efficacy assessments. Both were multicenter, double-blind, randomized, active comparator-controlled, parallel-group studies that evaluated the safety and efficacy of aprepitant in the prevention of PONV in surgical patients. Although the two studies were of similar design, they differed in terms of study hypotheses, efficacy analyses and geographic location.

The study populations consisted of patients scheduled to receive general anesthesia for an open abdominal surgery requiring at least an overnight hospital stay. Eligible patients were assigned to one of the following three treatment arms using a computer generated randomization schedule. Patients were treated with a single dose of study medications only on Day 1, preoperatively.

Table 11
Treatment Arms

Treatment Group	*Bottle A (PO)*	*Vial B (I.V.)*
I	Aprepitant 125 mg PO Placebo Aprepitant 40mg PO	Placebo Ondansetron 4mg
II	Aprepitant 40mg PO Placebo Aprepitant 125 mg PO	Placebo Ondansetron 4mg
III	Placebo Aprepitant 125 mg PO Placebo Aprepitant 40mg PO	Ondansetron 4mg

Limitations of the Study Design

The enrollment criteria included male and female patients receiving general anesthesia. However, based on the specific eligibility criteria, open abdominal surgery that required an overnight hospital stay, the majority of patients were expected to consist of women undergoing a gynecological surgery. The study population was acceptable. It is similar to the population enrolled in the two pivotal trials that provided the basis for approval of oral ondansetron for the prevention of PONV: women undergoing general and gynecological surgery requiring overnight hospitalization.

As with the prior studies used to support approval of the HEC and MEC induced nausea and vomiting indication, this Reviewer is concerned that the results of these two studies may not be generalizable to both male and female patients since the vast majority of enrolled patients were female.

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 surgical patients.

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<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

The question of possible treatment-by-gender interaction was not resolved during the MEC development program. The single study (Study 071) used to support the indication for prevention of moderately emetogenic CINV enrolled greater than 99% female patients.

Although it ultimately did not have an impact on my final recommendation, to be thorough, it is worth noting that this Reviewer questioned whether the studies used in calculating the non-inferiority margin, for the second primary endpoint were acceptable.

Table 13
Studies Used in Non-Inferiority Calculation
Ondansetron PONV Prevention Trials

Study Population	Drug	Complete Response		Odds Ratio
		Placebo	Active	
Women Out-patients	Ondansetron I.V.	64/139 46%	103/136 76%	3.66
Women Out-patients	Ondansetron I.V.	63/143 44%	86/136 63%	2.18
Women In-patients	Ondansetron PO	105/327 32%	179/343 52%	2.31
Women In-patients	Ondansetron PO	54/204 26%	112/207 54%	3.27
Ref. Modified Table 5-5 Protocol 091				

Study 091 utilized an *intervenous* formulation of ondansetron in a patient population that had a surgical procedure which required an *over-night hospitalization*. None of the studies used in calculating the non-inferiority margin evaluated an appropriate combination of drug formulation and surgical procedure.

The comparative *intravenous* ondansetron studies were performed on patients who had an *out-patient surgery*. It is unlikely that an outpatient surgery would have the same emetogenic potential as a more complicated surgery that required an over-night hospitalization.
The comparative studies that were performed on patients who required an *over-night hospitalization* evaluated the *oral formulation* of ondansetron.

6.1.4 Efficacy Findings

The Division verified the Applicant's data and concurs with the results of the major efficacy analyses. The primary efficacy analyses were performed on the modified intention to treat (mITT) population. The interpretation of the efficacy results requires some clinical judgment since Study 090 failed to satisfy its primary hypothesis. Because of this, the Sponsor amended Protocol 091, resulting in the two protocols having different study hypotheses. Since the two protocols had different study hypotheses, and one study succeeded while the other failed, the studies will first be reviewed separately.

Protocol 090

Primary Endpoint

The primary endpoint in Study 090 was Complete Response for 24-hours after surgery. The Complete Response endpoint is a composite end-point that includes two measured variables: "No Vomiting" and "No Rescue therapy". For Study 090 to succeed for its primary endpoint, aprepitant would need to be statistically significantly better than ondansetron for both variables (No Vomiting and No Rescue therapy).

Study 090 did not successfully satisfy its primary hypothesis that aprepitant (125 mg, 40 mg) is superior to ondansetron in the prevention of PONV as measured by the proportion of patients with Complete Response (no Vomiting and No Rescue Therapy) in the 24 hours following end of surgery. The reason the study failed was that the treatment group difference between the aprepitant groups and the ondansetron group were not statistically significant for one of the two composite variables, "No Rescue Therapy".

Table 14
Study 090
Select Efficacy Endpoints
(Modified- Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant vs Ondansetron	
		Δ	p-Value
Complete Response (Primary Endpoint) (no emesis and no rescue therapy, 0 to 24 hours)			
Aprepitant 40 mg	111/248 (44.8)	2.5	N.S.
Aprepitant 125 mg	103/239 (43.1)	0.8	N.S.
Ondansetron	104/246 (42.3)		
No Vomiting (Secondary Endpoint) (no emetic episodes, 0 to 24 hours)			
Aprepitant 40 mg	223/248 (89.9)	16.3	<0.001*
Aprepitant 125 mg	227/239 (95.0)	21.4	<0.001*
Ondansetron	181/246 (73.6)		
No Use of Rescue Medication (Secondary Endpoint) (for established emesis or nausea, 0 to 24 hours)			
Aprepitant 40 mg	112/248 (45.2)	-0.7	N.S.
Aprepitant 125 mg	106/239 (44.4)	-1.5	N.S.
Ondansetron	113/246 (45.9)		
No Vomiting (Secondary Endpoint) (no emetic episodes, 0 to 48 hours)			
Aprepitant 40 mg	209/247 (84.6)	17.7	<0.001*
Aprepitant 125 mg	220/236 (93.2)	26.3	<0.001*
Ondansetron	164/245 (66.9)		

Ref: Study 090.pdf Page 21 of 1851
Δ Treatment Group Difference Aprepitant vs. Ondansetron.
N.S.=Not Significant
* Not statistically significant based on Sponsor's data analysis plan
n/m= Number of patients responder/number of patients in analysis.

Secondary Endpoint:

Study 090, successfully demonstrated that both dose levels of aprepitant were clinically significantly superior to ondansetron with respect to the "No Vomiting" secondary endpoint during the first 24 hours after surgery. The use of 40 mg aprepitant (proposed dose) was associated with a 16% improvement over ondansetron for the No Vomiting endpoint. Even more impressive, the treatment group differences for the No Vomiting variable were maintained for the first 48 hours after surgery (18%). However, due to the pre-specified data analysis plan, these results cannot be considered statistically significant. However, clinical consideration must be given since the prevention of post operative vomiting is an important outcome.

Furthermore, even in the patients who vomited (treatment failures), the aprepitant patients faired better. In both aprepitant groups, a greater proportion of patients who vomited experienced only one emetic episode (76% in the aprepitant 40 mg group, and 83% in the aprepitant 125 mg group). In contrast, only 52% of the ondansetron-treated patients who vomited suffered a single emetic event.

Protocol 091

After Study 091 was initiated, the protocol was amended and the Data Analysis Plan revised. The Primary Efficacy Hypothesis was changed from superiority of aprepitant over ondansetron for Complete Response to the superiority of aprepitant over ondansetron for the No Vomiting endpoint in the 24 hours following end of surgery. The revisions were based on the results of Study 090, which failed to satisfy its primary hypothesis.

Primary Endpoint

Study 091 included six statistical null/alternative hypotheses that comprised the primary efficacy analyses. These were evaluated in a step-wise fashion, employing a closed testing procedure designed to control the overall Type I error rate at the 0.05 level.

The first primary efficacy endpoint was a superiority analysis for "No Vomiting in the 24-hours following the end of surgery." The results of the No Vomiting endpoint were statistically significantly higher in both of the aprepitant groups compared to the ondansetron group. These data and analyses were confirmed by the Agency.

The second primary efficacy endpoint included two efficacy hypotheses. The first hypothesis was that aprepitant was non-inferior to ondansetron for the Complete Response endpoint (No Vomiting and No Rescue Therapy). Based on the protocol defined non-inferiority margin, both aprepitant doses were non-inferior to ondansetron for the endpoint Complete Response. These data and analyses were also confirmed by the Agency.

Since the first (non inferiority) hypothesis of the second *primary* efficacy endpoint was successful, the second hypothesis was tested: the superiority of aprepitant over ondansetron with respect to the Complete Response endpoint. The Sponsor reported that, based on the protocol defined data analysis plan, both aprepitant doses were also superior to ondansetron for the Complete Response endpoint. However, the Agency's Statistical team does not agree with the Sponsor's analysis. The Agency's Statistical team agrees that Study 091 succeeded in demonstrating non-inferiority; however, for the superiority analyses, statistical significance was not maintained based upon one-sided test using a more appropriate 2.5% significance level and using the multiplicity adjustment method proposed by the sponsor. The issues regarding the calculation of the non-inferiority margin are discussed in detail in the review of Protocol 091 (Appendix B) as well at the Statistical Review (Dr. Wen-Jen Chen).

Table 15
Study 091
Response Rates for Primary Endpoints
Agency's Analyses
(Modified- Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant vs Ondansetron	
		Δ	Analysis
Primary Endpoints			
No Vomiting (Superiority) (no emetic episodes, 0 to 24 hours)			
Aprepitant 40 mg	246/293 (84.0)	12.6%	p<0.001
Aprepitant 125 mg	253/293 (86.3)	14.9%	p<0.001
Ondansetron	200/280 (71.4)		
Complete Response (Non-inferiority) LB of 95% CI > 0.65 (no emesis and no rescue therapy, 0 to 24 hours)			
Aprepitant 40 mg	187/293 (63.8)	8.8%	LB = 1.04
Aprepitant 125 mg	184/293 (62.8)	7.8%	LB = 1.08
Ondansetron	154/280 (55.0)		
Complete Response (Superiority) LB of 95% CI >1.0 (no emesis and no rescue therapy, 0 to 24 hours)			
Aprepitant 40 mg	187/293 (63.8)	8.8%	LB = 1.04*
Aprepitant 125 mg	184/293 (62.8)	7.8%	LB = 1.08*
Ondansetron	154/280 (55.0)		
Secondary Endpoint			
No Vomiting (Superiority) (no emetic episodes, 0 to 48 hours)			Odds Ratio[Ŧ]
Aprepitant 40 mg	238/292 (81.5)	15.2%	2.3
Aprepitant 125 mg	246/290 (84.8)	18.5%	2.9
Ondansetron	185/279 (66.3)		

Ref: Study 091.pdf Modified Table 7-1 and 7-9
Δ Treatment Group Difference Aprepitant vs. Ondansetron.
LB = lower bound of the 1-sided 95% confidence interval.
*P value <0.05
Ŧ: Estimated odds ratio for Aprepitant versus Ondansetron. A value of >1 favors Aprepitant over Ondansetron.
n/m= Number of patients responder/number of patients in analysis.

Combined Tables

Table 16
Select Efficacy Endpoints*
Studies 090 and 091
(Modified- Intention-to-Treat Population)

Treatment	Study 090	Study 091
Complete Response (no emesis and no rescue therapy, 0 to 24 hours)		
Aprepitant 40 mg	111/248 (44.8)	187/293 (63.8)
Aprepitant 125 mg	103/239 (43.1)	184/293 (62.8)
Ondansetron	104/246 (42.3)	154/280 (55.0)
No Vomiting (no emetic episodes, 0 to 24 hours)		
Aprepitant 40 mg	223/248 (89.9)	246/293 (84.0)
Aprepitant 125 mg	227/239 (95.0)	253/293 (86.3)
Ondansetron	181/246 (73.6)	200/280 (71.4)
No Use of Rescue Medication (for established emesis or nausea, 0 to 24 hours)		
Aprepitant 40 mg	112/248 (45.2)	197/293 (67.2)
Aprepitant 125 mg	106/239 (44.4)	190/293 (64.8)
Ondansetron	113/246 (45.9)	176/280 (62.9)
No Vomiting (no emetic episodes, 0 to 48 hours)		
Aprepitant 40 mg	209/247 (84.6)	238/292 (81.5)
Aprepitant 125 mg	220/236 (93.2)	246/290 (84.8)
Ondansetron	164/245 (66.9)	185/279 (66.3)

n/m= Number of patients responder/number of patients in analysis.
* Side by Side Comparison of Efficacy Results (Different Endpoints)
Study 090 Primary Endpoint: Complete Response (24 Hours)
Study 091 Primary Endpoint: No Vomiting (24 Hours)
Complete Response (non-inferior)
Complete Response (superior)

6.1.5 Clinical Microbiology

Not Applicable

6.1.6 Efficacy Conclusions

In this Reviewer's opinion, both studies (Protocols 090, 091) successfully demonstrate that aprepitant provided effective protection against PONV. The interpretation of these results requires some clinical judgment since Study 090 failed to satisfy its primary hypothesis. The primary endpoint in Study 090 was Complete Response, a composite end-point that included "No Vomiting" and "No Rescue therapy". The reason the Study 090 failed was that the treatment group differences for the "No Rescue" endpoint failed to reach statistical significance.

Study 090, however, did demonstrate that the use of 40 mg aprepitant (proposed dose) was associated with a 16% improvement over ondansetron for the No Vomiting endpoint. Even more impressive, the treatment group differences for the No Vomiting endpoint persisted for 48 hours after surgery (18%). This Reviewer acknowledges the that due to the pre-specified data analysis plan, these results cannot be considered statistically significant; however, the results are clinically meaningful.

Unlike Chemotherapy Induced Nausea and Vomiting (CINV), which is associated with repeat cycles of "Acute and Delayed" nausea and vomiting lasting 5 days or longer, in this Reviewer's opinion, the success of the No Vomiting endpoint is the most clinically important measure of efficacy in surgical patients. The most serious complications associated with PONV are directly related to the vomiting process (i.e. wound disruption, increased intraabdominal, intraocular and intracranial pressures, esophageal tears, electrolyte imbalance, and pulmonary aspiration. Whether of not a patient required rescue therapy is not as clinically important as the prevention of postoperative vomiting.

Study 091 satisfied both of it's primary hypotheses, that aprepitant is superior to ondansetron in the prevention of post operative vomiting and was non inferior to ondansetron as measured by the Complete response endpoint. The success of these endpoints and considerations of the other efficacy variables support that both dose levels of aprepitant were effective in the prevention of PONV.

Study 091 demonstrated that the use of aprepitant was associated with a 13% improvement over ondansetron for No Vomiting 24 hours after surgery (Primary Endpoint). This treatment group difference persisted in favor of aprepitant through 48 hours after surgery (Secondary endpoint). The use of aprepitant was associated with a 15% improvement over ondansetron for No Vomiting 48 hours after surgery As in Study 090, this represents a clinically significant improvement over a drug considered a standard of care by many institutions.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

A detailed review of the clinical sections of S-NDA 21-549 /010 was performed utilizing applicant submitted data.

7.1.1 Deaths

Three deaths were reported during the PONV studies: 1 patient (0.2%) in the aprepitant 40 mg group, 1 patient (0.2%) in the aprepitant 125-mg group, and 1 patient (0.2%) in the ondansetron group.

(b) (6) (aprepitant 40 mg), a 75 year-old, White male died of myeloproliferative disorder 28 days after administration of study therapy.

(b) (6) (aprepitant 125-mg group), a 44 year-old, Black female died of arrhythmia 7 days after administration of study therapy.

(b) (6) (ondansetron group), a 46 year-old, multi-racial woman experienced coagulopathy and multi-organ failure, and died 11 days after administration of study therapy.

None of these fatal serious adverse events were considered drug related by the investigator. A review of the CRFs did not suggest the events were related to study drug.

7.1.2 Other Serious Adverse Events

In general, the incidence and type of serious adverse events were similar among treatment groups. The safety analyses did not suggest that the use of aprepitant adversely affected the safety profile of the anesthesia or surgical procedure.

Serious Adverse Events by Body System

Table 17
Select Serious Adverse Events by Body System
(Incidence >0%)
Safety Population Studies 090 and 091

Adverse Experience	Treatment Group		
	Aprepitant 40mg (N=564)	Aprepitant 125mg (N=556)	Ondansetron (N=538)
≥ 1 Serious Adverse Event	**49 (8.7)**	**43 (7.7)**	**50 (9.3)**
Blood and Lymphatic System	**2 (0.4)**	**2 (0.4)**	**2 (0.4)**
Anemia	2 (0.4)	2 (0.4)	1 (0.2)
Coagulopathy	0 (0.0)	0 (0.0)	1 (0.2)
Cardiac Disorders	**0 (0.0)**	**3 (0.5)**	**2 (0.4)**
Arrhythmia	0 (0.0)	1 (0.2)	0 (0.0)
Cardio-Respiratory Arrest	0 (0.0)	0 (0.0)	1 (0.2)
Tachycardia / Sinus Tachycardia	0 (0.0)	1 (0.2)	1 (0.2)
Supraventricular Tachycardia	0 (0.0)	1 (0.2)	0 (0.0)
Gastrointestinal Disorders	**9 (1.6)**	**15 (2.7)**	**14 (2.6)**
Abdominal Distention	0 (0.0)	2 (0.4)	0 (0.0)
Abdominal Hematoma	0 (0.0)	1 (0.2)	0 (0.0)
Abdominal Pain / Abdominal Pain Upper	**2 (0.4)**	2 (0.4)	0 (0.0)
Constipation	2 (0.4)	1 (0.2)	2 (0.4)
Gastrointestinal Necrosis	0 (0.0)	0 (0.0)	1 (0.2)
Ileus / Ileus Paralytic	2 (0.4)	5 (0.9)	2 (0.4)
Intra-abdominal hemorrhage	1 (0.2)	0 (0.0)	0 (0.0)
Peritonitis	0 (0.0)	1 (0.2)	1 (0.2)
Vomiting	0 (0.0)	1 (0.2)	1 (0.2)
Infections and Infestations	**7 (1.2)**	**6 (1.1)**	**10 (1.9)**
Abdominal wall abscess	0 (0.0)	0 (0.0)	1 (0.2)
Hematoma infection	1 (0.2)	0 (0.0)	0 (0.0)
Pelvic abscess	1 (0.2)	1 (0.2)	1 (0.2)
Pneumonia	1 (0.2)	1 (0.2)	0 (0.0)
Wound Infection	2 (0.4)	0 (0.0)	4 (0.7)
Postoperative infection	2 (0.4)	1 (0.2)	1 (0.2)
Sepsis	0 (0.0)	0 (0.0)	1 (0.2)

Ref: Modified Table 2.7.4:17 ISS

Table 17 (cont)
Select Serious Adverse Events by Body System
(Incidence >0%)
Safety Population Studies 090 and 091

Adverse Experience (cont)	Treatment Group		
	Aprepitant 40mg (N=564)	Aprepitant 125mg (N=556)	Ondansetron (N=538)
Injury and Procedural Complications	**11 (2.0)**	**8 (1.4)**	**7 (1.3)**
Anastomotic leak	0 (0.0)	0 (0.0)	1 (0.2)
Postoperative wound complication	0 (0.0)	0 (0.0)	1 (0.2)
Wound dehiscence	2 (0.4)	2 (0.4)	1 (0.2)
Wound evisceration	0 (0.0)	0 (0.0)	1 (0.2)
Nervous System Disorders	**1 (0.2)**	**3 (0.5)**	**2 (0.4)**
Sedation	1 (0.2)	0 (0.0)	0 (0.0)
Respiratory, and Thoracic Disorders			
Respiratory Rate Decreased	1 (0.2)	0 (0.0)	0 (0.0)
Hypoventilation	0 (0.0)	0 (0.0)	1 (0.2)
Respiratory Arrest	0 (0.0)	2 (0.4)	0 (0.0)
Respiratory Depression	1 (0.2)	0 (0.0)	0 (0.0)
Ref: Modified Table 2.7.4:17 ISS			

The most common criteria for defining an AE as serious was prolonged hospitalization. The most common serious adverse events were Gastrointestinal Disorders: aprepitant 40-mg group 9 (1.6%), aprepitant 125-mg group 15 (2.7%), and ondansetron group 14 (2.6%).

Three serious adverse events were considered by the investigator as possibly drug related.

(b) (6) (aprepitant 125-mg): experienced mild constipation the day after surgery and lasted for 4 days which prolonged the hospitalization.

(b) (6) (aprepitant 125-mg): developed a sub ileus two days after surgery that lasted 5 days and prolonged the hospitalization.

(b) (6) (ondansetron group): experienced moderate constipation two days after surgery and lasted for 7 days, causing prolongation of the hospitalization.

7.1.3 Dropouts and Other Significant Adverse Events

Four of the 1658 (0.2%) randomized patients who received study drug experienced an adverse event that resulted in discontinuation from the study. No patients were discontinued due to laboratory adverse events. A review of the CRFs of patients who discontinued from the studies did not suggest a safety signal.

7.1.4 Other Search Strategies

The safety data from each study was reviewed independently and outlined. The results of this safety analysis were then compared to the Sponsor's integrated summary of safety. The Safety data from these studies were then compared to safety data in the original NDA to see if any new safety signals were identified. The narratives of all serious adverse events were reviewed.

7.1.5 Common Adverse Events

Table 18
Select Adverse Events by Body System
(Incidence ≥ 2%)
Safety Population Study 090 and 091

Adverse Experience	Treatment Group		
	Aprepitant 40mg (N=564) n/(%)	Aprepitant 125mg (N=556) n/(%)	Ondansetron (N=538) n/(%)
Patients with No Adverse Event(s)	**228 (40.4)**	**202 (36.3)**	**194 (36.1)**
Patients with Adverse Event(s)	**336 (59.6)**	**354 (63.7)**	**344 (63.9)**
Blood and Lymphatic System	**18 (3.2)**	**23 (4.1)**	**24 (4.5)**
Anemia	17 (3.0)	23 (4.1)	23 (4.3)
Cardiac Disorders	**34 (6.0)**	**41 (7.4)**	**41 (7.6)**
Bradycardia	25 (4.4)	22 (4.0)	21 (3.9)
Sinus Tachycardia/ Tachycardia	4 (0.7)	11 (2.0)	9 (1.7)
Gastrointestinal Disorders	**148 (26.2)**	**145 (26.1)**	**145 (27.0)**
Abdominal distension	9 (1.6)	13 (2.3)	9 (1.7)
Constipation	48 (8.5)	34 (6.1)	41 (7.6)
Nausea	48 (8.5)	46 (8.3)	46 (8.6)
Vomiting	14 (2.5)	10 (1.8)	21 (3.9)
Infections, Infestations	**55 (9.8)**	**54 (9.7)**	**58 (10.8)**
Urinary tract Infection	13 (2.3)	17 (3.1)	17 (3.2)
Wound Infection	10 (1.8)	7 (1.3)	11 (2.0)
Nervous System Disorders	**54 (9.6)**	**72 (12.9)**	**58 (10.8)**
Headache	28 (5.0)	45 (8.1)	35 (6.5)
Respiratory, and Thoracic Disorders	**55 (9.8)**	**43 (7.7)**	**56 (10.4)**
Vascular Disorders	**56 (9.9)**	**58 (10.4)**	**49 (9.1)**
Hypotension	32 (5.7)	36 (6.5)	25 (4.6)
Hypertension	12 (2.1)	10 (1.8)	17 (3.2)

Ref: Modified Table 2.7.4:12 Integrated Summary of Safety
a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

The incidence and type of adverse events was similar among the three treatment groups. This analysis did not suggest that the use of aprepitant adversely affected the safety profile of the anesthesia or surgical procedure. The most common adverse events were in the category of gastrointestinal disorders. Adverse events of ileus, ileus paralytic, sub ileus and postoperative ileus, when combined, occurred with similar incidence: aprepitant 40-mg group (1.4%), aprepitant 125-mg group (2.0%) and the ondansetron group (1.3%). The incidence of gastrointestinal obstruction, intestinal obstruction, and small intestinal obstruction, when combined, occurred with slightly lower incidence in the aprepitant groups compared with the ondansetron [aprepitant 40-mg (0.2%), aprepitant 125-mg group (0.7%), and ondansetron group (1.5%)].

The incidences of infections and infestations were also similar in each treatment group, and none were considered drug related by the investigators Overall wound infections (wound infection, suture line infection, inflammation of wound, wound complication, postoperative wound complication, incision site complication, wound secretion, wound evisceration, wound dehiscence) when combined, occurred with similar incidences across treatment groups: [aprepitant 40-mg (3.4%), aprepitant 125-mg group (4.3%), and ondansetron group (3.7%)].

The overall incidence of hemorrhage-related adverse events (hemorrhage, shock hemorrhagic, incision site hemorrhage, wound hemorrhage, operative hemorrhage, post procedural hemorrhage, genital hemorrhage, uterine hemorrhage, vaginal hemorrhage, intra-abdominal hemorrhage) was similar across treatment groups: [aprepitant 40-mg (2.0%), aprepitant 125-mg group (3.6%), and ondansetron group (3.0%)].

7.1.6 Less Common Adverse Events

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

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Criteria for identifying Clinically Significant Laboratory Abnormalities (CSLA) were pre-defined in the protocol.

Table 19
Number (%) of Patients With Clinically Significant Laboratory Abnormalities (CSLA) by Treatment Group (24 Hours Postsurgery)
Pooled PONV Studies—Protocols 091 – 090

Lab Test	Predefined Limit of Change	Treatment	n/N (%)‡
WBC 10^3/microL	Value ≤0.642 * LLN and Decrease >0	Aprepitant 40 mg	0/486 (0)
		Aprepitant 125 mg	0/490 (0)
		Ondansetron	0/480 (0)
	Value ≥1.49 * ULN and Increase >0	Aprepitant 40 mg	18/486 (3.7)
		Aprepitant 125 mg	24/490 (4.9)
		Ondansetron	18/480 (3.8)
Hematocrit (%)	Value ≤0.941 * LLN and Decrease >0	Aprepitant 40 mg	108/469 (23.0)
		Aprepitant 125 mg	96/473 (20.3)
		Ondansetron	118/461 (25.6)
Hemoglobin (gm/dL)	Value ≤0.819 * LLN and Decrease >0	Aprepitant 40 mg	78/486 (16.0)
		Aprepitant 125 mg	77/490 (15.7)
		Ondansetron	91/480 (19.0)
ALT	Value ≥3 * ULN and Increase >0	Aprepitant 40 mg	10/512 (2.0)
		Aprepitant 125 mg	7/500 (1.4)
		Ondansetron	5/495 (1.0)
AST	Value ≥3 * ULN and Increase >0	Aprepitant 40 mg	6/498 (1.2)
		Aprepitant 125 mg	5/486 (1.0)
		Ondansetron	4/474 (0.8)
Alk Phos	Value ≥3 * ULN and Increase >0	Aprepitant 40 mg	0/525 (0)
		Aprepitant 125 mg	0/514 (0)
		Ondansetron	0/514 (0)
Total Bilirubin (mg/dL)	Value ≥1.667 * ULN and Increase >0	Aprepitant 40 mg	8/520 (1.5)
		Aprepitant 125 mg	3/505 (0.6)
		Ondansetron	1/504 (0.2)

Ref: Modified Table 2.7.4:20 ISS
ULN = Upper limit of normal range
LLN = Lower limit of normal range
‡ Total number of patients with valid values of the laboratory or vital sign test.

7.1.7.2 Standard analyses and explorations of laboratory data

Overall the incidence and type of laboratory adverse events were similar between treatment groups and did not suggest a safety signal. There was a slight increased incidence of CSLA for hepatic laboratory studies in the aprepitant group compared to the ondansetron group. However, the number of patients with CSLA is too small to draw any conclusions. The clinical significance of this finding is unknown. A review of the safety data from the HEC and MEC development program did not suggest that the use of aprepitant adversely affected the liver.

7.1.7.2.1 Marked outliers and dropouts for laboratory abnormalities

Two laboratory adverse events were reported as serious and both occurred in the ondansetron group. There were no laboratory adverse events reported that resulted in discontinuation from the study.

7.1.8 Vital Signs

Vital signs, including measurements for systolic and diastolic blood pressure, pulse, temperature, and respiratory rate were recorded at baseline, every 15 minutes in the recovery room and at 2, 6, and 24 hours after the end of surgery.

The protocol defined criteria for identifying Clinically Significant Vital Sign Abnormalities (CSVA). The incidence of CSVA was generally similar between treatment groups. Numerically, more patients in the aprepitant 40-mg group had a decrease in diastolic blood pressure compared to ondansetron. The significance of this is unknown since the incidence of diastolic hypotension in the aprepitant 125-mg group was lower than that in the ondansetron group. Similarly, more patients in the aprepitant 40-mg group had a decrease in pulse rate compared to ondansetron; however, the frequency of this side effect was not dose-dependent either. Numerically, more patients in the ondansetron group had an increase in respiratory rate above 18 compared with the aprepitant groups.

Table 20
Clinically Significant Vital Sign Abnormality
Safety Population Studies 090 and 091

Vital Sign	Treatment Group		
	Aprepitant 40mg n (%)	Aprepitant 125mg n (%)	Ondansetron n (%)
Systolic Blood Pressure			
≥180 mmHg and ≥20 mmHg Inc.	11/560 (2.0)	11/548 (2.0)	14/538 (2.6)
≤90 mmHg and ≥20 mmHg Dec.	41/560 (7.3)	48/548 (8.8)	44/538 (8.2)
Diastolic Blood Pressure			
≥105 mmHg and ≥15 mmHg Inc.	6/560 (1.1)	11/548 (2.0)	11/538 (2.0)
≤50 mmHg and ≥15 mmHg Dec.	83/560 (14.8)	58/ 548 (10.6)	66/538 (12.3)
Pulse Rate (bpm)			
≥120 bpm and ≥15 bpm Inc.	8/560 (1.4)	9/548 1.6)	10/538 (1.9)
≤50 bpm and ≥15 bpm Dec.	18/560 (3.2)	14/548 (2.6)	11/538 (2.0)
Respiratory Rate (rpm)			
>18 rpm	306/559 (54.7)	307/548 (56.0)	323/538 (60.0)
<8 rpm	6/559 (1.1)	10/548 (1.8)	5/538 (0.9)

REF: Modified Table 2.7.4:21 ISS
Inc.=Increase
Dec.=Decrease
n/m = Number of randomized patients in each treatment group with a CSVA/number of randomized

7.1.8.1.1 Analyses focused on measures of central tendencies

The most common abnormalities were respiratory rate above 18, a decrease in diastolic blood pressure, and systolic blood pressure at or below 90 with a decrease from baseline of ≥20. Results were generally similar among the three treatment groups and did not suggest any safety signal.

7.1.8.1.2 Marked outliers and dropouts for vital sign abnormalities

There were no vital sign abnormalities reported as serious adverse events or that resulted in discontinuation from the study.

7.1.9 Electrocardiograms (ECGs)

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.

During Studies 090 and 091 12-lead ECGs were preformed at baseline, and approximately 24 hours postoperatively. All ECGs were sent to a Central Assessment Center.

7.1.9.1 Analyses focused on measures of central tendency

Table 21
12-Lead Electrocardiogram (ECG)
(24 Hours Postsurgery)
Safety Population Studies 090 and 091

12-Lead Electrocardiogram	Treatment Group		
	Aprepitant 40mg	Aprepitant 125mg	Ondansetron
PR interval (msec)			
Mean	148.38	147.02	146.20
Standard Deviation	23.60	22.03	22.97
QTc interval (msec)			
Mean	416.16	418.15	419.27
Standard Deviation	30.36	25.54	31.36
Ref: Modified Tables 2.7.4:22 ISS			

Summary statistics (mean and standard deviation) for the PR interval and QTc were performed 24 hours after the end of surgery. The results of these analyses were similar among treatment groups.

7.1.9.1.1 Marked outliers and dropouts for ECG abnormalities

The percentages of patients with clinically significant QTc interval prolongations at 24 hours after surgery were similar among treatment groups and did not suggest a safety signal. More patients in the ondansetron group had QTc prolongation > 60 msec compared to the aprepitant groups.

Five patients had a QTc value at 24 hours after surgery that exceeded the baseline QTc and was > 500 msec [aprepitant 40-mg group (3), aprepitant 125-mg group (1), ondansetron group (1)]. One additional patient, (b) (6) in the ondansetron group, had a QTc value at 16 days after the end of surgery that exceeded the baseline value and was > 500 msec. These data do not suggest that the use aprepitant is associated with QTc effect.

Table 22
12-Lead Electrocardiogram (ECG)
(24 Hours Postsurgery)
Safety Population Studies 090 and 091

12-Lead Electrocardiogram	Treatment Group		
	Aprepitant 40mg (N= 564) n/m (%)	Aprepitant 125mg (N= 556) n/m (%)	Ondansetron (N= 538) n/m (%)
QTc Interval Prolongation†			
Prolongation <30 msec	221/524 (42.2)	225/516 (43.6)	199/514 (38.7)
Prolongation 30 to 60 msec	46/524 (8.8)	46/516 (8.9)	52/514 (10.1)
Prolongation >60 msec	5/524 (1.0)	4/516 (0.8)	12/514 (2.3)

Ref: Modified Tables 2.7.4:23 ISS
† Largest increase from baseline during treatment phase.
N = Number of randomized patients who took at least one dose of active study medication.
n = Number of randomized patients who took at least one dose of active study medication meeting the predefined criteria.
m = Number of randomized patients who took at least one dose of active study medication and had at least one post baseline QTc
measurement.
% = Percentage (n/m * 100) of patients meeting the predefined criteria.

7.1.10 Immunogenicity

The S-NDA 21-549/010 application did not include studies that evaluated the immunogenicity potential of oral aprepitant.

7.1.11 Human Carcinogenicity

The S-NDA 21-549/010 application 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.

7.1.12 Special Safety Studies

The S-NDA 21-549/010 application did not include any special safety studies.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Aprepitant has no known potential for drug abuse or dependence.

7.1.14 Human Reproduction and Pregnancy Data

Pregnant and lactating females were excluded from participation in the PONV and CINV 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.

7.1.15 Assessment of Effect on Growth

The S-NDA 21-549/010 application did not include any studies that evaluated the effect of oral aprepitant on growth.

7.1.16 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.

7.1.17 Postmarketing Experience

Aprepitant is currently approved in 50 countries including the United States (US), and the European Union (EU) for the prevention of chemotherapy-induced nausea and vomiting (CINV) in combination with other antiemetics. It was first approved in the US for the prevention of CINV associated with highly emetogenic chemotherapy on March 6, 2003. It was then approved for the prevention of CINV associated with moderately emetogenic chemotherapy in November 2005.

Its marketing has not been suspended, revoked, or withdrawn by any Agency in any country. The April 25, 2006 Periodic Adverse Experience Report did not suggest any specific safety signal.

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

The PONV development program (Protocols 091 and 090) randomized a total of 1727 patients, of whom 1658 patients received active study drug [40mg group (564), 125mg group (556), ondansetron group (538)]. Both trials were multicenter, double-blind, randomized, active comparator-controlled, parallel-group studies. Both trials included 3 arms: aprepitant 125 mg PO, aprepitant 40 mg PO, and ondansetron 4 mg I.V.

The study population of both protocols consisted of patients receiving general anesthesia for open abdominal surgery requiring overnight, postsurgery hospital stay. The majority of patients were women undergoing gynecological surgeries.

7.2.1.2 Demographics

Protocol 090 enrolled 805 patients in the US whereas Protocol 091 enrolled 922 patients from 16 countries worldwide including the US. The three treatment groups were similar with respect to baseline patient demographics, type of surgical procedure and past medical histories. Overall, 92.4% of the patients were females and the mean age was 45.4 ± 10.95 years.

Table 23
Demographics
Studies 090 and 091

Demographics	Treatment Group		
	Aprepitant 40 mg (N=564) n/%	Aprepitant 125 mg (N=556) n/%	Ondansetron (N=538) n/%
Sex			
Female	519 (92.0)	510 (91.7)	503 (93.5)
Male	45 (8.0)	46 (8.3)	35 (6.5)
Race			
Caucasian	329 (58.3)	305 (54.9)	311 (57.8)
Black	78 (13.8)	101 (18.2)	75 (13.9)
Asian	32 (5.7)	35 (6.3)	36 (6.7)
Hispanic	76 (13.5)	73 (13.1)	76 (14.1)
Other	11 (2.0)	2 (0.4)	3 (0.6)
Age			
Mean	46.1	45.1	45.0
Median	45.0	45.0	44.0
SD	11.35	10.26	11.18
Age ≥ 65 years	46 (8.2)	34 (6.1)	37 (6.8)
Ref: Modified Table 2.7.4:3 Integrated Summary of Safety			

7.2.1.3 Extent of exposure (dose/duration)

In the pooled PONV studies, 1658 patients were treated with active study drug (aprepitant or ondansetron) as randomized [aprepitant 40mg (564), aprepitant 125mg (556), and ondansetron (538). Study medication was administered as a single dose prior to surgery. Aprepitant capsules (or placebo) were given 1 to 3 hours prior to induction of anesthesia, while ondansetron IV (or placebo) was given immediately before induction of anesthesia.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The safety data from the original NDA as well as S-NDA 21-549/008 were reviewed and compared to the data in this current submission. The April 25, 2006 Periodic Adverse Experience Report was reviewed and considered during this safety review.

Utilizing the Agency's on-line databases and resources, a search of the current literature did not identify any specific safety concerns. Adverse events reported through AERS were also reviewed to evaluate aprepitant's safety profile.

7.2.3 Adequacy of Overall Clinical Experience

The PONV development program included an adequate number of randomized patients to assess the safety and efficacy of aprepitant in the prevention of PONV. The studies were appropriately designed to allow for detailed analyses of safety and efficacy. Overall, Studies 090 and 091 successfully demonstrated that aprepitant is as safe and as well tolerated as ondansetron when used to prevent PONV.

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

S-NDA 21-549/010 included two clinical pharmacology studies which evaluated the metabolism and clearance of aprepitant: Protocols 107 and 108. Study 107 investigated the bioavailability and food effect on Emend 40 mg capsules while Study 108 was a drug interaction study with IV midazolam. The results of these studies are outlined in Section 5 of this review.

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 studies were appropriately designed to allow for detailed analyses of safety. Overall, Studies 090 and 091 successfully demonstrated that aprepitant is as safe and as well tolerated as ondansetron when used to prevent PONV.

As previously noted, Aprepitant has a complex metabolism. It is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. Due to this complex metabolic profile, this Reviewer recommended additional drug interaction studies (See Section 1.2 and 9.3 of this review).

7.2.8 Assessment of Quality and Completeness of Data

Other than the limitations previously discussed (>90% female patients), the data necessary to perform a through safety review were included and well organized in the SNDA. The quality of the 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 April 25, 2006 Periodic Adverse Experience Report was reviewed and considered during this safety review. Adverse events reported through AERS were also reviewed to evaluate aprepitant's safety profile. No new safety concerns have been identified.

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

Overall, the incidence and type of adverse events that were reported as drug related was similar among the 3 treatment groups and did not suggest a safety signal.

Table 24
Select Drug Related Adverse Events by Body System
(Incidence >0%)
Safety Population Study 090 and 091

Adverse Experience	Treatment Group		
	Aprepitant 40mg (N=564) n (%)	Aprepitant 125mg (N=556) n (%)	Ondansetron (N=538) n (%)
≥ 1 Drug Related Adverse Event	24 (4.3)	30 (5.4)	33 (6.1)
Cardiac Disorders	**3 (0.5)**	**5 (0.9)**	**2 (0.4)**
Bradycardia	3 (0.5)	4 (0.7)	1 (0.2)
Nodal Rhythm	0 (0.0)	0 (0.0)	1 (0.2)
Ventricular Extrasystoles	0 (0.0)	1 (0.2)	0 (0.0)
Gastrointestinal Disorders	**10 (1.8)**	**12 (2.2)**	**10 (1.9)**
Nausea	2 (0.4)	2 (0.4)	0 (0.0)
Vomiting	1 (0.2)	1 (0.2)	2 (0.4)
Diarrhea	0 (0.0)	0 (0.0)	1 (0.2)
Vascular Disorders	**1 (0.2)**	**3 (0.5)**	**1 (0.2)**
Hypertension	1 (0.2)	1 (0.2)	1 (0.2)
Hypotension	0 (0.0)	2 (0.4)	0 (0.0)
Ref: Modified Table 2.7.4:13 ISS			

Adverse events of bradycardia, defined by the investigator as drug-related, were slightly more common in the aprepitant groups compared with the ondansetron group. However, the overall incidences of bradycardia were similar across treatment groups: 25 patients (4.4%) in the aprepitant 40-mg group, 22 patients (4.0%) in the aprepitant 125-mg group, and 21 patients (3.9%) in the ondansetron group. The clinical significance of this finding is unknown.

A review of adverse events reported as drug-related did not suggest did not suggest a safety signal. The data do not suggest that the use of aprepitant adversely affected the safety profile of the anesthesia or the surgical procedure.

7.4 General Methodology

The review of S-NDA 21-259/010 included becoming familiar with the safety and efficacy data used to support the original NDA approval as well as the more recent approval for the MEC indication. This Reviewer worked closely with the Agency's Statistician to confirm the efficacy analyses and to evaluate the quality of the data.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Studies 090 and 091 were reviewed independently and summarized (see Appendix). The results of these reviews were then compared to the Sponsor's integrated summaries of safety and efficacy.

Based on the Sponsor's analyses, the efficacy results from Study 091 differed from Study 090. In Study 090 aprepitant failed to demonstrate *superiority* over ondansetron for the "Complete Response" endpoint. The Sponsor reported that Study 091 successfully demonstrated that both aprepitant doses were superior to ondansetron for the Complete Response endpoint. However, the Agency's Statistical team does not agree with the Sponsor's superiority analysis. The Agency's Statistical team verified that Study 091 succeeded in demonstrating non-inferiority for the Complete Response endpoint; however, for the superiority analyses, statistical significance was not maintained based upon one-sided test, using a more appropriate 2.5% significance level, applying the multiplicity adjustment method proposed by the sponsor.

In trying to identify why the results from the two studies differed, this Reviewer noted that the use and type of postoperative analgesics in Study 091 was very different than Study 090. In Study 091, 96% patients received an *opioid* class analgesic post operatively, compared to greater than 99% of the patients in Study 090. The most common analgesic used in both studies was morphine, a drug known to be associated with nausea and vomiting.

The use of morphine was much higher in Study 090 (failed study) compared to 091 [Study 090 (83.4%), Study 091(48.7%)]. Additionally, the use of non-opioid postoperative analgesics was more common in Study 091 compared to Study 090 (78.4% versus 67.0%). These differences in postoperative analgesics use may account for some of the differences in efficacy results. These differences in analgesics use may be related geography. Protocol 090 enrolled 805 patients in the US whereas Protocol 091 enrolled 922 patients from 16 countries worldwide including the US.

Explorations for drug-demographic interactions

Table 25
Complete Response By Age Group, Gender, Race and by Treatment Group in the 24 Hours Following End of Surgery
MITT Population
Pooled PONV Studies– Protocols 090 – 091

Demographics	Treatment Group		
	Aprepitant 40 mg n/(%)	Aprepitant 125 mg n/(%)	Ondansetron n/(%)
Overall	298/541 (55.1)	287/532 (53.9)	258/526 (49.0)
Sex			
Female	265/499 (53.1)	251/489 (51.3)	233/494 (47.2)
Male	33/42 (78.6)	36/43 (83.7)	25/32 (78.1)
Race			
Caucasian	160/321 (49.8)	139/292 (47.6)	142/308 (46.1)
Black	37/73 (50.7)	52/96 (54.2)	30/70 (42.9)
Hispanic	43/69 (62.3)	40/69 (58.0)	38/73 (52.1)
Other	58/78 (74.4)	56/75 (74.7)	48/75 (64.0)
Age (years)			
Age < 65	265/498 (53.2)	258/499 (51.7)	233/490 (47.6)
Age ≥ 65	33/43 (76.7)	29/33 (87.9)	25/36 (69.4)
Age < 75	288/529 (54.4)	283/528 (53.6)	251/516 (48.6)
Age ≥ 75 years	10/12 (83.3)	4/4 (100.0)	7/10 (70.0)

Ref: Modified Table 2.7.3 :27 Integrated Summary of Efficacy

Since it is this Reviewer's opinion that the success of the No Vomiting endpoints are the most clinically meaningful demonstration of efficacy in PONV trials, the following Table show patients with No Vomiting by Gender, Race and Age Group in the 24 hours following the end of surgery.

Table 26
No Vomiting By Age Group, Gender, Race and
by Treatment Group in the 24 Hours Following End of Surgery
MITT Population
Pooled PONV Studies– Protocols 090 – 091

Demographics	Treatment Group		
	Aprepitant 40 mg n/(%)	Aprepitant 125 mg n/(%)	Ondansetron n/(%)
Overall	469/541 86.7	480/532 90.2	381/526 72.4
Sex			
Female	431/499 (86.4)	439/489 (89.8)	354/494 (71.7)
Male	38/42 (90.5)	41/43 (95.3)	27/32 (84.4)
Race			
Caucasian	280/321 (87.2)	262/292 (89.7)	214/308 (69.5)
Black	60/73 (82.2)	87/96 (90.6)	53/70 (75.7)
Hispanic	62/69 (89.9)	62/69 (89.9)	57/73 (78.1)
Other	67/78 (85.9)	69/75 (92.0)	57/75 (76.0)
Age (years)			
Age < 65	427/498 (85.7)	449/499 (90.0)	351/490 (71.6)
Age ≥ 65	42/43 (97.7)	31/33 (93.9)	30/36 (83.3)
Age < 75	457/529 (86.4)	476/528 (90.2)	374/516 (72.5)
Age ≥ 75 years	12/12 (100.0)	4/4 (100.0)	7/10 (70.0)
Ref: Modified Table 2.7.3 :26 Integrated Summary of Efficacy			

Supplemental NDA 21-549/010 did not identify any significant treatment by treatment-by-age or race interaction for the endpoints Complete Response or No Vomiting. Overall, the results of the subgroup analyses suggest that aprepitant was efficacious in regard to the No Vomiting endpoint regardless of age or race. The limited number of older patients precludes any meaningful statistical interpretation with respect to advanced age. Across treatment groups, the response rate was lower for the Black race than for the other racial groups.

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 safety signal. The safety profile observed in the PONV development program is similar to that of ondansetron for the PONV indication.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dose for the prevention of PONV is a single 40 mg capsule within 3 hours prior to induction of anesthesia. The Sponsor stated that this dose was based on dose ranging data from the CINV development program.

The following table shows the currently approved dosing recommendation for CINV.

Table 27
Approved Dosing Regimen

Day 1	Days 2 to 3
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)
Moderately Emetogenic Chemotherapy	
Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 16mg PO	Aprepitant 80 mg PO Daily

8.2 Drug-Drug Interactions

No new clinical issues were identified 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 (b) (4) of age. This submission is reviewed and signed off in DFS (October 19, 2004).

In S-NDA 21-549 /008 Merck requested a (b) (4) *waiver* for performing studies in pediatric patients (b) (4) of age. To be consistent with recent pediatric study requests for other antiemetics used in the prevention of CINV, this request (b) (4) was denied (Review in DFS: May, 4, 2005). Merck was encouraged to evaluate pediatric patients 6 months of age or younger.

Merck submitted a revised "Proposed Pediatric Study Request (PPSR)" to IND 50,283/392 on February 14, 2006. Merck proposed the following two pediatric studies (age group 6 months - 17 years) as a basis for the Agency's issuance of a Written Request.

Study # 1

Merck reports that this adolescent study is currently in progress and was initiated in April 2004, following the submission of protocol for review and comments (IND 50,283/335) on February 27, 2004.

> Adolescents (12 - 17 years):
>
> A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety,

Tolerability, and Efficacy of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated with Emetogenic Chemotherapy in Adolescent Patients (N = 30; aged 12 to 17 years).

Study # 2

Infants and Young Children (6 months to 12 years):

Following the availability of the aprepitant PK data from the adolescent study, an open-label two-part study will be initiated in younger pediatric patients receiving emetogenic chemotherapy (both HEC and MEC) with a rapidly disintegrating tablet (RDT) of aprepitant suspended in water.

Part I of the study will be conducted in two steps. Step A will initiate with a single dose based on preliminary data from the adolescent study (not to exceed 47 mg/m^2, corresponding to a fixed adult dose of 80 mg), and roughly corresponding to 65% of the recommended adult dose on day 1 of chemotherapy (125 mg). Based on the pharmacokinetic profile and tolerability of the single dose in Step A, a higher or lower dose will be tested in Step B.

Part II of the study will investigate a 3 day regimen of aprepitant in combination with a 5-HT_3 antagonist (dosed in accordance with age appropriate prescribing information), using a dosing regimen to be decided based on the results of Part I, and is intended to be confirmatory. Overall, approximately 48 patients receiving both HEC and MEC will be enrolled in the study. All attempts will be made to enroll at least 10 infants (6 months <2 years).

The Division is currently working on generating a Written Request (WR) for Emend. It is anticipated that this WR will be similar to recent WR issued for other antiemetics.

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 submitted data from Studies 090 and 091 are sufficient to support the approval of aprepitant for the prevention of Post-Operative Nausea and Vomiting. This recommendation is based on the studies demonstrating clinically meaningful results that are supported in part by statistically significant findings in Study 091.

Although Study 090 failed to satisfy its primary efficacy hypothesis, the data are supportive of aprepitant's efficacy in the prevention of PONV. The study demonstrated that both dose levels of aprepitant (40mg and 125mg) were clinically significantly superior to ondansetron with respect to the secondary endpoint "No Vomiting" during the first 24 hours after surgery. In Study 090, the use of 40mg aprepitant (proposed dose) was associated with a 16% improvement over ondansetron for the No Vomiting endpoint 24 hours after surgery. However, due to the pre-specified data analysis plan, these results cannot be considered statistically significant.

Study 091 satisfied both of it's primary hypotheses, that aprepitant is superior to ondansetron in the prevention of post operative vomiting and was non inferior to ondansetron as measured by the Complete response endpoint. The success of these endpoints and considerations of the other efficacy variables support that both dose levels of aprepitant were effective in the prevention of PONV.

Study 091 demonstrated that the use of aprepitant was associated with a 13% improvement over ondansetron for No Vomiting 24 hours after surgery (Primary Endpoint). This treatment group difference persisted in favor of aprepitant through 48 hours after surgery (Secondary endpoint). The use of aprepitant was associated with a 15% improvement over ondansetron for No Vomiting 48 hours after surgery As in Study 090, this represents a clinically significant improvement over a drug considered a standard of care by many institutions.

It is this Reviewer's opinion that, for the PONV indication, the success of the No Vomiting endpoint is the most clinically meaningful demonstration of efficacy. All of the serious complications associated with PONV are directly related to the vomiting process (i.e. wound disruption, increased intraabdominal, intraocular and intracranial pressures, esophageal tears, electrolyte imbalance, and pulmonary aspiration. The use of rescue therapy is not as clinically meaningful in the postoperative surgical patient as is the prevention of vomiting.

The safety analysis did not identify any new safety concerns. Overall, Studies 090 and 091 successfully demonstrated that aprepitant is as safe and as well tolerated as ondansetron when

used to prevent PONV. The incidence and type of adverse and serious adverse events was similar among the three treatment groups and did not suggest that the use of aprepitant adversely affected the safety profile of the anesthesia or surgical procedure

9.2 Recommendation on Regulatory Action

The submitted data from Studies 090 and 091 are sufficient to support the approval of aprepitant for the prevention of Post-Operative Nausea and Vomiting.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Not Applicable

9.3.2 Required Phase 4 Commitments

1) A significant treatment-by-gender interaction was identified in one of the two pivotal trials submitted with the original aprepitant NDA (prevention HEC CINV). This issue was not resolved in S-NDA 21-549 /008 (prevention of MEC CINV), which enrolled greater than 99% female patients. There is currently an outstanding Phase IV commitment requested to evaluate the safety and efficacy of aprepitant in a patient population which includes more male patients for the prevention of CINV in patients receiving MEC.

   In this submission, 92% of the patients enrolled in the PONV trials were female. There are insufficient data available to perform a meaningful treatment by gender analysis. Although the limited number of male patients precludes any meaningful statistical interpretation, the analyses suggests that for the Complete Response endpoint, aprepitant may not be as efficacious as ondansetron in male patients. Since this remains an unanswered question, it is this Reviewer's opinion that approval of the PONV indication should be contingent on Merck agreeing to perform a study to further evaluate the safety and efficacy of aprepitant in male patients undergoing surgery.

2. Aprepitant has a complex metabolism. Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. Following a *three* day regimen of aprepitant, patients on warfarin had an 11% decrease in their International Normalized Ratio (INR) on Day 8 and their S-warfarin trough plasma concentration decreased by as much as 34%.

This information is currently included in the PRECAUTIONS section of the label. With this new indication, the Sponsor proposes the following revisions to this section of the label (underlined portion)

> 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, or following administration of a single 40 mg dose of EMEND for the prevention of postoperative nausea and vomiting (see PRECAUTIONS, *Drug Interaction*
> (Ref: Proposed Label)

In this Reviewer's opinion, there are insufficient data to support that a single 40mg dose of aprepitant will affect the efficacy of warfarin.

Although the proposed wording in the PRECAUTIONS section is safe and acceptable, it may result in requiring post operative patients to present to the hospital or lab numerous times during the post operative period to have their INR "monitored closely for 2 weeks". Since it is unknown whether this is necessary, this Reviewer/Clinician is concerned that the label require patients with recent major surgery (i.e. abdominal surgery or joint replacement) be transported to have lab work performed which may not be necessary. It is this Reviewer's opinion that approval of the PONV indication should be contingent on Merck agreeing to perform a study to evaluate whether a single 40mg dose of aprepitant will have a clinically important effect on warfarin.

3. Similarly, data from the original NDA has shown that coadministration of aprepitant and hormonal contraceptives may effect the efficacy of the birth control. The following information is currently included in the PRECAUTIONS section of the label.

> *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.

This Reviewer/Clinician is concerned for the following reasons; for scheduled elective surgeries, patients will most likely be prescribed aprepitant by the anesthesia department during their preoperative screening visit, with instructions to take the medication just prior to going to the hospital, since the drug must be given "within 3 hours prior to induction of anesthesia." The treating surgeon may not know the patient was premedicated with aprepitant, therefore his discharge instructions will not include the recommendation that "back-up methods of contraception" be used for a month after surgery. Even if this information is conveyed to the patient during their preoperative screening visit (as much as 2 weeks before surgery), the patient may not remember after surgery.

Although the proposed wording in the PRECAUTIONS section is safe and acceptable, it may not apply to a single 40mg dose of aprepitant. There are insufficient data to support that a single 40mg dose of aprepitant will have a clinically important effect on hormonal contraceptives. To aid treating physicians in the safe use of this drug, approval of the PONV indication should be contingent on Merck agreeing to perform a study to evaluate whether a single 40mg dose of aprepitant will have a clinically important effect on the efficacy of the birth control.

9.4 Labeling Review

A multidisciplinary detailed labeling review is currently being performed. All pertinent Labeling issues will be addressed in the Team Leader supplemental review (See Hugo Gallo-Torres M.D., Ph.D., P.N.S Review).

10 APPENDICES

10.1 Review of Individual Study Reports

Appendix A: Study 090 (filed in DFS)
Appendix B: Study 091 (filed in DFS)

10.2 Line-by-Line Labeling Review

To Be Filed in DFS (Pending Discussion with Sponsor)

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/s/

Gary DellaZanna
6/1/2006 08:16:16 AM
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Hugo Gallo Torres
6/1/2006 08:56:03 AM
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Protocol 090

Aprepitant

A Randomized, Double-Blind, Active Comparator-Controlled, Parallel Group Study, Conducted Under In-House Blinding Conditions to Examine the Safety, Tolerability, and Efficacy of 2 Doses of Aprepitant for the Prevention of Postoperative Nausea and Vomiting

Clinical Phase III

Study Period: Start: September 26, 2003
End: November 24, 2004

Study Design:

Study 090 was a multicenter (29), randomized, double-blind, parallel-group, active comparator, controlled trial with in-house blinding designed to assess the safety and efficacy of two dose levels of aprepitant for the prevention of Post Operative Nausea and Vomiting (PONV) in patients undergoing an open abdominal surgery, requiring overnight hospital stay.

Eligible patients were assigned to one of the following three treatment arms using a computer generated randomization schedule,. Patients received a single dose of study medications preoperatively (Day 1).

Table 1
Treatment Arms

Treatment Group	Bottle A (PO)	Vial B (I.V.)
I	Aprepitant 125 mg PO Placebo Aprepitant 40mg PO	Placebo Ondansetron 4mg
II	Aprepitant 40mg PO Placebo Aprepitant 125 mg PO	Placebo Ondansetron 4mg
III	Placebo Aprepitant 125 mg PO Placebo Aprepitant 40mg PO	Ondansetron 4mg

Ref: Table 5-1 Protocol 090

All aspects of surgery were recorded, including type of surgery, type and duration of anesthesia, and duration of recovery. After surgery, patients were permitted to take "rescue therapy" for established nausea or vomiting. Emetic episodes, rescue medications and severity of nausea were recorded in the Case Report Form (CRF).

Patients were issued a diary card to record emetic episodes, use of rescue medications, and pain medications for any out-patient period of the study for up to 48 hours following end of surgery.

Study Objectives:

Merck defined the following Study Objectives for Protocol 090:

Primary Objectives

To demonstrate that aprepitant (125 mg, 40 mg) is *superior* to ondansetron in the prevention of PONV as measured by the proportion of patients with Complete Response in the 24 hours following end of surgery.

To evaluate the safety and tolerability of aprepitant (125 mg, 40 mg) in patients undergoing surgery.

Secondary Objectives

To demonstrate that aprepitant (125 mg, 40 mg) is superior to ondansetron in the prevention of PONV as measured by the proportion of patients with:

1. No Vomiting (0 to 24 hours)
2. No Rescue (0 to 24 hours)
3. No Vomiting (0 to 48 hours)

Exploratory Objectives

To demonstrate that aprepitant (125 mg, 40 mg) is superior to ondansetron in the prevention of PONV in terms of the distribution of:

1. Peak Nausea Score (0 to 24 hours)
2. Time to first vomiting episode in the 0 to 48 hours time frame
3. Time to first use of rescue in the 0 to 24 hours time frame
4. To compare the 125-mg and 40-mg treatment groups for the endpoint of complete response (0 to 24 hours)

Medical Officer Comment:
The treatment arms and study design were acceptable for this Phase III study. The Study Design should be able to meet the study objectives.

The study design is similar to the studies that led to the approval of ondansetron for prevention of PONV indication. The active comparator, ondansetron, has a well characterized risk/benefit profile in the prevention of PONV and is one of the most commonly used antiemetics for prevention of PONV.

It is important to note that Merck specifically designed Protocol 090 to demonstrate that aprepitant is superior to ondansetron in the prevention of PONV.

Schedule of Clinical Observations:

Table 2
Schedule of Clinical Observations and Laboratory Measurements

Procedure	Pre-study[†]	Day of Surgery: Preoperative Phase -3 Hours	Surgery Phase Clock Stops[¶¶]	Postoperative Phase (Hours) 0	2	6	24	48	Follow-Up[§]
Medical history	X[¶]								
Informed consent	X[¶]								
Laboratory tests[‖]	X						X[†††]		X[‡‡]
Urine pregnancy test		X[‡]							
Alcohol use	X[¶]								
Tobacco use	X[¶]								
Patient reminder card/Instruction							X		
Vital signs	X[#]	X		X	X	X	X		X
Physical exam	X[¶]								X
Electrocardiogram (central vendor)	X						X		X[‡‡]
Aprepitant (or placebo) dosing		X[##]							
Ondansetron (or placebo) dosing			X[‡‡‡]						
Postanesthesia recovery score				X[§§]	----------	----------	X[§§]		
Nausea assessment using VRS[‖‖]		X			X	X	X	X	
Emetic episodes				X	----------	----------	----------	X	
Rescue medication				X	----------	----------	----------	X	
Patient telephone contact								X[††]	X[††]
AE monitoring	X				X				

-3: 3 hours before induction of anesthesia.
0: End of surgery when last suture/staple placed.
24: 24 hours after last suture/staple placed.
48: 48 hours after last suture/staple placed.
† Within 3 weeks of surgery.
‡ Urine pregnancy test obtained prior to study drug administration.
§ Within 3 weeks after surgery.
‖ Includes serum pregnancy test in women of childbearing potential. Laboratory tests need to be repeated before beginning surgery only if patient's clinical status is changed.
¶ Informed consent, medical history and physical exam performed within 1 month of surgery may be used.
# Weight and height measured only at prestudy visit.
†† Patients discharged from the hospital will be contacted via telephone 48 hours postsurgery to collect nausea VRS, emetic episodes, rescue medications, and pain medications. Patients will also be called ~3 weeks postsurgery to complete follow-up procedures, only if the patient cannot return for the follow-up visit.
‡‡ ECG and laboratory tests will be repeated at follow-up only if clinically significant abnormalities were noted and reported as adverse events at the 24 hours postsurgery assessment.
§§ Postanesthesia recovery score assessed in recovery room every 15 minutes until a score of ≥8 is reached.
‖‖ Nausea VRS will also be assessed prior to offering rescue medication, and if the patient complains of nausea.
¶¶ The beginning of surgery is defined as the time of ondansetron/placebo administration. The timing for preoperative procedures are based on the beginning of surgery. Postoperative procedures are based on the end of surgery (T_{zero}).
Aprepitant to be administered 1 to 3 hours prior to induction of anesthesia.
††† Serum pregnancy test at 24 hours postsurgery.
‡‡‡ Ondansetron to be administered immediately prior to induction of anesthesia.

Ref Table 5-2 Protocol 090

Medical Officer Comment:
The scheduled safety and efficacy assessments were acceptable for this Phase III trial.

Protocol Amendments:

Medical Officer Comment:
Protocol 090 was amended twice. The first amendment eliminated a planned genetic analysis. It also established an External Review Board to review an interim analysis for futility. This interim analysis was discussed with the Agency's Biostatistical Division. This analysis did not require a statistical adjustment or penalty.

The second amendment provided evaluation of aprepitant plasma concentrations in a subset of surgical patients enrolled at two study sites (Site 006, and Site 020).

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. These changes did not affect inclusion/exclusion criteria, and should not affect the efficacity analysis. The final protocol and amendments were acceptable.

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 reported that one of their study sites was identified as being non-compliant with some/all requirements of Good Clinical Practice (Dr. Paul White – Dallas, Texas, 090-0024).

With the exception of this investigator, Merck certified that Study 090 was conducted in conformance with Good Clinical Practice standards and/or local statutes and regulations regarding informed consent, and the protection of the rights and welfare of human subjects participating in biomedical research.

Additionally, one patient [redacted] (b) (6) *was enrolled during a 7-day lapse in the study site's IRB approval. This was communicated to Merck after all data had been entered and preliminary analyses were conducted. As a result, the IRB allowed the data from this patient to remain in the analyses. Inclusion of this patient was acceptable.*

Investigators:

Medical Officer Comment:
Twenty nine U.S. centers participated in Study 090. As stated above, one site was identified as non-compliant with the requirements of Good Clinical Practice (Dr. Paul White – Dallas, Texas, Site 0024). Merck determined that the data from this site were unreliable. Therefore, the efficacy data from this site were not included in the efficacy analyses (19 patients). These patients were included in the safety analysis. Merck performed and provided an analysis of the primary efficacy endpoint with and without including these 19 patients.

Table 3
Patients with Complete Response
24 hours Following Surgery
(Modified- Intention-to-Treat Population with and without Site 0024)

Treatment	n/m (%)	Aprepitant vs Ondansetron	
		Δ	p-Value
Complete Response (Primary Endpoint) (Excluding Site 0024)			
Aprepitant 40 mg	111/248 (44.8)	2.5	0.611
Aprepitant 125 mg	103/239 (43.1)	0.8	0.866
Ondansetron	104/246 (42.3)		
Complete Response (Primary Endpoint) (Including Site 0024)			
Aprepitant 40 mg	115/254 (45.3)	3	0.533
Aprepitant 125 mg	108/0.703 (44.1)	1.8	0.703
Ondansetron	107/253 (42.3)		
Ref: Study 090.pdf Modified Tables Page 21 and 1840 of 1851 Δ Treatment Group Difference Aprepitant vs. Ondansetron.			

Removing these patients from the primary efficacy analysis did not effect the interpretation of the results.

Dose Selection:

Medical Officer Comment:
The dose selection for this Phase III study was acceptable. The two dose levels of aprepitant evaluated in Study 090 (125mg and 40mg) were based on dose ranging data from the CINV development program.

Study Population Selection

Medical Officer Comment:
The study population consisted of male and female patients receiving general anesthesia for open abdominal surgery requiring overnight hospital stay. Based on the specific eligibility criteria, the majority of patients were expected to consist of women undergoing a gynecological surgery.

This should be acceptable since female gender and gynecological surgery are known risk factors for developing PONV and Male patients were not excluded. However, a treatment-by-gender analysis should be performed to see if both genders respond to therapy.

Enrollment Criteria

Inclusion Criteria

male or female ≥18 years of age
able to understand study procedures
written informed consent
scheduled to undergo open abdominal surgery requiring overnight hospital stay
scheduled to receive the following general anesthetic regimen:

- Premedication with benzodiazepine (e.g., I.V. midazolam 1 to 3 mg) or nil
- Induction with any anesthetic agent
- Narcotics (e.g., fentanyl, morphine, or hydromorphone)
- Neuromuscular blocking agents
- Maintenance with N_2O (50 to 70%) with volatile anesthetic
- Neostigmine 2 to 5 mg (A minimum dose of 2.5 mg was recommended.)

scheduled to receive postoperative opioids (e.g., morphine, or fentanyl) by intramuscular (I.M.) or intravenous (I.V.), or patient controlled analgesia (PCA)
premenopausal female patients: demonstrate negative pregnancy test and agree to use a barrier form of contraception for at least 14 days before and after surgery
American Society of Anesthesia (ASA) physical status of I–III

Exclusion Criteria

scheduled to receive propofol for maintenance of anesthesia
(Note: Propofol was permitted for induction of anesthesia)
nasogastric or oral gastric tube intra- or postoperatively
allergic to any protocol medications or any other 5-HT_3 antagonists
expected to receive neuroaxial anesthesia (e.g., epidural, spinal)
expected to receive opioid antagonists
expected Intensive Care Unit (ICU) admission after surgery
clinically significant respiratory, metabolic, hepatic, renal, or cardiovascular condition

history of any illness, including morbid obesity that in the opinion of the investigator might have confounded the results or posed unwarranted risk to the patient
vomiting from any organic etiology (e.g., small bowel obstruction).
vomited within 24 hours prior to surgery
mentally incapacitated or significant emotional or psychiatric disorder
any illicit drug use, or current evidence of alcohol abuse
taking, or had taken within 7 days of surgery the following

CYP3A4 substrates:
- Terfenadine
- Cisapride
- Astemizole
- Pimozide

CYP3A4 inhibitors:
- Clarithromycin
- Ketoconazole, itraconazole

taking, or had taken within 30 days of surgery the following

CYP3A4 inducers:
- Phenytoin or carbamazepine
- Barbiturates
- Rifampicin or rifabutin

abnormal laboratory values
-- AST >2.5 x upper limit of normal
-- ALT >2.5 x upper limit of normal
-- Bilirubin >1.5 x upper limit of normal
-- Creatinine >1.5 x upper limit of normal

pregnancy or breast feeding
participated in a study with aprepitant
taken a non-approved (investigational) drug within the last 4 weeks
taken an antiemetic within 24 hours before surgery, or scheduled to receive an antiemetic during the study

Medical Officer Comment:
The enrollment criteria were acceptable for this Phase III study. The CYP3A4 medications listed in the exclusion criteria are acceptable for this Phase III study.

Rescue Therapy

Patients were instructed to take rescue therapy for established nausea or vomiting. Study personnel were to offer the rescue therapy if the patient:

- specifically asked for rescue medication for established nausea
- experienced >1 episode of vomiting or retching
- experienced nausea for more than 15 minutes

Medical Officer Comment:
The Sponsor reports that patients who took rescue medication for "established" nausea or vomiting were considered as failures according to the primary endpoint. However, patients who took rescue medication without established nausea or vomiting were considered protocol violators.

Since this was a blinded study, the protocol defined use of rescue medication is acceptable and should not have resulted in a bias in favor of either treatment arm.

Prior and Concomitant Therapy

All prescribed and over-the-counter drugs taken by the patient within 30 days of surgery, during and after the treatment phase, and through the follow-up visit were recorded by the study coordinator.

In addition to the medications prohibited by the exclusion criteria, the protocol specifically prohibited the following drugs that have antiemetic activity within 24 hours of surgery:

- 5-HT3 antagonists (e.g., ondansetron, granisetron, dolasetron)
- Phenothiazines (e.g., prochlorperazine, fluphenazine, perphenazine)
- Thiethylperazine (e.g., chlorpromazine, promethazine)
- Butyrophenones (e.g., haloperidol or droperidol)
- Benzamide (e.g., metoclopramide or alizapride)
- Domperidone
- Cannabinoids
- Corticosteroids (e.g., dexamethasone, methylprednisolone, or prednisone)
- Scopolamine
- Cyclizine

Medical Officer Comment:
The assessments for Prior and Concomitant Therapies, as well as the protocol defined list of prohibited medications, were acceptable.

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
Any other reason, in the opinion of the investigator that precluded further participation by the patient.

Medical Officer Comment:
The protocol defined reasons for discontinuation from the study were acceptable.

Study Medication Administration and Blinding

Aprepitant was manufactured in the United States and was provided by Merck. The commercially available intravenous ondansetron hydrochloride (ZOFRAN™) was manufactured by Glaxo SmithKline and was provided by Merck.

Aprepitant capsules (or placebo) were supplied in 1 bottle (Bottle A), and ondansetron (or placebo) was dispensed in 1 vial (Vial B). Each bottle contained two capsules (aprepitant 125 mg and placebo, or aprepitant 40 mg and placebo, or two placebo capsules). Patients received the oral study drug 1 to 3 hours before induction of anesthesia. Patients were then treated with the intravenous study medication (ondansetron, or placebo) immediately before induction of anesthesia.

Each investigative site designated an unblinded pharmacists to receive, store and prepare the ondansetron and saline placebo. The investigators, study coordinators, and patients all remained blinded to the study medications.

An interim futility analysis was performed by an unblinded Merck statistician, who was otherwise uninvolved with the project. The Merck Clinical Monitor and all other Merck personnel involved with the conduct of the study remained blinded to treatment allocations.

Medical Officer Comment:
The randomization process, blinding procedures, and medication administration were acceptable. The interim futility analysis did not effect the collection or interpretation of the efficacy data.

Treatment Compliance

Medical Officer Comment:
Study 090 was a single-dose study in which therapy was administered by study personnel before induction of anesthesia, treatment compliance was therefore expected to be 100%.

Efficacy Assessments

Vomiting Assessment

A vomiting episode was defined as expulsion of stomach contents through the mouth or retching, defined as a non-productive attempt to vomit. Vomiting episodes were considered distinct if separated by the absence of vomiting and retching for at least 1 minute.

Nausea Assessment

Nausea was assessed using 11 point nausea Verbal Rating Score (VRS). Zero (0) corresponded to "no nausea", and 10 represented nausea "as bad as it could be." Nausea assessments were recorded by study personnel at prespecified times: 2, 6, 24, and 48 hours postsurgery. Nausea was also assessed at unscheduled times prior to any offering of rescue medication. If a patient was discharged prior to the 48 hour nausea assessment, the assessment was completed over the phone by the study coordinator.

Rescue Therapy

The type of rescue therapy, time and dosage was recorded by the study coordinator while in the hospital or by the patient for any out-patient period of the study for up to 48 hours following end of surgery.

Medical Officer Comment:
The protocol stipulated definitions and efficacy assessments were acceptable. Study coordinators documented these assessments during the hospitalization period of the study. After discharge, patients recorded efficacy assessments for any out-patient period of the study for up to 48 hours following end of surgery.

Efficacy Endpoints:

Treatment comparisons were performed between the aprepitant groups and the ondansetron group for all statistical analyses. Additionally, the two aprepitant groups (125 mg and 40 mg) were compared to each other for the primary end-point Complete Response during the first 24 hours to see if one dose level was significantly more efficacious. The time points of 24 hours and 48 hours refer the end of surgery, defined as the time the last suture/staple was placed on the surgical incision.

Medical Officer Comment:
The protocol definition for "end of surgery" was recommended by the Division so a time to recovery analysis could be performed. It was unknown whether aprepitant would affect the metabolism of the anesthetics used.

Primary Efficacy Endpoint:

Complete Response: No Vomiting and No Rescue in the 24 hours following the end of surgery

Secondary Efficacy Endpoints:

No Vomiting in the 24 hours following the end of surgery
No Rescue in the 24 hours following the end of surgery
No Vomiting in the 48 hours following the end of surgery

Medical Officer Comment:
The efficacy endpoints were acceptable. The Primary Endpoint (Complete Response) is a composite end-point that includes the end-points No Vomiting and No Rescue therapy. To succeed for the primary endpoint both variables would need to be statistically significant.

It is important to note that neither the primary nor secondary endpoints included an assessment for nausea. The nausea variable was evaluated only as a exploratory endpoint.

Exploratory Efficacy Endpoints:

In addition to the primary and secondary efficacy endpoints, the Sponsor analyzed the following prespecified and non-prespecified exploratory endpoints:

Prespecified Exploratory Endpoints

Complete Response (0 to 24 hours) in the aprepitant 125mg versus 40 mg treatment
Peak nausea scores in the 0 to 24 hours following the end of surgery
Time to first vomiting in the 0 to 48 hours following the end of surgery
Time to first use of rescue in the 0 to 24 hours following the end of surgery

Not Prespecified Exploratory Endpoints

Summary of number of PONV risk factors per patient by treatment group
Summary statistics for overall duration of anesthesia
Post-Hoc Non inferiority analysis for the primary endpoint

Safety Endpoints

The Protocol defined the following Safety Endpoint Analyses:

Primary Safety Endpoint Analyses:

Clinical or laboratory *adverse event* within 14 days of aprepitant therapy
Clinical or laboratory *drug-related adverse event* within 14 days of aprepitant therapy.
Clinical or laboratory *serious adverse event* within 14 days of aprepitant therapy.
Discontinuation of treatment due to a clinical or laboratory adverse experience

Secondary Safety Endpoint Analyses:

Clinical or laboratory *adverse event* occurring in 5% of patients in at least 1 of the comparison treatment groups

Medical Officer Comment:
The protocol defined safety endpoints and safety assessment were acceptable.

Patient Enrollment:

A total of 903 patients were screened, resulting in 805 patients being randomized in to one of three treatment groups [aprepitant 40mg (272), aprepitant 125mg (263), ondansetron (270)].

Medical Officer Comment:
Of the 98 patients not randomized, 68 patients did not meet the eligibility criteria, 25 withdrew consent, 1 patient was lost to follow-up, and 4 patients were screened after the trial had been closed. The most common reasons for exclusion were that the patients were not scheduled to undergo open abdominal surgery.

Patient Accountability:

Of the 805 randomized patients, 752 (93.4%) patients completed the study. Fifty-three (6.6%) patients discontinued from the study [aprepitant 40mg group (14), aprepitant 125mg group (23) and ondansetron group (16)].

Table 4
Disposition of Randomized Patients

Patients Randomized	Treatment Group		
	Aprepitant 40mg (N=272)	Aprepitant 125mg (N=263)	Ondansetron (N=270)
Patients completed	258	240	254
Patients discontinued	14	23	16
lost to follow-up	3	6	1
moved	0	1	0
withdrew consent	3	5	6
other	8	11	9
Ref. Modified Table 6-1 Protocol 090			

Medical Officer:
The number of patients who discontinued from the study and the reasons for discontinuation were similar between treatment groups and did not suggest a safety signal. The Sponsor reports that no patients discontinued due to a clinical or a laboratory adverse event.

In addition to these patients, the data from the nineteen patients randomized at Study Site 024 (UT South Western Medical Center, Dallas, TX), were not included in the efficacy analysis

Defined Study Populations:

Medical Officer Comments:
Two patient populations were defined for the efficacy analysis: a modified intention-to-treat (MITT) population and the per-protocol population (PP). The primary efficacy analysis was performed on the MITT population.

Modified Intention-to-Treat Population:

The Modified Intention-to-Treat Population included all patients who received study drug (one dose from both Bottle A and Vial B), had undergone protocol-defined surgery (open abdominal surgery under general anesthesia), and had at least one post operative assessment.

The following Table displays the number of patients excluded from the MITT population and the justification for exclusion.

Table 5
Randomized Patients Excluded From the MITT Analyses

Exclusion	Treatment Group		
	Aprepitant 40mg (N=272)	Aprepitant 125mg (N=263)	Ondansetron (N=270)
Total Excluded	**24 (8.8)**	**24 (9.1)**	**24 (8.8)**
No study medication	9 (3.3)	10 (3.8)	12 (4.4)
Incomplete study medication (had surgery)	5 (1.8)	2 (0.8)	1 (0.4)
Incomplete study medication (no surgery)	1 (0.4)	3 (1.1)	2 (0.7)
Complete study medication (no surgery)	1 (0.4)	0 (0.0)	0 (0.0)
No efficacy data	0 (0.0)	2 (0.8)	0 (0.0)
Incorrect study medication	2 (0.7)	1 (0.4)	2 (0.7)
Study Site 024	6 (2.2)	6 (2.3)	7 (2.6)
Ref. Modified Table 6-5 Protocol 090 Number (%)			

Medical Officer:
The protocol definition for the MITT population was acceptable. The number of patients excluded from the MITT analyses and the reasons for being excluded were acceptable. Excluding these patients should not affect the interpretation of the efficacy data or result in a bias in favor of aprepitant.

Protocol violations resulted in 72 patients being excluded from the MITT analyses, 24 patients from each treatment group. Of these patients, 31 were excluded because they were discontinued from the study prior to receiving study drug. The most common reason for discontinuation prior to administration of study drug was a change in surgical plan that made the patient no longer eligible for the study (i.e. laparoscopic procedure). These exclusions are not expected to result in any unfair bias (see Table 5).

Per-Protocol Population:

Protocol violation criteria and protocol violators were identified prior to breaking the blind and no data were imputed in the per-protocol analysis. The Sponsor performed a per-protocol analysis as supportive evidence of efficacy. The following Table shows the number of patients and reasons for exclusion from the Per-Protocol Efficacy Analyses during the 24-hour follow-up period.

Table 6
Patients Excluded From the Per-Protocol Efficacy Analyses
24 Hours Following End of Surgery

Exclusion	Treatment Group		
	Aprepitant 40mg (N=248)	Aprepitant 125mg (N=239)	Ondansetron (N=246)
Total Excluded	**14 (5.6)**	**15 (6.3)**	**23 (9.3)**
No Nitrous Oxide	3 (1.2)	5 (2.0)	3 (1.2)
No post-operative opioids	1 (0.4)	1 (0.4)	2 (0.8)
Propofol for maintenance of anesthesia	0 (0.0)	0 (0.0)	1 (0.4)
NG/OG tube	4 (1.6)	6 (2.5)	6 (2.4)
Neuroaxial anesthesia	1 (0.4)	0 (0.0)	3 (1.2)
Prophylactic anti-emetic (up to 24 hours post-surgery)	10 (4.0)	5 (2.0)	13 (5.2)

Ref. Modified Table 6-6 Protocol 090
Number (%)

Medical Officer:
The protocol defined per-protocol population was acceptable. During the first 24-hour follow-up period 52 patients were excluded from the PP population. The number of excluded patients increased to 62 when assessed for the 48-hour follow-up period.

A slightly higher proportion of patients in the ondansetron group were identified as protocol violators. However, since protocol violators were identified prior to breaking the blind, this should not result in a bias in favor of any treatment arm.

Demographics and Characteristics

Table7
Demographics

Demographics	Treatment Group		
	Aprepitant 40 mg (N=261)	Aprepitant 125 mg (N=252)	Ondansetron (N=253)
Sex			
Female	245 (93.9)	238 (94.4)	239 (94.5)
Male	16 (6.1)	14 (5.6)	14 (5.5)
Race			
Caucasian	185 (70.9)	161 (63.9)	167 (66.0)
Black	45 (17.2)	63 (25.0)	49 (19.4)
Asian	3 (1.1)	4 (1.6)	6 (2.4)
Hispanic	24 (9.2)	24 (9.5)	29 (11.5)
Other	4 (1.5)	0 (0.0)	2 (0.7)
Age			
Mean	45.9	44.0	44.9
Median	45.0	44.0	44.9
Min-Max	22 to 83	23 to 78	18 to 82
Age ≥ 65 years	18 (6.9)	10 (4.0)	16 (6.3)
Ref: Modified Table 6-8 Study 090			

Medical Officer Comment:
The majority of the patients in Study 090 were Caucasian (67%) females (94%) between the ages of 35 to 54 years. The three treatment groups were generally similar with respect to known risk factors for developing nausea and vomiting (female gender, history of PONV or motion sickness, non smoking status, and use of postoperative opioids). The number of randomized male patients was too small to perform any meaningful analysis.

Primary Diagnosis and Type of Surgery

Table 8
Number (%) of Patients With Specific Types of Surgery
by Surgery Category
MITT Population

Select Surgeries	Treatment Group		
	Aprepitant 40mg (N=248)	Aprepitant 125mg (N=239)	Ondansetron (N=246)
Non-Gynecological Surgery	**20 (8.1)**	**15 (6.3)**	**23 (9.3)**
Gynecological Surgery	**228 (91.9)**	**224 (93.7)**	**223 (90.7)**
Hysterectomy / Salpingo Oophorectomy	127 (51.2)	112 (46.9)	107 (43.5)
Hysterectomy	68 (27.4)	78 (32.6)	78 (31.7)
Salpingo-oophorectomy	10 (4.0)	8 (3.3)	13 (5.3)
Myomectomy	11 (4.4)	17 (7.1)	10 (4.1)
Ovarian/Adnexal Cystectomy	6 (2.4)	10 (4.2)	6 (2.4)
Intestinal Resection	11 (4.4)	10 (4.2)	16 (6.5)
Ref. Modified Table 6-11 Protocol 090 Number (%)			

Medical Officer Comment:
The specific types of surgery were generally similar across treatment groups. Overall, 675 patients (92.1 %) underwent a gynecological surgery. The most common category of surgery was hysterectomy plus salpingo-oophorectomy (47.2%).

The incidence of bowel surgery was slightly higher in the ondansetron group compared to both aprepitant groups. Since this type of surgery requires prolonged, direct surgical manipulation of the bowel, it may make these patients more prone to ileus and PONV. This may have resulted in a slight bias in favor of the aprepitant group. However, in Study 091, bowel surgery was more common in the aprepitant groups, so these slight differences should not be important in the integrated efficacy analysis.

Preexisting Diagnosis

Medical Officer Comment:
As part of a through review of efficacy, preexisting medical conditions which may have affected the incidence of PONV were reviewed. The incidence and type of preexisting medical conditions were similar between treatment groups and should not have resulted in a bias. The most common preexisting medical conditions involved the reproductive system and breast disorders (68.5%).

Handling of Dropouts or Missing Data

Based on the protocol, patients meeting all 4 of the following criteria were excluded from the MITT analysis:

1) discharged from the hospital prior to 23 hours following surgery
2) lost to follow-up prior to 23 hours following surgery
3) did not vomit prior to loss to follow-up
4) did not receive rescue medications prior to loss to follow-up

Medical Officer Comment:
Two patients (b) (6) *and* (b) (6) *both in the aprepitant 125-mg group, received study therapy, and underwent surgery, but did not have any post operative efficacy data. These patients were excluded from the MITT analyses.*

Safety Population

Medical Officer Comment:
The protocol defined safety population included all patients who were randomized and received study drug. However, the Data Analysis Plan did not stipulate how patients who received incorrect study therapy would be handled. Prior to unblinding, Merck incorporated the following post-hoc approach to patients who received incorrect study therapy.

> *Patients who received two active study drugs (i.e. aprepitant 40 mg + ondansetron) or two inactive study drugs (i.e. placebo for aprepitant 40 mg + placebo for ondansetron) were excluded from the safety analyses and the MITT analyses.*
>
> *Adverse events experienced by patients who received two active study drugs were to be described separately in each safety subsection of the Clinical Study Report.*

This post-hoc approach is acceptable and should not result in any bias. Considering that aprepitant is currently approved for use in conjunction with $5HT_3$ receptor antagonists, the patients who mistakenly received two active study drugs should not be at an unacceptable risk.

Concomitant and Prior Medical Therapy

All medications taken in the 30 days prior to study entry and during the 4 days following study were recorded in the CRF.

Medical Officer Comment:
The use of prior medical therapy was similar between treatment groups and should not have affected the efficacy analysis (Ref. Table 6-13). Of the 766 randomized patients who received active study drug, 682 (89%) patients had taken at least 1 medication in the 30 days prior to study entry. The three most commonly reported prior medications were in the categories of

vitamins, analgesics, and antiinflammatory and antirheumatic products. This study differed from Study 091 which had psycholeptics, antibacterials, and drugs for acid related disorders as the most common prior medical therapies.

Anesthesia-Related Medications

Table 9
Summary Statistics for Duration of Anesthesia by Treatment Group

Duration (Hours)	Treatment Group		
	Aprepitant 40mg (N=248)	Aprepitant 125mg (N=238*)	Ondansetron (N=246)
Mean	2.0	2.0	2.2
Standard deviation	1.0	1.0	1.2
Median	1.8	1.8	1.8
Minimum	0.6	0.5	0.5
Maximum	6.5	6.0	8.6

Ref. Modified Table 6-15 Protocol 090
* One patient (b) (6) had incomplete anesthesia information and was not included in this calculation

Medical Officer Comment:
The type and duration of anesthesia was analyzed to see if it resulted in a significant interaction on the safety and/or efficacy results. Overall, the type, dose and duration of anesthesia were similar among the three treatment groups and should not have resulted in a bias in any of the treatment arms.

It is generally accepted that the use of nitrous oxide can contribute to the development of PONV. More than 98% of the patients in the MITT population received nitrous oxide. The mean dose of nitrous oxide was balanced [54.00 ± 6.96 in the aprepitant 40-mg group, 53.74 ± 6.6 in the aprepitant 125-mg group, and 54.06 ± 7.19 in the ondansetron group].

Postoperative Analgesics

Medical Officer Comment:
Since the type and use of post operative analgesics could effect the incidence of PONV, these data were collected and analyzed. Greater than 99% of the patients received one or more opioid class analgesic medication post operatively. The most common post operative analgesics were morphine (83.4 %), ketorolac (50.6 %) and fentanyl (27.3 %). Overall, the type and dose of post operative analgesics were similar in the three treatment groups and should not have resulted in a bias in favor of any of the treatment arms.

The type of postoperative analgesics in Study 090 was very different than Study 091. In Study 091, 95.7% patients received one or more opioid class analgesic medication post operatively. In Study 090 greater than 99% of the patients received one or more opioid class analgesic medication post operatively.

The most common analgesic used in both studies was morphine. However, the use of morphine was much higher in Study 090 compared to 091 [Study 090 (83.4%), Study 091(48.7%)] Additionally, the use of postoperative non-opioid analgesics was 67.0% in Study 090, compared to78.4% in Study 091.

The use of morphine is a known risk factor for the development of PONV. These differences in the use of postoperative analgesics may account for some of the difference in efficacy observed between Studies 090 and 091.

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.

In section 6.5.3.4 of the Study Summary, it states the following:

> *Table 6-17 displays all antiemetic rescue medications administered during the first 24 hours after surgery for treatment of established nausea, or vomiting. Since administration of rescue therapy is an efficacy end-point, the table displays only rescue therapies administered to patients who were evaluable for efficacy (MITT population). Medications with antiemetic properties administered for prevention of nausea and vomiting, or other reasons are reported as "Other Concomitant Therapies" in Table 6-18.*

It is not clear why the Sponsor reported "Rescue medications" and "medications with antiemetic properties administered for prevention of nausea and vomiting" separately. In table 6-17, the use of rescue medication was similar in all three treatment groups [aprepitant 40-mg (54.8%), aprepitant 125-mg group (55.6%), and ondansetron group (54.1%)]. However, there was a slight increase in use of antiemetics reported in the Aprepitant groups in Table 6-18.

Table 10
Number (%) of Patients With Specific Concomitant Therapies
(Incidence 5% in One or More Treatment Groups) by Drug Category

Select Concomitant Medications	Treatment Group		
	Aprepitant 40mg (N=261)	Aprepitant 125mg (N=252)	Ondansetron (N=253)
Patients ≥ 1 Concomitant therapies	260 (99.6)	251 (99.6)	252 (99.6)
Antiemetics and Antinauseants	**24 (9.2)**	**24 (9.5)**	**20 (7.9)**
Ondansetron	23 (8.8)	22 (8.7)	18 (7.1)
Drugs with Antiemetic Activity Reported in Other Classes			
Functional Gastrointestinal Disorders	**96 (36.8)**	**96 (38.1)**	**86 (34.0)**
Metoclopramide	17 (6.5)	16 (6.3)	16 (6.3)
Respiratory System			
Promethazine	17 (6.5)	13 (5.2)	20 (7.9)

Ref. Modified Table 6-18 Protocol 090
Number (%)

Additionally, It is not clear how the Applicant determined the Drug Category in Table 6-18. For example, Promethazine (Phenergan®) is listed as a Respiratory System therapy. Phenergan has an approved indication for "Antiemetic therapy in postoperative patients" (Ref. Phenergan® Label)

Regardless of this finding, the use of medications with antiemetic properties should not have affected the efficacy analysis since their use were generally similar in the three treatment groups. The differences were small and should not have affected the interpretation of efficacy data.

Protocol Deviations

Table 11
Protocol Deviations
Affecting Analysis Populations

Protocol Deviations	Treatment Group		
	Aprepitant 40mg (N=261)	Aprepitant 125mg (N=252)	Ondansetron (N=253)
Prime Therapy Deviations			
No Study Therapy[A]	9	10	12
Incorrect Study Therapy[A]	2	1	2
Incomplete Study Therapy[A]	6	5	3
Surgery Deviations			
No Surgery[A]	1	0	0
Nasogastric/Oral gastric Tube[B]	4	6	6
Neuroaxial Anesthesia[B]	1	0	3
No N_2O[B]	3	5	3
Propofol for Maintenance[B]	0	0	1
Post-Surgery Deviations			
No Postoperative Opioids[B]	1	1	2
Prohibited Medication			
Antiemetic for Other than Rescue[B]	12	12	15
CYP3A4 substrates/ inducers/ inhibitors	0	0	1

Ref. Section 6.2.2 and Modified Table 6-3 Protocol 090
[A] excluded from MITT analyses.
[B] Included in MITT analysis, but excluded from PP analysis

Medical Officer Comment:
Protocol deviations and violations were identified prior to unblinding the study. The type and number of protocol deviations were similar across treatment groups and should not result in a bias. The Sponsor's justification for including/excluding patients from the primary efficacy analyses were acceptable.

Efficacy Results

Table 12
Response Rates for Primary and Secondary Endpoints
(Modified- Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant vs Ondansetron	
		Δ	p-Value
Complete Response (Primary Endpoint) (no emesis and no rescue therapy, 0 to 24 hours)			
Aprepitant 40 mg	111/248 (44.8)	2.5	N.S.
Aprepitant 125 mg	103/239 (43.1)	0.8	N.S.
Ondansetron	104/246 (42.3)		
No Vomiting (no emetic episodes, 0 to 24 hours)			
Aprepitant 40 mg	223/248 (89.9)	16.3	<0.001
Aprepitant 125 mg	227/239 (95.0)	21.4	<0.001
Ondansetron	181/246 (73.6)		
No Use of Rescue Medication (for established emesis or nausea, 0 to 24 hours)			
Aprepitant 40 mg	112/248 (45.2)	-0.7	N.S.
Aprepitant 125 mg	106/239 (44.4)	-1.5	N.S.
Ondansetron	113/246 (45.9)		
No Vomiting (no emetic episodes, 0 to 48 hours)			
Aprepitant 40 mg	209/247 (84.6)	17.7	<0.001*
Aprepitant 125 mg	220/236 (93.2)	26.3	<0.001*
Ondansetron	164/245 (66.9)		

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Δ Treatment Group Difference Aprepitant vs. Ondansetron.
N.S.= Not statistically significant
* Not statistically significant after multiplicity adjustment
n/m= Number of patients responder/number of patients in analysis.

Medical Officer Comment:
Study 090 failed to satisfy its Primary Hypothesis that aprepitant (125 mg, 40 mg) is superior to ondansetron in the prevention of PONV as measured by the proportion of patients with Complete Response (no Vomiting and No Rescue Therapy) in the 24 hours following end of surgery.

The study failed for its primary endpoint because the treatment group differences between the aprepitant groups and the ondansetron group were not statistically significant for the "No Rescue" variable.

The Study, however, did demonstrate that both dose levels of aprepitant were both clinically and statistically significantly superior to ondansetron with respect to the "No Vomiting" secondary endpoint. The treatment group differences for the No Vomiting variable during the first 48 hours

after surgery was even larger. However, due to the prespecified data analysis plan, these results cannot be considered statistically significant.

In this Reviewer's opinion, the success of the No Vomiting endpoint is more clinically meaningful than the failure of the primary endpoint. The most serious complications associated with PONV are directly related to the vomiting process (i.e. wound disruption, increased intraabdominal, intraocular and intracranial pressures, esophageal tears, electrolyte imbalance, and pulmonary aspiration.

The treatment group differences remained clinically meaningful even in the patients who were classified as treatment failures, based on the vomiting endpoint. In both aprepitant groups, a greater proportion of patients who vomited, experienced only one emetic episode [aprepitant 40 mg group (76%), and aprepitant 125 mg group (83%)]. In contrast, only 52% of the ondansetron-treated patients who vomited suffered a single emetic event.

Table 13
Number of Vomiting Episodes Per Patients by Treatment Group

Emetic Episodes	Treatment Group		
	Aprepitant 40mg (N=248)	Aprepitant 125mg (N=239)	Ondansetron (N=246)
0	89.9	95.0	73.6
1	7.7	4.2	13.8
2	1.6	0	5.3
3	0.4	0	3.3
4	0	0.4	2.0
5	0	0.4	0.8
6	0.4	0	0.4
7	0	0	0.4
10	0	0	0.4
Ref. Modified Table 7-5 Protocol 090			

Nausea Severity:

Severity of nausea was recorded using a verbal rating score (VRS). The VRS consisted of a 11 point linear scale, anchored at 0 and 10. Patients were asked "On a scale of 0 to 10, with 0 equal to no nausea and 10 equal to nausea as bad as it could be, how much nausea have you had over the last 24 hours?"

Medical Officer Comment:
At each pre-specified time point and every time a patient requested rescue therapy, the patient's nausea severity was assessed using the VRS. The planned analysis used the peak measurement

over all values recorded in the first 24 hours. The pattern of distribution of nausea severity prior to rescue was similar across treatment groups.

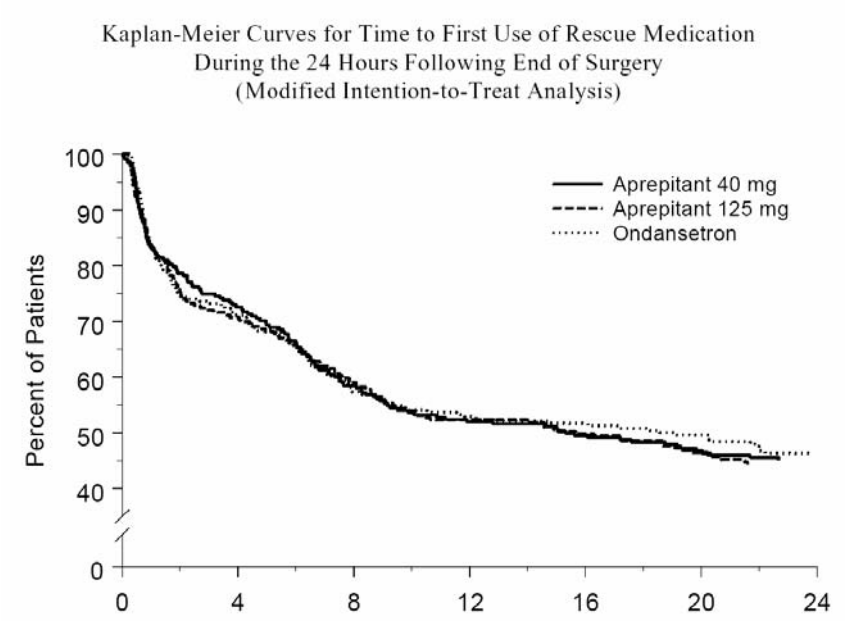
Select Exploratory Endpoints:

Complete Response (0 to 24 Hours) between the Aprepitant Treatment Groups

Medical Officer Comment:
The Sponsor performed a comparison between the aprepitant 40-mg and 125-mg treatment groups to see if one dose level was more effective. Based on the primary endpoint, there was no significant difference in efficacy between the two aprepitant dose levels (p-value=0.737).

Time to First Use of Rescue Medication (0 to 24 Hours)

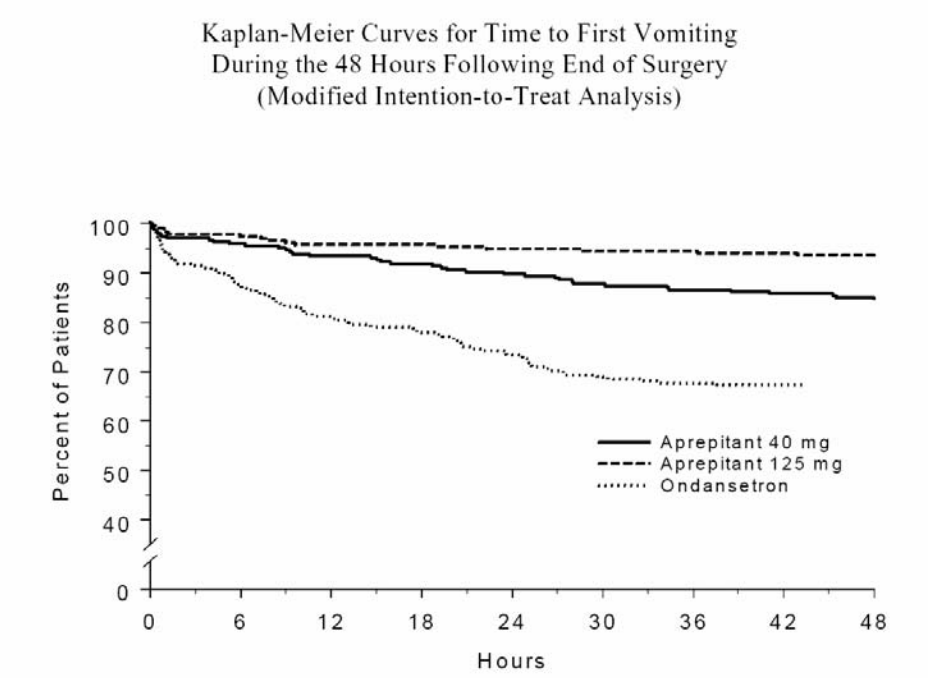
Figure 1



(Ref: Figure 7-2 Study 090.pdf)

Time to First Vomiting (0 to 48 Hours)

Figure 2



Medical Officer Comment:
Using the Sponsor's analyses, the use of aprepitant (40 mg or 125 mg) did not effect the time to first use of rescue medication when compared to ondansetron (p-values 0.906 and 0.769, respectively). However, compared to the ondansetron group, both dose levels of aprepitant delayed the time to first vomiting (p-values <0.001).

Additional Analysis:

Since Study 090 failed to demonstrate that aprepitant (125 mg, 40 mg) was *superior* to ondansetron for the Complete Response endpoint (primary hypothesis), the Sponsor performed a *post-hoc* Non-Inferiority analysis to support that aprepitant is as effective as ondansetron in the prevention of PONV.

Table 14
Post-Hoc Non-Inferiority Analysis
Patients with Complete Response by Treatment Group
in the 24 Hours Following End of Surgery
(Modified-Intention-to-Treat Analysis)

Treatment	With Complete Response	Aprepitant vs Ondansetron	
	n/m (%)	Odds Ratio‡	Lower bound of One-sided 95% CI
Aprepitant 40 mg	111/248 (44.8)	1.1	0.81
Aprepitant 125 mg	103/239 (43.1)	1.0	0.76
Ondansetron	104/246 (42.3)		

Ref. Table 7-10 Protocol 090

‡ Estimated odds ratio for Aprepitant versus Ondansetron. A value of >1 favors Aprepitant over Ondansetron.
The model included terms for treatment and investigative sites.
n/m = Number of patients with desired response/number of patients included in analysis.
CI = Confidence interval.

Medical Officer Comment:
This post-hoc Non-Inferiority analysis is of limited value. The fact that the Non-Inferiority Margin was calculated post-hoc makes these results suspect of bias. Furthermore, this reviewer is not convinced that the studies used to calculate the non-inferiority margin are acceptable for the following reasons. None of the comparative studies used to calculate the margin evaluated an appropriate combination of drug formulation and surgical procedure.

The comparative intravenous ondansetron studies were performed on patients who had an out-patient surgery. It is unlikely that an outpatient surgery would have the same emetogenic potential as a more complicated surgery that required an over-night hospitalization. Additionally, the comparative studies that were performed on patients who required an over-night hospitalization evaluated the oral formulation of ondansetron. This Reviewer questions whether the submitted studies could be used to accurately calculate a non-inferiority margin.

Table 15
Studies Used in Non-Inferiority Calculation
Ondansetron PONV Prevention Trials

Study Population	Drug	Complete Response		Odds Ratio
		Placebo	Active	
Women Out-patients	Ondansetron I.V.	64/139 46%	103/136 76%	3.66
Women Out-patients	Ondansetron I.V.	63/143 44%	86/136 63%	2.18
Women In-patients	Ondansetron PO	105/327 32%	179/343 52%	2.31
Women In-patients	Ondansetron PO	54/204 26%	112/207 54%	3.27
Ref. Modified Table 5-5 Protocol 090				

Subgroup Analysis

Table 16
Complete Response
by Subgroup (Age, and Race)
24 Hours Following End of Surgery
(Modified-Intention-to-Treat Population)

	Treatment Group		
	Aprepitant 40mg n/m (%)	Aprepitant 125mg n/m (%)	Ondansetron n/m (%)
Age Group (Years)			
Age < 65	100/230 (43.5)	96/230 (41.7)	94/230 (40.9)
Age ≥ 65	11/18 (61.1)	7/9 (77.8)	10/16 (62.5)
Age <75	106/241 (44.0)	102/238 (42.9)	100/241 (41.5)
Age ≥ 75	5/7 (71.4)	1/1 (100.0)	4/5 (80.0)
Race Group			
Black	19/40 (47.5)	30/59 (50.8)	19/44 (43.2)
Hispanic	12/22 (54.5)	14/24 (58.3)	11/28 (39.3)
White	75/180 (41.7)	55/152 (36.2)	72/166 (43.4)
Other	5/6 (83.3)	4/4 (100.0)	2/8 (25.0)
Ref. Modified Table 7-11 Protocol 090 n/m = Number of patients with desired response/number of patients included in analysis.			

Medical Officer Comment:
Regardless of age category, aprepitant was similar to ondansetron with respect to the Complete Response endpoint. There were some variations observed in treatment differences among racial groups. Interestingly, in the defined Race analyses, Caucasians in the 125mg aprepitant group demonstrated the lowest Complete Response rate (36.2). The clinical significance of this finding

is unknown considering that the 40mg aprepitant group was higher (41.7) and was similar to the ondansetron group (43.4).

The Sponsor also performed analyses to determine whether the efficacy of aprepitant was effected by the following variables: smoking status, duration of surgery, history of PONV, and history of motion sickness. None of these treatment interaction analyses were statically significant.

Treatment by Gender Analysis:

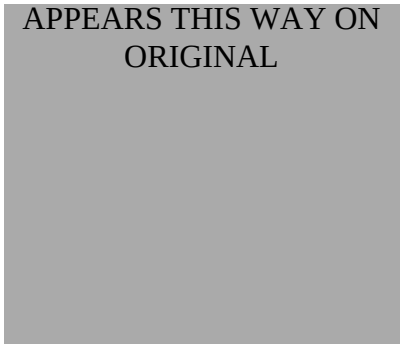
Medical Officer Comment:
The protocol's data analysis plan stated that a treatment-by-gender analysis would be included in the efficacy models if the percentage of male patients exceeded 10%. Since, the percentage of male patients (5.7%) did reach the pre-specified 10%, the submission did not include this analysis. Do to the question of a treatment-by-gender interaction identified in the original NDA, this analysis was requested. The Sponsor submitted these results as a response to an information request.

Table 17
Complete Response By Gender and
by Treatment Group in the 24 Hours Following End of Surgery
(Modified-Intention-to-Treat Analysis)

Treatment	n/m (%)	Aprepitant vs Ondansetron	
		Δ	Odds Ratio‡
Gender (p= 0.557)			
Female			
Aprepitant 40 mg	98/232 42.2	1.7%	1.1
Aprepitant 125 mg	95/226 42.0	1.5%	1.1
Ondansetron	94/232 40.5		
Male			
Aprepitant 40 mg	13/16 81.3	9.9%	2.0
Aprepitant 125 mg	8/13 61.5	-9.9%	0.8‡
Ondansetron	10/14 71.4		

Ref: Sec_1 11 3.pdf Table 2
Δ Treatment Group Difference Aprepitant vs. Ondansetron
‡ Estimated odds ratio for Aprepitant versus Ondansetron. A value of >1 favors Aprepitant over Ondansetron.
n/m= Number of patients responder/number of patients in analysis.

Although the limited number of male patients precludes any meaningful statistical interpretation, this analyses suggests that for the Complete Response endpoint, Aprepitant 125mg may not be as efficacious as ondansetron in male patients. A similar finding was noted in Study 091; however, this occurred in the Aprepitant 40mg group.



Safety Evaluation and Results

Exposure:

Of the 805 randomized patients, 766 patients received active study drug and were included in the safety analyses [aprepitant 40-mg (261), aprepitant 125-mg (252), and ondansetron (253)]. Three (3) patients (b) (6) and (b) (6) inadvertently received both active aprepitant and active ondansetron. These patients were excluded from the safety tables; however the adverse events experienced by these patients were described separately in each safety sub-section.

Patients were treated with study medications *only* on Day 1, preoperatively. Adverse events occurring up to 14 days after study drug administration were reported.

Adverse Experiences

Table 18
Adverse Events Summary
Study 090

Adverse Experience	Treatment Group		
	Aprepitant 40mg (N=261)	Aprepitant 125mg (N=252)	Ondansetron (N=253)
Patients with No Adverse Event(s)	81 (31.0)	77 (30.6)	64 (25.3)
Patients with Adverse Event(s)	180 (69.0)	175 (69.4)	189 (74.7)
Patients with Serious Adverse Event(s)	23 (8.8)	12 (4.8)	20 (7.9)
Death	1 (0.4)	0	0
Discontinued from Study due to AE	0	0	0
Ref: Modified Table 8-2, Study 090.pdf			

Medical Officer Comment:
The overall incidence of adverse and serious adverse events was similar among the 3 treatment groups. The incidence of both serious and non-serious adverse events was slightly higher in the ondansetron group; however, these differences were not statistically significant.

One patient in the aprepitant 40-mg group died 30 days after surgery. This event was reported as a progression of his underlying malignant disease (myeloproliferative disorder). No patients discontinued the study due a clinical adverse experience.

Adverse Events by Body System

Five hundred forty-four (544) of 766 patients (71.01%) who received either aprepitant or ondansetron experienced a adverse event [aprepitant 40 mg (69.0%), aprepitant 125 mg (69.4%), and ondansetron (74. 7%)].

Table 19
Select Adverse Events by Body System
(Incidence ≥ 2%)
Safety Population Study 090

Adverse Experience	Treatment Group		
	Aprepitant 40mg (N=261)	Aprepitant 125mg (N=252)	Ondansetron (N=253)
Blood and Lymphatic System	**8 (3.1)**	**14 (5.6)**	**13 (5.1)**
Anemia	7 (2.7)	14 (5.6)	13 (5.1)
Cardiac Disorders	**17 (6.5)**	**14 (5.6)**	**23 (9.1)**
Bradycardia	10 (3.8)	3 (1.2)	10 (4.0)
Tachycardia	4 (1.5)	8 (3.2)	9 (3.6)
Gastrointestinal Disorders	**93 (35.6)**	**81 (32.1)**	**89 (35.2)**
Constipation	27 (10.3)	21 (8.3)	23 (9.1)
Nausea	35 (13.4)	30 (11.9)	37 (14.6)
Vomiting	7 (2.7)	5 (2.0)	12 (4.7)
Diarrhea	4 (1.5)	5 (2.0)	2 (0.8)
Small Bowel Obstruction	0	2 (0.8)	5 (2.0)
Skin and Subcutaneous Tissue	**44 (16.9)**	**41 (16.3)**	**47 (18.6)**
Pruritus	39 (14.9)	33 (13.1)	39 (15.4)
Infections and Infestations	**31 (11.9)**	**27 (10.7)**	**27 (10.7)**
Wound Infection	7 (2.7)	4 (1.6)	6 (2.4)
Nervous System Disorders	**25 (9.6)**	**35 (13.9)**	**33 (13.0)**
Headache	17 (6.5)	24 (9.5)	20 (7.9)
Urinary Retention	8 (3.1)	7 (2.8)	11 (4.3)
Respiratory, and Thoracic Disorders	**29 (11.1)**	**22 (8.7)**	**27 (10.7)**
Hypoxia	8 (3.1)	7 (2.8)	4 (1.6)
Vascular Disorders	**33 (12.6)**	**29 (11.5)**	**27 (10.7)**
Hypertension	7 (2.7)	5 (2.0)	9 (3.6)
Hypotension	22 (8.4)	22 (8.7)	17 (6.7)
Ref: Modified Table 8-4, Study 090.pdf			

Medical Officer Comment:
The overall incidence and type of adverse events was similar among the 3 treatment groups. The most common adverse events were pruritus, constipation, and nausea. Episodes of nausea or vomiting were only reported as adverse events if they occurred more than 48 hours after surgery. Prior to that time nausea or vomiting were reported as efficacy end-points.

The aprepitant group had a higher incidence of hypoxia than the ondansetron group [aprepitant 40-mg (3.1%), aprepitant 125-mg (2.8%), and ondansetron (1.6%)]. The clinical significance of

this finding is unknown considering hypoventilation was reported as a Serious Adverse event only in the ondansetron group.

Additional analyses did not suggest that aprepitant affected the safety profile of the anesthetics used in the study or the surgical procedure.

The adverse events reported by the 3 patients who received both aprepitant and ondansetron (not included in the above table) include the following:

(b) (6) *(received aprepitant 40 mg plus ondansetron), experienced suture-related complications*

(b) (6) *(received aprepitant 125 mg plus ondansetron) experienced a serious adverse event of left lower lobe pneumonia.*

Neither adverse event was considered by the investigator to be related to study drugs. The third patient, (b) (6) *(received aprepitant 40 mg plus ondansetron), did not experience any adverse events.*

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Serious Adverse Events:

Table 20
Select Serious Adverse Events by Body System
(Incidence >0%)
Safety Population Study 090

Adverse Experience	Treatment Group		
	Aprepitant 40mg (N=261)	Aprepitant 125mg (N=252)	Ondansetron (N=253)
Blood and Lymphatic System	**2 (0.8)**	**1 (0.4)**	**0 (0.0)**
Anemia	2 (0.8)	**1 (0.4)**	**0 (0.0)**
Gastrointestinal Disorders	**5 (1.9)**	**6 (2.4)**	**7 (2.8)**
Abdominal Pain	1 (0.4)	0	0
Constipation	1 (0.4)	1 (0.4)	1 (0.4)
Ileus	2 (0.8)	2 (0.8)	0
Ileus Paralytic	0	1 (0.4)	0
Intestinal Obstruction	1 (0.4)	0	0
Retroperitoneal Edema	0	0	1 (0.4)
Small Bowel Obstruction	0	2 (0.8)	5 (2.0)
Infections and Infestations	**2 (0.8)**	**2 (0.8)**	**5 (2.0)**
Wound Infection	1 (0.4)	0	3 (1.2)
Postoperative infection	1 (0.4)	0	1 (0.4)
Staphylococcal infection	0	0	1 (0.4)
Nervous System Disorders	**0**	**1 (0.4)**	**1 (0.4)**
Cerebrovascular accident	0	0	1 (0.4)
Convulsion	0	1 (0.4)	0
Respiratory, and Thoracic Disorders	**3 (1.1)**	**1 (0.4)**	**2 (0.8)**
Hypoventilation	0	0	1 (0.4)
Atelectasis	1 (0.4)	0	0
Pulmonary Embolism	1 (0.4)	0	0
Respiratory Arrest	0	1 (0.4)	0
Vascular Disorders	**1 (0.4)**	**0**	**1 (0.4)**
Deep Vein Thrombosis	0	0	1 (0.4)
Hematoma	1 (0.4)	0	0
Ref: Modified Table 8-4, Study 090.pdf			

Medical Officer Comment:
The narratives of patients with serious adverse events were reviewed. In general, the incidence and type of serious adverse events were similar among treatment groups. The most common serious adverse events were Gastrointestinal Disorders [aprepitant 40-mg (1.9%), aprepitant 125-mg (2.4%), and ondansetron (2.8%)]. Serious adverse events of ileus were small, but were only reported in the aprepitant groups. The clinical significance of this finding is unknown since this did not occur in Study 091.

Serious adverse events of small intestinal obstruction were slightly more common in the ondansetron group compared with the aprepitant groups. The one report of respiratory arrest (aprepitant 125mg group) occurred in a 24 year old female with depression and ovarian cancer.

The narrative describes that the patient experienced a seizure the day after surgery. The patient experienced an episode of apnea and then cardiac arrest while undergoing a CT. The investigator reported that the seizure was the initial event, and all of the other events were related to the seizure.

Only one (1) serious adverse event was considered by the investigator as possibly related to study therapy: [redacted] *in aprepitant 125-mg group experienced mild constipation that started the day after surgery and lasted for 4 days causing a prolongation of the hospitalization.*

Discontinued Due to Adverse Experiences

Medical Officer Comment:
No patients were discontinued from the study due to an adverse event.

Summary of Laboratory Adverse Experiences

Table 21
Summary of Laboratory Adverse Events
Safety Population Study 090

Laboratory Adverse Events	Treatment Group		
	Aprepitant 40mg (N=261)	Aprepitant 125mg (N=252)	Ondansetron (N=253)
≥ 1 Lab Test Post Baseline	**259 (99)**	**248 (98)**	**253 (100)**
No Lab Adverse Event	243 (93.8)	235 (94.8)	238 (94.1)
≥ 1 Lab Adverse Event	16 (6.2)	13 (5.2)	15 (5.9)
≥ 1 Lab Serious Adverse Event	0	0	1 (0.4)
Discontinued Due to Adverse Event	0	0	0
Ref: Modified Table 8-11, Study 090.pdf			

Medical Officer Comment:
Laboratory adverse events were reported in 44 of the 760 patients (5.7%) who received study drug. There were no apparent differences between the aprepitant (125 mg, 40 mg) groups and the ondansetron group for the incidence of laboratory adverse events. There was only 1 serious laboratory adverse event reported, which occurred in a patient in the ondansetron group.

Table 22
Select Laboratory Adverse Events
(Incidence >0%)
Safety Population Study 090

Laboratory Adverse Events	Treatment Group		
	Aprepitant 40mg (N=261)	Aprepitant 125mg (N=252)	Ondansetron (N=253)
≥ 1 Lab Adverse Event	16 (6.2)	13 (5.2)	15 (5.9)
Blood Chemistry Test	**8/256 (3.1)**	**6/245 (2.4)**	**6/251 (2.4)**
ALT increased	2/250 (0.8)	2/240 (0.8)	1/247 (0.4)
AST increased	1/247 (0.4)	2/238 (0.8)	1/245 (0.4)
Bilirubin increased	1/253 (0.4)	0	0
Alk Phos. Increased	1/253 (0.4)	0	0
Magnesium decreased	2/4 (50.0)	0ψ	1/3 (33.3)
Phosphorus decreased	3/4 (75.0)	0ψ	0/1 (0.0)
Potassium decreased	1/252 (0.4)	2/244 (0.8)	3/250 (1.2)
Hematology Laboratory Test	**8/248 (3.2)**	**8/243 (3.3)**	**8/248 (3.2)**
Hematocrit decreased	2/242 (0.8)	1/240 (0.4)	2/239 (0.8)
Hemoglobin decreased	7/248 (2.8)	7/243 (2.9)	7/248 (2.8)
White blood cell count increased	0	0	1/248 (0.4)

Ref: Modified Table 8-13, Study 090.pdf
ψ Indicates there were no patients for whom the laboratory test was recorded

Medical Officer Comment:
Overall, the incidence of laboratory adverse events were small and did not suggest a safety signal. The most frequent laboratory abnormality reported as an adverse event was a decreased hemoglobin, which occurred in 7 patients in each treatment group.

With respect to the adverse events experienced by the three patients who received both aprepitant and ondansetron, and were not included in safety population, only one patient experienced a laboratory adverse event: (b) (6) *experienced a decreased serum calcium. This laboratory value did not meet the criteria for a serious adverse event and was not considered by the investigator to be related to study drugs.*

Vital Signs, Physical Observations

Table 23
Clinically Significant Vital Sign Abnormalities
Safety Population Study 090

Vital Sign	Treatment Group		
	Aprepitant 40mg (N=260)	Aprepitant 125mg (N=248)	Ondansetron (N=253)
Diastolic Blood Pressure			
≤ 50 mmHg and decrease ≥ 15 mmHg	52 (20)	33 (13.3)	36 (14.2)
≥ 105 mmHg and increase ≥ 15 mmHg	2 (0.8)	4 (1.6)	3 (1.2)
Systolic Blood Pressure			
≤ 90 mmHg and decrease ≥ 20 mmHg	16 (6.2)	20 (8.1)	17 (6.7)
≥ 180 mmHg and increase ≥ 20 mmHg	4 (1.5)	2 (0.8)	6 (2.4)
Pulse Rate			
≤ 50 and decrease ≥ 15	8 (3.1)	7 (2.8)	4 (1.6)
≥ 120 and increase ≥ 15	4 (1.5)	6 (2.4)	3 (1.2)
Respiratory Rate			
<8	4 (1.5)	4 (1.6)	3 (1.2)
>18	134 (51.5)	141 (56.9)	148 (58.5)
Temperature			
≥ 38.33° C and increase ≥ 1.11° C	0	2 (0.8)	0
Ref: Modified Table 8-17, Study 090.pdf			

Medical Officer Comment:
The protocol predefined limits for Clinically Significant Vital Sign Abnormalities (CSVA). Overall, the incidence of CSVA was similar among treatment groups. The most common abnormalities were respiratory rate above 18, decrease in diastolic blood pressure, and decrease in systolic blood pressure.

Electrocardiogram (ECG)

Table 24
12-Lead Electrocardiogram (ECG)
(24 Hours Postsurgery)
Safety Population Study 090

12-Lead Electrocardiogram	Treatment Group		
	Aprepitant 40mg n/m (%)	Aprepitant 125mg n/m (%)	Ondansetron n/m (%)
PR interval (msec)			
Mean	147.96	147.06	145.98
Standard Deviation	22.25	22.35	23.35
QTc interval (msec)			
Mean	416.63	414.39	415.16
Standard Deviation	25.36	24.51	34.39
QTc Interval Prolongation†			
Prolongation <30 msec	96/236 (40.7)	88/232 (37.9)	89/239 (37.2)
Prolongation 30 to 60 msec	19/236 (8.1)	20/232 (8.6)	20/239 (8.4)
Prolongation >60 msec	2/236 (0.8)	3/232 (1.3)	3/239 (1.3)

Ref: Modified Tables 8-18 and 8-19, Study 090.pdf
† Largest increase from baseline during treatment phase.
n = Number of randomized patients who took at least one dose of active study medication meeting the predefined criteria.
m = Number of randomized patients who took at least one dose of active study medication and had at least one post baseline QTc measurement.
% = Percentage (n/m * 100) of patients meeting the predefined criteria.

Medical Officer Comment:
Summary statistics (mean and standard deviation) for the PR interval and QTc performed 24 hours after the end of surgery were similar among treatment groups. The percentages of patients with clinically significant QTc interval prolongations at 24 hours after surgery were also similar among treatment groups and did not suggest a safety signal.

Additional Safety Analyses

Since it was unknown whether aprepitant could affect to metabolism and or safety profile of the anesthetics used during surgery, the Agency requested that the protocol include additional analyses to evaluate the awakening time, the duration of recovery and any evidence of respiratory depression.

Table 25
Summary Statistics for Awakening Time and Duration of Recovery
Safety Population Study 090

Awakening Time Duration of Recovery	Treatment Group		
	Aprepitant 40mg	Aprepitant 125mg	Ondansetron
Awakening time (Hrs)			
Mean	0.20	0.19	0.19
Standard Deviation	0.18	0.15	0.17
Duration of recovery (Hrs)			
Mean	0.38	0.35	0.36
Standard Deviation	0.24	0.22	0.20
Ref: Modified Tables 8-20, Study 090.pdf			

Medical Officer Comment:
Mean awakening time and mean duration of recovery were similar among the three treatment groups, suggesting that aprepitant had no greater influence over CYP3A4 metabolism of the anesthetics than did ondansetron.

Serious adverse events of excessive sedation and respiratory depression were prespecified as adverse events of special interest. All serious adverse event reports were reviewed by two physicians not involved with the study. One of the two physicians did not consider any of the serious adverse events to be consistent with either excessive sedation, or respiratory depression.

According to the second physician, two patients, one in the aprepitant group and one in the ondansetron group, experienced a serious adverse events which may have been consistent with respiratory depression. None of these adverse experiences were reported as drug related by the investigators.

A review of these safety data does not suggest that aprepitant affected the safety profile of the anesthetics used in these surgeries.

Deaths

Medical Officer Comment:
As previously described in this review, One patient in the aprepitant 40 mg group died 30 days after surgery. This event was reported as a progression of his underlying malignant disease (myeloproliferative disorder) and not drug related.

Discussion:

The primary purpose of this study was to demonstrate that aprepitant provided effective protection against PONV and that it was safe and well tolerated by surgical patients. The active comparator arm, intravenous ondansetron, was an acceptable comparator since it is approved for the proposed indication and is one of the most commonly used antiemetics for prevention of PONV.

Efficacy:

Table 26
Response Rates for Primary and Secondary Endpoints
(Modified- Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant vs Ondansetron	
		Δ	p-Value
Complete Response (Primary Endpoint) (no emesis and no rescue therapy, 0 to 24 hours)			
Aprepitant 40 mg	111/248 (44.8)	2.5	0.611
Aprepitant 125 mg	103/239 (43.1)	0.8	0.866
Ondansetron	104/246 (42.3)		
No Vomiting (no emetic episodes, 0 to 24 hours)			
Aprepitant 40 mg	**223/248 (89.9)**	**16.3**	**<0.001**
Aprepitant 125 mg	**227/239 (95.0)**	**21.4**	**<0.001**
Ondansetron	181/246 (73.6)		
No Use of Rescue Medication (for established emesis or nausea, 0 to 24 hours)			
Aprepitant 40 mg	112/248 (45.2)	-0.7	0.829
Aprepitant 125 mg	106/239 (44.4)	-1.5	0.724
Ondansetron	113/246 (45.9)		
No Vomiting (no emetic episodes, 0 to 48 hours)			
Aprepitant 40 mg	**209/247 (84.6)**	**17.7**	**<0.001***
Aprepitant 125 mg	**220/236 (93.2)**	**26.3**	**<0.001***
Ondansetron	164/245 (66.9)		

Ref: Study 090.pdf Page 21 of 1851
Δ Treatment Group Difference Aprepitant vs. Ondansetron.
* Not statistically significant after multiplicity adjustment
n/m= Number of patients responder/number of patients in analysis.

Although Study 090 failed to satisfy its Primary Hypothesis (aprepitant is superior to ondansetron for the "Complete Response" endpoint, the study did demonstrate that both dose levels of aprepitant were clinically and statistically significantly superior to ondansetron with

respect to the "No Vomiting" endpoint (secondary endpoint) during the first 24 hours after surgery.

The Primary Endpoint (Complete Response) is a composite end-point that includes the end-points No Vomiting and No Rescue therapy. To succeed for the primary endpoint both variables would need to be statistically significant. The study failed for its primary endpoint because the treatment group difference for the "No Rescue" variable was not statistically significant.

In this Reviewer's opinion, the success of the No Vomiting endpoint is more clinically meaningful than the failure of one variable within the Primary Endpoint (No Rescue). The most serious complications associated with PONV are directly related to the vomiting process (i.e. wound disruption, bleeding, increased intraabdominal, intraocular and intracranial pressures, esophageal tears, electrolyte imbalance, and pulmonary aspiration.

The therapeutic effect for the No Vomiting endpoints were maintained in favor of aprepitant for 48 hours after surgery. However, due to the prespecified data analysis plan, the results at 48 hours cannot be considered statistically significant.

Furthermore, even in the patients who vomited, the aprepitant patients faired better. In both aprepitant groups, a greater proportion of patients who vomited, experienced only one emetic episode (76% in the aprepitant 40 mg group, and 83% in the aprepitant 125 mg group). In contrast, only 52% of the ondansetron-treated patients who vomited suffered a single emetic event. In this Reviewer's opinion, any therapy that can significantly decrease the number of vomiting episodes in surgical patients represents a clinically meaningful improvement over currently approved therapy.

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Safety:

Study 090 successfully demonstrated that aprepitant is as safe as ondansetron and was well tolerated when used to prevent PONV. The incidence and type of adverse and serious events was similar among the three treatment groups. Actually, the incidence of both serious and non-serious adverse events was slightly higher in the ondansetron group when compared to the aprepitant groups.

Table 27
Select Adverse Events by Body System
(Incidence ≥2%)
Safety Population Study 090

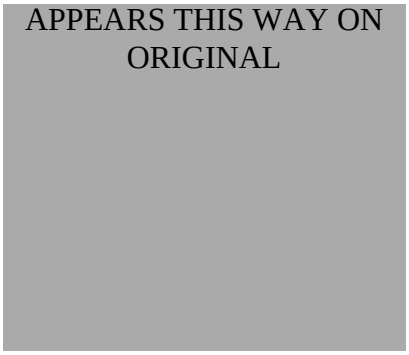
Adverse Experience	Treatment Group		
	Aprepitant 40mg (N=261)	Aprepitant 125mg (N=252)	Ondansetron (N=253)
Blood and Lymphatic System	**8 (3.1)**	**14 (5.6)**	**13 (5.1)**
Anemia	7 (2.7)	14 (5.6)	13 (5.1)
Cardiac Disorders	**17 (6.5)**	**14 (5.6)**	**23 (9.1)**
Bradycardia	10 (3.8)	3 (1.2)	10 (4.0)
Tachycardia	4 (1.5)	8 (3.2)	9 (3.6)
Gastrointestinal Disorders	**93 (35.6)**	**81 (32.1)**	**89 (35.2)**
Constipation	27 (10.3)	21 (8.3)	23 (9.1)
Nausea	35 (13.4)	30 (11.9)	37 (14.6)
Vomiting	7 (2.7)	5 (2.0)	12 (4.7)
Diarrhea	4 (1.5)	5 (2.0)	2 (0.8)
Small Bowel Obstruction	0	2 (0.8)	5 (2.0)
Skin and Subcutaneous Tissue	**44 (16.9)**	**41 (16.3)**	**47 (18.6)**
Pruritus	39 (14.9)	33 (13.1)	39 (15.4)
Infections and Infestations	**31 (11.9)**	**27 (10.7)**	**27 (10.7)**
Wound Infection	7 (2.7)	4 (1.6)	6 (2.4)
Nervous System Disorders	**25 (9.6)**	**35 (13.9)**	**33 (13.0)**
Headache	17 (6.5)	24 (9.5)	20 (7.9)
Urinary Retention	8 (3.1)	7 (2.8)	11 (4.3)
Respiratory, and Thoracic Disorders	**29 (11.1)**	**22 (8.7)**	**27 (10.7)**
Hypoxia	8 (3.1)	7 (2.8)	4 (1.6)
Vascular Disorders	**33 (12.6)**	**29 (11.5)**	**27 (10.7)**
Hypertension	7 (2.7)	5 (2.0)	9 (3.6)
Hypotension	22 (8.4)	22 (8.7)	17 (6.7)
Ref: Modified Table 8-4, Study 090.pdf			

Additionally, the safety profile of aprepitant was similar to ondansetron in terms of adverse events related to laboratory studies and 12 lead ECGs. The safety analyses did not suggest that the use of aprepitant adversely affected the safety profile of the anesthesia or surgical procedure.

Conclusion:

Although Study 090 failed to satisfy its Primary Hypothesis (aprepitant is superior to ondansetron for the "Complete Response" endpoint), the study did demonstrate that both dose levels of aprepitant were clinically and statistically significantly superior to ondansetron with respect to the "No Vomiting" endpoint (secondary endpoint) during the first 24 hours after surgery. Study 090 demonstrated that the use of 40mg aprepitant (proposed dose) was associated with a 16% improvement over ondansetron for the No Vomiting endpoint. Along with the other evidence of efficacy, this represents a clinically meaningful improvement over a drug many consider a standard of care.

Study 090 successfully demonstrated that aprepitant is as safe and as well tolerated as ondansetron when used to prevent PONV.



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/s/

Gary DellaZanna
6/1/2006 08:18:27 AM
MEDICAL OFFICER

Hugo Gallo Torres
6/1/2006 09:10:21 AM
MEDICAL OFFICER

Protocol 091

Aprepitant

A Randomized, Double-Blind, Active Comparator-Controlled, Parallel Group Study, Conducted Under In-House Blinding Conditions to Examine the Safety, Tolerability, and Efficacy of 2 Doses of Aprepitant for the Prevention of Postoperative Nausea and Vomiting

Clinical Phase III

Study Period: Start: May 28, 2004
End: April 20, 2005

Study Design:

Study 091 was a multicenter (42), randomized, double-blind, parallel-group, active comparator, controlled trial with in-house blinding designed to assess the safety and efficacy of two dose levels of aprepitant for the prevention of Post Operative Nausea and Vomiting (PONV) in patients receiving general anesthesia for open abdominal surgery requiring overnight hospital stay.

Eligible patients were assigned to one of the following three treatment arms using a computer generated randomization schedule. Patients were treated with study medications only on Day 1, preoperatively.

Table 1
Treatment Arms

Treatment Group	Bottle A (PO)	Vial B (I.V.)
I	Aprepitant 125 mg PO Placebo Aprepitant 40mg PO	Placebo Ondansetron 4mg
II	Aprepitant 40mg PO Placebo Aprepitant 125 mg PO	Placebo Ondansetron 4mg
III	Placebo Aprepitant 125 mg PO Placebo Aprepitant 40mg PO	Ondansetron 4mg

Ref: Table 5-1 Protocol 091

All aspects of surgery were recorded, including type of surgery, type and duration of anesthesia, and duration of recovery. After surgery, patients were permitted to take "rescue therapy" for established nausea or vomiting. Emetic episodes, rescue medications and severity of nausea were recorded in the Case Report Form (CRF).

Patients were issued a diary card to record emetic episodes, use of rescue medications, and pain medications for any out-patient period of the study for up to 48 hours following end of surgery.

Study Objectives:

Merck defined the following Study Objectives for Protocol 091:

Primary Objectives

1. To demonstrate that aprepitant (125 mg, 40 mg) is *superior* to ondansetron in the prevention of PONV as measured by the proportion of patients with No Vomiting in the 24 hours following end of surgery.

2. To demonstrate that aprepitant (125 mg, 40 mg) is *not inferior* to ondansetron in the prevention of PONV as measured by the proportion of patients with Complete Response in the 24 hours following the end of surgery.

3. To evaluate the safety and tolerability of aprepitant (125 mg, 40 mg) in patients undergoing surgery.

If the above was established, the protocol also defined that the following would be evaluated:

4. Compared to ondansetron, aprepitant (125 mg, 40 mg) will provide *superior* prevention of PONV as measured by the proportion of patients with Complete Response in the 24 hours following the end of surgery.

Secondary Objectives

To demonstrate that aprepitant (125 mg, 40 mg) is superior to ondansetron in the prevention of PONV as measured by the proportion of patients with No Vomiting in the 48 hours following end of surgery.

Exploratory Objectives

1. To assess the proportion of patients with No rescue (0 to 24 hours) in aprepitant (125 mg, 40 mg) and ondansetron groups.

2. To assess the distribution of peak nausea score (0 to 24 hours) in the aprepitant (125 mg, 40 mg) and ondansetron groups.

3. To assess the time to first vomiting episode in the 0 to 48 hours time frame in the aprepitant (125 mg, 40 mg) and ondansetron groups.

4. To assess the time to first vomiting episode, or first use of rescue in the 0 to 24 hours time frame in the aprepitant (125 mg, 40 mg) and ondansetron groups.

5. To assess the time frame to first use of rescue in the 0 to 24 hours time frame, in the aprepitant (125 mg, 40 mg) and ondansetron groups

Medical Officer Comment:
The treatment arms and study design were acceptable for this Phase III study.

After the study was initiated, the protocol was amended and the Data Analysis Plan revised. The Primary Efficacy Hypothesis was changed from superiority of aprepitant over ondansetron for Complete Response 24 hours after surgery to the superiority of aprepitant over ondansetron for the No Vomiting endpoint 24 hours after surgery.

The revisions were based on the results of Study 090, which failed to satisfy its primary hypothesis. The revisions were made prior to breaking the blind and are acceptable. In this Reviewer's opinion, the revised primary endpoints in Study 091 are more clinically meaningful than the primary endpoint used in Study 090 (Complete Response alone).

Considering all serious complications associated with PONV are directly related to the vomiting process (i.e. wound disruption, increased intraabdominal, intraocular and intracranial pressures, esophageal tears, electrolyte imbalance, and pulmonary aspiration), the "No Vomiting" endpoint is assessing a more clinically meaningful endpoint.

The study design, endpoints and patient population were acceptable. This study is similar to the studies that led to the approval of ondansetron for prevention of PONV indication. The active comparator, ondansetron, has a well characterized risk/benefit profile in the prevention of PONV and is one of the most commonly used antiemetics for prevention of PONV.

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Schedule of Clinical Observations:

Table 2
Schedule of Clinical Observations and Laboratory Measurements

Procedure	Pre-study[†]	Day of Surgery: Preoperative Phase -3 Hours	Day of Surgery: Surgery Phase Clock Stops[§]	Postoperative Phase (Hours) 0	2	6	24	48	Follow-Up[‡]
Medical history	X[‖]								
Informed consent	X[‖]								
Laboratory tests[¶]	X						X[#]		X[††]
Urine pregnancy test		X[‡‡]							
Alcohol use	X[‖]								
Tobacco use	X[‖]								
Patient reminder card/Instruction							X		
Vital signs	X[§§]	X		X	X	X	X		X
Physical exam	X[‖]								X
Electrocardiogram (central vendor)	X						X		X[††]
Aprepitant (or placebo) dosing		X[‖‖]							
Ondansetron (or placebo) dosing			X[¶¶]						
Postanesthesia recovery score				X[##]	----------	X[##]			
Nausea assessment using VRS[†††]		X			X	X	X	X	
Emetic episodes				X	----------			X	
Rescue medication				X	----------			X	

Procedure	Pre-study[†]	Day of Surgery: Preoperative Phase -3 Hours	Day of Surgery: Surgery Phase Clock Stops[§]	Postoperative Phase (Hours) 0	2	6	24	48	Follow-Up[‡]
Patient telephone contact								X[‡‡‡]	X[‡‡‡]
AE monitoring	X					X			

-3: 3 hours before induction of anesthesia.
0: End of surgery when last suture/staple placed.
24: 24 hours after last suture/staple placed.
48: 48 hours after last suture/staple placed.
† Within 3 weeks of surgery.
‡ Within 3 weeks after surgery.
§ The beginning of surgery is defined as the time of ondansetron/placebo administration. The timing for preoperative procedures are based on the beginning of surgery. Postoperative procedures are based on the end of surgery (T_{zero}).
‖ Informed consent, medical history and physical exam performed within 1 month of surgery may be used.
¶ Includes serum pregnancy test in women of childbearing potential. Laboratory tests need to be repeated before beginning surgery only if patient's clinical status is changed.
# Includes serum pregnancy test at 24 hours post-surgery.
†† ECG and laboratory tests will be repeated at follow-up only if clinically significant abnormalities were noted and reported as adverse events at the 24 hours post-surgery assessment.
‡‡ Urine pregnancy test obtained prior to study drug administration.
§§ Weight and height measured only at prestudy visit.
‖‖ Aprepitant to be administered 1 to 3 hours prior to induction of anesthesia.
¶¶ Ondansetron to be administered immediately prior to induction of anesthesia.
Postanesthesia recovery score assessed in recovery room every 15 minutes until a score of ≥8 is reached.
††† Nausea VRS will also be assessed prior to offering of rescue medication and if the patients complain of nausea
‡‡‡ Patients discharged from the hospital will be contacted via telephone 48 hours post-surgery to collect nausea VRS, emetic episodes, rescue medications, and pain medications. Patients will also be called ~3 weeks post-surgery to complete follow-up procedures if the patient cannot return for the follow-up visit.

Ref Table 5-2 Protocol 091

Medical Officer Comment:
The scheduled safety and efficacy assessments were acceptable for this Phase III trial.

Protocol Amendments:

Medical Officer Comment:
Protocol 091 was amended twice. The first amendment deleted a planned genetic analysis and included some editorial changes.

The second amendment provided for the changes to the Data Analysis Plan and study objectives that were outlined in the "Study Objectives" section of this review. The primary efficacy hypothesis was changed from superiority of aprepitant over ondansetron for the Complete Response endpoint to the superiority of aprepitant over ondansetron for the "No Vomiting" endpoint 24 hours following end of surgery.

This amendment also provided for a second primary endpoint that included two hypotheses: 1) aprepitant is non-inferior to ondansetron for the Complete Response endpoint, and if this hypotheses was satisfied, 2) aprepitant is superior to ondansetron for the Complete Response endpoint.

The safety and tolerability of aprepitant was also defined as a primary objective.

The second amendment also redefined the secondary objectives from:

(1) No Vomiting (0 to 24 hours)
(2) No Rescue (0 to 24 hours)
(3) No Vomiting (0 to 48 hours)

to No Vomiting in the 48 hours following end of surgery.

One of the original secondary objectives, "No rescue therapy" (0 to 24 hours), was re-defined as an exploratory objective and the comparison between the 125 mg and 40 mg aprepitant treatment groups for complete response was removed from the exploratory objectives.

Other defined exploratory objectives included:

time to first emetic episode (0 to 24 hours)
time to first use of rescue (0 to 24 hours)

The protocol amendments, as well as the final protocol, were reviewed and found acceptable. As previously noted, it is this Reviewer's opinion that the revised objectives in Study 091 were better designed to demonstrate a clinically meaningful treatment effect than the objectives used in Study 090.

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 reported that the following two study sites were identified as being non-compliant with some/all requirements of Good Clinical Practice:

Dr. John Moodie – Hamilton, New Zealand, 091-0002
Dr. Hector Alfaro – Mexico D.F., Mexico, 091-0029

With the exception of the above investigators, Merck certified that Study 091 was conducted in conformance with Good Clinical Practice standards and/or local statutes and regulations regarding informed consent, and the protection of the rights and welfare of human subjects participating in biomedical research. The efficacy data from these sites were not included in the primary efficacy analyses.

Investigators:

Medical Officer Comment:
Forty-two (42) centers participated in to Study 091, with only eight of the study sites located in the United States. The remaining thirty-four centers were located in the following countries: Austria, Brazil, Colombia, Costa Rica, France, Germany, Hong Kong, Italy, Mexico, New Zealand, Peru, Singapore, Spain, Switzerland, and the United Kingdom.

The geographical difference in this multinational study may account for some of the difference in efficacy between this Study (091) and Study 090 which was performed entirely in the United States.

Dose Selection:

Medical Officer Comment:
The dose selection for this Phase III study was acceptable. The two dose levels of aprepitant (125mg and 40mg) were based on dose ranging data from the CINV development program.

Study Population Selection

Medical Officer Comment:
The study population consisted of male and female patients receiving general anesthesia for open abdominal surgery that required an overnight hospital stay. Based on the specific eligibility criteria, the majority of patients were expected to consist of women undergoing a gynecological surgery.

This study population is acceptable since female gender and gynecological surgery are known risk factors for developing PONV and male patients were not excluded. This study population is similar to the population enrolled in the two pivotal trials that provided the basis for approval of oral ondansetron for the prevention of PONV: women undergoing general and gynecological surgery requiring overnight hospitalization.

Enrollment Criteria

Inclusion Criteria

male or female ≥18 years of age
able to understand study procedures
written informed consent
scheduled to undergo open abdominal surgery requiring overnight hospital stay
scheduled to receive the following general anesthetic regimen:

- Premedication with benzodiazepine (e.g., I.V. midazolam 1 to 3 mg) or nil
- Induction with any anesthetic agent
- Narcotics (e.g., fentanyl, morphine, or hydromorphone)
- Neuromuscular blocking agents
- Maintenance with N_2O (50 to 70%) with volatile anesthetic
- Neostigmine 2 to 5 mg (A minimum dose of 2.5 mg was recommended.)

scheduled to receive postoperative opioids (e.g., morphine, or fentanyl) by intramuscular (I.M.) or intravenous (I.V.), or patient controlled analgesia (PCA)
premenopausal female patients: demonstrate negative pregnancy test and agree to use a barrier form of contraception for at least 14 days before and after surgery
American Society of Anesthesia (ASA) physical status of I–III

Exclusion Criteria

scheduled to receive propofol for maintenance of anesthesia
(Note: Propofol was permitted for induction of anesthesia)
nasogastric or oral gastric tube intra- or postoperatively
allergic to any protocol medications or any other 5-HT_3 antagonists
expected to receive neuroaxial anesthesia (e.g., epidural, spinal)

expected to receive opioid antagonists
expected Intensive Care Unit (ICU) admission after surgery
clinically significant respiratory, metabolic, hepatic, renal, or cardiovascular condition
history of any illness, including morbid obesity, that in the opinion of the investigator might have confounded the results or posed unwarranted risk to the patient
vomiting from any organic etiology (e.g., small bowel obstruction).
vomited within 24 hours prior to surgery
mentally incapacitated or significant emotional or psychiatric disorder
any illicit drug use, or current evidence of alcohol abuse
taking, or had taken within 7 days of surgery the following

CYP3A4 substrates:
- Terfenadine
- Cisapride
- Astemizole
- Pimozide

CYP3A4 inhibitors:
- Clarithromycin
- Ketoconazole, itraconazole

taking, or had taken within 30 days of surgery the following

CYP3A4 inducers:
- Phenytoin or carbamazepine
- Barbiturates
- Rifampicin or rifabutin

abnormal laboratory values:

-- AST >2.5 x upper limit of normal
-- ALT >2.5 x upper limit of normal
-- Bilirubin >1.5 x upper limit of normal
-- Creatinine >1.5 x upper limit of normal

pregnancy or breast feeding
participated in a study with aprepitant
taken a non-approved (investigational) drug within the last 4 weeks
taken an antiemetic within 24 hours before surgery

Medical Officer Comment:
The enrollment criteria were acceptable for this Phase III study. The Sponsor reports "Patients were excluded if a nasogastric or oral gastric tube was routinely used for the type of surgery" and "if, during the course of surgery, a nasogastric or oral gastric tube was deemed medically necessary." If this occurred it was recorded on the worksheet, and the clinical monitor had to be notified immediately.

Excluding patients who receive a nasogastric or oral gastric tube during surgery is acceptable since it is a recognized therapy for PONV. Patients who have a nasogastric or oral gastric tube placed after surgery should be considered treatment failures. The CYP3A4 medications listed in the exclusion criteria are acceptable for this Phase III study.

Rescue Therapy

Patients were instructed to take rescue therapy for established nausea or vomiting. Study personnel were to offer the rescue therapy if the patient:

- specifically asked for rescue medication for established nausea
- experienced >1 episode of vomiting or retching
- experienced nausea for more than 15 minutes

Medical Officer Comment:
The protocol did not define which medications could be used as rescue therapy. The Sponsor did not supply the rescue therapy. The use of rescue therapy will be further discussed in the Efficacy section of this review.

Patients who took rescue medication for "established" nausea or vomiting were considered as failures according to the primary endpoint. However, patients who took rescue medication without established nausea or vomiting were considered protocol violators. Since this was a blinded study, the protocol defined use of rescue medication is acceptable and should not have resulted in a bias in favor of either treatment arm.

Prior and Concomitant Therapy

All prescribed and over-the-counter drugs taken by the patient within 30 days of surgery, during and after the treatment phase, and through the follow-up visit were recorded by the study coordinator.

In addition to the medications prohibited by the exclusion criteria, the protocol specifically prohibited the following drugs that have antiemetic activity within 24 hours of surgery:

- 5-HT_3 antagonists (e.g., ondansetron, granisetron, dolasetron)
- Phenothiazines (e.g., prochlorperazine, fluphenazine, perphenazine)
- Thiethylperazine (e.g., chlorpromazine, promethazine)
- Butyrophenones (e.g., haloperidol or droperidol)
- Benzamide (e.g., metoclopramide or alizapride)
- Domperidone
- Cannabinoids
- Corticosteroids (e.g., dexamethasone, methylprednisolone, or prednisone)
- Scopolamine
- Cyclizine

Medical Officer Comment:
The assessment for Prior and Concomitant Therapies, as well as the protocol defined list of prohibited medications, were acceptable.

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
Any other reason, in the opinion of the investigator that precluded further participation by the patient.

Medical Officer Comment:
The protocol defined reasons for discontinuation from the study were acceptable.

Study Medication Administration and Blinding

Aprepitant was manufactured in the United States and was provided by Merck. The commercially available intravenous ondansetron hydrochloride (ZOFRAN™) was manufactured by Glaxo SmithKline and was provided by Merck.

Aprepitant capsules (or placebo) were supplied in 1 bottle (Bottle A), and ondansetron (or placebo) was dispensed in 1 vial (Vial B). Each bottle contained two capsules (aprepitant 125 mg and placebo, or aprepitant 40 mg and placebo, or two placebo capsules).

Patients received the oral study drug 1 to 3 hours before induction of anesthesia. Patients were then treated with the intravenous study medication (ondansetron, or placebo) immediately before induction of anesthesia.

Each investigative site designated an unblinded pharmacists to receive, store and prepare the ondansetron and saline placebo. The investigators, study coordinators, and patients all remained blinded to the study medications.

Medical Officer Comment:
The randomization process, blinding procedures, and medication administration were acceptable.

Treatment Compliance

Medical Officer Comment:
Study 091 was a single-dose study in which therapy was administered by study personnel before induction of anesthesia, treatment compliance was therefore expected to be 100%.

Efficacy Assessments

Vomiting Assessment

A vomiting episode was defined as expulsion of stomach contents through the mouth or retching, defined as a non-productive attempt to vomit. Vomiting episodes were considered distinct if separated by the absence of vomiting and retching for at least 1 minute.

Nausea Assessment

Nausea was assessed using 11 point nausea Verbal Rating Score (VRS). Zero (0) corresponded with "no nausea", and 10 represented nausea "as bad as it could be." Nausea assessments were recorded by study personnel at prespecified times: 2, 6, 24, and 48 hours postsurgery. Nausea was also assessed at unscheduled times prior to any offering of rescue medication. If a patient was discharged prior to the 48 hour nausea assessment, the assessment was completed over the phone by the study coordinator.

Rescue Therapy

The patients were allowed to request rescue medication at any time after surgery for established nausea (nausea VRS >0), or vomiting. In addition, rescue therapy was offered to all patients who experienced more than one emetic episode, or patients who have nausea lasting for more than 15 minutes.

The type of rescue therapy, time and dosage was recorded by the study coordinator while in the hospital or by the patient for any out-patient period of the study for up to 48 hours following end of surgery.

Medical Officer Comment:
The protocol definitions for nausea and vomiting and efficacy assessments were acceptable. Study coordinators documented these assessments during the hospitalization period of the study. After discharge, patients recorded efficacy assessments for any out-patient period of the study for up to 48 hours following end of surgery.

Efficacy Endpoints:

Treatment comparisons were performed between the aprepitant groups and the ondansetron group for all statistical analyses. The time points of 24 hours and 48 hours following the end of surgery was relative to the time the last suture/staple was placed on the surgical incision.

Medical Officer Comment:
The protocol definition for "end of surgery" was recommended by the Division so a time to recovery analysis could be performed. It was unknown whether aprepitant would affect the metabolism of the anesthetics used.

Primary Efficacy Endpoint:

No Vomiting:	No Vomiting in the 24 hours following the end of surgery
Complete Response:	No Vomiting and No Rescue 24 hours following surgery

Secondary Efficacy Endpoints:

No Vomiting in the 48 hours following the end of surgery

Medical Officer Comment:
The efficacy endpoints were acceptable. The Primary and Secondary Endpoints were changed after the study was initiated, prior to breaking the blind. The revised endpoints were selected based on the results from Study 090.

The original Primary Endpoint was changed from a superiority analysis for Complete Response to two primary endpoints. The first primary endpoint was a superiority analysis for No Vomiting in the 24 hours following end of surgery.

The second primary endpoint included two hypotheses: 1) aprepitant is non-inferior to ondansetron for the Complete Response endpoint, and if this hypotheses was satisfied, 2) aprepitant is superior to ondansetron for the Complete Response endpoint.

In this Reviewer's opinion, the revised endpoints in Study 091 are more clinically meaningful than the primary endpoint used in Study 090 (Complete Response alone). Considering all serious complications associated with PONV are directly related to the vomiting process (i.e. wound disruption, increased intraabdominal pressure), the "No Vomiting" endpoint is more clinically meaningful than whether or not a patient used rescue therapy.
The second primary endpoint, included a non–inferiority analysis based on a non-inferiority margin (δ) calculated by the Sponsor. Merck based the calculation of this margin on placebo-controlled studies of ondansetron in surgical patients outlined in the following table.

Table 3
Studies Used in Non-Inferiority Calculation
Ondansetron PONV Prevention Trials

Study Population	Drug	Complete Response		Odds Ratio
		Placebo	Active	
Women Out-patients	Ondansetron IV	64/139 46%	103/136 76%	3.66
Thoi	Ondansetron IV	63/143 44%	86/136 63%	2.18
Women In-patients	Ondansetron PO	105/327 32%	179/343 52%	2.31
Women In-patients	Ondansetron PO	54/204 26%	112/207 54%	3.27
Ref. Modified Table 5-5 Protocol 091				

Merck states the following regarding their "Rationale for Selection of Non-Inferiority Margin"

> *The criterion used for selecting δ as a function of the relative effect of control to placebo was: select δ as one half of the relative effect of control to placebo on the log odds ratio scale. This criterion is meant to ensure that the treatment effect preserves at least half of the control effect.*
>
> *Applying this criterion to the studies mentioned above, a conservative non-inferiority boundary of δ=0.65 was identified as follows: The odds ratio (2.18) for the second study in Table 3 was selected as representing the most conservative estimate of treatment effect. The inverse of the odds ratio (1 / 2.18 = 0.459) was calculated so as to obtain the placebo / ondansetron value. The natural log of this value was then taken (0.459 = -0.779) to obtain the same scale that is used in the logistic regression analysis. Since the rationale is to preserve at least ½ of the effect, ½ of -0.779 was determined (-0.390). Finally, this value was exponentiated (0.677) to return it to the odds ratio scale. This value was rounded to 0.65 to obtain the non-inferiority margin.*
>
> *An odds ratio of 0.65 corresponds approximately to a difference in percentages of about 10 percentage points assuming the response rates are centered around 50% (as they are in the four historical ondansetron studies). This difference of 10 percentage points is consistent with ½ of the effect seen in the ondansetron studies and it also represents a conservative non-inferiority margin on this scale as other studies for prevention of nausea and vomiting have used a non-inferiority margin of 15 percentage points (see ALOXI Prescribing Information for prevention of CINV*

This reviewer is not convinced that the studies used to calculate the non-inferiority margin are acceptable for the following reasons.

Study 091 utilized an intervenous formulation of ondansetron in a patient population that had a surgical procedure which required an over-night hospitalization. None of the used in calculating the margin evaluated an appropriate combination of drug formulation and surgical procedure.

The comparative intravenous ondansetron studies were performed on patients who had an out-patient surgery. It is unlikely that an outpatient surgery would have the same emetogenic potential as a more complicated surgery that required an over-night hospitalization.

Additionally, the comparative studies that were performed on patients who required an over-night hospitalization evaluated the oral formulation of ondansetron. This Reviewer questions whether the submitted studies could be used to accurately calculate a non-inferiority analysis.

Exploratory Efficacy Endpoints:

Exploratory Endpoints (Pre-specified)

No use of rescue medication in the 0 to 24 hours
Peak nausea score in the 0 to 24 hours
Time to first vomiting episode in the 0 to 48 hours
Time to first vomiting or first use of rescue medication in the 0 to 24 hours
Time to first use of rescue medication in the 0 to 24 hours
Subgroup display: No Vomiting and Complete Response (0 to 24 hours) by age and race

Exploratory Endpoints (Not pre-specified)

Summary of number of PONV risk factors per patient by treatment group
Summary statistics for overall duration of anesthesia
Post-hoc subgroup display: No Vomiting (0 to 24 hours) by use of Ondansetron as rescue medication

Medical Officer Comment:
In addition to the primary and secondary efficacy endpoints, the Sponsor analyzed prespecified and non-prespecified exploratory endpoints. These analyses will be reviewed as supportive evidence of efficacy.

Safety Endpoints

The Protocol defined the following Safety Endpoint Analyses:

Primary Safety Endpoint Analyses:

Clinical or laboratory *adverse event* within 14 days of aprepitant therapy
Clinical or laboratory *drug-related adverse event* within 14 days of aprepitant therapy.
Clinical or laboratory *serious adverse event* within 14 days of aprepitant therapy.
Discontinuation of treatment due to a clinical or laboratory adverse experience

Secondary Safety Endpoint Analyses:

Clinical or laboratory *adverse event* occurring in >= 5% of patients in at least 1 of the comparison treatment groups

Medical Officer Comment:
The protocol defined safety endpoints and safety assessment were acceptable.

Patient Enrollment:

A total of 1004 patients were screened, resulting in 922 patients being randomized in to one of three treatment groups [aprepitant 40mg (307), aprepitant 125mg (313), ondansetron (302)].

Medical Officer Comment:
Of the 82 patients not randomized, 51 patients did not meet the eligibility criteria, 25 withdrew consent. The most common reasons for exclusion were that the patients were not scheduled to undergo open abdominal surgery.

Patient Accountability:

Table 4
Disposition of Randomized Patients

Patients Randomized	Treatment Group		
	Aprepitant 40mg (N=307)	Aprepitant 125mg (N=313)	Ondansetron (N=302)
Patients completed	301	298	285
Patients discontinued	6	15	17
adverse event	1	3	2
lost to follow-up	0	1	1
withdrew consent	1	1	2
other	4	10	12
Ref. Modified Table 6-1 Protocol 091			

Medical Officer:
Of the 922 randomized patients, 884 (95.9%) patients completed the study. Thirty-eight patients (4.12%) discontinued from the study [aprepitant 40mg group (6), aprepitant 125mg group (15) and ondansetron group (17)]. The number of patients who discontinued from the study and the reasons for discontinuation were similar between treatment groups and should not result in a bias.

The number of patients who discontinued due to an adverse event was small (6) and was similar between treatment groups. Two of the 6 patients did not receive any active study drug (b) (6) in the aprepitant 125-mg group and (b) (6) in the ondansetron group). No patients discontinued due to a laboratory adverse experience.

Twenty-six patients discontinued for "other reasons" [aprepitant 40mg group (4), aprepitant 125mg group (10) and ondansetron group (12)]. The status of "discontinuation for other reasons" was assigned most commonly because the surgery was canceled/rescheduled, the surgical/anesthesia plans changed, or the patient became "ineligible" for the study. Twenty of the 26 patients who discontinued for "other reasons" were discontinued prior to receiving study drug.

Defined Study Populations:

Medical Officer Comments:
Two patient populations were defined for the efficacy analysis: a modified intention-to-treat (MITT) population and the per-protocol population (PP). The primary efficacy analysis was performed on the MITT population.

Modified Intention-to-Treat Population:

The Modified Intention-to-Treat Population included all patients who received study drug (one dose from both Bottle A and Vial B), had undergone protocol-defined surgery (open abdominal surgery under general anesthesia), and had at least one post operative assessment.

The following Table displays the number of patients excluded from the MITT population and the justification for exclusion.

Table 5
Randomized Patients Excluded From the MITT Analyses
(0 - 24 hours)

Exclusion	Treatment Group		
	Aprepitant 40mg (N=307)	Aprepitant 125mg (N=313)	Ondansetron (N=302)
Included in MITT Analyses	**293/307 (95.4)**	**293/313 (93.6)**	**280/302 (92.7)**
Total Excluded	**14/307 (4.6)**	**20/313 (6.4)**	**22/302 (7.3)**
No study medication	4/307 (1.3)	9/313 (2.9)	17/302 (5.6)
Incomplete study medication or No post treatment efficacy data	3/307 (1.0)	4/313 (1.3)	0/302 (0.0)
Potentially unblinded at site	0/307 (0.0)	0/313 (0.0)	1/302 (0.3)
Study Site 02	3/307 (1.0)	2/313 (0.6)	2/302 (0.7)
Study Site 29	5/307 (1.6)	5/313 (1.6)	3/302 (1.0)
Ref. Modified Table 6-5 Protocol 091 Number (%)			

Medical Officer:
The protocol definition for the MITT population was acceptable. The number of patients excluded from the MITT analyses and the reasons for being excluded were acceptable. The Sponsor's justification for excluding the patients from Study Sites 02 and 29 is acceptable. Removing the patients from these sites should not affect the interpretation of the efficacy data or result in a bias in favor of aprepitant since the number of patients enrolled in these sites were small.

Of the 922 randomized patients, 56 patients were excluded from the MITT analyses [aprepitant 40mg group (14), aprepitant 125mg group (20) and ondansetron group (22)]. The most common reason for exclusion from the MITT analysis was the non-administration of active study medication. These exclusions are not expected to result in any unfair bias (see Table 5). Therefore, 866 randomized patients received study drug, underwent surgery, and had at least 1 posttreatment efficacy assessment. These patients were included in the MITT efficacy analyses for the 24-hour post-surgery endpoints.

Five additional patients were missing data for the secondary 48-hours post-surgery analysis [aprepitant 40mg group (1), aprepitant 125mg group (3) and ondansetron group (1)]. Therefore, 861 patients were included in the MITT analyses for the 48-hour endpoint analyses.

Per-Protocol Population:

Protocol violation criteria and protocol violators were identified prior to breaking the blind. No data were imputed in the per-protocol analysis. The Sponsor performed a per-protocol analysis as supportive evidence of efficacy. The following Table shows the number of patients and reasons for exclusion from the Per-Protocol Efficacy Analyses during the 24-hour follow-up period.

Table 6
Patients Excluded From the Per-Protocol Efficacy Analyses
24 Hours Following End of Surgery

Exclusion	Treatment Group		
	Aprepitant 40mg (N=293)	Aprepitant 125mg (N=293)	Ondansetron (N=280)
Total Excluded	34/293 (11.6)	23/293 (7.8)	31/280 (11.1)
No Nitrous Oxide	1/293 (0.3)	0/293 (0.0)	2/280 (0.7)
No post-operative opioids	14/293 (4.8)	14/293 (4.8)	9/280 (3.2)
Propofol for maintenance of anesthesia	1/293 (0.3)	0/293 (0.0)	0/280 (0.0)
NG/OG tube	7/293 (2.4)	2/293 (0.7)	3/280 (1.0)
Neuroaxial anesthesia	0/293 (0.0)	0/293 (0.0)	1/280 (0.3)
Prophylactic anti-emetic (up to 24 hours post-surgery)	11/293 (3.8)	8/293 (2.7)	18/280 (6.4)
Vomited within 24 hours prior to study entry	2/293 (0.7)	0/293 (0.0)	1/280 (0.3)
Ref. Modified Table 6-6 Protocol 091 Number (%)			

Medical Officer:
The protocol defined per-protocol population was acceptable. During the first 24-hour follow-up period 88 patients were excluded from the PP population. The number of excluded patients increased to 110 when assessed for the 48-hour follow-up period. Since protocol violators were identified prior to breaking the blind, this should not result in a bias in favor of any treatment arm. Approximately 10% of the study population was defined as protocol violators. The number of violators was similar between treatment groups.

Demographics and Characteristics

Table 7
Demographics

Demographics	Treatment Group		
	Aprepitant 40 mg (N=303)	Aprepitant 125 mg (N=304)	Ondansetron (N=285)
Sex			
Female	274 (90.4)	272 (89.5)	264 (92.6)
Male	29 (9.6)	32 (10.5)	21 (7.4)
Race			
Caucasian	144 (47.5)	144 (47.4)	144 (50.5)
Black	33 (10.9)	38 (12.5)	26 (9.1)
Asian	29 (9.6)	31 (10.2)	30 (10.5)
Hispanic	52 (17.2)	49 (16.1)	47 (16.5)
Other	7 (2.3)	2 (0.7)	1 (0.4)
Age			
Mean	46.3	46.1	45.0
Median	45.0	45.0	44.0
Min-Max	19 - 84	18 - 84	21 - 84
Age ≥ 65 years	28 (9)	24 (8)	21 (7)

Ref: Modified Table 6-8 Study 091

Table 8
Number of Risk Factors† per Patient
by Treatment Group

Risk Factors	Treatment Group		
	Aprepitant 40 mg (N=303)	Aprepitant 125 mg (N=304)	Ondansetron (N=285)
0	1 (0.3)	1 (0.3)	1 (0.4)
1	15 (5.0)	17 (5.6)	13 (4.6)
2	80 (26.4)	82 (27.0)	65 (22.8)
3	152 (50.2)	161 (53.0)	153 (53.7)
4	55 (18.2)	43 (14.1)	53 (18.6)

Ref: Modified Table 6-10 Study 091
† Risk Factors: non-smoker, female, history of PONV and/or history of motion sickness and use of postoperative opioids.

Medical Officer Comment:
The majority of the patients in Study 091 were Caucasian (48%) females (91%) between the ages of 35 to 54 years. The three treatment groups were generally similar with respect to known risk factors for developing nausea and vomiting (female gender, history motion sickness, non smoking status, and use of postoperative opioids). The number of randomized male patients was be too small to perform any meaningful analysis.

The ondansetron group had a slightly higher incidence of a history of PONV [aprepitant 40mg group (16%), aprepitant 125mg group (13%) and ondansetron group (18%)]. However, this should not result in a bias in favor of the aprepitant group since there were no differences among the 3 treatment groups with respect to the overall number of risk factors for PONV.

Primary Diagnosis and Type of Surgery

Table 9
Patients With Specific Types of Surgery
MITT Population

Select Surgeries	Treatment Group		
	Aprepitant 40mg (N=248)	Aprepitant 125mg (N=239)	Ondansetron (N=246)
Non-Gynecological Surgery	**56 (19.1)**	**56 (19.1)**	**49 (17.5)**
Gynecological Surgery	**237 (80.9)**	**237 (80.9)**	**231 (82.5)**
Hysterectomy / Salpingo Oophorectomy	113 (38.6)	105 (35.8)	93 (33.2)
Hysterectomy	80 (27.3)	99 (33.8)	96 (34.3)
Salpingo-oophorectomy	13 (4.4)	3 (1.0)	5 (1.8)
Myomectomy	30 (10.2)	21 (7.2)	25 (8.9)
Ovarian/Adnexal Cystectomy	8 (2.7)	4 (1.4)	2 (0.7)
Intestinal Resection	17 (5.8)	15 (5.1)	10 (3.6)

Ref. Modified Table 6-11 Protocol 091
Number (%)

Medical Officer Comment:
The types of surgery procedures were similar across treatment groups. Over 81% of the patients underwent a gynecological surgery. The most common category of surgery was hysterectomy plus salpingo-oophorectomy (36%). The incidence of bowel surgery was higher in both aprepitant groups compared to the ondansetron group. Since this type of surgery requires prolonged, direct surgical manipulation of the bowel, it may make these patients more prone to ileus and PONV. This may have resulted in a slight bias in favor of the ondansetron group. However, in Study 090, bowel surgery was more common in the ondansetron group, so these slight differences should not be important in the integrated efficacy analysis.

Preexisting Diagnosis

Medical Officer Comment:
As part of the review of efficacy, preexisting medical conditions which may have affected the incidence of PONV were analyzed. The incidence and type of preexisting medical conditions were similar between treatment groups and should not have resulted in a bias. The most common preexisting medical conditions involved the reproductive system and breast disorders (42%).

Handling of Dropouts or Missing Data

For the primary efficacy analyses, patients who at sometime during the 23 hours following surgery were both discharged *and* also lost to follow-up, *and* who in addition neither vomited nor used rescue medication, were to be excluded from the primary endpoint analyses.

Medical Officer Comment:
None of the patients met these criteria.

Safety Population

Medical Officer Comment:
The protocol defined safety population was acceptable. It included all patients who were randomized and received a study drug (one dose from Bottle A or vial B).

Concomitant and Prior Medical Therapy

All medications taken in the 30 days prior to study entry and during the14 days following study were recorded in the CRF.

Medical Officer Comment:
The use of prior medical therapy was similar between treatment groups and should not have affected the efficacy analysis (Ref. Table 6-13). Of the 892 randomized patients who received active study drug, 742 (83.2%) patients had taken at least 1 medication in the 30 days prior to

study entry. The three most commonly reported prior medications in Study 091 were in the categories of psycholeptics, antibacterials, and drugs for acid related disorders. This study differed from Study 090 which had vitamins, analgesics, and antiinflammatory products as the most commonly reported prior medications.

Anesthesia-Related Medications

Table 10
Summary Statistics for Duration of Anesthesia by Treatment Group

Duration (Hours)	Treatment Group		
	Aprepitant 40mg (N=292)*	Aprepitant 125mg (N=293)	Ondansetron (N=279)*
Mean	2.0	1.9	1.8
Standard deviation	1.0	1.0	0.9
Median	1.8	1.7	1.6
Minimum	0.5	0.4	0.4
Maximum	6.9	6.9	5.7

Ref. Modified Table 6-15 Protocol 091
* Two patients had incomplete anesthesia information and was not included in this calculation

Medical Officer Comment:
The type and duration of anesthesia was analyzed to see if it resulted in a significant interaction on the efficacy results. Overall, the type, dose and duration of anesthesia were similar among the three treatment groups and should not have resulted in a bias in any of the treatment arms.

It is generally accepted that the use of nitrous oxide can contribute to the development of PONV. All but 3 patients received nitrous oxide (b) (6) *from aprepitant 40-mg group, and* (b) (6) *and* (b) (6) *from the ondansetron group). The use of nitrous oxide was similar across treatment groups (mean percentages): [aprepitant 40-mg (54.10 ± 6.27%), aprepitant 125-mg(53.65 ± 5.92%), and ondansetron (53.69 ± 5.91%).*

Postoperative Analgesics

Medical Officer Comment:
Since the use and type of post operative analgesics could effect the incidence of PONV, these data were collected and analyzed. Overall, the type and dose of post operative analgesics were similar in the three treatment groups and should not have resulted in a bias in favor of any of the treatment arms.

The type of postoperative analgesics used in Study 091 was very different than Study 090. In Study 091, 95.7% patients received one or more opioid class analgesic medication post operatively. In Study 090 greater than 99% of the patients received one or more opioid class analgesic medication post operatively.

The most common analgesic used in both studies was morphine. However, the use of morphine was much higher in Study 090 compared to 091 [Study 090 (83.4%), Study 091(48.7%)] Additionally, the use of postoperative non-opioid analgesics was 78.4% in Study 091, compared to 67.0% in Study 090. The use of morphine is a known risk factor for the development of PONV. These differences in the use of postoperative analgesics may account for some of the difference in efficacy observed between Study 090 and 091.

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. The use of rescue medication was similar between treatment groups [aprepitant 40-mg (32.8%), aprepitant 125-mg (35.2%) and ondansetron (37.1%)].

This reviewer also analyzed the use of Concomitant Therapies that may have antiemetic properties that were not administered as rescue therapy.

Table 11
Patients With Specific Concomitant Therapies
(Incidence 5% in One or More Treatment Groups) by Drug Category

Select Concomitant Medications	Treatment Group		
	Aprepitant 40mg (N=303)	Aprepitant 125mg (N=304)	Ondansetron (N=285)
Patients ≥ 1 Concomitant therapies	303 (100.0)	301 (99.0)	285 (100.0)
Drugs with Antiemetic Activity Reported in Other Classes			
Functional Gastrointestinal Disorders			
Metoclopramide	19 (6.3)	18 (5.9)	24 (8.4)
Nervous System			
Adiphenine Hydrochloride (+) Dipyrone (+) Promethazine	18 (5.9)	21 (6.9)	15 (5.3)

Ref. Modified Table 6-18 Protocol 091
Number (%)

The use of medications with antiemetic properties should not have resulted in a bias in favor of aprepitant. Metoclopramide, a drug approved for the prevention of PONV, was used more often in the ondansetron group than aprepitant group. The use of other drugs with antiemetic properties were generally similar between treatment groups.

Protocol Deviations

Table 12
Protocol Deviations
Affecting Analysis Populations
0 to 24 Hours Postoperatively

Protocol Deviations	Treatment Group		
	Aprepitant 40mg (N=307)	Aprepitant 125mg (N=313)	Ondansetron (N=302)
Prime Therapy Deviations			
No Study Therapy[A]	4	9	17
Incomplete Study Therapy[A]	3	4	0
Potential Premature Unblinding[A]	0	0	1
Pre-Surgery Deviations			
Vomited within 24 hours before surgery[B]	2	0	1
Surgery Deviations			
Nasogastric/Oral gastric Tube[B]	7	2	3
Neuroaxial Anesthesia[B]	0	0	1
No N_2O[B]	1	0	2
Propofol for Maintenance[B]	1	0	0
Post-Surgery Deviations			
No Postoperative Opioids[B]	14	14	9
Prohibited Medication			
Antiemetic within 24 hours before surgery OR for other than Rescue[B]	11	8	18
Site Data Excluded			
Study Site 2[A]	3	2	2
Study Site 29[A]	5	5	3

Ref. Table 5 Information Request March 2006
[A] excluded from MITT analyses.
[B] Included in MITT analysis, but excluded from PP analysis

Medical Officer Comment:
Protocol deviations and violations were identified prior to unblinding the study. The type and number of protocol deviations were generally similar across treatment groups and should not result in a bias. The Sponsor's justification for including/excluding patients from the primary efficacy analyses were acceptable.

Efficacy Results

Primary Endpoints:

Table 13
Response Rates for Primary Endpoints
(Modified- Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant vs Ondansetron	
		Δ	Analysis
Primary Endpoints			
No Vomiting (Superiority) (no emetic episodes, 0 to 24 hours)			
Aprepitant 40 mg	246/293 (84.0)	12.6%	p<0.001
Aprepitant 125 mg	253/293 (86.3)	14.9%	p<0.001
Ondansetron	200/280 (71.4)		
Complete Response (Non-inferiority) 95% CI 0.65 (no emesis and no rescue therapy, 0 to 24 hours)			
Aprepitant 40 mg	187/293 (63.8)	8.8%	LB = 1.04
Aprepitant 125 mg	184/293 (62.8)	7.8%	LB = 1.08
Ondansetron	154/280 (55.0)		
Complete Response (Superiority) 95% CI >1.0 (no emesis and no rescue therapy, 0 to 24 hours)			
Aprepitant 40 mg	187/293 (63.8)	8.8%	LB = 1.04*
Aprepitant 125 mg	184/293 (62.8)	7.8%	LB = 1.08*
Ondansetron	154/280 (55.0)		

Ref: Study 091.pdf Table 7-1
Δ Treatment Group Difference Aprepitant vs. Ondansetron.
LB = lower bound of the 1-sided 95% confidence interval.
*P value <0.05
n/m= Number of patients responder/number of patients in analysis.

Medical Officer Comment:
The 6 statistical null/alternative hypotheses that comprise the primary efficacy analyses were evaluated in a step-wise fashion employing a closed testing procedure designed to control the overall Type I error rate at the 0.05 level.

The first primary efficacy endpoint was a superiority analysis for No Vomiting, defined as the absence of vomiting episodes, retching or dry heaves, regardless of whether or not the patient took rescue medication. The proportions of patients with No Vomiting in the 24-hours following the end of surgery were significantly higher in both the aprepitant groups compared to the ondansetron group. The per-protocol analysis for No Vomiting (0 to 24 hours) endpoint demonstrated similar results.

The second primary efficacy endpoint included two hypotheses: 1) aprepitant is non-inferior to ondansetron for the Complete Response endpoint, and if this hypotheses was satisfied, 2) aprepitant is superior to ondansetron for the Complete Response endpoint.

Non-inferiority was defined as having the lower bound of the 1-sided 95% confidence interval for the odds ratio, comparing aprepitant to ondansetron, exceed the pre-specified non-inferiority margin of 0.65. Based on the Sponsor's calculations, and confirmed by the Agency's statistician, both aprepitant doses were non-inferior to ondansetron for the primary endpoint Complete Response.

Based on the data analysis plan, since the first (non inferiority) hypothesis of the second primary efficacy endpoint was successful, the second hypothesis was tested: the superiority of aprepitant over ondansetron with respect to the Complete Response endpoint. The Sponsor reported that, based on the protocol defined data analysis plan, both aprepitant doses were also superior to ondansetron for the Complete Response endpoint. However, the Agency's Statistical team does not agree with their analysis. The team agrees that Study 091 succeeded in demonstrating non-inferiority; however, for the superiority analyses, statistical significance was not maintained based upon one-sided test using a more appropriate 2.5% significance level and using the multiplicity adjustment method proposed by the sponsor.

As previously noted in this review, this Reviewer questioned whether the studies used to calculate the non-inferiority margin were acceptable. Although this may be an important consideration when evaluating the Statistical Significance of these results, the study clearly demonstrated that both dose levels of aprepitant were significantly superior to ondansetron with respect to the No Vomiting primary endpoint during the first 24 hours after surgery as well as for the secondary endpoint, 0 to 48 hour time period.

It is this Reviewer's opinion that the success of the No Vomiting endpoints are the most clinically meaningful demonstration of efficacy in the PONV population. All of the serious complications in this population are directly related to the vomiting process (i.e. wound disruption, increased intraabdominal, intraocular and intracranial pressures, esophageal tears, electrolyte imbalance, and pulmonary aspiration.

Furthermore, the treatment group differences were clinically meaningful even in the patients who were classified as treatment failures, based on the vomiting endpoint. In both aprepitant groups, a greater proportion of patients who vomited, experienced only one emetic episode [aprepitant 40 mg group (66%), and aprepitant 125 mg group (65%)]. In contrast, only 50% of the ondansetron-treated patients who vomited suffered a single emetic event.

Table 13
Number of Vomiting Episodes Per Patients by Treatment Group

Emetic Episodes	Treatment Group		
	Aprepitant 40mg (N=293)	Aprepitant 125mg (N=293)	Ondansetron (N=280)
0	246 (84.0)	253 (86.3)	200 (71.4)
1	31 (10.6)	26 (8.9)	40 (14.3)
2	11 (3.8))	9 (3.1	24 (8.6)
3	4 (1.4)	4 (1.4)	7 (2.5)
4	1 (0.3)	1 (0.3)	7 (2.5)
5	0 (0.0)	0 (0.0)	1 (0.4)
6	0 (0.0)	0 (0.0)	1 (0.4)
Ref. Modified Table 7-4 Protocol 091			

Secondary Endpoint:

Table 14
Response Rates for Secondary Endpoint
(Modified- Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant vs Ondansetron	
		Δ	Analysis
Secondary Endpoint			
No Vomiting (Superiority) (no emetic episodes, 0 to 48 hours)			
Aprepitant 40 mg	238/292 (81.5)	15.2%	p<0.001
Aprepitant 125 mg	246/290 (84.8)	18.5%	p<0.001
Ondansetron	185/279 (66.3)		
Ref: Study 091.pdf Table 7-1 Δ Treatment Group Difference Aprepitant vs. Ondansetron. LB = lower bound of the 1-sided 95% confidence interval. *P value <0.05 n/m= Number of patients responder/number of patients in analysis.			

Medical Officer Comment:
The proportions of patients with No Vomiting in the 48 hours following the end of surgery were significantly higher in both aprepitant groups than in the ondansetron group. The per-protocol analysis for the No Vomiting (0 to 48 hours) endpoint demonstrated similar results.

Select Exploratory Endpoints:

No Rescue Medication (0 to 24 hours) Following End of Surgery

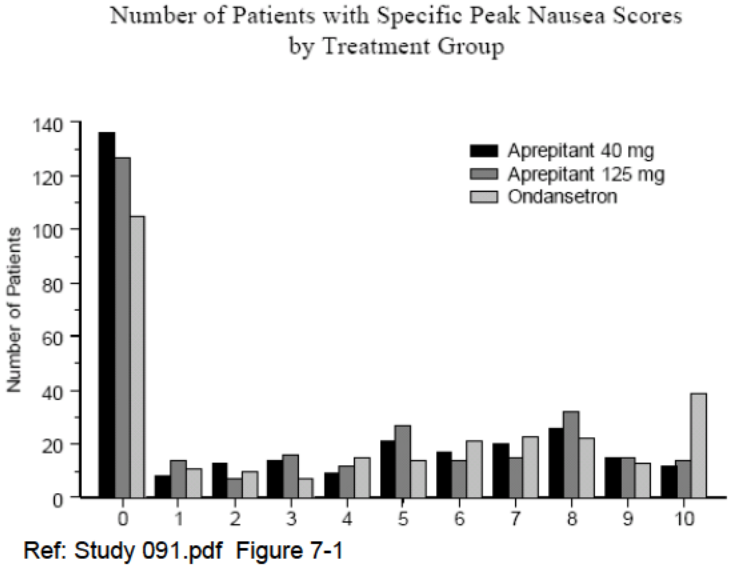
Table 15
Patients With No Use of Rescue Medication
24 Hours Following End of Surgery
(Modified-Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant vs Ondansetron	
		Δ	p-Value
Exploratory Endpoint			
No Use of Rescue Medication (0 to 24 hours)			
Aprepitant 40 mg	197/293 (72.6)	9.7%	0.299
Aprepitant 125 mg	190/293 (64.8)	1.9%	0.628
Ondansetron	176/280 (62.9)		

Ref: Study 091.pdf Table 7-11
Δ Treatment Group Difference Aprepitant vs. Ondansetron.
n/m= Number of patients responder/number of patients in analysis.

Medical Officer Comment:
The use of rescue therapy was numerically higher in the ondansetron group; however this treatment group difference failed to reach statistical significance.

Figure 1

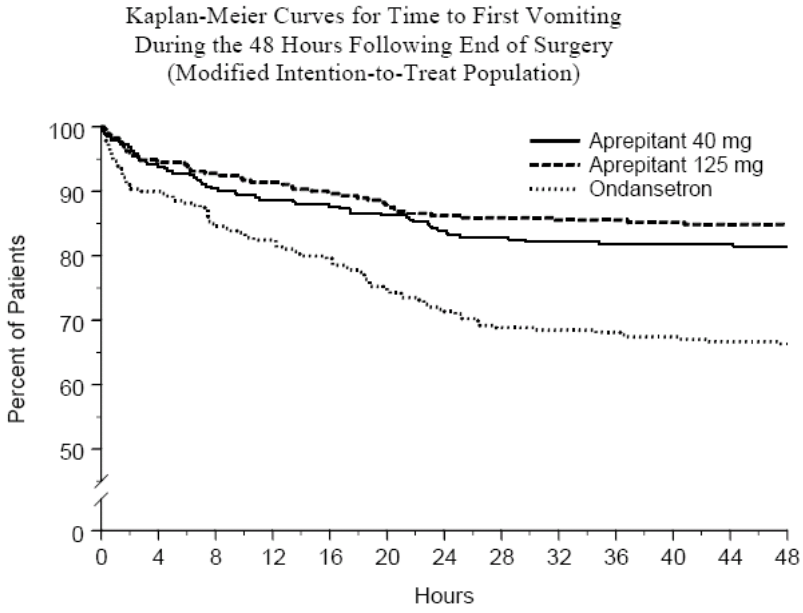


Ref: Study 091.pdf Figure 7-1

Medical Officer Comment:
The severity of nausea was assessed by a Verbal Rating Score (VRS) on a scale of 0 to 10. Overall, 303 patients received rescue medications. Compared to the ondansetron treatment group, more patients in the aprepitant groups (125 mg, 40 mg) reported no nausea (VRS = 0), while fewer patients on aprepitant reported nausea "as bad s it could be" (VRS = 10).

Time to First Vomiting (0 to 48 Hours)

Figure 2



Ref: Study 091.pdf Figure 7-2

Medical Officer Comment:
Using the Sponsor's analyses, the use of aprepitant (40 mg or 125 mg) did not effect the time to first use of rescue medication when compared to ondansetron. However, compared to the ondansetron group, both dose levels of aprepitant delayed the time to first vomiting.

Subgroup Analysis

Table 16
No Vomiting
by Subgroup (Age, and Race)
24 Hours Following End of Surgery
(Modified-Intention-to-Treat Population)

	Treatment Group		
	Aprepitant 40mg n/m (%)	Aprepitant 125mg n/m (%)	Ondansetron n/m (%)
Age Group (Years)			
Age < 65	221/268 (82.5)	231/269 (85.9)	184/260 (70.8)
Age ≥ 65	25/25 (100.0)	22/24 (91.7)	16/20 (80.0)
Age <75	241/288 (83.7)	250/290 (86.2)	197/275 (71.6)
Age ≥ 75	5/5 (100.0)	3/3 (100.0)	3/5 (60.0)
Race Group			
Black	23/33 (69.7)	29/37 (78.4)	14/26 (53.8)
Hispanic	43/47 (91.5)	39/45 (86.7)	37/45 (82.2)
White	118/141 (83.7)	120/140 (85.7)	97/142 (68.3)
Other	62/72 (86.1)	65/71 (91.5)	52/67 (77.6)

Ref. Modified Table 7-13 Protocol 091
n/m = Number of patients with desired response/number of patients included in analysis.

Medical Officer Comment:
Overall, the results of the subgroup analyses suggest that aprepitant was efficacious in regard to the No Vomiting primary endpoint regardless of age or race. The limited number of older patients precludes any meaningful statistical interpretation with respect to advanced age. Across treatment groups, the response rate was lower for the Black race than for the other racial groups.

Table 17
Complete Response
by Subgroup (Age, and Race)
24 Hours Following End of Surgery
(Modified-Intention-to-Treat Population)

	Treatment Group		
	Aprepitant 40mg n/m (%)	Aprepitant 125mg n/m (%)	Ondansetron n/m (%)
Age Group (Years)			
Age < 65	165/268 (61.6)	162/269 (60.2)	139/260 (53.5)
Age ≥ 65	22/25 (88.0)	22/24 (91.7)	15/20 (75.0)
Age <75	182/288 (63.2)	181/290 (62.4)	151/275 (54.9)
Age ≥ 75	5/5 (100.0)	3/3 (100.0)	3/5 (60.0)
Race Group			
Black	18/33 (54.5)	22/37 (59.5)	11/26 (42.3)
Hispanic	31/47 (66.0)	26/45 (57.8)	27/45 (60.0)
White	85/141 (60.3)	84/140 (60.0)	70/142 (49.3)
Other	53/72 (73.6)	52/71 (73.2)	46/67 (68.7)

Ref. Modified Table 7-14 Protocol 091
n/m = Number of patients with desired response/number of patients included in analysis.

Medical Officer Comment:
Regardless of age category or Race, the results for the Complete Response endpoint were numerically higher in the aprepitant groups than ondansetron group.

The Sponsor also performed analyses to determine whether the efficacy of aprepitant was effected by the following variables: smoking status, duration of surgery, history of PONV, and history of motion sickness. None of these treatment interaction analyses were statically significant.

Treatment by Gender Analysis:

Medical Officer Comment:
The protocol's data analysis plan stated that a treatment-by-gender analysis would be included in the efficacy models if the percentage of male patients exceeded 10%. Since, the percentage of male patients did reach the pre-specified 10%, the submission did not include this analysis.

Since one of the studies in the original NDA demonstrated a treatment-by-gender interaction, in spite of the small number of male patients, a gender analysis was requested. The Sponsor submitted these results as a response to an information request.

Table 19
No Vomiting By Gender
24 Hours Following End of Surgery
(Modified-Intention-to-Treat Analysis)

Treatment	n/m (%)	Aprepitant vs Ondansetron	
		Δ	Odds Ratio‡
Gender (p=0.887)			
Female			
Aprepitant 40 mg	223/267 (83.5%)	12.9%	2.1
Aprepitant 125 mg	225/263 (85.6%)	15.0%	2.5
Ondansetron	185/262 (70.6%)		
Male			
Aprepitant 40 mg	23/26 (88.5%)	5.2%	1.4
Aprepitant 125 mg	28/30 (93.3%)	10.0%	2.5
Ondansetron	15/18 (83.3%)		

Ref: Sec_1 11 3.pdf Table 3
Δ Treatment Group Difference Aprepitant vs. Ondansetron
‡ Estimated odds ratio for Aprepitant versus Ondansetron. A value of >1 favors Aprepitant over Ondansetron.
n/m= Number of patients responder/number of patients in analysis.

Table 18
Complete Response By Gender
24 Hours Following End of Surgery
(Modified-Intention-to-Treat Analysis)

Treatment	n/m (%)	Aprepitant vs Ondansetron	
		Δ	Odds Ratio‡
Gender (p=0.189)			
Female			
Aprepitant 40 mg	167/267 (62.5)	9.4%	1.5
Aprepitant 125 mg	156/263 (59.3)	6.2%	1.3
Ondansetron	139/262 (53.1)		
Male			
Aprepitant 40 mg	20/26 (76.9)	- 6.4%	0.6‡
Aprepitant 125 mg	28/30 (93.3)	10%	2.6
Ondansetron	15/18 (83.3)		

Ref: Sec_1 11 3.pdf Table 2
Δ Treatment Group Difference Aprepitant vs. Ondansetron
‡ Estimated odds ratio for Aprepitant versus Ondansetron. A value of >1 favors Aprepitant over Ondansetron.
n/m= Number of patients responder/number of patients in analysis.

Although the limited number of male patients precludes any meaningful statistical interpretation, these analyses suggest, that for the Complete Response endpoint, Aprepitant 40 mg may not be as efficacious as ondansetron in male patients. These results differ from Study 090 where this occurred in the Aprepitant 125mg group.

The results for the No Vomiting endpoint were numerically higher in both aprepitant groups than the ondansetron group, but there was a larger treatment group difference in female patients, suggesting that aprepitant may not be as efficacious in male patients.

Safety Evaluation and Results

Exposure:

Of the 922 randomized patients, 892 patients received active study drug per their treatment allocation and were included in the safety analyses [aprepitant 40-mg (303), aprepitant 125-mg (304), and ondansetron (285)]. Patients were treated with study medication *only* on Day 1, preoperatively. Adverse events occurring up to 14 days after study drug administration were reported.

Adverse Experiences

Table 19
Adverse Events Summary
Study 091

Adverse Experience	Treatment Group		
	Aprepitant 40mg (N=303)	Aprepitant 125mg (N=304)	Ondansetron (N=285)
Patients with No Adverse Event(s)	147 (48.5)	125 (41.1)	130 (45.6)
Patients with Adverse Event(s)	156 (51.5)	179 (58.9)	155 (54.4)
Patients with Serious Adverse Event(s)	26 (8.6)	31 (10.2)	30 (10.5)
Death	0 (0.0)	1 (0.3)	1 (0.4)
Discontinued from Study due to AE	1 (0.3)	2 (0.7)	1 (0.4)
Discontinued from Study due to SAE	0 (0.0)	1 (0.3)	1 (0.4)
Ref: Modified Table 8-2, Study 091.pdf			

Medical Officer Comment:
The incidence of adverse and serious adverse events was similar among the 3 treatment groups.

Adverse Events by Body System

Four hundred ninety (490) of the 892 patients (54.9%) who received active study drug experienced a adverse event: [aprepitant 40 mg (51.5%), aprepitant 125 mg (58.9%), and ondansetron (54.4%)].

Table 20
Select Adverse Events by Body System
(Incidence ≥ 2%)
Safety Population Study 091

Adverse Experience	Treatment Group		
	Aprepitant 40mg (N=303)	Aprepitant 125mg (N=304)	Ondansetron (N=285)
Blood and Lymphatic System	**10 (3.3)**	**9 (3.0)**	**11 (3.9)**
Anemia	10 (3.3)	9 (3.0)	10 (3.5)
Cardiac Disorders	**17 (5.6)**	**27 (8.9)**	**18 (6.3)**
Bradycardia	15 (5.0)	19 (6.3)	11 (3.9)
Sinus Tachycardia/ Tachycardia	0 (0.0)	3 (1.0)	3 (1.1)
Gastrointestinal Disorders	**55 (18.2)**	**64 (21.1)**	**56 (19.6)**
Abdominal distension	4 (1.3)	9 (3.0)	7 (2.5)
Abdominal pain	2 (0.7)	3 (1.0)	3 (1.1)
Constipation	21 (6.9)	13 (4.3)	18 (6.3)
Diarrhea	0 (0.0)	4 (1.3)	4 (1.4)
Bowel Obstruction	0 (0.0)	0 (0.0)	3 (1.1)
Nausea	13 (4.3)	16 (5.3)	9 (3.2)
Vomiting	7 (2.3)	5 (1.6)	9 (3.2)
Infections, Infestations, Pyrexia, Pain			
Pyrexia	21 (6.9)	20 (6.6)	31 (10.9)
Pain	4 (1.3)	5 (1.6)	3 (1.1)
Postoperative Infection	3 (1.0)	1 (0.3)	1 (0.4)
Urinary tract Infection	5 (1.7)	9 (3.0)	12 (4.2)
Wound Infection	3 (1.0)	3 (1.0)	5 (1.8)
Nervous System Disorders			
Headache	11 (3.6)	21 (6.9)	15 (5.3)
Respiratory, and Thoracic Disorders			
Respiratory rate increased	1 (0.3)	0 (0.0)	3 (1.1)
Bronchospasm	4 (1.3)	4 (1.3)	7 (2.5)
Dyspnea	4 (1.3)	1 (0.3)	1 (0.4)
Pharyngolaryngeal Pain	1 (0.3)	1 (0.3)	3 (1.1)
Vascular Disorders	**23 (7.6)**	**29 (9.5)**	**22 (7.7)**
Hypotension	10 (3.3)	14 (4.6)	8 (2.8)
Hypertension	5 (1.7)	5 (1.6)	8 (2.8)
Hypertension Crisis	0 (0.0)	4 (1.3)	0 (0.0)
Hemorrhage			
Genital Hemorrhage	3 (1.0)	4 (1.3)	4 (1.4)
Operative hemorrhage	4 (1.3)	3 (1.0)	1 (0.4)

Ref: Modified Table 8-4, Study 091.pdf

Medical Officer Comment:
The incidence and type of adverse events was similar among the 3 treatment groups. This analysis did not suggest that the use of aprepitant adversely affected the safety profile of the anesthesia or surgical procedure.

For example, the incidence of "postoperative infection" was slightly higher in the aprepitant group compared to the ondansetron group [aprepitant 40 mg (1.0%), aprepitant 125 mg (0.3%), and ondansetron (0.4%)]. However, the incidence of "wound infection" was higher in the ondansetron group [aprepitant 40 mg (1.0%), aprepitant 125 mg (1.0%), and ondansetron (1.8%)]. Also, the incidence of postoperative fever was slightly higher in the ondansetron group compared to the aprepitant group[aprepitant 40 mg (6.9%), aprepitant 125 mg (6.6%), and ondansetron (10.9%)]. These findings suggest that aprepitant is as safe as ondansetron in patients undergoing a surgical procedure.

The most commonly reported adverse events were pyrexia, constipation and headache. Episodes of nausea or vomiting were only reported as adverse events if they occurred more than 48 hours after surgery. Prior to that time nausea or vomiting were reported as efficacy end-points. The incidence of nausea and vomiting reported as an adverse event was similar among the 3 treatment groups.

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Serious Adverse Events:

Table 21
Select Serious Adverse Events by Body System
(Incidence >0%)
Safety Population Study 091

Adverse Experience	Treatment Group		
	Aprepitant 40mg (N=303)	Aprepitant 125mg (N=304)	Ondansetron (N=285)
≥ 1 Serious Adverse Event	**26 (8.6)**	**31 (10.2)**	**30 (10.5)**
Blood and Lymphatic System	**0 (0.0)**	**1 (0.3)**	**2 (0.7)**
Anemia	0 (0.0)	1 (0.3)	1 (0.4)
Coagulopathy	0 (0.0)	0 (0.0)	1 (0.4)
Gastrointestinal Disorders	**4 (1.3)**	**9 (3.0)**	**7 (2.5)**
Abdominal Distention	0 (0.0)	2 (0.7)	0 (0.0)
Constipation	1 (0.3)	0 (0.0)	1 (0.4)
Ileus	0 (0.0)	1 (0.3)	2 (0.7)
Ileus Paralytic	0 (0.0)	1 (0.3)	0 (0.0)
Intestinal Obstruction	0 (0.0)	0 (0.0)	3 (1.1)
Small Intestinal Obstruction	0 (0.0)	1 (0.3)	0 (0.0)
Gastrointestinal necrosis	0 (0.0)	0 (0.0)	1 (0.4)
Intra-abdominal hemorrhage	1 (0.3)	0 (0.0)	0 (0.0)
Abdominal Pain	0 (0.0)	2 (0.7)	0 (0.0)
Peritonitis	0 (0.0)	1 (0.3)	1 (0.4)
Vomiting	0 (0.0)	1 (0.3)	1 (0.4)
Infections, Infestations, Pyrexia, Pain			
Pyrexia	2 (0.7)	4 (1.3)	5 (1.8)
Abdominal wall abscess	0 (0.0)	0 (0.0)	1 (0.4)
Urinary tract Infection	0 (0.0)	0 (0.0)	1 (0.4)
Hematoma infection	1 (0.3)	0 (0.0)	0 (0.0)
Pelvic abscess	1 (0.3)	0 (0.0)	1 (0.4)
Vaginal abscess	0 (0.0)	1 (0.3)	0 (0.0)
Wound Infection	1 (0.3)	0 (0.0)	1 (0.4)
Postoperative infection	1 (0.3)	1 (0.3)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	1 (0.4)

Ref: Modified Table 8-9, Study 091.pdf

Table 21 (cont)
Select Serious Adverse Events by Body System
(Incidence >0%)
Safety Population Study 091

Adverse Experience (cont)	Treatment Group		
	Aprepitant 40mg (N=303)	Aprepitant 125mg (N=304)	Ondansetron (N=285)
Injury and Procedural Complications	**7 (2.3)**	**6 (2.0)**	**6 (2.1)**
Anastomotic leak	0 (0.0)	0 (0.0)	1 (0.4)
Operative hemorrhage	2 (0.7)	0 (0.0)	0 (0.0)
Post procedural hemorrhage	1 (0.3)	1 (0.3)	1 (0.4)
Postoperative wound complication	0 (0.0)	0 (0.0)	1 (0.4)
Wound dehiscence	2 (0.7)	1 (0.3)	0 (0.0)
Wound evisceration	0 (0.0)	0 (0.0)	1 (0.4)
Nervous System Disorders			
Cerebrovascular accident	0 (0.0)	0 (0.0)	1 (0.4)
Sedation	1 (0.3)	0 (0.0)	0 (0.0)
Respiratory, and Thoracic Disorders			
Respiratory depression	1 (0.3)	0 (0.0)	0 (0.0)
Pulmonary Embolism	1 (0.3)	0 (0.0)	1 (0.4)
Respiratory Arrest	0 (0.0)	1 (0.3)	0 (0.0)
Vascular Disorders			
Hemorrhage	0 (0.0)	1 (0.3)	1 (0.4)
Hematoma	0 (0.0)	1 (0.3)	0 (0.0)
Ref: Modified Table 8-9, Study 091.pdf			

Medical Officer Comment:
The narratives of patients with serious adverse events were reviewed. Eighty-seven (87) of the 892 randomized patients who received active study drug had one or more serious adverse events. In general, the incidence and type of serious adverse events were similar among treatment groups, with a slightly lower incidence of serious events in the aprepitant 40-mg group (26 patients, 8.6%) compared with the aprepitant 125-mg group (31 patients, 10.2%) and the ondansetron group (30 patients, 10.5%).

The analysis of serious adverse events did not suggest that the use of aprepitant adversely affected the safety profile of the anesthesia or surgical procedure. The most common serious adverse events were Gastrointestinal Disorders [aprepitant 40-mg (1.3%), aprepitant 125-mg (3.0%), and ondansetron (2.5 %)]. The incidence of "Infection" related serious adverse events and "Procedural Complications" were balanced between treatment groups and did not suggest a safety signal.

Only two of the serious adverse events were considered by the investigators to be possibly related to study therapy. Patient (b) (6) *(aprepitant 125-mg group) developed a sub ileus 2 days after surgery which lasted for 5 days, causing prolongation of the hospitalization. Patient* (b) (6) *(ondansetron group) developed moderate constipation 2 days after surgery which lasted 7 days, causing a prolongation of the hospitalization.*

Discontinued Due to Adverse Experiences

Medical Officer Comment:
Four patients developed adverse events which resulted in discontinuation from the study. These cases were reviewed and did not suggest a safety signal. One patient in the aprepitant 40-mg group developed gastroenteritis and pyrexia prior to receiving study drug and was discontinuation from the study.

One patient in the aprepitant 125-mg group developed postoperative vomiting which was considered by the investigator to be possibly drug related and the patient was discontinuation from the study. Two patients, one patient in the aprepitant 125-mg group and one in the ondansetron group, experienced a serious adverse event which resulted in death, causing discontinuation from the study. These cases will be discussed under the "Deaths" section of this review.

Summary of Laboratory Adverse Experiences

Table 22
Summary of Laboratory Adverse Events
Safety Population Study 091

Laboratory Adverse Events	Treatment Group		
	Aprepitant 40mg (N=303)	Aprepitant 125mg (N=304)	Ondansetron (N=285)
≥ 1 Lab Test Post Baseline	**302**	**299**	**284**
No Lab Adverse Event	259 (85.8)	251 (83.9)	242 (85.2)
≥ 1 Lab Adverse Event	43 (14.2)	48 (16.1)	42 (14.8)
≥ 1 Lab Serious Adverse Event	0 (0.0)	0 (0.0)	1 (0.4)
Discontinued Due to Adverse Event	0	0	0
Ref: Modified Table 8-11, Study 091.pdf			

Medical Officer Comment:
Laboratory adverse events were reported in 133 of the 885 patients (15.0%) who received study drug. No patients discontinued the study due to a laboratory adverse event. Overall the incidence and type of laboratory adverse events were similar between treatment groups.

There was only 1 serious laboratory adverse event reported, which occurred in a patient in the ondansetron group. [redacted] *(ondansetron group) had three serious laboratory adverse events 6 days after surgery: increased alanine aminotransferase, increased aspartate aminotransferase, and increased gamma glutamyltransferase. All three adverse events were reported as possibly related to study drugs by the investigator.*

Table 23
Select Laboratory Adverse Events
(Incidence >0%)
Safety Population Study 091

Laboratory Adverse Events	Treatment Group		
	Aprepitant 40mg (N=303)	Aprepitant 125mg (N=304)	Ondansetron (N=285)
≥ 1 Lab Adverse Event	43/302 (14.2)	48/299 (16.1)	42/284 (14.8)
Blood Chemistry Test	**27/301 (9.0)**	**23/295 (7.8)**	**23/284 (8.1)**
ALT increased	6/293 (2.0)	5/288 (1.7)	7/274 (2.6)
AST increased	6/291 (2.1)	5/283 (1.8)	7/270 (2.6)
Bilirubin increased	4/293 (1.4)	4/288 (1.4)	2/276 (0.7)
Alk Phos. Increased	0 (0)	0 (0)	0 (0)
Hematology Laboratory Test	**16/279 (5.7)**	**24/285 (8.4)**	**21/271 (7.7)**
Hematocrit decreased	5/272 (1.8)	5/272 (1.8)	5/265 (1.9)
Hemoglobin decreased	13/279 (4.7)	21/285 (7.4)	15/271 (5.5)
White blood cell count increased	2/279 (0.7)	0/282 (0.0)	4/270 (1.5)
Ref: Modified Table 8-13, Study 091.pdf			

Medical Officer Comment:
There were no apparent differences between the aprepitant (125 mg, 40 mg) groups and the ondansetron group for the incidence of laboratory adverse events. The incidence of laboratory adverse events were small and did not suggest a safety signal. The most frequent laboratory abnormality reported as an adverse event was a decreased hemoglobin [aprepitant 40-mg (4.7%), aprepitant 125-mg (7.4%), and ondansetron (5.5 %)].

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Vital Signs, Physical Observations

Table 24
Clinically Significant Vital Sign Abnormalities 24 Hours Post-Surgery
Safety Population Study 091

Vital Sign	Treatment Group		
	Aprepitant 40mg n/N (%)	Aprepitant 125mg n/N (%)	Ondansetron n/N (%)
Diastolic Blood Pressure			
≤ 50 mmHg and decrease ≥ 15 mmHg	31/300 (10.3)	26/300 (8.7)	30/285 (10.5)
≥ 105 mmHg and increase ≥ 15 mmHg	4/300 (1.3)	7/300 (2.3)	9/285 (3.2)
Systolic Blood Pressure			
≤ 90 mmHg and decrease ≥ 20 mmHg	25/300 (8.3)	28/300 (9.3)	27/285 (9.5)
≥ 180 mmHg and increase ≥ 20 mmHg	7/300 (2.3)	9/300 (3.0)	8/285 (2.8)
Pulse Rate			
≤ 50 and decrease ≥ 15	10/300 (3.3)	7/300 (2.3)	7/285 (2.5)
≥ 120 and increase ≥ 15	4/300 (1.3)	3/300 (1.0)	7/285 (2.5)
Respiratory Rate			
<8	2/299 (0.7)	6/300 (2.0)	2/285 (0.7)
>18	172/299 (57.5)	166/300 (55.3)	175/285 (61.4)
Temperature			
≥ 38.33° C and increase ≥ 1.11° C	0/299 (0.0)	4/297 (1.3)	3/282 (1.1)
Ref: Modified Table 8-17, Study 091.pdf			

Medical Officer Comment:
The protocol predefined limits for Clinically Significant Vital Sign Abnormalities (CSVA). Overall, the incidence of CSVA was similar between treatment groups and did not suggest a safety signal. The use of aprepitant appears to have had no greater effect on vital signs than ondansetron.

Electrocardiogram (ECG)

Table 24
12-Lead Electrocardiogram (ECG)
(24 Hours Postsurgery)
Safety Population Study 091

12-Lead Electrocardiogram	Treatment Group		
	Aprepitant 40mg n/N (%)	Aprepitant 125mg n/N (%)	Ondansetron n/N (%)
PR interval (msec)			
Mean	149.49	146.26	146.39
Standard Deviation	24.58	21.85	22.66
QTc interval (msec)			
Mean	417.66	419.40	422.93
Standard Deviation	34.51	25.67	27.94
QTc Interval Prolongation†			
Prolongation <30 msec	125/288 (43.4)	137/284 (48.2)	110/275 (40.0)
Prolongation 30 to 60 msec	27/288 (9.4)	26/284 (9.2)	32/275 (11.6)
Prolongation >60 msec	3/288 (1.0)	1/284 (0.4)	9/275 (3.3)

Ref: Modified Tables 8-18 and 8-19, Study 091.pdf
† Largest increase from baseline during treatment phase.
n/N = Randomized patients/ patients with ≥ 1one post baseline QTc measurement who took at least one dose of active study medication meeting the predefined criteria.
N = Number of randomized patients who took at least one dose of active study medication and had at least one post baseline QTc measurement.
% = Percentage (n/m * 100) of patients meeting the predefined criteria.

Medical Officer Comment:
Summary statistics (mean and standard deviation) for the PR interval and QTc, performed 24 hours after surgery, were similar among the three treatment groups. The percentages of patients with clinically significant QTc prolongations were generally similar among treatment groups and did not suggest a safety signal. The percentage of patients with QTc prolongation >60 msec was higher in the ondansetron group compared to the aprepitant (125 mg, 40 mg) groups.

Four patients had a QTc value 24 hours after surgery that exceeded the baseline QTc and was >500 msec [aprepitant 40mg (2), aprepitant 125mg (1), and ondansetron (1)]. One additional patient (b) (6) *in the ondansetron group) had a QTc value measured 16 days after surgery that exceeded the baseline value and was > 500 msec. The clinical significance of these findings is unknown; however, these results do not suggest a safety signal.*

Additional Safety Analyses

Since it was unknown whether aprepitant could affect the metabolism and or safety profile of the anesthetics used during surgery, the Agency requested that the protocol include additional analyses to evaluate the awakening time, the duration of recovery and any evidence of respiratory depression.

Table 25
Summary Statistics for Awakening Time and Duration of Recovery
Safety Population Study 091

Awakening Time Duration of Recovery	Treatment Group		
	Aprepitant 40mg	Aprepitant 125mg	Ondansetron
Awakening time (Hrs)			
Mean	0.23	0.22	0.21
Standard Deviation	0.24	0.19	0.16
Duration of recovery (Hrs)			
Mean	0.42	0.40	0.38
Standard Deviation	0.35	0.30	0.30
Ref: Modified Tables 8-20, Study 091.pdf			

Medical Officer Comment:
In Study 091 the mean awakening time and mean duration of recovery were similar among the three treatment groups, suggesting that aprepitant had no greater effect on the metabolism of the anesthetics than did ondansetron.

Serious adverse events of excessive sedation and respiratory depression were prespecified as adverse events of special interest. All serious adverse event reports were reviewed in a blinded fashion by two physicians not involved with the study.

Both physicians considered 3 patients to have developed an adverse event consistent with respiratory depression (b) (6) *and* (b) (6) *in the aprepitant 40-mg group and* (b) (6) *in the aprepitant 125-mg group). In addition to these three patients, one of the two physician considered* (b) (6) *in the aprepitant 40-mg group developed excessive sedation.*

The clinical significance of three, possibly four, cases of excessive sedation in the aprepitant groups is uncertain. This finding was not observed in Study 090. The incidence is too small to draw any specific conclusion. Additionally, none of these events were reported as drug related by the primary investigators.

Deaths

Medical Officer Comment:
As previously described in this review, two patients died during the course of this study; one patient (in the ondansetron group) experienced multi-organ failure and coagulopathy which resulted in death 11 days after surgery and one patient (in the aprepitant 125-mg group) experienced an arrhythmia which resulted in death 7 days after surgery. Neither death was considered drug-related by the investigator. A review of these cases did not suggest that either event was drug related.

Discussion:

The primary purpose of Study 091 was to demonstrate that aprepitant provided effective protection against PONV and that it was safe and well tolerated by surgical patients. The active comparator arm, intravenous ondansetron, was an acceptable comparator since it is approved for the proposed indication and is one of the most commonly used antiemetics for prevention of PONV.

Efficacy:

Table 26
Response Rates for Primary Endpoints
(Modified- Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant vs Ondansetron	
		Δ	Analysis
Primary Endpoints			
No Vomiting (Superiority) (no emetic episodes, 0 to 24 hours)			
Aprepitant 40 mg	246/293 (84.0)	12.6%	p<0.001
Aprepitant 125 mg	253/293 (86.3)	14.9%	p<0.001
Ondansetron	200/280 (71.4)		
Complete Response (Non-inferiority) 95% CI 0.65 (no emesis and no rescue therapy, 0 to 24 hours)			
Aprepitant 40 mg	187/293 (63.8)	8.8%	LB = 1.04
Aprepitant 125 mg	184/293 (62.8)	7.8%	LB = 1.08
Ondansetron	154/280 (55.0)		
Complete Response (Superiority) 95% CI >1.0 (no emesis and no rescue therapy, 0 to 24 hours)			
Aprepitant 40 mg	187/293 (63.8)	8.8%	LB = 1.04*
Aprepitant 125 mg	184/293 (62.8)	7.8%	LB = 1.08*
Ondansetron	154/280 (55.0)		

Ref: Study 091.pdf Table 7-1
Δ Treatment Group Difference Aprepitant vs. Ondansetron.
LB = lower bound of the 1-sided 95% confidence interval.
*P value <0.05
n/m= Number of patients responder/number of patients in analysis.

Unlike Study 090, which failed to satisfy its primary hypothesis (aprepitant is superior to ondansetron for the Complete Response endpoint), Study 091 succeeded for its "redefined" two primary endpoints.

The first primary efficacy endpoint was a superiority analysis for "No Vomiting" in the 24-hours following the end of surgery. The results of the No Vomiting endpoint were statistically significantly higher in both of the aprepitant groups compared to the ondansetron group.

The second primary efficacy endpoint included two efficacy hypotheses. The first hypothesis was that aprepitant was *non-inferior* to ondansetron for the Complete Response endpoint (No Vomiting and No Rescue Therapy). Based on the protocol defined non-inferiority margin, both aprepitant doses were non-inferior to ondansetron for the endpoint Complete Response. These data and analyses were confirmed by the Agency.

Since the non inferiority hypothesis of the second primary endpoint was successful, the second hypothesis was tested: the superiority of aprepitant over ondansetron with respect to the Complete Response endpoint. Although the Sponsor reported that both aprepitant doses were also superior to ondansetron for the Complete Response endpoint, the Agency's Statistical team does not agree. The Agency agrees that Study 091 succeeded in demonstrating non-inferiority for the Complete Response endpoint; however, for the superiority analyses, statistical significance was not maintained based upon a one-sided test, using a more appropriate 2.5% significance level and applying the multiplicity adjustment method proposed by the sponsor.

In trying to identify why the results from this study differed from Study 090, this Reviewer noted that the use and type of postoperative analgesics in Study 091 was very different than Study 090. In Study 091, 96% patients received an opioid class analgesic post operatively, compared to greater than 99% of the patients in Study 090. The most common analgesic used in both studies was morphine, a drug known to be associated with nausea and vomiting.

The use of morphine was much higher in Study 090 (failed study) compared to 091 [Study 090 (83.4%), Study 091(48.7%)]. The use of non-opioid postoperative analgesics was higher in Study 091 compared to Study 090 (78.4% versus 67.0%). These differences in postoperative analgesics use may account for some of the differences in results.

These differences in analgesics use may be related geography. Protocol 090 enrolled 805 patients in the US whereas Protocol 091 enrolled 922 patients from 16 countries worldwide including the US.

Regardless of the differences in postoperative analgesics use, it remains this Reviewer's opinion that the success of the No Vomiting endpoints are the most clinically meaningful demonstration of efficacy. All of the serious complications associated with PONV are directly related to the vomiting process (i.e. wound disruption, increased intraabdominal, intraocular and intracranial pressures, esophageal tears, electrolyte imbalance, and pulmonary aspiration. The use of rescue therapy is not as clinically meaningful in the postoperative surgical patient as is the prevention of vomiting. Study 091 demonstrated that the use of aprepitant was associated with a 13%

improvement over ondansetron for the No Vomiting endpoint. This represents a clinically significant improvement over a drug many consider a standard of care.

Safety:

Study 091 successfully demonstrated that aprepitant is as safe and as well tolerated as ondansetron when used to prevent PONV. The incidence and type of adverse and serious events was similar among the three treatment groups The safety analyses did not suggest that the use of aprepitant adversely affected the safety profile of the anesthesia or surgical procedure.

Table 27
Adverse Events Summary
Study 091

Adverse Experience	Treatment Group		
	Aprepitant 40mg (N=303)	Aprepitant 125mg (N=304)	Ondansetron (N=285)
Patients with No Adverse Event(s)	147 (48.5)	125 (41.1)	130 (45.6)
Patients with Adverse Event(s)	156 (51.5)	179 (58.9)	155 (54.4)
Patients with Serious Adverse Event(s)	26 (8.6)	31 (10.2)	30 (10.5)
Death	0 (0.0)	1 (0.3)	1 (0.4)
Discontinued from Study due to AE	1 (0.3)	2 (0.7)	1 (0.4)
Discontinued from Study due to SAE	0 (0.0)	1 (0.3)	1 (0.4)
Ref: Modified Table 8-2, Study 091.pdf			

Two patients died during the course of this study; one patient (ondansetron group) experienced multi-organ failure and coagulopathy which resulted in death 11 days after surgery and one patient (aprepitant 125-mg group) experienced an arrhythmia which resulted in death 7 days after surgery. Neither death was considered drug-related by the investigator. A review of the CRFs also did not suggest them to be drug related.

Conclusion:

Study 091 demonstrated that aprepitant provided effective protection against PONV and is safe and well tolerated by surgical patients. Study 091 satisfied it's primary hypotheses, that aprepitant is superior to ondansetron in the prevention of post operative vomiting. It also succeeded in demonstrating that aprepitant was non inferior to ondansetron as measured by the Complete response endpoint. The success of these endpoints and considerations of the other efficacy variables support that both dose levels of aprepitant were effective in the prevention of PONV.

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/s/

Gary DellaZanna
6/1/2006 08:20:59 AM
MEDICAL OFFICER

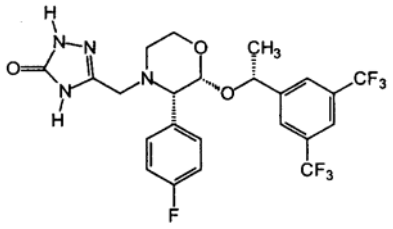
Hugo Gallo Torres
6/1/2006 09:14:16 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21549Orig1s010

PRODUCT QUALITY 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 SE1-010	Dates August 29, 2005
8. Supplement Provides for: Qualification of a 40 mg strength capsule (dosage form marketed currently are 80 and 125 mg capsules).		9. Amendments & Other (Reports, etc.) Dates: January 30, 2006 (labeling)	
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: None

CC: NDA 21-549
HFD-180/Div File/NDA 21-549
ONDQA/DPE/VIII/VJimenez
ONDQA/DPE/VIII/RFrankewich
R/D init: HPatel

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.		June 5, 2006

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

/s/

Ray Frankewich
6/8/2006 03:37:15 PM
CHEMIST
This is an efficacy supplement from what was HFD-180 which also is submitted to qualify a new 40 mg capsule dosage strength.

David Lewis
6/8/2006 03:42:12 PM
CHEMIST
Concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21549Orig1s010

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS
DIVISION OF BIOMETRICS II

STATISTICAL REVIEW AND EVALUATION

NDA:	21549
DATE RECEIVED BY CENTER:	August 29, 2005
DRUG NAME:	Emend (Aprepitant) Capsules 40 mg/125 mg
INDICATION:	Prevention of postoperative nausea and vomiting
SPONSOR:	Merck and Co., INC.
DOCUMENT REVIEWED:	Electronic submissions dated August 29, 2005
STATISTICAL REVIEWER:	Wen-Jen Chen, Ph.D. (HFD-725)
STATISTICAL TEAM LEADER:	Stella Grosser, Ph.D. (HFD-725)
BIOMETRICS DIVISION DIRECTOR:	Stephen Wilson, Ph.D. (HFD-725)
MEDICAL DIVISION:	Gastroenterology Products
CLINICAL REVIEWER:	Gary Della'Zanna, MD (HFD-180)
PROJECT MANAGER:	Betsy Scroggs, Pharm.D. (HFD-180)
STATISTICAL KEYWORDS:	Clinical studies; NDA review; Non-inferiority.

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1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

Following the efficacy assessments for the two Studies (P090 and P091), presented in sub-section 1.3, only Study P091 demonstrated that Aprepitant 125 mg and Aprepitant 40 mg were non-inferior to Ondansetron assessed by the primary endpoint (complete response in the 24 hours following end of surgery) and were also superior to Ondansetron assessed by no vomiting. However, since less than 10% of patients enrolled in Study P091 were males, the non-inferiority of Aprepitant to Ondansetron shown in Study P091 may not apply to male patients.

It is noted that the effectiveness of Aprepitant shown in Study P091 was not established by Study P090. Study P090 did not provide efficacy evidence to support the use of Aprepitant in the prevention of postoperative nausea and vomiting. Accordingly, from the statistical perspective, the two studies overall did not provide substantial evidence to support the use of Aprepitant in the prevention of postoperative nausea and vomiting.

1.2 Brief Overview of Clinical Studies

Two phase-III Studies P090 and P091 are submitted by the applicant to support Aprepitant regimen in the prevention of postoperative nausea and vomiting (PONV). The two trials were multi-center, randomized, double-blind, active comparator-controlled, and parallel-group clinical studies. In these two studies, Aprepitant was compared with Ondansetron for the prevention of postoperative nausea and vomiting in 1658 patients (766 for study P090 and 892 for Study P091) undergoing open abdominal surgery. Patients were randomized to receive 40 mg Aprepitant, 125 mg Aprepitant, or 4 mg Ondansetron.

For Study P090, the primary objective was to demonstrate that Aprepitant (125 mg, 40 mg) was superior to Ondansetron in the prevention of PONV as measured by the proportion of patients with no vomiting and no rescue therapy (complete response) in the 24 hours following end of surgery. However, for Study P091, the primary objectives were to demonstrate that Aprepitant (125 mg, 40 mg) was superior to Ondansetron in the prevention of PONV as measured by the proportion of patients with no vomiting in the 24 hours following end of surgery and to demonstrate that Aprepitant (125 mg, 40 mg) was not inferior to Ondansetron in the prevention of PONV as measured by the proportion of patients with complete response in the 24 hours following end of surgery. If the non-inferiority of Aprepitant versus Ondansetron was established, the following will also be evaluated: compared to Ondansetron, Aprepitant (125 mg, 40 mg) would provide superior prevention of PONV as measured by the proportion of patients with complete response in the 24 hours following end of surgery.

For Study P090, the primary endpoint was the complete response defined as no vomiting and no rescue therapy in the 24 hours following end of surgery. However, for Study P091, no vomiting was selected as the first primary endpoint and complete response (no vomiting and no rescue therapy) in the 24 hours following end of surgery was the second primary endpoint. In addition,

the non-inferiority margin of 0.65 on odds ratio of Aprepitant versus Ondansetron IV assessed by complete response was selected by the applicant. However, the non-inferiority margin of 0.65 was not submitted to the agency for review before Study P091 was conducted.

1.3 Statistical Issues and Findings

1.3.1 Study P090

- Since the primary hypothesis of Aprepitant (125 mg, 40 mg) superior to Ondansetron (4 mg IV) assessed by the primary endpoint (complete response in 24 hours following end of surgery) was not met, according to the pre-specified multiplicity adjustment technique, the testing procedure was terminated and Aprepitant was judged not superior to Ondansetron for the secondary and exploratory endpoints. In addition, since Type I error rate of 2.5% was totally spent for testing the primary hypothesis, no Type I error rate was left for the analyses of the secondary and exploratory endpoints. Consequently, based upon the results of the pre-specified superiority analysis for the primary, secondary, and exploratory endpoints and Type I error rate was totally spent for the primary endpoint analysis, Study P090 did not provide efficacy evidence to support the use of Aprepitant regimen in the prevention of postoperative nausea and vomiting.
- After superiority of Aprepitant to Ondansetron failed for the primary endpoint the proportion of patients with complete response during the first 24 hours after surgery, the non-inferiority margin selected by the applicant for this study is a post-hoc manner and has the following statistical issues.

  i) Loss of credibility on the selection of non-inferiority margin
  ICH E10 states that ‘prior to the trial, an equivalence or non-inferiority margin 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.

  ii) Loss of position as confirmatory hypothesis
  As indicated by the applicant’s submission, Study P090 was a phase III study to support Aprepitant regimen in the prevention of postoperative nausea and vomiting. 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 postoperative nausea and vomiting. Therefore, if the applicant decided on applying non-inferiority analysis to confirm that Aprepitant regimen is effective for the proposed indication, the null hypothesis of inferiority 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 the null hypothesis of inferiority is not formulated before conducting the trial, but also the selected margin is data dependent and is biased. Accordingly, the null hypothesis of inferiority including a margin influenced by data of the current study (Study P090) is a post-hoc hypothesis and can not be regarded as a confirmatory hypothesis.

iii) Significance level of the non-inferiority analysis inflated
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 Ondansetron is inflated.

In conclusion, from 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.

1.3.2 Study P091

- As commented upon in the section of "Reviewer's Comments", treatment effectiveness assessed by no vomiting in 24 hours following end of surgery is confounded with that of the rescue therapy and the primary endpoint for the previous approved drugs for this application was also the complete response. Consequently, from statistical perspective and previous NDA experiences, it seems that complete response in 24 hours following end of surgery is more appropriate to be employed as the primary endpoint than no vomiting in the assessment for prevention of postoperative nausea and vomiting.
- The appropriateness for the four historical studies used by the applicant to identify the non-inferiority margin with respect to the complete response is questioned by the medical reviewer Dr Della'Zanna. The non-inferiority margin selected by the applicant using the four questionable historical studies may not accurately reflect the effective size of Ondansetron assessed by the primary endpoint (complete response in the 24 hours following end of surgery). However, the two lower bounds for the one-sided 97.5% confidence interval on odds ratios of Aprepitant 125 mg versus Ondansetron and Aprepitant 40 mg versus Ondansetron are high (respectively, 0.99 and 1.02). Consequently, both Aprepitant 125 mg and Aprepitant 40 mg are regarded to be non-inferior to Ondansetron assessed by complete response in the 24 hours following end of surgery. However, due to less than 10% of patients enrolled for males in Study P091, the non-inferiority of Aprepitant to Ondansetron shown in Study P091 may not be able to apply to male patients.
- As commented upon in the sub-section of "Non-inferiority analysis and comments", since higher dose 125 mg for Aprepitant is failed to demonstrate superior to Ondansetron assessed by the complete response in the 24 hours following end of surgery, by the step-wise multiplicity adjustment method proposed by the applicant, the superior test based

upon the complete response is ceased and Aprepitant 40 mg is judged not superior to Ondansetron. Therefore, the superiority of Aprepitant versus Ondansetron assessed by complete response in the 24 hours following end of surgery is not supported. However, since the primary hypothesis of Aprepitant non-inferior to Ondansetron was met, the secondary hypothesis regarding Aprepitant superior to Ondansetron assessed by no vomiting was pursued. Based upon the result of the applicant's superiority analysis with respect to no vomiting, both Aprepitant 125 mg and Aprepitant 40 mg are superior to Ondansetron ($p< 0.001$).

2.0 INTRODUCTION

2.1 Overview

In the introduction of the clinical study report, the applicant wrote the following:

> Postoperative nausea and vomiting (PONV) are amongst the most common complications of surgery. PONV occurring after the first 24 hours appears to be affected primarily by post-surgical factors, such as the use of postoperative opiates, but its incidence is poorly characterized. In one study conducted in patients receiving general anesthesia for surgery at high risk of PONV, 35% of the patients experienced nausea and vomiting more than 24 hours following surgery. Delayed PONV may be especially troublesome for out-patients who have less access to medical care and cannot resume their normal daily activities.
>
> The most commonly used anti-emetic for prophylaxis of PONV is a 5-HT3 receptor antagonist. However, there is a sound rationale for the development of the NK1 antagonist, Aprepitant, for prevention of PONV: (i) PONV is an unmet medical need; (ii) NK1 antagonists have been demonstrated to be effective for both the prevention and treatment of PONV; (iii) Aprepitant is effective against centrally acting emetogens (including opiates) with a broader spectrum of anti-emetic activity pre-clinically than 5-HT3 receptor antagonists; (iv) Aprepitant has a long duration of action, and a well characterized drug interaction profile; and (v) Aprepitant is generally well tolerated.

Two phase-III Studies P090 and P091 are submitted by the applicant to support Aprepitant regimen in the prevention of postoperative nausea and vomiting (PONV).

For Study P090, the primary objective was to demonstrate that Aprepitant (125 mg, 40 mg) was superior to Ondansetron in the prevention of PONV as measured by the proportion of patients with no vomiting and no rescue therapy (complete response) in the 24 hours following end of surgery. However, for Study P091, the primary objectives were to demonstrate that Aprepitant (125 mg, 40 mg) was superior to Ondansetron in the prevention of PONV as measured by the proportion of patients with no vomiting in the 24 hours following end of surgery and to demonstrate that Aprepitant (125 mg, 40 mg) was not inferior to Ondansetron in the prevention of PONV as measured by the proportion of patients with complete response in the 24 hours following end of surgery. If the non-inferiority of Aprepitant versus Ondansetron was established, the following would also be evaluated: compared to Ondansetron, Aprepitant (125 mg, 40 mg) would provide superior prevention of PONV as measured by the proportion of patients with complete response in the 24 hours following end of surgery.

For Study P090, the primary endpoint was the complete response defined as no vomiting and no rescue therapy in the 24 hours following end of surgery. However, for Study P091, no vomiting was selected as the first primary endpoint and complete response (no vomiting and no rescue therapy) in the 24 hours following end of surgery was the second primary endpoint. In addition, the non-inferiority margin of 0.65 on odds ratio of Aprepitant versus Ondansetron IV assessed by complete response was selected by the applicant. However, the non-inferiority margin of 0.65 was not submitted to the agency for review before Study P091 was conducted.

2.2 Data Sources

To assess the clinical efficacy of Aprepitant regimen in prevention of postoperative nausea and vomiting, this reviewer reviewed electronic NDA supplement (SNDA) submission, dated August 29, 2005. In addition, data used by this reviewer's statistical analysis was also submitted by the applicant on August 29, 2005 and located at "\\cdsesub1\evsprod\n021549\0000\m5". However, for nausea analysis performed in Study P091, data was submitted by the applicant on March 9, 2006.

3.0 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study P090

Study Design and Endpoints

The primary objectives of the study were to demonstrate Aprepitant (125 mg, 40 mg) superior to Ondansetron in the prevention of PONV as measured by the proportion of patients with complete response in the 24 hours following end of surgery and to evaluate the safety and tolerability of Aprepitant (125 mg, 40 mg) in patients undergoing surgery.

This was a multi-center (29 centers in United States participated), randomized, double-blind, parallel group, active-comparator controlled trial with in-house blinding to assess the safety and efficacy of two different doses of Aprepitant for the prevention of PONV in patients undergoing open abdominal surgery requiring overnight hospital stay.

The study population consisted of patients receiving general anesthesia for open abdominal surgery requiring overnight hospital stay. Based on the specific eligibility criteria, the majority of patients were expected to consist of women undergoing gynecological surgeries. Eligible patients who met the inclusion but not exclusion criteria were randomized to one of the three treatment groups (Table 3.1.1.1).

Table 3.1.1.1 (Applicant's) Treatment Regimen

Treatment Group	Bottle A (PO)	Vial B (IV)
I	Aprepitant 125 mg (1 capsule) Placebo for aprepitant 40 mg (1 capsule)	Placebo for ondansetron 4 mg
II	Placebo for aprepitant 125 mg (1 capsule) Aprepitant 40 mg (1 capsule)	Placebo for ondansetron 4 mg
III	Placebo for aprepitant 125 mg (1 capsule) Placebo for aprepitant 40 mg (1 capsule)	Ondansetron 4 mg

For randomizing patients to treatment groups, the applicant indicated that patients were allocated to each treatment group within each clinical site using a computer-generated random allocation schedule. To ensure in-house blinding, the randomization schedule was generated by an assistant statistician who was uninvolved with the study. The investigators, study coordinators, and patients all remained blinded to the study medications. Blinded allocation schedules and blinded supplies of Aprepitant were supplied by Merck. Patients in this study were stratified at randomization according to gender (stratum A for males; stratum B for females).

Efficacy parameters included emetic episodes, use of rescue medication, and severity of nausea. Assessments of efficacy were performed until 48 hours after end of surgery. During the hospitalization period of the study, efficacy parameters were captured by the study coordinator or investigator onto the study worksheets, or by hospital staff in the patient-chart. Following hospital discharge, patients were issued a reminder card to record emetic episodes, rescue medications, and pain medications for any out-patient period of the study for up to 48 hours following end of surgery. Finally, the time frame of the study included pre-study phase (within 3 weeks of surgery), pre-operative phase (3 hours before surgery), surgery phase, post-operative phase (0 to 48 hours after last suture/staple placed), and follow-up phase (within 3 weeks after surgery).

Statistical Methodologies

The primary endpoint analysis was the complete response defined as no vomiting and no rescue therapy in the 24 hours following the end of surgery.

The secondary endpoint analyses were as follows:

- No vomiting in the 24 hours following the end of surgery;
- No use of rescue medication in the 24 hours following the end of surgery; and
- No vomiting in the 48 hours following the end of surgery.

The exploratory endpoint analyses (pre-specified) were as follows:

- Complete Response (0 to 24 hours) in the Aprepitant 125 mg versus 40 mg treatment groups;
- Peak nausea scores in the 0 to 24 hours following the end of surgery;
- Time to first vomiting in the 0 to 48 hours following the end of surgery;
- Time to first use of rescue medication in the 0 to 24 hours following the end of surgery; and

- Subgroup displays.

Two patient populations were considered for the efficacy analysis: the modified intention-to-treat (MITT) population and the per-protocol (PP) population. The MITT population for efficacy included all patients who were randomized, took study drug, underwent protocol-defined surgery, and had at least one post-treatment assessment. This was the primary population used to assess efficacy.

The PP population is the MITT population without those patients who were identified as protocol violators prior to un-blinding and no imputation was done for missing values. This population was also considered for the evaluation of the primary endpoint. Since 7.1% of MITT patients were protocol violators, a per-protocol analysis was also carried out for all the secondary endpoints.

The applicant indicated that the primary and secondary end-point analyses were performed using logistic regression at two-sided significance level of .05. Treatment comparisons were made using logistic regression models that included terms for treatment and investigative sites (1-5 defined below) and no interaction terms. Gender was not included in the model because the number of male patients was small (<10%). Treatment-by-investigative sites was evaluated at the 10% level (reported if $p<0.1$).

Since this study was conducted at a large number of sites, in order to avoid small cells in the logistic model, sites were pooled based on the size of the sites as follows: all sites with 24, 25-30, 31-40, 41-59, and 60 patients were pooled together as group 1-5, respectively.

For the exploratory endpoint analysis, Kaplan-Meier curves were generated for each of the treatment groups to describe the time to first vomiting and time to first use of rescue medication to treat established nausea or vomiting. The time interval for vomiting was 0 to 48 hours following the end of surgery, and for use of rescue medication it was 0 to 24 hours following the end of surgery. A log-rank test was used for treatment comparisons. Patients who did not have the event (vomiting or rescue) were followed up to the end of the relevant time period (48 hours for vomiting, 24 hours for rescue).

For the nausea analysis, an individual peak nausea score was calculated over the first 24 hours following the end of surgery. All scheduled and unscheduled nausea assessments over the first 24 hours were included in this calculation. The single highest VRS (verbal rating score) score was used as the peak value. The Wilcoxon rank-sum test was used in comparing the treatment groups.

Patients meeting all 4 of the following criteria were planned to be excluded from the MITT analysis of complete response in the 24 hours following the end of surgery: 1) discharged from the hospital prior to 23 hours following surgery; 2) lost to follow-up prior to 23 hours following surgery; 3) did not vomit prior to loss to follow-up; and 4) did not receive rescue medications prior to loss to follow-up. However, for the analysis of peak nausea, all patients with at least one nausea assessment after surgery were included. For time to event analyses, all patients were included. For the per-protocol analysis, no imputations were made.
The applicant indicated that since there was only one primary efficacy endpoint with one primary time point, no multiplicity adjustments were required. However, a step-down procedure was used to account for multiple tests (two doses compared to Ondansetron) within the primary hypothesis. The

primary hypothesis is formulated by testing whether or not the efficacy of Aprepitant (125 mg, 40 mg) is superior to that of Ondansetron IV evaluated by the proportion of patients with complete response in the 24 hours following end of surgery. Specifically, this closed-testing procedure involves two steps. In Step 1, the comparison between Aprepitant 125-mg and Ondansetron (with respect to the complete response endpoint) was tested at the 0.05 level of significance. If the p-value was less than 0.05, then the difference is declared statistically significant. Step 2 is then carried out. In Step 2, the comparison between Aprepitant 40 mg and Ondansetron was tested at the 0.05 level of significance. The step-down procedure ensures that the overall type 1 error rate was controlled at the 0.05 level.

A similar multiplicity strategy was employed to account for the two treatment comparisons for each of the secondary hypotheses. Additionally, the same closed testing procedure was also used to account for the multiple secondary hypotheses. That is, assuming the primary hypothesis has been met, the first secondary hypothesis that Aprepitant (125 mg, 40 mg) is superior to Ondansetron with respect to no vomiting in the 24 hours following the end of surgery was tested at the 5% significance level. Subsequent secondary hypotheses, no rescue (0 to 24 hours) and no vomiting (0 to 48 hours), were tested at the 5% level as long as the previous secondary hypothesis was declared significant. However, except for the complete response (0 to 24 hours) in the Aprepitant 125 mg versus 40 mg treatment groups, no multiplicity adjustment technique was pre-specified for the exploratory endpoint analyses. Nominal p-values are displayed for all treatment comparisons.

Subgroup analyses for the primary endpoint of complete response in the 24 hours following the end of surgery were performed for the following variables:

- Relevant risk factors, such as smoking status, duration of surgery, history of PONV and/or motion sickness;
- Age (<65 years, 65 years; <75 years, 75 years);
- Race.

In addition, since males represented only 5.8% of the MITT population, a display by gender was not included.

Finally, the applicant also performed a post-hoc non-inferiority analysis using a post-hoc delta margin of 0.65 to compare the efficacy of Aprepitant (125 mg, 40 mg) to that of Ondansetron with respect to the primary efficacy endpoint (complete response of no vomiting and no use of rescue in the 24 hours following end of surgery).

A total of 740 patients (approximately, 247 patients per treatment group) were to be randomized to yield a total of 720 MITT evaluable patients (approximately, 240 patients per treatment group), assuming approximately 3% dropout rate. Patient randomization was stratified according to gender.

Based on a sample size of 240 MITT evaluable patients per treatment group and assuming a significance level of 0.05 (two-sided) for testing the primary efficacy hypothesis, it is anticipated that the present study has 99% power to detect a 15 percentage-point difference (e.g., 80% versus 65%) for the 125-mg dose. Given the uncertain estimate of the response rate for

Ondansetron in this population, the study was designed to provide 90% power to detect a difference of 15 percentage points: for a 50% response rate for Ondansetron (that is, the rate with the largest variability), and a rate of 65% for the Aprepitant group in the proportion of patients reporting a complete response at 24 hours following the end of surgery.

Patient Disposition

The accounting of patients randomized into the study was presented in Table 3.1.1.1.

Table 3.1.1.1 (Applicant's) Overall disposition for all randomized patients

Patients Randomized	Aprepitant 40 mg (N=272)	Aprepitant 125 mg (N=263)	Ondansetron (N=270)	Total (N=805)
Patients completed	258	240	254	752
Patients discontinued	14	23	16	53
lost to follow-up	3	6	1	10
moved	0	1	0	1
withdrew consent	3	5	6	14
other	8	11	9	28

Overall, 805 patients were randomized in the study. Of these, 752 (93.4%) patients completed the study, and 53 (6.6%) patients discontinued from the study: 14 patients in the Aprepitant 40-mg group, 23 patients in the Aprepitant 125-mg group and 16 patients in the Ondansetron group.

The applicant indicated that no patient discontinued due to a clinical, or a laboratory adverse event. Eleven patients (3 in the Aprepitant 40-mg group, 7 in the Aprepitant 125-mg group, and 1 in the Ondansetron group) did not undergo the follow-up visits, or the follow-up phone calls within 3 weeks of surgery. Hence they were reported as lost to follow-up even though they had completed the in-patient portion of the study and were included in the efficacy analyses. One of these patients moved before the follow-up visit occurred. In addition, fourteen patients discontinued because they withdrew consent (3 in the Aprepitant 40-mg group, 5 in Aprepitant 125-mg group, and 6 in the Ondansetron group). Finally, twenty-eight patients (8 patients in the Aprepitant 40-mg group, 11 patients in the Aprepitant 125-mg group, and 9 patients in the Ondansetron group) discontinued for "other reasons".

Demographics and Baseline Characteristics

Table 3.1.1.2 displayed the baseline patient demographics (gender, age, and race) while Table 3.1.1.3 displayed baseline patient characteristics, including known risk factors for PONV (history of PONV, history of motion sickness, and tobacco use), and the American Society of Anesthesiology (ASA) status. These two tables included all randomized patients who received active study drug and were included in the safety displays and analyses.

Table 3.1.1.2 (Applicant's) Baseline patient demographics by treatment groups (All randomized patients who received active study drug)

	Aprepitant 40 mg (N=261)		Aprepitant 125 mg (N=252)		Ondansetron (N=253)		Total (N=766)	
	n	(%)	n	(%)	n	(%)	n	(%)
Gender								
Female	245	(93.9)	238	(94.4)	239	(94.5)	722	(94.3)
Male	16	(6.1)	14	(5.6)	14	(5.5)	44	(5.7)
Age								
17 and under	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
18 to 24	4	(1.5)	4	(1.6)	4	(1.6)	12	(1.6)
25 to 34	31	(11.9)	32	(12.7)	35	(13.8)	98	(12.8)
35 to 44	88	(33.7)	103	(40.9)	104	(41.1)	295	(38.5)
45 to 54	93	(35.6)	85	(33.7)	64	(25.3)	242	(31.6)
55 to 64	27	(10.3)	18	(7.1)	30	(11.9)	75	(9.8)
65 to 74	11	(4.2)	8	(3.2)	11	(4.3)	30	(3.9)
Over 74	7	(2.7)	2	(0.8)	5	(2.0)	14	(1.8)
Mean	45.9		44.0		44.9		45.0	
SD	11.21		9.38		11.21		10.66	
Median	45.0		44.0		43.0		44.0	
Range	22 to 83		23 to 78		18 to 82		18 to 83	
Race								
Asian	3	(1.1)	4	(1.6)	6	(2.4)	13	(1.7)
Black	45	(17.2)	63	(25.0)	49	(19.4)	157	(20.5)
Hispanic American	24	(9.2)	24	(9.5)	29	(11.5)	77	(10.1)
White	185	(70.9)	161	(63.9)	167	(66.0)	513	(67.0)
Other*	4	(1.5	0	(0.0)	2	(0.7)	6	(0.8)
* Other includes European, Indian and Native American								

From Table 3.1.1.2, the applicant indicated that the three treatment groups were similar with respect to baseline patient demographics. Overall, 94% of the patients were females and the mean age was 45 ± 11 years.

Table 3.1.1.3 (Applicant's) Baseline patient characteristics by treatment groups (All randomized patients who received active study drug)

	Aprepitant 40 mg (N=261)		Aprepitant 125 mg (N=252)		Ondansetron (N=253)		Total (N=766)	
	n	(%)	n	(%)	n	(%)	n	(%)
History of Postoperative Nausea and Vomiting								
Yes	79	(30.3)	83	(32.9)	81	(32.0)	243	(31.7)
No	182	(69.7)	169	(67.1)	172	(68.0)	523	(68.3)
History of Motion Sickness								
Yes	76	(29.1)	62	(24.6)	64	(25.3)	202	(26.4)
No	185	(70.9)	190	(75.4)	189	(74.7)	564	(73.6)
Tobacco Use								
Never	147	(56.3)	175	(69.4)	152	(60.1)	474	(61.9)
Current	64	(24.5)	45	(17.9)	54	(21.3)	163	(21.3)
Ex-user	50	(19.2)	32	(12.7)	47	(18.6)	129	(16.8)
ASA Status								
P1	55	(21.1)	64	(25.4)	61	(24.1)	180	(23.5)
P2	171	(65.5)	152	(60.3)	160	(63.2)	483	(63.1)
P3	35	(13.4)	36	(14.3)	32	(12.6)	103	(13.4)
ASA = American Society of Anesthesiology P1 = A normal healthy person P2 = A patient with mild systemic disease P3 = A patient with severe systemic disease								

Similarly, based upon the results of Table 3.1.1.3, the applicant indicated that the baseline-patient characteristics were similar across treatment groups.

Applicant's Efficacy Analysis Results and Conclusions

Primary endpoint analysis

Table 3.1.1.4 displayed the results for the percentages of patients with complete response in the 24 hours following end of surgery using MITT population.

Table 3.1.1.4 (Applicant's) Number of patients with complete response† by treatment in the 24 hours following end of surgery using MITT population

	With Complete Response			Aprepitant Versus Ondansetron	
Treatment	n/m	%	95% CI	Odds Ratio‡	p-Value
Aprepitant 40 mg	111/248	44.8	(38.5, 51.2)	1.1	0.611
Aprepitant 125 mg	103/239	43.1	(36.7, 49.6)	1.0	0.866
Ondansetron	104/246	42.3	(36.0, 48.7)		

† Complete Response = No vomiting and no use of rescue medication for vomiting or nausea.
‡ Estimated odds ratio for Aprepitant versus Ondansetron; the model included terms for treatment and investigative sites.
n/m = Number of patients with desired response/number of patients included in analysis.
CI = Confidence interval.

Based upon Table 3.1.1.4, the applicant indicated that the differences on the proportions of patients with complete response between the Aprepitant groups and the Ondansetron group were not statistically significant, but numerically comparable.

In addition, the applicant indicated that for the primary efficacy outcome, the treatment interactions with investigative center and risk factors such as age, smoking status, duration of surgery, history of PONV and/or motion sickness were tested individually at the 10% significance level using logistic models. The interactions between treatment and investigative center, treatment and age, and treatment and duration of surgery were not significant (p-value = 0.354, 0.673 and 0.481, respectively). Similarly, the interactions between treatment and smoking status, and treatment and history of PONV and/or motion sickness were also not significant (p>0.10), indicating that the effect of Aprepitant relative to Ondansetron was similar among risk groups.

In support of the MITT analysis, a per-protocol analysis was performed focusing on the patients without protocol violations. The per-protocol population consisted of the MITT population with the exclusion of protocol violators (52 patients or 7.1% of the MITT population) and no imputation for missing data. However, the applicant indicated that the results of the per-protocol analysis were nearly identical to those of the MITT analysis.

Secondary endpoint analysis

For no vomiting (0 to 24) defined as the absence of vomiting episodes retching, or dry heaves, regardless of whether or not the patient took rescue medication to treat established nausea or vomiting, the applicant indicated that the percentages were 90.0 in the Aprepitant 40-mg group, 95.0 in the Aprepitant 125-mg group and 74.0 in the Ondansetron group by MITT population.

The proportions of patients with no vomiting in the 24 hours following the end of surgery were higher ($p<0.001$) in both the Aprepitant 40-mg and 125-mg groups than in the Ondansetron group. Based upon the result, the applicant concluded that regardless of the use of rescue medication, Aprepitant (125 mg, 40 mg) controlled vomiting better than Ondansetron in the 24 hours following end of surgery.

For no rescue defined as no use of rescue medication, the results showed that the percentages were 45.0 in the Aprepitant 40-mg group, 44.0 in the Aprepitant 125-mg group and 46.0 in the Ondansetron group using MITT population. The differences between the Aprepitant groups and the Ondansetron group were not statistically significant ($p=0.830$ and 0.720 respectively for Aprepitant 40mg vs. Ondansetron and 125 mg vs. Ondansetron). There is insufficient evidence to support that Aprepitant (125 mg or 40 mg) is superior to Ondansetron with respect to the efficacy endpoint of no rescue in the 24 hours following end of surgery.

Finally, for no vomiting (0 to 48), the percentages of patients were 84.6 in the Aprepitant 40-mg group, 93.2 in the Aprepitant 125-mg group and 66.9 in the Ondansetron group using MITT population. These results suggest that, regardless of the use of rescue medication, more patients in the Aprepitant (125 mg, 40 mg) groups reported no vomiting than did the patients in the Ondansetron group in the 48 hours following end of surgery. However, the applicant indicated that since the previous hypothesis of no rescue (0 to 24 Hours) was not met at the significance level of 5%, the findings for no vomiting (0-48 hours) were no considered statistically significant.

Results of the per protocol analysis for the secondary end point of no vomiting in the 48 hours following the end of surgery were similar to those of the MITT analysis.

Exploratory endpoint analysis

For complete response in the 24 hours following surgery, the comparison between Aprepitant 125-mg and Aprepitant 40-mg groups was performed using logistic regression with treatment and investigator sites as the parameters. The result indicated that the percentages between treatment groups were not significant ($p=0.740$).

For peak nausea score (0 to 24 Hours), there were no significant differences in the distribution of peak nausea verbal rating score (VRS) between Aprepitant 40 mg and Ondansetron ($p=0.190$) and between Aprepitant 125 mg and Ondansetron ($p=0.660$) using Wilcoxon rank-sum tests.

For time to first vomiting (0 to 48 Hours), compared to the Ondansetron group, Aprepitant 40 mg and Aprepitant 125 mg delayed the time to first vomiting (p-values <0.001 based on the log-rank test).

For time to first use of rescue medication (0 to 24 Hours), there was no apparent evidence to support that Aprepitant 40 mg and Aprepitant 125 mg delay the time to first use of rescue medication compared to Ondansetron (p-values 0.906 and 0.769, respectively, based on log-rank test).

Post Hoc Non-Inferiority Analysis

Based upon the post hoc non-inferiority margin of 0.65, the applicant indicated that the lower bounds (0.81 and 0.76 respectively, for Aprepitant 40 mg vs. Ondansetron and 125 mg vs Ondansetron) of the one-sided 95% confidence interval for the odds ratio comparing Aprepitant (125 mg and 40 mg) to Ondansetron are above 0.65, the non-inferiority margin.

Statistical Reviewer's Comments

In this section, this reviewer makes comments on the following two issues: 1) superiority analysis results regarding the primary and secondary endpoints based upon the multiplicity adjustment method proposed by the applicant and 2) the post-hoc non-inferiority analysis.

1) Comments on the superiority analysis results

The results from the superiority analysis pre-specified in the protocol P090 indicate that the efficacy of Aprepitant 125 mg (p=0.87) and Aprepitant 40 mg (p=0.61) are not superior to that of Ondansetron 4mg IV assessed by the primary endpoint the proportion of patients with complete response during the first 24 hours after surgery. Since the primary hypothesis of Aprepitant (125 mg, 40 mg) superior to Ondansetron 4 mg IV assessed by the primary endpoint was not met, according to the pre-specified multiplicity adjustment technique, the testing procedure was terminated and Aprepitant was judged not superior to Ondansetron for the secondary and exploratory endpoints.

On the other hand, since the two-sided Type I error rate of 5% was totally spent for testing the primary hypothesis, no Type I error rate was left for the analyses of the secondary and exploratory endpoints. Consequently, based upon the results of the superiority analyses for the primary, secondary, and exploratory endpoints judged by the multiplicity adjustment method pre-specified in the protocol and Type I error rate totally spent for the primary endpoint analysis, Study P090 did not provide evidence to support the use of Aprepitant in the prevention of postoperative nausea and vomiting.

2) Comments on the post-hoc non-inferiority analysis

After superiority of Aprepitant to Ondansetron failed for the primary endpoint the proportion of patients with complete response during the first 24 hours after surgery, the non-inferiority margin selected in the post-hoc non-inferiority analysis presented by the applicant in this study has the following statistical issues.

i) 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.

ii) Loss of position as confirmatory hypothesis

As indicated by the applicant's submission, Study P090 was a phase III study to support Aprepitant regimen in the prevention of postoperative nausea and vomiting. 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 postoperative nausea and vomiting. Therefore, if the applicant decided on applying non-inferiority analysis to confirm that Aprepitant regimen was effective for the proposed indication, the inferiority null hypothesis along with its non-inferiority margin should have been pre-specified during the protocol stage. In the contrast, if the non-inferiority margin was selected after inspecting data, not only the inferiority null hypothesis was not formulated before conducting the trial, but also the selected margin was data dependent and was biased. Accordingly, the inferiority null hypothesis, including a margin influenced by the current trial (Study P090) data, was a post-hoc hypothesis and could not be deemed as a confirmatory hypothesis.

iii) 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 was 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.

In conclusion, from a statistical perspective, since the non-inferiority analysis along with its margin was not pre-specified in the protocol but specified 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.

3.1.2 Study P091

Study Design and Endpoints

This was a multi-center, randomized, double-blind, parallel group, active comparator controlled trial with in-house blinding to assess the safety and efficacy of two different doses of Aprepitant for the prevention of postoperative nausea and vomiting (PONV) in patients undergoing open abdominal surgery requiring overnight hospital stay.

The primary objectives of the study were to demonstrate that Aprepitant (125 mg, 40 mg) was superior to Ondansetron in the prevention of PONV as measured by the proportion of patients with no vomiting in the 24 hours following end of surgery and to demonstrate that Aprepitant (125 mg, 40 mg) was not inferior to Ondansetron in the prevention of PONV as measured by the proportion of patients with complete response in the 24 hours following end of surgery. If the non-inferiority of Aprepitant versus Ondansetron was established, the superiority of Aprepitant (125 mg, 40 mg) to Ondansetron as measured by the proportion of patients with complete response in the 24 hours following end of surgery would also be evaluated.

For the information on the study population, treatment regimen, randomization skill, efficacy parameter assessments, and study time frame, refer to the section of "Study Design and Endpoints" depicted in Study P090.

The applicant further indicated that no vomiting in the 24 hours following end of surgery was selected as the first primary efficacy endpoint because it was an objective and clinically relevant assessment. Complete response (no emesis and no rescue) in the 24 hours following end of surgery was selected as the second primary efficacy endpoint as it is an effective index of control of PONV.

Statistical Methodologies

For the definitions of MITT and Per-protocol (PP) patient populations, refer to the section of "Statistical Methodologies" in Study P090. The PP population was also considered for the evaluation of the primary endpoints. Since 6% of the patients were excluded from the MITT population, the per-protocol population was also used for the analysis of the secondary endpoint. The per-protocol analyses were considered supportive of the MITT analyses.

To ensure comparability between treatment groups, patients were randomized to 1 of the 3 treatment groups (Aprepitant 125 mg, 40 mg, or Ondansetron) at each investigative site using a stratified randomization schedule by gender. The applicant indicated that female gender is an important risk factor for PONV and, based on the specific eligibility criteria, the vast majority of study patients were expected to be female.

Unlike Study P090, there were two primary endpoint analyses: no vomiting in the 24 hours following the end of surgery and complete response (no vomiting and no use of rescue medication) in the 24 hours following the end of surgery. For no vomiting in the 24 hours following the end of surgery, compared to Ondansetron IV, Aprepitant (125 mg, 40 mg) will

provide superior prevention of PONV while for complete response in the 24 hours following the end of surgery, Aprepitant (125 mg, 40 mg) will provide non-inferior prevention of PONV to Ondansetron IV. If this is established the following hypothesis will also be tested: compared to Ondansetron IV, Aprepitant (125 mg, 40 mg) will provide superior prevention of PONV as measured by the proportion of patients with complete response in the 24 hours following end of surgery.

Unless stated otherwise, all tests of hypotheses used a two-sided significance level of 5%. The major emphasis of the statistical conclusions was based on the results from the logistic regression analyses. In addition, this study was conducted at a large number of sites (42 investigational sites: 34 from ex-U.S. and 8 in U.S.). In order to avoid small cells in the logistic model, sites were pooled based on geographical region: Asia (Hong Kong, Singapore, New Zealand); Europe (Switzerland, Spain, United Kingdom, France, Austria, Germany, Italy); North America (United States, Mexico, Costa Rica); South America (Brazil, Columbia, Peru).

For the superiority analysis with regard to the primary endpoint of no vomiting, the applicant indicated that treatment comparisons were made using logistic regression models that included terms for treatment and investigative sites and no interaction terms. Gender was not included in the model because the number of male patients was small (<10%). Treatment-by-investigative site interaction was evaluated at the 10% level ($p<0.1$).

For the non-inferiority analysis with regard to the primary endpoint of complete response, the non-inferiority margin was determined by the efficacy of Ondansetron versus placebo shown on the four historical women studies which were summarized in Table 3.1.2.1.

Table 3.1.2.1 (Applicant's) Ondansetron PONV Historical Prevention Trials

Study Population	Drug	Complete Response		Odds Ratio
		Placebo	Active	
Women Out-patients	Ondansetron IV	64/139 46%	103/136 76%	3.66
Women Out-patients	Ondansetron IV	63/143 44%	86/136 63%	2.18
Women In-patients	Ondansetron PO	105/327 32%	179/343 52%	2.31
Women In-patients	Ondansetron PO	54/204 26%	112/207 54%	3.27

The applicant indicated that the criterion used for selecting the relative effect of control to placebo was: select as one half of the relative effect of control to placebo on the log odds ratio scale. This criterion is meant to ensure that the treatment effect preserves at least half of the control effect. Based upon Table 3.1.2.1, applying this criterion to the studies mentioned above, a non-inferiority boundary of =0.65 was identified as follows: the odds ratio (2.18) for the second study in Table 3.1.2.1 was selected as representing the most conservative estimate of treatment effect. The inverse of the odds ratio (1 / 2.18 = 0.459) was calculated so as to obtain the placebo / Ondansetron value. The natural log of this value was then taken (0.459 = -0.779) to

obtain the same scale that is used in the logistic regression analysis. Since the rationale is to preserve at least ½ of the effect, ½ of -0.779 was determined (-0.390). Finally, this value was exponentiated (0.677) to return it to the odds ratio scale. This value was rounded to 0.65 to obtain the non-inferiority margin.

The secondary endpoint analysis was no vomiting in the 48 hours following the end of surgery.

The exploratory endpoint analyses (pre-specified) were as follows:

- No use of rescue medication in the 0 to 24 hours following the end of surgery;
- Peak nausea score in the 0 to 24 hours following the end of surgery;
- Time to first vomiting episode in the 0 to 48 hours following the end of surgery;
- Time to first vomiting or first use of rescue medication in the 0 to 24 hours following the end of surgery;
- Time to first use of rescue medication in the 0 to 24 hours following the end of surgery;
- Subgroup display: No Vomiting (0 to 24 hours) and Complete Response (0 to 24 hours) by age and race.

Refer to the section of statistical Methodologies in Study P090 for the statistical analysis methods applied to the secondary and exploratory endpoints.

This study was powered to achieve a minimum of 80% on both primary hypotheses. A total of 880 patients were to be randomized to yield 840 patients with data (approximately 280 MITT evaluable patients per treatment group), assuming 5% dropout rate. Patient randomization was stratified according to gender.

Based on a sample size of 280 evaluable (MITT) patients per treatment group and assuming a significance level of 0.05 (two-sided) for testing the first primary efficacy hypothesis relating to the no vomiting endpoint, it was anticipated that the present study had 99% power to detect a 15 percentage-point difference (e.g., 90% versus 75%).

Based on the same sample size and assuming a significance level of 0.05 (one-sided) for testing the second primary efficacy hypothesis relating to the complete response endpoint, it is anticipated that the present study had 80% power to declare non-inferiority for Aprepitant, using a non-inferiority margin of 0.65 (for odds ratio) and a rate of 45% for the active control group in the proportion of patients reporting complete response in 24 hours following end of surgery.

In order to control Type-I error rate of 0.05, the applicant indicated that the two stated primary hypotheses actually map to a set of six statistical null/alternative hypotheses that were evaluated in a step-wise fashion employing a closed testing procedure designed to control the overall Type I error rate at the 0.05 level. Specifically, this procedure involved the following 6 steps.
For endpoint of no vomiting (0 to 24 hours) following end of surgery:
Step 1 HA: Aprepitant 125 mg superior to Ondansetron using two-sided test with alpha = .05;
Step 2 HA: Aprepitant 40 mg superior to Ondansetron using two-sided test with alpha = .05.

For endpoint of complete response (0 to 24 hours) following end of surgery:
Step 3 HA: Aprepitant 125 mg non-inferior to Ondansetron using one-sided test with alpha = .05;
Step 4 HA: Aprepitant 40 mg non-inferior to Ondansetron using one-sided test with alpha = .05;
Step 5 HA: Aprepitant 125 mg superior to Ondansetron using one-sided test with alpha = .05;
Step 6 HA: Aprepitant 40 mg superior to Ondansetron using one-sided test with alpha = .05.
HA = Statistical alternative hypothesis.

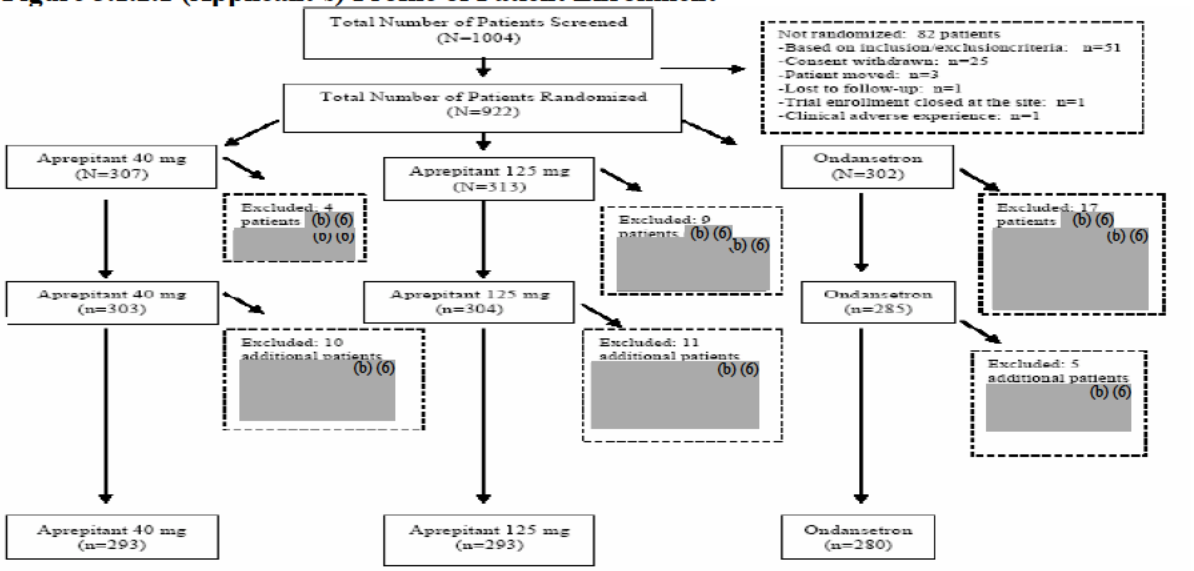
The statistical evaluation described in Steps 2 and 3 occurred only if the preceding step resulted in a significant finding that rejected the statistical null hypothesis in favor of the explicitly stated alternative hypothesis. The statistical evaluation described in Steps 4 and 5 occurred simultaneously and only if Step 3 resulted in a significant finding that rejected the statistical null hypothesis in favor of the explicitly stated alternative hypothesis. The statistical evaluation described in Step 6 occurred only if Steps 4 and 5 resulted in a significant finding that rejected the statistical null hypothesis in favor of the explicitly stated alternative hypothesis.

Tests of non-inferiority (Steps 3 and 4) were conducted by comparing the lower bound of the confidence interval for the specified odds ratio to the value of 0.65. If the lower bound exceeded 0.65, then non-inferiority was concluded. The tests of superiority described in Steps 5 and 6 were conducted by comparing the lower bound of the confidence interval for the specified odds ratio to the value of 1.0. If the lower bound exceeded 1.0, then superiority was concluded. This step-down procedure ensures that the overall Type I error rate is controlled at the 0.05 level.

Patient Disposition

Figure 3.1.2.1 displays the profile of study enrollment and summarizes the number of patients in each of the populations analyzed.

Figure 3.1.2.1 (Applicant's) Profile of Patient Enrollment



Based upon Figure 3.1.2.1, the applicant indicated that of the 1004 patients screened for inclusion in the study, 82 patients were excluded during screening and not randomized. Out of the excluded patients, 51 patients did not meet the eligibility criteria. In addition, 25 patients withdrew consent, 3 patients moved, 1 patient was not enrolled due to a clinical adverse event, one patient was lost to follow-up, and 1 patient was not enrolled because trial enrollment was closed at the site.

The remaining 922 patients who met the eligibility criteria at the screening visit were enrolled in the study and randomized into one of three treatment groups (307 for Aprepitant 40-mg, 313 for Aprepitant 125-mg, and 302 for Ondansetron). Of the 922 randomized patients, 56 patients were excluded from the MITT analyses: 14 from the Aprepitant 40 mg group, 20 from the Aprepitant 125 mg group, and 22 from the Ondansetron group. That is, of the 866 remaining patients in the MITT population, 293 patients received Aprepitant 40 mg, 293 patients received Aprepitant 125 mg, and 280 patients received Ondansetron.

Thirty of these 56 were excluded from MITT analysis because they did not receive study drug: 25 were excluded because they were discontinued from the study prior to receiving study drug, and 5 patients were excluded because they received partial study drug which was determined to be inactive after un-blinding. A total of 26 patients were not included in the MITT efficacy analyses because: 18 patients were excluded due to unreliable efficacy data, 7 patients were excluded because received incomplete study therapy and no post-treatment efficacy assessments, and 1 patient was potentially un-blinded by study site personnel.

Demographics and Baseline Characteristics

For baseline patient demographics, the applicant indicated that the distributions of the three treatment groups (Aprepitant 40 mg, Aprepitant 125 mg, and Ondansetron) with respect to

gender, age, and race were similar. Overall, 91% of patients were females and the mean age was 46 ± 11years.

For patient baseline characteristics, the applicant indicated that the distributions for the history of PONV, history of motion sickness, tobacco use, and the American Society of Anesthesiology (ASA) status were similar across treatment groups. Table 3.1.2.2 presented baseline patient characteristics using all randomized patients who received active study drug.

Table 3.1.2.2 (Applicant's) Baseline Patient Characteristics by Treatment Groups

	Aprepitant 40 Mg (N=303)		Aprepitant 125 Mg (N=304)		Ondansetron (N=285)		Total (N=892)	
	n	(%)	n	(%)	n	(%)	n	(%)
History of Postoperative Nausea and Vomiting								
Yes	50	(16.5)	40	(13.2)	52	(18.2)	142	(15.9)
No	253	(83.5)	264	(86.8)	233	(81.8)	750	(84.1)
History of motion Sickness								
Yes	42	(13.9)	44	(14.5)	40	(14.0)	126	(14.1)
No	261	(86.1)	260	(85.5)	245	(86.0)	766	(85.9)
Tobacco Use								
Never	211	(69.6)	208	(68.4)	200	(70.2)	619	(69.4)
Current	46	(15.2)	58	(19.1)	54	(18.9)	158	(17.7)
Ex-user	46	(15.2)	38	(12.5)	31	(10.9)	115	(12.9)
ASA Status								
P1	171	(56.4)	163	(53.6)	151	(53.0)	485	(54.4)
P2	125	(41.3)	132	(43.4)	123	(43.2)	380	(42.6)
P3	7	(2.3)	9	(3.0)	11	(3.9)	27	(3.0)

ASA = American Society of Anesthesiology; P1 = A normal healthy person; P2 = A patient with mild systemic disease; P3 = A patient with severe systemic disease.

Applicant's Efficacy Analysis Results and Conclusions

Primary endpoint analysis

Table 3.1.2.3 displayed the results for the percentages of patients with no vomitting in the 24 hours following end of surgery using MITT population.

Table 3.1.2.3 (Applicant's) Number of patients with no vomiting by treatment in the 24 hours following end of surgery using MITT population

	With No Vomiting			Aprepitant Versus Ondansetron	
Treatment	n/m	%	95% CI	Odds Ratio[†]	p-Value
Aprepitant 40 mg	246/293	84.0	(79.2, 88.0)	2.1	<0.001
Aprepitant 125 mg	253/293	86.3	(81.9, 90.1)	2.5	<0.001
Ondansetron	200/280	71.4	(65.8, 76.6)		

[†] Estimated odds ratio for Aprepitant versus Ondansetron. A value of >1 favors Aprepitant over Ondansetron. The model included terms for treatment and investigative sites.
n/m= Number of patients with desired response/number of patients included in analysis.
CI = Confidence Interval.

For the first primary efficacy endpoint of no vomiting, the applicant indicated that the percentages of patients with no vomiting in the 24 hours following end of surgery were significantly higher in both

the Aprepitant 125 mg (step 1 of the closed testing procedure, p<0.001) and Aprepitant 40 mg (step 2 of the closed testing procedure, p<0.001) groups than in the Ondansetron group. There was no significant interaction (p>0.1) between treatment and investigative center groupings.

Table 3.1.2.4 displayed the results for the percentages of patients with complete response in the 24 hours following end of surgery, along with the odds ratios and respective one-sided 95% lower confidence bound for the odds ratios using MITT population.

Table 3.1.2.4 (Applicant's) Number of patients with complete response by treatment in the 24 hours following end of surgery using MITT population

	With Complete Response		Aprepitant Versus Ondansetron	
Treatment	n/m	%	Odds Ratio‡	1-sided 95% CI Lower Bound
Aprepitant 40 mg	187/293	63.8	1.4	1.08*
Aprepitant 125 mg	184/293	62.8	1.4	1.04*
Ondansetron	154/280	55.0		

† Complete Response = No vomiting and no use of rescue.
‡ Estimated odds ratio for Aprepitant versus Ondansetron. A value of >1 favors Aprepitant over Ondansetron.
The model included terms for treatment and investigative sites.
n/m= Number of patients with desired response/number of patients included in analysis.
CI = Confidence Interval.
*P value <0.05

The applicant indicated that the criteria of non-inferiority was defined as having the lower bound of the one-sided 95% confidence interval for the odds ratio, comparing Aprepitant to Ondansetron, exceed the pre-specified non-inferiority margin of 0.65. Based upon Table 3.1.2.4, the applicant alleged that compared Aprepitant to Ondansetron, both of the lower bounds for Aprepitant 125 mg (step 3 of the closed testing procedure) and Aprepitant 40 mg (step 4 of the closed testing procedure) exceed 0.65. Therefore, both Aprepitant doses were non-inferior to Ondansetron.

For the superiority analysis with respect to the complete response endpoint in the 24 hours following end of surgery, the applicant emphasized that as shown in Table 3.1.2.4, the one-sided 95% lower bound exceeds 1.0 for Aprepitant 125 mg (step 5, p=0.029) and Aprepitant 40 mg (step 6, p=0.018) compared to Ondansetron. Therefore, both Aprepitant doses are superior to Ondansetron.

Finally, the applicant indicated that the results of the per-protocol analysis for complete response (0 to 24 hours) following end of surgery support those of the MITT analysis.

Secondary/Exploratory endpoint analysis

For no vomiting in the 48 hours following end of surgery, the applicant indicated that the percentages of patients with no vomiting for Aprepitant 125 mg and 40 mg were respectively, 85% and 82% and both were significantly higher (p<0.001) than 66% for the Ondansetron group.

For no rescue therapy in the 24 hours following end of surgery, Table 3.1.2.5 displayed the results for the proportion of patients with no use of rescue medication.

Table 3.1.2.5 (Applicant's) Number of patients with no use of rescue therapy by treatment in the 24 hours following end of surgery using MITT population

	With No Use of Rescue Medication			Aprepitant Versus Ondansetron	
Treatment	n/m	%	95% CI	Odds Ratio[†]	p-Value
Aprepitant 40 mg	197/293	67.2	(61.5, 72.6)	1.2	0.299
Aprepitant 125 mg	190/293	64.8	(59.1, 70.3)	1.1	0.628
Ondansetron	176/280	62.9	(56.9, 68.5)		

[†] Estimated odds ratio for Aprepitant versus Ondansetron. A value of >1 favors Aprepitant over Ondansetron. The model included terms for treatment and investigative sites.
n/m= Number of patients with desired response/number of patients included in analysis.
CI = Confidence Interval.

Based upon the non-significant results in Table 3.1.2.5, the applicant declared that the rates of no use of rescue medication were similar across treatment groups.

For peak nausea VRS scores (verbal rating score - 0 being no nausea and 10 being bad nausea) in 24 hours following end of surgery, the applicant reported that for the Aprepitant groups (125 mg, 40 mg), the median peak nausea VRS scores were half and the 75th percentiles were slightly lower than those of the Ondansetron group. The distribution of peak nausea was lower in both the Aprepitant (125 mg, 40 mg) groups compared to the Ondansetron group ($p<0.05$ for both comparisons).

For time to first vomiting episode or first use of rescue Medication in 24 hours following end of surgery, the applicant showed that based upon the log rank test, there was evidence to suggest Aprepitant 40 mg and 125 mg ($p=0.043$ and $p=0.047$, respectively) delayed the combination of onset of vomiting or initiation of rescue medication, compared to Ondansetron.

For time to first use of rescue medication in 24 hours following end of surgery, the applicant claimed that there was no apparent difference among the three treatment groups with respect to time to first use of rescue medication.

Statistical Reviewer's Comments and Analysis

In order to validate the applicant's efficacy claim, this reviewer first performs the following two analyses using MITT population: 1) efficacy comparison by center based upon complete response and 2) efficacy comparison based upon nausea. Then, this reviewer comments on the following three issues: 1) switching primary endpoint, 2) non-inferiority analysis, and 3) overall efficacy of Aprepitant.

Reviewer's analysis

1.) Efficacy comparison by center based upon complete response

In order to explore whether the efficacy of Aprepitant to Ondansetron, as assessed by the primary endpoint complete response in 24 hours following end of surgery, was dominated by any one site, this reviewer analyzes the differences in proportions with regard to the primary endpoint by site to compare the efficacy among three treatments using MITT population. The sites used in this analysis are the sites provided by the data set submitted by the applicant. Table 3.1.2.6 presents the result.

Table 3.1.2.6 (Reviewer's) Complete response in 24 hours following end of surgery by treatment group and site using MITT patient population

SITE NUMBER	APREPITANT 40MG % (n/N)	APREPITANT 125 MG % (n/N)	ONDAN-SETRON % (n/N)	SITE NUMBER	APREPITANT 40MG % (n/N)	APREPITANT 125 MG % (n/N)	ONDAN-SETRON % (n/N)
Site 1	58.3 (7/12)	72.7 (8/11)	70.0 (7/10)	Site 24	60.0 (9/15)	66.7 (10/15)	53.8 (7/13)
Site 3	52.9 (9/17)	33.3 (6/18)	47.4 (9/19)	Site 25	66.7 (2/3)	60.0 (3/5)	60.0 (3/5)
Site 4	68.8 (11/16)	76.9 (10/13)	64.3 (9/14)	Site 31	50.0 (4/8)	83.3 (5/6)	62.5 (5/8)
Site 5	87.5 (7/8)	37.5 (3/8)	62.5 (5/8)	Site 33	75.0 (3/4)	100.0 (2/2)	50.0 (1/2)
Site 6	85.7 (6/7)	83.3 (5/6)	40.0 (2/5)	Site 34	75.0 (3/4)	25.0 (1/4)	100.0 (2/2)
Site 7	40.0 (2/5)	50.0 (3/6)	50.0 (2/4)	Site 36	50.0 (2/4)	100.0 (4/4)	75.0 (3/4)
Site 8	100.0 (1/1)	0.0 (0/0)	0.0 (0/0)	Site 37	66.7 (6/9)	77.8 (7/9)	100.0 (8/8)
Site 9	0.0 (0/6)	25.0 (1/4)	33.3 (2/6)	Site 38	72.7 (8/11)	81.8 (9/11)	60.0 (6/10)
Site 11	85.0 (17/20)	78.9 (15/19)	57.9 (11/19)	Site 39	50.0 (2/4)	25.0 (1/4)	40.0 (2/5)
Site 12	53.1 (17/32)	53.1 (17/32)	38.7 (12/31)	Site 40	55.6 (5/9)	66.7 (6/9)	83.33 (5/6)
Site 13	55.6 (5/9)	55.6 (5/9)	62.5 (5/8)	Site 41	100.0 (2/2)	66.7 (2/3)	33.3 (1/3)
Site 15	100.0 (1/1)	0.0 (0/0)	0.0 (0/0)	Site 42	100.0 (1/1)	0.0 (0/2)	0.0 (0/2)
Site 16	80.0 (4/5)	100.0 (4/4)	80.0 (4/5)	Site 43	20.0 (2/10)	27.3 (3/11)	27.3 (3/11)
Site 17	84.6 (11/13)	84.6 (11/13)	50.0 (6/12)	Site 44	0.0 (0/0)	50.0 (1/2)	0.0 (0/2)
Site 18	80.0 (8/10)	70.0 (7/10)	77.8 (7/9)	Site 45	66.7 (4/6)	42.9 (3/7)	50.0 (3/6)
Site 19	90.0 (9/10)	80.0 (8/10)	80.0 (8/10)	Site 46	100.0 (1/1)	50.0 (1/2)	100.0 (1/1)
Site 20	66.7 (2/3)	75.0 (3/4)	50.0 (2/4)	Site 48	25.0 (1/4)	50.0 (2/4)	0.0 (0/5)
Site 21	50.0 (1/2)	100.0 (4/4)	66.7 (2/3)	Site 49	60.0 (3/5)	75.0 (3/4)	60.0 (3/5)
Site 22	80.0 (4/5)	83.3 (5/6)	60.0 (3/5)	Site 50	66.7 (2/3)	50.0 (2/4)	50.0 (1/2)
Site 23	33.3 (1/3)	20.0 (1/5)	33.3 (1/3)	Site 51	60.0 (3/5)	100.0 (5/5)	60.0 (3/5)

Note: Overall complete response rates for Aprepitant 40 mg, 125 mg, and Ondansetron were respectively, 63.8% (187/293), 62.8% (184/293), and 55.0% (154/280).

Table 3.1.2.6 indicates that for the three large sites (11, 12, and 17) each with MITT patients larger than 35, the complete response rates for patients in the two Aprepitant groups were more than 20%, 14%, and 34% higher than that of the patients in the Ondansetron group respectively, for sites 11, 12, and 17. However, Breslow-Day tests show that the effects of site on the treatment efficacy comparisons are not significantly different for both Aprepitant 40 mg versus Ondansetron (p=0.82) and Aprepitant 125 mg versus Ondansetron (p=0.60).

2) Efficacy comparison based upon nausea

In this NDA submission, except for peak nausea score, the applicant did not further report the efficacy assessment based upon the proportion of patients with no nausea. However, prevention of nausea is a part of the proposed indication. In order to assess the efficacy of Aprepitant on nausea, this reviewer compares the efficacy of Aprepitant versus Ondansetron assessed by the proportion of patients with no nausea. Since in the protocol, the applicant pre-specified peak nausea as an exploratory endpoint, this reviewer also treats the nausea analysis as an exploratory analysis without multiplicity adjustment for the two efficacy comparisons (Aprepitant 125 mg versus Ondansetron and Aprepitant 40 mg versus Ondansetron). The purpose of this nausea analysis is to explore (not confirm) whether Aprepitant has effect on the prevention of nausea.

The statistical method used to perform the nausea analysis is the one the applicant used for the vomiting analysis. The analysis result of nausea is presented in Table 3.1.2.7.

Table 3.1.2.7 (Reviewer's) Number of patients with no nausea in the 24 hours following end of surgery using MITT population

	No Nausea		Aprepitant Versus Ondansetron	
Treatment	n/m	%	Odds Ratio †	P-value
Aprepitant 40 mg	138/293	47.0	1.46	0.025
Aprepitant 125 mg	127/293	43.0	1.27	0.170
Ondansetron	105/280	38.0		

†: Estimated odds ratio for Aprepitant versus Ondansetron A value of >1 favors Aprepitant over Ondansetron

The model included terms for treatment and investigative sites n/m= Number of patients with desired response/number of patients included in analysis

Table 3.1.2.7 shows that the p-value (p=0.025) only for the efficacy comparison of Aprepitant 40 mg versus Ondansetron is less than 0.05, assessed by no nausea. It indicates that Aprepitant 40 mg may be better than Ondansetron on prevention of nausea. However, the applicant may need to conduct another phase III study to confirm that Aprepitant 40 mg is superior to Ondansetron on prevention of nausea.

Similarly, for no-significant nausea, the analysis result shows that Aprepitant 40 mg may be better than Ondansetron on prevention of significant nausea (p=0.031).

Reviewer's Comments

1) Issue on switching primary endpoint

Noted by this reviewer, as Study P090, the primary endpoint for the original protocol P091 was still the complete response in 24 hours following end of surgery. However, after learning the superiority of Aprepitant to Ondansetron failed assessed by complete response shown in Study P090, in Study P091, the applicant amended no vomiting to be the first primary endpoint and devalued complete response as the secondary primary endpoint, before completing the study and un-blinding the database.

However, unlike the complete response (no vomiting and no rescue therapy) assessment, no vomiting evaluated a patient without vomiting as treatment success regardless of him taking the rescue therapy. Thus, the treatment success assessed by no vomiting was confounded with the effect of the rescue therapy. The contribution of drug interaction effect (confounding effect) of Aprepitant with the rescue therapy to the treatment success may be different from that of Ondansetron with the rescue therapy. Consequently, the different confounding effects between Aprepitant and Ondansetron induce an unfair/biased efficacy comparison for study drug Aprepitant versus the comparator Ondansetron.

In addition, the primary endpoint for registration of studies of previously approved drugs including Kytril injection submitted by Hoffmann-La Roche Inc. under NDA 20239/S-008 and Ondansetron submitted by Glaxo Inc. on September 19, 1994 under NDA 20103/S-005 were also complete response. By light of selecting complete response as the primary endpoint for the previously approved drugs, the complete response was deemed better than no vomiting in characterizing the clinical benefit in the prevention of postoperative nausea and vomiting.

Accordingly, from the comment on the confounding effect induced by no vomiting and the clinical experiences from the previous NDA submissions, the complete response in 24 hours following end of surgery appears more scientifically sound than no vomiting to be employed as the first primary endpoint.

2) Issue on the non-inferiority analysis

Noted by this reviewer, in Table 3.1.2.4, the applicant applied the lower bound of the one-sided 95% confidence interval to test whether the odds of Aprepitant was greater than that of Ondansetron assessed by the primary endpoint (complete response in 24 hours following end of surgery). However, since this hypothesis was a one-sided testing hypothesis, instead of using 95% one-sided confidence interval, the lower bound for the one-sided 97.5% confidence interval of odds ratios with regard to the complete response in 24 hours following end of surgery for Aprepitant versus Ondansetron should have been used for the non-inferiority analysis to compare the efficacy between Aprepitant and Ondansetron.

In addition, for the non-inferiority margin selection, the applicant provided four placebo-control historical studies (odds ratios summarized in Table 3.1.2.1) to explore the effectiveness of Ondansetron used to prevent postoperative nausea and vomiting. Instead of using upper bound of the point estimate of odds ratio, the applicant employed the point estimate of odds ratio of placebo versus Ondansetron from the second study listed in Table 3.1.2.1 to develop the non-inferiority margin. The point estimate of odds ratio did not address the uncertainty regarding the validity of assay constancy assumption (more comments followed in the subsection of “Non-inferiority margin selection”) on the effectiveness of Ondansetron versus placebo. Therefore, the effect size of Ondansetron versus placebo estimated by a point estimate was not stable and was very likely overestimated.

In order to correct the non-inferiority analysis conducted by the applicant, this reviewer first selects the non-inferiority margin based upon the principle of ICH guidance and then, performs the non-inferiority analysis based upon the primary endpoint of complete response in 24 hours following end of surgery using MITT population. Finally, the comments of medical reviewer, Dr. Della'Zanna, on non-inferiority margin are highlighted.

Non-inferiority margin selection

Noted by this reviewer, the active control drug used by the applicant to assess the efficacy of Aprepitant was Ondansetron IV. The medical reviewer commented that the effect size of oral Ondansetron on prevention of postoperative nausea and vomiting may be different from that of intravenous Ondansetron. For detail, refer to the sub-section of "Medical reviewer's comments on non-inferiority margin".

However, of the four historical studies submitted by the applicant to demonstrate the assay sensitivity of Ondansetron, only the first two trials (in Table 3.1.2.1) explored the effectiveness of Ondansetron IV. As a result, the first two trials in Table 3.1.2.1 are used by this reviewer to establish the non-inferiority margin based upon the complete response to assess the non-inferiority of Aprepitant versus Ondansetron IV. In addition, as for the principle of margin selection, ICH E10 indicates 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 when compared with placebo in the setting of the planned trial. ICH E10 also emphasizes that the determination of the margin in a non-inferiority trial should reflect uncertainties in the evidence on which the choice is based, and should be suitably conservative.

From Table 3.1.2.1, one notes that there is a large difference between the two odds ratios (3.66 versus 2.18) recorded in the first two trials. Based upon the principle of margin selection stated by ICH E10, using data from the first two trials, this reviewer applies the weighted random effect method to generate the upper bound of the two-sided 95% confidence interval for the odds ratio of placebo versus Ondansetron on complete response using the first two trials. Then, based upon the sponsor's algorithm for margin selection, the non-inferiority margin is identified as 0.77 using the upper bound of the two-sided 95% confidence interval generated by the data from the first two trials.

Non-inferiority analysis and comments

Table 3.1.2.8 presents the non-inferiority analysis results on complete response in 24 hours following end of surgery using MITT population.

Table 3.1.2.8 (Reviewer's) Number of patients with complete response by treatment in the 24 hours following end of surgery using MITT population

	With Complete Response		Aprepitant Versus Ondansetron	
Treatment	n/m	%	Odds Ratio †	1-sided 97.5% CI Lower Bound
Aprepitant 40 mg	187/293	63.8	1.4	1.02
Aprepitant 125 mg	184/293	62.8	1.4	0.99
Ondansetron	154/280	55.0		

Complete Response = No vomiting and no use of rescue; †: Estimated odds ratio for Aprepitant versus Ondansetron A value of >1 favors Aprepitant over Ondansetron

The model included terms for treatment and investigative sites n/m= Number of patients with desired response/number of patients included in analysis

Non-inferiority margin: 0.77.

From Table 3.1.2.8, one notes that the lower bounds of one-sided 97.5% confidence interval on the odds ratio of Aprepitant 125 mg versus ondasnsetron and Aprepitant 40 mg versus Ondansetron are respectively, 0.99 and 1.02, greater than the non-inferiority margin of 0.77. Therefore, at significance level of 0.025, the efficacy of Aprepitant 125 mg and Aprepitant 40 mg are not inferior to that of Ondansetron in the sense that the odds of the two test drugs Aprepitant 125 mg and 40 mg assessed by complete response in the 24 hours following end of surgery are not less than 0.77 times that of Ondansetron.

However, the lower bound of one-sided 97.5% confidence interval on odds ratio of Aprepitant 125 mg versus ondasnsetron is 0.99, less than 1. As a result, at significance level of 0.025, the efficacy of Aprepitant 125 mg is not superior to that of Ondansetron assessed by complete response in the 24 hours following end of surgery. Since higher dose 125 mg for Aprepitant failed to demonstrate the superiority to Ondansetron, by the step-wise multiplicity adjustment method proposed by the applicant, the superior test based upon complete response is ceased and Aprepitant 40 mg is judged not superior to Ondansetron.

Finally, it is noted that more than 90% of patients enrolled in this study were females. Due to lack of male patients, the non-inferiority of Aprepitant to Ondansetron shown in the study may not be able to apply to male patients.

Medical reviewer's comments on non-inferiority margin

For the four historical studies provided by the applicant to identify the size of Ondansetron IV, the medical reviewer, Dr. Della'Zanna, indicates that he is not convinced that the studies used to calculate the non-inferiority margin are accurate for the following reasons.

Study P091 utilized an intravenous formulation of Ondansetron in a patient population that had a surgical procedure which required an over-night hospitalization. Neither of the comparative studies listed evaluated an appropriate combination of drug formulation and surgical procedure.

For the historical studies, the intravenous Ondansetron formulation was administered to patients who had an out-patient surgery. It is unlikely that an outpatient surgery would have the same emetogenic potential as a more complicated surgery that required hospitalization. Additionally,

the comparative studies that were performed on patients who required in-patient care evaluated the oral formulation of Ondansetron. Dr. Della'Zanna then, questions whether the submitted studies could be used to accurately calculate a non-inferiority margin.

In order to precisely identify the smallest size of the effectiveness of the active control drug, ICH E10 further recommends that for a planned non-inferiority trial to be similarly sensitive to drug effects, it is essential that the trial have critical design characteristics similar to those of the historical trials. These design characteristics include, for example, the entry criteria (severity of medical condition, concomitant illness, and method of diagnosis), dose and regimen (including drug formulation) of control drug, surgical procedure, concomitant treatments used, the endpoint measured and timing of assessments, and the use of a washout period to exclude selected patients.

Accordingly, based upon the comments made by the medical reviewer regarding the issue of the combination of drug formulation and surgical procedure, the critical design characteristics of the four historical studies might not be similar to that of the two current trials (P090 and P091). Following the principle recommended by the ICH E10, the non-inferiority margin calculated by the applicant using the four historical studies is questionable, as the medical reviewer commented.

3) Overall assessment on the efficacy of Aprepitant

As commented upon in the section of "Reviewer's Comments", treatment effectiveness assessed by no vomiting is confounded with that of the rescue therapy and the primary endpoint of registration studies of previously approved drugs for the proposed indication was also the complete response. From the statistical perspective and previous NDA experience, it seems that the complete response is more appropriate to be employed as the first primary endpoint than no vomiting in the assessment for the prevention of postoperative nausea and vomiting. Thus, to evaluate the efficacy of Aprepitant in prevention of postoperative nausea and vomiting, this reviewer is primarily based upon the complete response in the 24 hours following end of surgery. However, for the primary endpoint the complete response in the 24 hours following end of surgery, the two trials P090 and P091 failed to demonstrate the superiority of Aprepitant (40 mg and 125 mg) to Ondansetron.

As to the non-inferiority analysis based upon the complete response, for Study P090, the non-inferiority analysis was proposed after inspecting data. As a result, the non-inferiority analysis was a post-hoc analysis and was not able to assess the efficacy of Aprepitant versus Ondansetron.

For Study P091, as commented upon by the medical reviewer Dr Della'Zanna, the non-inferiority margin selected by the applicant using the four questionable historical studies may not accurately reflect the effective size of Ondansetron assessed by the primary endpoint the complete response in the 24 hours following end of surgery. However, the two lower bounds for the one-sided 97.5% confidence interval on odds ratios of Aprepitant 125 mg versus

Ondansetron and Aprepitant 40 mg versus Ondansetron are high (respectively, 0.99 and 1.02). As a result, both Aprepitant 125 mg and Aprepitant 40 mg are deemed to be non-inferior to Ondansetron assessed by the complete response. In other words, the efficacy result of the non-inferiority analysis can only be acknowledged for Study P091. Yet, due to less than 10% of patients enrolled for males in Study P091, the non-inferiority of Aprepitant to Ondansetron shown in Study P091 may not be able to apply to male patients.

As to the efficacy analysis based upon no-vomiting in the 24 hours following end of surgery, for Study P090, since the significance level of 2.5% was totally spent for testing the primary null hypothesis that the efficacy of Aprepitant was not superior to that of Ondansetron assessed by the complete response in the 24 hours following end of surgery, no more significance level was left for the efficacy comparison of Aprepitant versus Ondansetron assessed by no vomiting. In addition, based upon the applicant's multiplicity adjustment method, due to the primary hypothesis for the superiority of Aprepitant versus Ondansetron assessed by the primary endpoint the complete response in the 24 hours following end of surgery failed, the testing procedure was terminated and Aprepitant was judged not superior to Ondansetron assessed by the secondary endpoint no vomiting in the 24 hours following end of surgery.

For Study P091, although the superiority of Aprepitant versus Ondansetron assessed by the complete response in the 24 hours following end of surgery was not supported, the primary hypothesis of Aprepitant non-inferior to Ondansetron was met. The secondary hypothesis regarding Aprepitant superior to Ondansetron assessed by no vomiting in the 24 hours following end of surgery was pursued. Based upon the result of the applicant's superiority analysis in regard with no vomiting in the 24 hours following end of surgery, both Aprepitant 125 mg and Aprepitant 40 mg are superior to Ondansetron ($p< 0.001$).

Following above efficacy assessments for the two studies (P090 and P091), only one study (Study P091) is deemed to demonstrate that Aprepitant 125 mg and Aprepitant 40 mg are non-inferior to Ondansetron assessed by the primary endpoint the complete response in the 24 hours following end of surgery and are superior to Ondansetron assessed by no vomiting in the 24 hours following end of surgery. However, the effectiveness of Aprepitant shown by Study P091 was not established by Study P090.

3.2 Evaluation of Safety

3.2.1 Study P090

The applicant indicated that of the 805 randomized patients, 766 patients (261 in the Aprepitant 40-mg group, 252 in the Aprepitant 125-mg group, and 253 in the Ondansetron group) received active study drug as per their treatment allocation and are included in all safety displays and analyses. Three patients inadvertently received both active Aprepitant and active Ondansetron were excluded from all safety tables. Adverse events occurring up to 14 days after study drug administration (or related to events with onset within 14 days of dosing) were reported.

The statistical comparison of Aprepitant (125 mg, 40 mg) with Ondansetron with respect to the summary of clinical adverse event is presented in Table 3.2.1.1.

Table 3.2.1.1 (Applicant's) Clinical adverse event summary with percentage differences for Aprepitant versus Ondansetron

	n (%)		Aprepitant Versus Ondansetron†		
			Difference‡ (%)	95% CI§	p-Value
With one or more adverse experiences					
Aprepitant 40 mg (N=261)	180	(69.0)	-5.7	(-13.5, 2.1)	0.170
Aprepitant 125 mg (N=252)	175	(69.4)	-5.3	(-13.1, 2.6)	0.198
Ondansetron (N=253)	189	(74.7)			
With drug-related adverse experiences‖					
Aprepitant 40 mg (N=261)	11	(4.2)	-2.1	(-6.3, 1.9)	0.326
Aprepitant 125 mg (N=252)	9	(3.6)	-2.8	(-6.9, 1.1)	0.218
Ondansetron (N=253)	16	(6.3)			
With serious adverse experiences					
Aprepitant 40 mg (N=261)	23	(8.8)	0.9	(-4.0, 5.8)	0.752
Aprepitant 125 mg (N=252)	12	(4.8)	-3.1	(-7.7, 1.2)	0.200
Ondansetron (N=253)	20	(7.9)			
Discontinued due to adverse experiences					
Aprepitant 40 mg (N=261)	0	(0.0)	0.0	(-1.5, 1.5)	
Aprepitant 125 mg (N=252)	0	(0.0)	0.0	(-1.5, 1.5)	
Ondansetron (N=253)	0	(0.0)			

† Aprepitant was compared with Ondansetron (Aprepitant - Ondansetron) using Fisher's exact test.
‡ Difference (%) = Percentage Point Difference.
§ 95% CI computed using a method by Miettinen and Nurminen.
‖ Determined by the investigator to be possibly, probably, or definitely drug related.
Although a patient may have had 2 or more clinical adverse events, a patient is only counted once within a category. The same patient may appear in different categories.
N = number of patients who took at least one dose of study medication.
n = number of patients who took at least one dose of study medication and had at least one adverse event in a given category.
% = 100 (n/N).
CI = Confidence interval.

Based up on Table 3.2.1.1, the applicant indicated that the overall incidence of clinical adverse events was similar among the three treatment groups. In addition, clinical adverse events determined by the investigator to be possibly, probably, or definitely drug related were more common in the Ondansetron group compared with the Aprepitant 40mg and 125mg groups. However, the differences were not statistically significant.

Serious clinical adverse events occurred with similar incidence in the Aprepitant 40 mg group and the Ondansetron group, and with lower incidence in the Aprepitant 125 mg group. However, there were no statistically significant differences between the Aprepitant groups and the Ondansetron group for the incidence of patients with serious clinical adverse events.

One of the serious clinical adverse events in the Aprepitant 125-mg group was determined by the investigator to be related to study drug. This was a case of mild constipation that prolonged the hospitalization. One patient with myeloproliferative disorder (Aprepitant 40-mg group) died due to progression of the underlying malignant disease 30 days after surgery. No patients discontinued the study due a clinical adverse event.

3.2.2 Study P091

Of the 922 randomized patients, 892 (303 in the Aprepitant 40 mg group, 304 in the Aprepitant 125 mg group, and 285 in the Ondansetron group) received active study drug as per treatment allocation and are included in all safety displays and analyses. Adverse events occurring within 14 days after last study drug administration (or related to events with onset occurring up to 14 days of dosing) were reported.

The statistical comparison of Aprepitant (125 mg, 40 mg) with Ondansetron with respect to the summary of clinical adverse event is presented in Table 3.1.2.2.1.

Table 3.2.2.1 (Applicant's) Clinical adverse event summary with percentage differences for Aprepitant versus Ondansetron

	n (%)	Aprepitant Versus Ondansetron†		
		Difference‡ (%)	95% CI §	p-value
With one or more adverse experiences				
Aprepitant 40 mg (N=303)	156 (51.5)	-2.9	(-10.9, 5.2)	0.509
Aprepitant 125 mg (N=304)	179 (58.9)	4.5	(-3.5, 12.5)	0.280
Ondansetron (N=285)	155 (54.4)			
With drug-related adverse experiences‖				
Aprepitant 40 mg (N=303)	13 (4.3)	-1.7	(-5.5, 2.0)	0.454
Aprepitant 125 mg (N=304)	21 (6.9)	0.9	(-3.2, 5.0)	0.738
Ondansetron (N=285)	17 (6.0)			
With serious adverse experiences				
Aprepitant 40 mg (N=303)	26 (8.6)	-1.9	(-6.9, 2.9)	0.483
Aprepitant 125 mg (N=304)	31 (10.2)	-0.3	(-5.4, 4.7)	1.000
Ondansetron (N=285)	30 (10.5)			
Discontinued due to adverse experiences				
Aprepitant 40 mg (N=303)	1 (0.3)	0.0	(-1.7, 1.5)	1.000
Aprepitant 125 mg (N=304)	2 (0.7)	0.3	(-1.4, 2.1)	1.000
Ondansetron (N=285)	1 (0.4)			

† Aprepitant was compared with Ondansetron (Aprepitant - Ondansetron) using Fisher's exact test.
‡ Difference (%) = Percentage Point Difference.
§ 95% CI computed using a method by Miettinen and Nurminen.
‖ Determined by the investigator to be possibly, probably, or definitely drug related.
Although a patient may have had 2 or more clinical adverse events, a patient is only counted once within a category. The same patient may appear in different categories.
N = number of patients who took at least one dose of study medication.
n = number of patients who took at least one dose of study medication and had at least one adverse event in a given category.
% = 100 (n/N).
CI = Confidence interval.

Based upon Table 3.2.2.1, the applicant indicated that clinical adverse events defined by the investigator as possibly, probably, or definitely drug related were also less common in the Aprepitant 40mg group compared with the Aprepitant 125mg group and the Ondansetron group. However, there was no statistically significant difference between the Aprepitant 40mg group and the Ondansetron group.

Serious clinical adverse events occurred with similar incidence in the Aprepitant 125mg group and the Ondansetron group, and with a lower incidence in the Aprepitant 40mg group. The difference between the Aprepitant 40mg group and Ondansetron group was not statistically significant. Two of the serious clinical adverse events were defined by the investigator to be related to study drug. One in the Aprepitant 125mg group was a subileus which prolonged the

hospitalization and was determined by the investigator to be another important medical event. One in the Ondansetron group was a case of constipation which prolonged the hospitalization.
Two patients died during the course of this study. One patient (in the Ondansetron group) experienced multi-organ failure and coagulopathy which resulted in death 11 days after surgery. One patient experienced an arrhythmia (in the Aprepitant 125mg group) which resulted in death 7 days after surgery. Neither death was considered drug-related by the investigator.

Four patients discontinued the study due to clinical adverse events. This includes the two patients who died during the course of the study. In addition, one patient in the Aprepitant 40mg group experienced gastroenteritis and fever which were determined by the investigator not to be related to study drug. One patient in the Aprepitant 125mg group experienced vomiting which the investigator determined to be possibly related to study drug.

4.0 SUBGROUP ANALYSIS

4.1 Gender, Race, and Age

In order to assess the consistency of the non-inferiority of the Aprepitant regimen to the Ondansetron therapy across subgroups, this reviewer performs subgroup analysis on the primary endpoint (complete response in 24 hours following end of surgery) using MITT patient population. Since the non-inferiority of Aprepitant versus Ondansetron for Study P090 is a post-hoc analysis and is not acceptable, the subgroup analysis is only for Study P091.

In addition, for Study P091, more than 90% of MITT patients were females and were with ages under 65. The subgroup analyzed is only for Race group (Caucasian vs. 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) Number of patients with complete response in the 24 hours following end of surgery by treatment group using MITT population

Caucasian

Treatment	With Complete Response		Aprepitant Versus Ondansetron	
	n/m	%	Odds Ratio †	1-sided 97.5% CI Lower Bound
Aprepitant 40 mg	85/141	60.0	1.50	0.92
Aprepitant 125 mg	84/140	60.0	1.50	0.92
Ondansetron	70/142	49.3		

N0n-Caucasian

Treatment	With Complete Response		Aprepitant Versus Ondansetron	
	n/m	%	Odds Ratio †	1-sided 97.5% CI Lower Bound
Aprepitant 40 mg	102/152	67.0	1.28	0.81
Aprepitant 125 mg	100/153	65.0	1.22	0.75
Ondansetron	84/138	60.9		

Complete Response = No vomiting and no use of rescue; †: Estimated odds ratio for Aprepitant versus Ondansetron A value of >1 favors Aprepitant over Ondansetron

The model included terms for treatment and investigative sites n/m= Number of patients with desired response/number of patients included in analysis

Non-inferiority margin: 0.77.

Table 4.1.1 shows that for Caucasian group, the lower bounds of one-sided 97.5% confidence interval for odds ratio of Aprepitant 40 mg versus Ondansetron (0.92) and Aprepitant 125 mg versus Ondansetron (0.92) are greater than the non-inferiority margin of 0.77. Thus, for Caucasian group, the non-inferioriority of Aprepitant 40 mg and apepitant 125 mg to Ondansetron are supported when assessed by the complete response in the 24 hours following end of surgery using MITT population.

However, for Non-Caucasian group, only the lower bound of one-sided 97.5% confidence interval for odds ratio of Aprepitant 40 mg versus Ondansetron (0.81) is greater than the non-inferiority margin of 0.77. Therefore, for Non-Caucasian group, the non-inferiority only for Aprepitant 40 mg versus Ondansetron assessed by the complete response in the 24 hours following end of surgery is supported using MITT population.

4.2 Other Special/Subgroup Populations- Not applicable

5.0 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Study P090

- Since the primary hypothesis of Aprepitant (125 mg, 40 mg) superior to Ondansetron (4 mg IV) assessed by the primary endpoint (complete response in 24 hours following end of surgery) was not met, according to the pre-specified multiplicity adjustment technique, the testing procedure was terminated and Aprepitant was judged not superior to Ondansetron for the secondary and exploratory endpoints. In addition, since Type I error

rate of 2.5% was totally spent for testing the primary hypothesis, no Type I error rate was left for the analyses of the secondary and exploratory endpoints. Consequently, based upon the results of the pre-specified superiority analysis for the primary, secondary, and exploratory endpoints and Type I error rate being totally spent for the primary endpoint analysis, Study P090 did not provide efficacy evidence to support the use of Aprepitant regimen in the prevention of postoperative nausea and vomiting.

- After superiority of Aprepitant to Ondansetron failed for the primary endpoint the proportion of patients with complete response during the first 24 hours after surgery, the non-inferiority margin was selected by the applicant for this study in a post-hoc manner and has the following statistical issues.

i) Loss of credibility on the selection of non-inferiority margin
ICH E10 states that 'prior to the trial, an equivalence or non-inferiority margin 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.

ii) Loss of position as confirmatory hypothesis
As indicated by the applicant's submission, Study P090 was a phase III study to support Aprepitant regimen in the prevention of postoperative nausea and vomiting. 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 postoperative nausea and vomiting. Therefore, if the applicant decided on applying non-inferiority analysis to confirm that Aprepitant regimen is effective for the proposed indication, the null hypothesis of inferiority 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 the null hypothesis of inferiority is not formulated before conducting the trial, but also the selected margin is data dependent and is biased. Accordingly, the null hypothesis of inferiority including a margin influenced by data of the current study (Study P090) is a post-hoc hypothesis and can not be regarded as a confirmatory hypothesis.

iii) Significance level of the non-inferiority analysis inflated
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 Ondansetron is inflated.

In conclusion, from 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.

5.1.2 Study P091

- As commented upon in the section of "Reviewer's Comments", treatment effectiveness assessed by no vomiting in 24 hours following end of surgery is confounded with that of the rescue therapy and the primary endpoint for the previous approved drugs for this application was also the complete response. Consequently, from statistical perspective and previous NDA experiences, it seems that complete response in 24 hours following end of surgery is more appropriate to be employed as the primary endpoint than no vomiting in the assessment for prevention of postoperative nausea and vomiting.
- The appropriateness for the four historical studies used by the applicant to identify the non-inferiority margin with respect to the complete response is questioned by the medical reviewer Dr Della'Zanna. The non-inferiority margin selected by the applicant using the four questionable historical studies may not accurately reflect the effective size of Ondansetron assessed by the primary endpoint (complete response in the 24 hours following end of surgery). However, the two lower bounds for the one-sided 97.5% confidence interval on odds ratios of Aprepitant 125 mg versus Ondansetron and Aprepitant 40 mg versus Ondansetron are high (respectively, 0.99 and 1.02). Consequently, both Aprepitant 125 mg and Aprepitant 40 mg are regarded to be non-inferior to Ondansetron assessed by complete response in the 24 hours following end of surgery. However, since less than 10% of patients enrolled in Study P091were males, the non-inferiority of Aprepitant to Ondansetron shown in Study P091 may not apply to male patients.
- As commented upon in the sub-section of "Non-inferiority analysis and comments", since higher dose 125 mg for Aprepitant failed to demonstrate superior to Ondansetron assessed by the complete response in the 24 hours following end of surgery, by the step-wise multiplicity adjustment method proposed by the applicant, the superior test based upon the complete response is ceased and Aprepitant 40 mg is judged not superior to Ondansetron. Therefore, the superiority of Aprepitant versus Ondansetron assessed by complete response in the 24 hours following end of surgery is not supported. However, since the primary hypothesis of Aprepitant non-inferior to Ondansetron was met, the secondary hypothesis regarding Aprepitant superior to Ondansetron assessed by no vomiting was pursued. Based upon the result of the applicant's superiority analysis with respect to no vomiting, both Aprepitant 125 mg and Aprepitant 40 mg are superior to Ondansetron ($p< 0.001$).

5.2 Conclusions and Recommendations

Following the efficacy assessments for the two Studies (P090 and P091), presented in sub-section 1.3, only Study P091 demonstrated that Aprepitant 125 mg and Aprepitant 40 mg were non-inferior to Ondansetron assessed by the primary endpoint (complete response in the 24 hours following end of surgery) and were also superior to Ondansetron assessed by no vomiting. However, since less than 10% of patients enrolled in Study P091 were males, the non-inferiority of Aprepitant to Ondansetron shown in Study P091 may not apply to male patients.

It is noted that the effectiveness of Aprepitant shown in Study P091 was not established by Study P090. Study P090 did not provide efficacy evidence to support the use of Aprepitant in the prevention of postoperative nausea and vomiting. Accordingly, from the statistical perspective, the two studies overall did not provide substantial evidence to support the use of Aprepitant in the prevention of postoperative nausea and vomiting.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21549Orig1s010

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-549/S-010	Submission Date(s): 8/29/05
Brand Name	Emend
Generic Name	Aprepitant
Reviewer	Sue-Chih Lee, Ph.D.
Team Leader	Dennis Bashaw, Pharm.D.
OCPB Division	Division of Clinical Pharmacology III
OND division	Division of Gastroenterology Products
Sponsor	Merck
Submission Type	Efficacy Supplement
Formulation; Strength(s)	Capsules, 40 mg
Dosing regimen	Single 40 mg administered within 3 hrs prior to induction of anesthesia.
Indication	Prevention of postoperative nausea and vomiting (PONV)

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1. EXECUTIVE SUMMARY

Emend® (aprepitant 80-mg and 125-mg capsules), in combination with other antiemetic agents, have been approved for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy (CINV). In this efficacy supplement, the sponsor is seeking approval of Emend® 40-mg capsules for the prevention of postoperative nausea and vomiting (PONV).

In support of this efficacy supplement, the sponsor submitted two clinical studies (Protocols 90 and 91) and two clinical pharmacology and biopharmaceutics studies (Protocols 107 and 108). In addition, the sponsor referenced two drug interaction studies, which were provided in the original NDA, in order to include the information related to the 40-mg dose in the package insert.

Protocols 90 and 91 are two pivotal clinical trials with the same study design but with different analysis plans on efficacy assessment. The aprepitant doses studied in these trials were 40 mg and 125 mg.

Clinical pharmacology and biopharmaceutics studies:

- Protocol 107 is a single-dose, 3-period crossover study to evaluate the food effect on the pharmacokinetics of aprepitant following oral administration of the 40-mg to-be-marketed capsule formulation. (This study also investigated under fasting conditions the bioavailability of the to-be-marketed formulation relative to a colloidal suspension formulation.)

- Protocol 108 is a single-dose, 2-period, crossover, drug interaction study to assess the effect of oral aprepitant 125 mg on the pharmacokinetics of intravenous midazolam 2 mg.

- Previous drug interaction studies referenced provide the following information:
  (1) The effect of oral aprepitant 40 mg on the pharmacokinetics of oral midazolam 2 mg (Protocol 041); and
  (2) The effect of oral aprepitant 40 mg on the pharmacokinstis of oral dexamethasone 20 mg.

The proposed Emend 40-mg capsule is an exact formulation weight multiple of the approved 80-mg and 125-mg capsules. This formulation was used in all the pivotal clinical trials and clinical pharmacology studies.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed this supplemental NDA and found that the overall Clinical Pharmacology Section is *acceptable* provided that a mutually satisfactory agreement can be reached between the sponsor and Agency regarding the labeling language.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Dose Selection

Only two aprepitant doses (40 mg and 125 mg) were studied in the clinical trials for PONV. These doses were modeled from previous CINV trials. The efficacy assessment for PONV indicated that any differentiation between these two doses was not clinically meaningful. Therefore, no dose-response relationship can be established for efficacy. Although the adverse event profiles for the two doses appeared similar, the selection of the 40 mg dose over the 125 mg is important at least from the drug-drug interaction view point.

Single-dose PK of Emend 40-mg capsules

Following single oral administration of Emend 40 mg under fasting conditions, (arithmetic) mean AUC was 7997 ng.hr/mL and mean Cmax was 712.8 ng/mL occurring at approximately 3 hours postdose (Table 1). A second, lower peak appeared at approximately 11 hours postdose, likely to be due to enterohepatic recycling. The bioavailability of the 40-mg capsules was close to that of a colloidal suspension (96%; see results of A/C in Table 2), but the absolute bioavailability was not determined.

Table 1: Aprepitant PK Parameters Following Single Oral Dose of Emend 40 mg (Study 107)

Statistics	$AUC_{0-\infty}$ (ng hr/mL)	Cmax (ng/mL)	Tmax (hr)
Arithmetic Mean	7997.2	712.8	3.1
SD	2081	235.9	2-4 (range)
%CV	26.0	33.1	-

Food Effect

Previous studies showed that the food effect is dose-dependent with greater effects at higher doses. For the 40-mg dose, high-fat breakfast delayed Tmax for 2 hours and decreased Cmax by 18% but did not alter the extent of absorption (See results of B/A in Table 2). Note: Food effect is not critical for the proposed PONV indication since patients are supposed to be fasted before surgery.

Table 2: Summary of Aprepitant PK Parameters for Three Treatments (Study 107)
(A: 40-mg capsule/fasted; B: 40-mg capsule/fed: C: colloidal suspension/fasted)

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	B/A	A/C	B/A	A/C	B/A	A/C
$AUC_{0-\infty}$ (ng•hr/mL)	7751	7999	8092	1.03	0.96	(0.94, 1.13)	(0.88, 1.05)	> 0.250	> 0.250
C_{max} (ng/mL)	675	552	684	0.82	0.99	(0.69, 0.97)	(0.84, 1.16)	0.049	> 0.250
Tmax (hr)	3.0	5.0	4.0	-	-	-	-	-	-
Half-life (hr)	9.0	10.0	9.7	-	-	-	-	-	-

† 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 Tmax 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.

Treatment A: A single, oral dose of a 40 mg aprepitant FMC capsule administered in a fasted state.
Treatment B: A single, oral dose of a 40 mg aprepitant FMC capsule administered following a standard breakfast.
Treatment C: A single, 40 mg oral dose of the aprepitant colloidal dispersion 25 mg/mL administered in a fasted state.

Multiple-dose PK

The multiple dose PK was not conducted as the 40-mg capsules will be administered for PONV as a single dose only.

Drug Interactions

Several drug interaction studies were submitted in the original NDA and the information is included in the current Emend® label. The sponsor conducted one new drug interaction study with IV midazolam and referenced two previous studies as the information from these studies is currently not included in the approved label.

Midazolam

Study 108:

Aprepitant is a CYP3A4 inhibitor. Concomitant administration of Emend® 125 mg increased the bioavailability of midazolam IV 2.0 mg (Cmax: ↑20.3%; AUC: ↑47.1%).

Study 041:

Oral aprepitant 125 mg (on Day 1 of a 5 day regimen) produced a 2.27-fold increase in the midazolam AUC following a 2- mg oral dose. Therefore, at a dose of 125 mg, aprepitant is considered a moderate inhibitor.

Aprepitant given at a 40-mg dose (on Day 1 of a 5 day regimen), produced a 1.22-fold increase in the AUC of midazolam 2 mg PO (Table 3). Therefore, aprepitant at a 40 mg dose level is considered a weak inhibitor and is not expected to have a clinically important effect on IV midazolam.

As the differences in midazolam pharmacokinetics is more prominent following concomitant oral administration, the interaction is considered to be due to effects on first pass metabolism. With IV dosing of midazolam, no dosage adjustment is necessary when it is coadministered with Emend 40 mg. Dosage adjustment may be needed when midazolam IV is coadministered with Emend 125 mg, depending on the clinical situation and degree of monitoring available.

Table 3: Effect of Oral Aprepitant (125 mg and 40 mg) on the AUC of Midazolam 2 mg (PO and IV)

		Geometric Mean Ratio†			Geometric Mean Ratio†	
Aprepitant Dose	N	AUC Oral Midazolam With Oral Aprepitant/ Oral Midazolam Alone and 95%CI	Inhibitor Category	N	AUC IV Midazolam With Oral Aprepitant/ IV Midazolam Alone and 90%CI	Inhibitor Category
125 mg oral	16	2.27 (1.64, 3.14)‡	moderate	12	1.47 (1.36, 1.59) §	weak
40 mg oral	12	1.22 (0.93, 1.61)‡	weak	--	Not studied	--

† Geometric means, geometric mean ratios, and CIs back-transformed from least-squares means from ANOVA. The CI for P041 are 95% CI and for P108 are 90% CI.
‡ P041 (from the original EMEND filing)
§ P108 (refer to section 2.7.2.3)

Dexamethasone

The effect of oral aprepitant 40 mg on oral dexamethasone 20 mg (on Day 1 of a 5 day regimen) was evaluated in a study submitted to the original NDA. The relevant data relate to two treatments: the aprepitant 40-mg oral treatment with dexamethasone 20 mg oral and ondansetron 32 mg IV on Day 1, and the reference treatment which included dexamethasone 20 mg oral and ondansetron 32 mg IV on Day 1. Aprepitant 40 mg orally increased the dexamethasone AUC to 1.45-fold (90% CI of 1.31, 1.61) and Cmax to 1.20-fold. No dosage adjustment for dexamethasone is recommended in view of the single dose use of Emend 40 mg for PONV.

2. QUESTION-BASED REVIEW

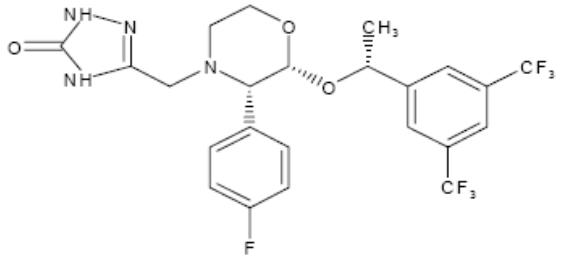
2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physicochemical properties of the drug substance and drug product?

Drug Substance:

Chemical name:

5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one



Aprepitant

Empirical formula:	$C_{23}H_{21}F_7N_4O_3$
Molecular weight:	534.43
Solubility:	Practically insoluble in water

Formulation:
The proposed 40 mg capsule (Table 4) is an exact formulation weight multiple of the approved 80-mg and 125-mg capsule formulations.

Table 4: Components and Composition of Emend® 40-mg, 80-mg and 125-mg capsules

(b) (4)

[redacted]

2.1.2 What are the proposed mechanism of action, therapeutic indication and dosage recommendations?

Aprepitant is a brain-penetrant nonpeptide NK1-receptor antagonist that blocks the emetic reflex induced by substance P. It has been approved, in combination with other

antiemetics, for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy. The sponsor is pursuing the use of single 40-mg dose for the prevention of post-operative nausea and vomiting (PONV).

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical trials?

The two pivotal clinical trials (Protocol 091 and Protocol 090) had an identical study design. Both trials were multicenter, double-blind, randomized, active comparator-controlled, parallel-group studies. Both trials included 3 arms: aprepitant 125 mg PO, aprepitant 40 mg PO, and ondansetron 4 mg IV. Patients requiring open abdominal surgery which required overnight, postsurgery hospital stay were enrolled (N=922 for Protocol 91 and 805 for Protocol 090). In these trials, aprepitant was administered as single dose to patients 1 to 3 hours before the expected induction of anesthesia.

2.2.2 What are the response endpoints and how are they measured in clinical studies?

The original primary efficacy hypothesis was identical for both Protocol 091 and Protocol 090. The hypothesis was that aprepitant is superior to ondansetron with respect to Complete Response during the first 24 hours after surgery. Protocol 90 completed enrollment first, and did not meet the primary efficacy hypothesis. In Protocol 090, the use of rescue medications for established nausea and/or vomiting was higher than expected, and the nausea severity prior to rescue administration was highly variable, hence limiting the sensitivity of the Complete Response endpoint. Subsequently, the primary efficacy end point for Protocol 091 was revised.

Protocol 091 had two primary efficacy hypotheses:
(1) Aprepitant is superior to ondansetron as measured by the proportion of patients with No Vomiting in the 24 hours following end of surgery; and
(2) Aprepitant is non-inferior to ondansetron as measured by the proportion of patients with Complete Response in the 24 hours following end of surgery.
If this hypothesis is met, the following hypothesis would be evaluated:
Aprepitant, compared to ondansetron, is superior as measured by the proportion of patients with Complete Response in the 24 hours following end of surgery.

In both Protocol 091 and Protocol 090, efficacy assessment consisted of episodes of vomiting, use of rescue therapy, and severity of nausea. The definitions for these terms are given below:

- No Vomiting was defined as the absence of vomiting episodes, retching, or dry heaves, regardless of whether or not the patient took rescue medication to treat established nausea or vomiting.

- Rescue therapy was offered to: (i) patients who requested it; (ii) patients who experienced more than 1 emetic episode; or (iii) patients who had nausea lasting for more than 15 minutes. No Rescue was defined as no use of rescue medications for established nausea or vomiting.

- Patients who did not vomit and did not take rescue medications were defined as patients with Complete Response.

2.2.3 How are the dose and dosing regimen determined?

Only two doses were studied in the two pivotal trials for PONV. These doses were modeled from the CINV trials. The efficacy assessment indicated that any differentiation between the aprepitant 40 mg and 125 mg was not clinically meaningful (Figures 1 and 2). Although the adverse event profiles for the two doses were similar (Table 5), from the drug-drug interaction view point, the 40 mg dose is more favorable as aprepitant at the 125-mg dose level is a moderate CYP3A4 inhibitor while 40 mg of aprepitant is considered only a weak CYP3A4 inhibitor. Therefore, the selection of the 40 mg dose over the 125 mg is favored from a drug interaction standpoint. It should be pointed out, however, that doses lower than 40 mg were not studied.

(Note: Although Protocols 090 and 091 had different primary efficacy end points, the same type of analyses were performed for Protocol 090 post hoc. The pattern of complete response across treatment groups was similar in the 2 studies (Figure 2). However, the complete response rates among all treatment groups were ~20% higher in Protocol 091 compared to Protocol 090.**)**

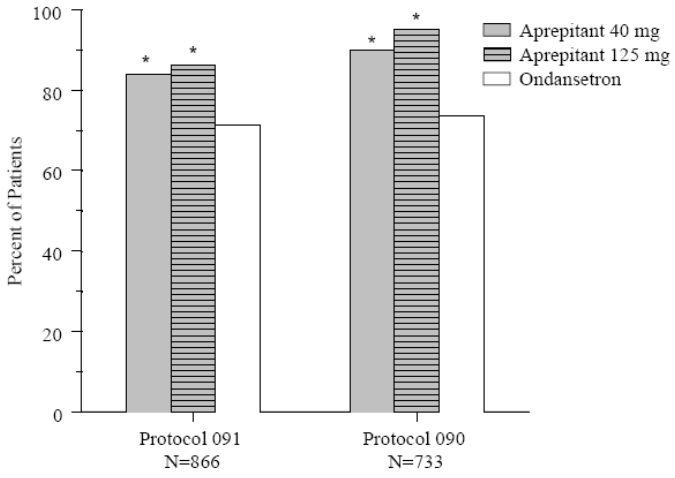


Figure 1 : Proportion of Patients With No Vomiting 0 to 24 Hours Following End of Surgery (Modified-Intention-to-Treat Analysis)

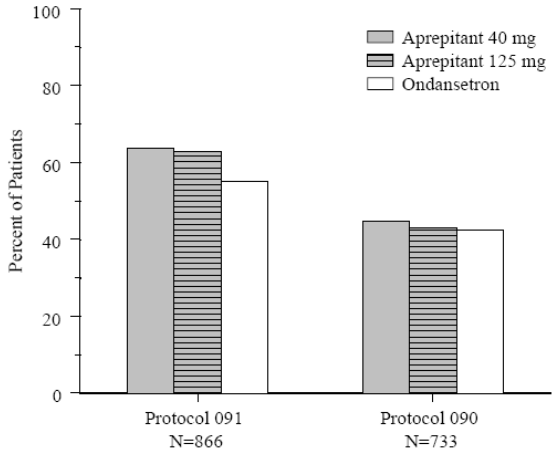


Figure 2: Proportion of Patients With Complete Response 0 to 24 Hours Following End of Surgery (Modified-Intention-to-Treat Analysis)

Table 5: Clinical Adverse Experience Summary for Pooled PONV Studies - Protocols 090 & 091

	Aprepitant 40 mg (N = 564)		Aprepitant 125 mg (N = 556)		Ondansetron (N = 538)	
	n	(%)	n	(%)	n	(%)
Number (%) of patients:						
With one or more adverse experiences	336	(59.6)	354	(63.7)	344	(63.9)
With no adverse experience	228	(40.4)	202	(36.3)	194	(36.1)
With drug-related adverse experiences†	24	(4.3)	30	(5.4)	33	(6.1)
With serious adverse experiences	49	(8.7)	43	(7.7)	50	(9.3)
With serious drug-related adverse experiences	0	(0.0)	2	(0.4)	1	(0.2)
Who died	1	(0.2)	1	(0.2)	1	(0.2)
Discontinued due to adverse experiences	1	(0.2)	2	(0.4)	1	(0.2)
Discontinued due to drug-related adverse experiences	0	(0.0)	1	(0.2)	0	(0.0)
Discontinued due to serious adverse experiences	0	(0.0)	1	(0.2)	1	(0.2)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably or definitely drug related.

2.2.4 What are the pharmacokinetic parameters of aprepitant 40 mg in healthy young subjects?

Single-Dose PK

Following single oral administration of Emend 40 mg under fasting conditions, (arithmetic) mean AUC was 7997 ng.hr/mL and mean Cmax was 712.8 ng/mL occurring at approximately 3 hours postdose. A second, lower peak appeared at approximately 11 hours postdose (Figure 3). The sponsor did not explain why but it was likely to be due to enterohepatic recycling as there was evidence of this phenomenon in animal studies*. The absolute bioavailability of the 40-mg capsules was not determined because previous

experiences indicated that the injection formulation containing polysorbate 80 was not well tolerated due to hypersensitivity reactions. Instead, the sponsor conducted a relative bioavailability study comparing the 40-mg capsules to a suspension. It would have been helpful to have a relative bioavailability study comparing the 40-mg capsule/dose to the 80-mg or 125-mg capsule/dose.

*Reference:
Huskey SE, Dean BJ, Doss GA, Wang Z, Hop CE, Anari R, Finke PE, Robichaud AJ, Zhang M, Wang B, Strauss JR, Cunningham PK, Feeney WP, Franklin RB, Baillie TA, Chiu SH., "The metabolic disposition of aprepitant, a substance P receptor antagonist, in rats and dogs" Drug Metab Dispos. 2004 Feb;32(2):246-58.

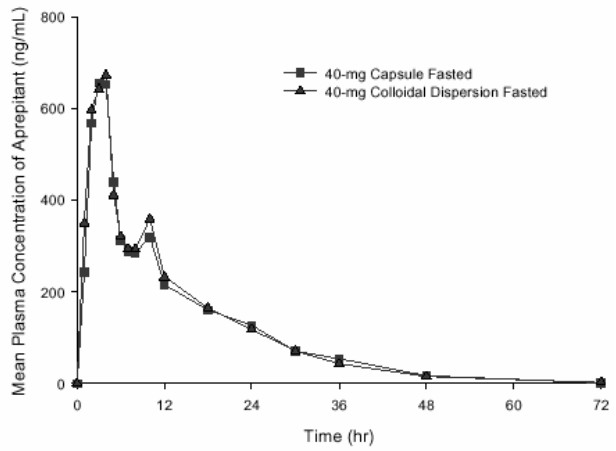


Figure 3. Mean Plasma Concentration versus Time Profiles of Aprepitant Following 40 mg Single Capsule Dose Given Fasted and 40 mg Single Colloidal Dispersion Dose Given Fasted

Table 6: PK Parameters Following Single Oral Dose of Emend 40 mg (Study 107)

Statistics	$AUC_{0-\infty}$ (ng hr/mL)	Cmax (ng/mL)	Tmax (hr)
Arithmetic Mean	7997.2	712.8	3.1
SD	2081	235.9	2-4 (range)
%CV	26.0	33.1	-

Multiple-Dose PK

The sponsor did not provide multiple dose PK data for the 40-mg dose. Since the 40-mg capsules will be administered for PONV as a single dose only, the multiple dose data are not required.

2.2.5 How do the pharmacokinetics of aprepitant in healthy volunteers compare to that in the target patient population?

The pharmacokinetics in the target patient population was not studied in this supplement.

2.3 Intrinsic Factors

The sponsor has evaluated intrinsic factors in the original NDA and the information is reflected in the current Emend® label.

2.4 Extrinsic Factors

Drug-Drug Interaction

2.4.1 What is the new drug-drug interaction information to be added to the package insert?

The new drug-drug interaction information to be added to the package insert is related to interaction with midazolam and dexamethasone. Aprepitant is a CYP3A4 inhibitor and both midazolam and dexamethasone are CYP3A4 substrates. With respect to midazolam, the sponsor conducted a new interaction study with midazolam IV and referenced an earlier interaction study with oral midazolam. For dexamethasone, the sponsor referenced a study submitted in the original NDA. Coadministration of aprepitant increased midazolam and dexamethasone plasma concentrations.

Midazolam

New study (Protocol 108): This was a randomized, open-label, 2-period, crossover study to evaluate the effect of single 125-mg dose of aprepitant on the pharmacokinetics of midazolam IV 2 mg. Thirteen healthy subjects (10 females & 3 males; age: 27.6 yrs (20-36 yrs); wt: 69.5 kg (54-87.4 kg)) participated and 12 completed the study. Midazolam was administered over 2 minutes either alone or 1 hour after the aprepitant dose. There was at least 14 days between the two treatment periods and each treatment was administered after an overnight fast.

Mean plasma midazolam concentration-time profiles with and without coadministrastion of oral aprepitant are presented in Figure 4 and the midazolam PK parameters are listed in Table 6. Administration of oral aprepitant 125 mg increased the bioavailability of midazolam IV 2.0 mg (Cmax: ↑20.3%; AUC: ↑47.1%). Dosage adjustment for intravenous midazolam may be needed when it is coadministered with Emend 125 mg, depending on the clinical situation (e.g., elderly patients) and degree of monitoring available.

Figure 4: Mean Midazolam Plasma Profiles following IV Administration of Midazolam 2.0 mg With and Without 125 mg Oral Aprepitant

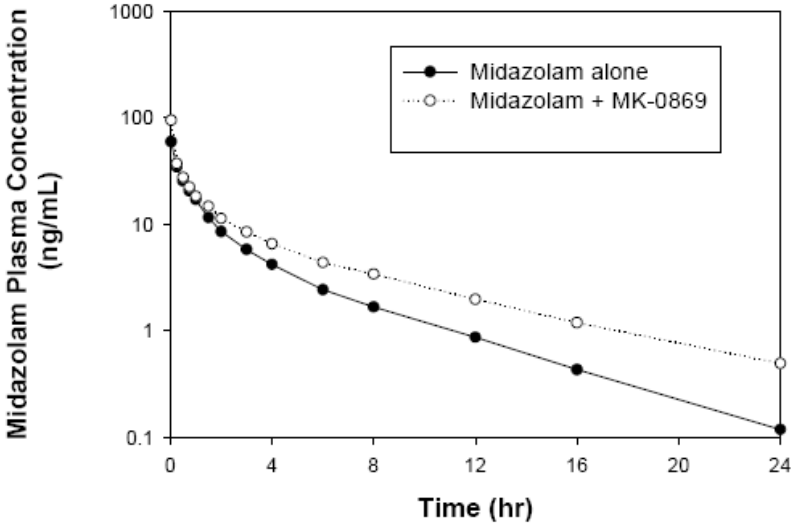


Table 6: Midazolam PK parameters With and Without Coadministration of Oral Aprepitant

Variable (units)	Geometric Means[†‡] Midazolam With Aprepitant	Geometric Means[†‡] Midazolam Alone	Geometric Mean Ratio[†] (Midazolam With Aprepitant/ Midazolam Alone) and 90% CI	p-Value[§]	MSE[‖]
$AUC_{0-\infty}$ (ng•hr/mL)	110.3	75.0	1.47 (1.36, 1.59)	< 0.001	0.0103
Cl_p (mL/min)	302.1	444.5	0.68 (0.63, 0.73)	< 0.001	0.0103
C_{max} (ng/mL)	71.8	59.7			
T_{max} (hr)	0.14	0.15			
$t_{½}$ (hr)	5.2	3.7			

† Geometric means, geometric mean ratios, and CIs back-transformed from least-squares means from ANOVA.
‡ Median for T_{max}, harmonic mean for $t_{½}$.
§ Tests null hypothesis of no between-treatment difference versus two-sided alternative.
‖ Mean square error on natural log scale.

Referenced study (Protocol 041): This study was submitted to the original NDA which was reviewed at that time by Drs. Venkat Jarugula and Myong-Jin Kim of OCP. The study investigated the effect of aprepitant (both 125-mg and 40-mg doses) on oral midazolam 2 mg. Oral aprepitant 125 mg (on Day 1 of a 5 day regimen) produced a 2.27-fold increase in the midazolam AUC. As such, aprepitant 125 mg is considered a moderate inhibitor. The observed effect is greater on oral midazolam 2 mg (2.27-fold in Study 041) compared to IV midazolam 2 mg (1.47-fold in Study 108) most likely due to inhibition of gut metabolism and first-pass effect for oral midazolam.

Aprepitant given at the 40-mg dose (on Day 1 of a 5 day regimen), produced a 1.22-fold increase in the AUC of midazolam 2 mg PO. Therefore, aprepitant 40 mg is considered a weak inhibitor and is not expected to have a clinically important effect on IV midazolam.

Table 7: Summary of the Effects of 125-mg and 40-mg Oral Aprepitant on the AUC of Midazolam given as a 2 mg oral or a 2 mg IV dose in Healthy Young Subjects

Aprepitant Dose	N	Geometric Mean Ratio† AUC Oral Midazolam With Oral Aprepitant/ Oral Midazolam Alone and 95%CI	Inhibitor Category	N	Geometric Mean Ratio† AUC IV Midazolam With Oral Aprepitant/ IV Midazolam Alone and 90%CI	Inhibitor Category
125 mg oral	16	2.27 (1.64, 3.14)‡	moderate	12	1.47 (1.36, 1.59)§	weak
40 mg oral	12	1.22 (0.93, 1.61)‡	weak	--	Not studied	--

† Geometric means, geometric mean ratios, and CIs back-transformed from least-squares means from ANOVA. The CI for P041 are 95% CI and for P108 are 90% CI.
‡ P041 (from the original EMEND filing)
§ P108 (refer to section 2.7.2.3)

Dexamethasone

The effect of oral aprepitant 40 mg on the pharmacokinetics of oral dexamethasone 20 mg was evaluated in a study submitted to the original NDA, which was reviewed at that time by Drs. Venkat Jarugula and Myong-Jin Kim of OCP. The treatment of aprepitant 40 mg PO with dexamethasone 20 mg PO and ondansetron 32 mg IV on Day 1 was compared to the treatment of dexamethasone 20 mg oral and ondansetron 32 mg IV on Day 1. Aprepitant 40 mg orally increased the dexamethasone AUC to 1.45-fold (90% CI of 1.31, 1.61) and Cmax to 1.25-fold (90% CI: 1.03-1.52). Dosage adjustment for dexamethasone is not considered necessary when coadministered with aprepitant 40 mg.

2.5 General Biopharmaceutics

2.5.1 What dosing recommendations should be made regarding administration in relation to meals?

For the proposed indication, patients are supposed to be fasted before surgery. Therefore, food effect is not critical for the indication. Nevertheless, the sponsor conducted a food effect study and the information is presented below.

Protocol 107 was an open-label, single-dose, 3-period crossover study in 12 healthy volunteers. One of the objectives was to evaluate the effect of food on the pharmacokinetics of aprepitant following single oral doses of the 40-mg final market composition capsule formulation. For fed conditions, subjects were given a high-fat breakfast (2 scrambled eggs, 2 slices of toast with 2 pats of butter, 2 strips of bacon, 113 gm of hash brown potatoes, 236 mL of whole milk).

Mean plasma aprepitant concentrations under fasted (Treatment A) and fed (Treatment B) conditions are presented in Figure 5. The high fat breakfast delayed Tmax for 2 hours and decreased Cmax by 18% but had little effect on the AUC (Table 7).

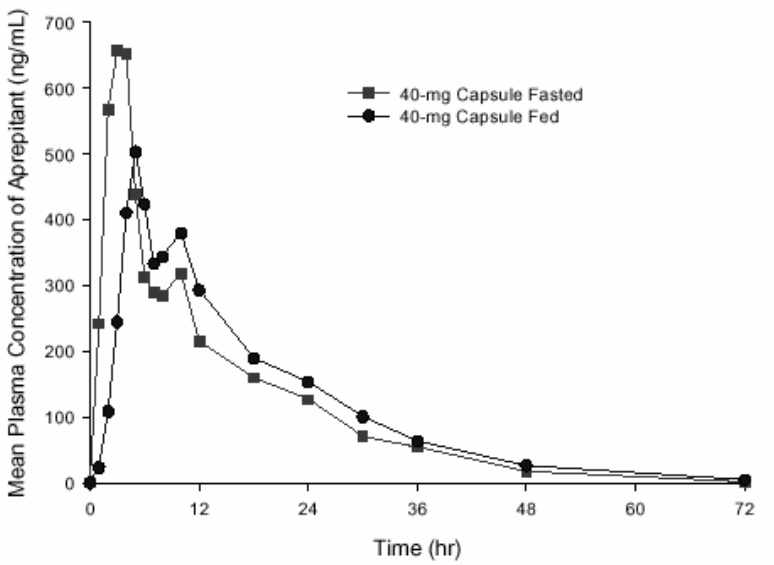


Figure 5. Mean Plasma Concentration versus Time Profiles of Aprepitant Following 40 mg Single Oral Capsule Dose Given Fasted and Fed

Table 7: Summary of Plasma Aprepitant PK Parameters Under Fasted and Fed Conditions

Parameter	Geometric Mean		Mean Ratio	90% CI for Mean Ratio
	Fasted	Fed	Fasted/Fed	Fasted/Fed
AUC (ng hr/mL)	7751	7999	1.03	(0.94, 1.13)
Cmax (ng/mL)	675	552	0.82	(0.69, 0.97)
Tmax (hr)	3.0	5.0	-	-
T ½ (hr)	9.0	10.0	-	-

2.5.2 Has the Applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

The sponsor's proposed dissolution method and specification are described below, which are the same as those for the 80-mg and 125-mg capsules.

Apparatus: Apparatus II (Paddle), 100 rpm
Medium: 2.2% sodium dodecyl sulfate; 37°C
Specification: Q = (b)(4)% at 20 minutes

Figure 6 shows the comparative dissolution profiles for the 40-mg, 80-mg and 125-mg capsules at product release. Figure 7 shows the comparative dissolution profiles for 3 lots of Emend 40-mg capsules at product release (0 week) and at 225 weeks after release.

Reviewer's Comment: Dissolution is faster for the lower strengths. Based on Figure 7, it appears that the specification for the 40-mg capsules should be tightened possibly to Q = (b)(4)% at 15 minutes if the above dissolution method is used. This comment has been communicated to Drs. Raymond Frankewich and David Lewis of ONDQA.

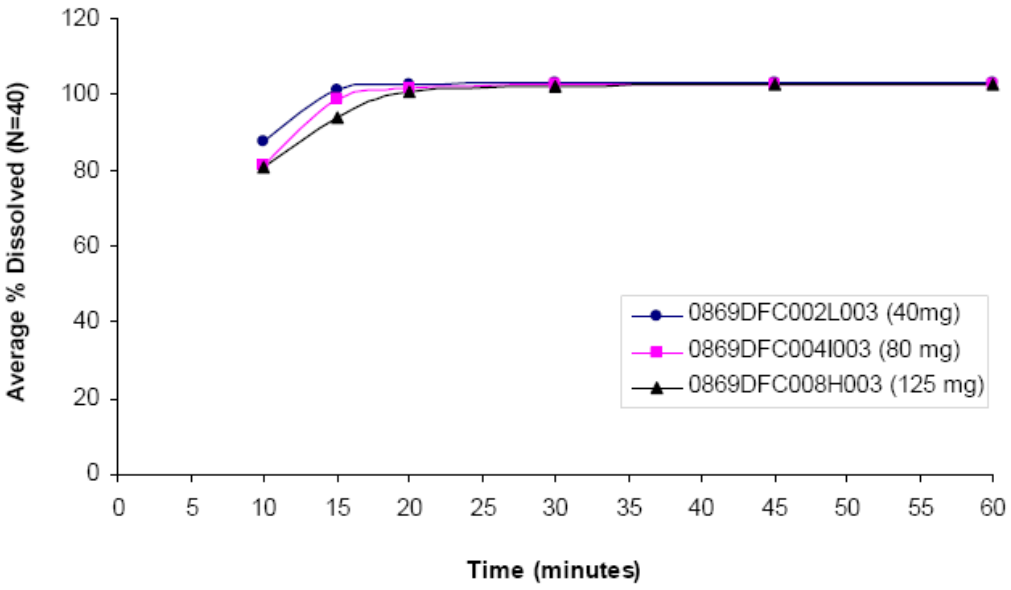


Figure 6: Comparative dissolution profiles for the 40 mg, 80 mg and 125 mg capsules at product release

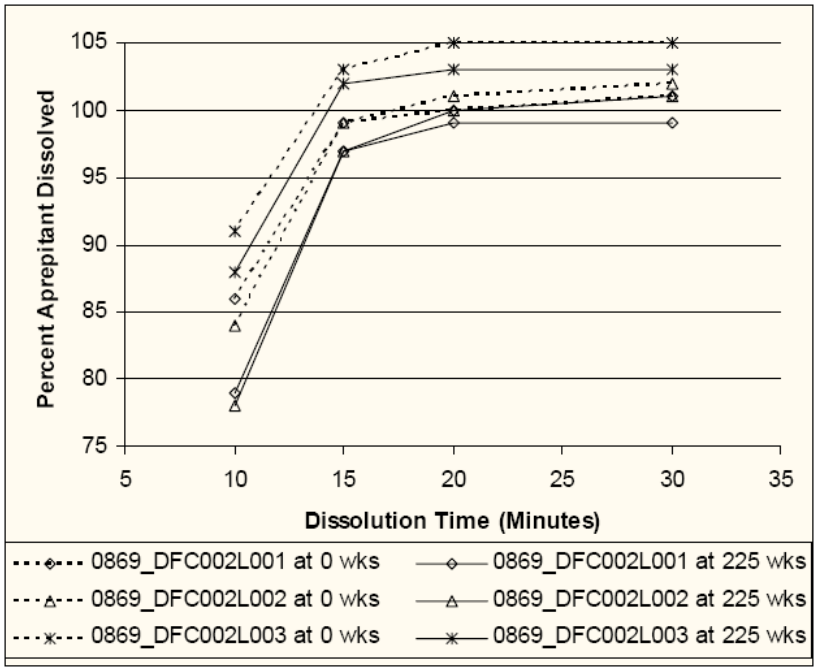


Figure 7: Comparative dissolution profiles for 3 lots of Emend 40 mg capsules at release (0 week) and at 225 weeks after release.

2.5.3 Is the proposed to-be-marketed formulation same as the formulation used in the PK studies?

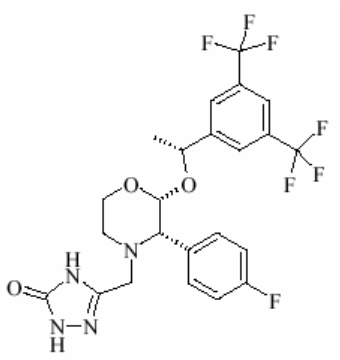
Yes.

2.6 Analytical Method -

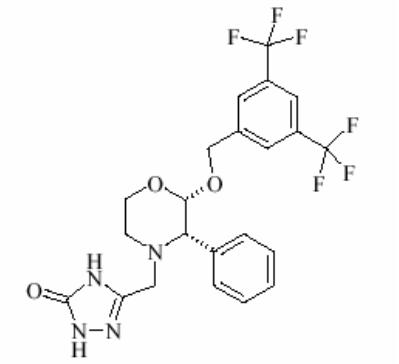
2.6.1 Was the assay method appropriately validated?

Yes. The analytical method uses liquid-liquid extraction for analyte isolation and LC-MS/MS detection. The internal standard used was L-742694. The precursor→product ion combinations of m/z 535→277 and 503→259 were used to quantify aprepitant (L-754030) and L-742694, respectively, in multiple reaction monitoring mode.

(Aprepitant)



(L-742694)



The validation results are as follows:

LOQ:	10 ng/mL
Intra-day (Table 8):	Precision (%CV): 1.6-6.8%; Accuracy: 92-104%
Inter-day:	Precision (%CV): <5%; Accuracy: ±5% (difference)
Linearity:	R^2 ≥0.9985 (10-5000 ng/mL)
Selectivity:	Aprepitant and the internal standard were chromatographically separated from each other and endogenous interferences.

Table 8: Intra-day Precision and Accuracy of Replicate Analysis (n=5) of MK-0869 in Five Different Lots of Human Control Plasma

Nominal Concentration (ng/mL)	Mean[a] Concentration (ng/mL)	Precision[b] C.V.%	Accuracy[c] (%)
10	10.2	5.3	102
25	22.9	5.0	92
50	51.1	5.9	102
100	101.4	3.7	101
500	502.4	1.6	100
1000	1004.4	2.7	100
2500	2432.0	6.8	97
5000	5176.0	1.9	104

Protocol 107:
An Open-Label, Single-Dose, 3-Period Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics of Aprepitant Following Single Oral Doses of the 40 mg Final Market Composition (FMC) Capsule Formulation

Objectives:
(1) To investigate the effect of food on the pharmacokinetics of the 40 mg aprepitant final market composition (FMC) capsule in healthy, young male and female subjects, and
(2) To compare the pharmacokinetics of aprepitant, when administered to healthy, young male and female subjects in the fasting state, as a single oral 40 mg FMC capsule dose and as a single 40 mg oral dose of nanoparticle colloidal dispersion.

Study design:
This was an open-label, single-dose, 3-period crossover study. Subjects were randomized to receive 1 of 3 different treatments (A, B, and C) in each study period. There was a minimum 7-day washout interval between each treatment period. A total of 13 subjects (5 males & 8 females) participated and 12 completed the study.
Note: The sponsor indicated that the aprepitant IV formulation was not used to assess the absolute bioavailability of the 40-mg capsules formulation because the IV formulation (containing polysorbate 80 at (b) (4) *was not well tolerated in a previous study due to symptoms consistent with known polysorbate hypersensitivity reactions*.

The 3 treatments were:
Treatment A: A single, oral, 40 mg aprepitant FMC capsule administered in a fasted state
Treatment B: A single, oral, 40 mg aprepitant FMC capsule administered following a standard breakfast.
Treatment C: A single, oral, 40 mg dose of aprepitant colloidal dispersion (25 mg/mL) administered in a fasted state.

The composition of the breakfast is:

- 2 scrambled eggs
- 2 slices of toast with 2 pats of butter
- 2 strips of bacon
- 113 gm hash brown potatoes
- 236 mL of whole milk

Pharmacokinetic blood samples were collected over 72 hours following dosing (pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 30, 36, 48, and 72 hours postdose) in each of the 3 treatment periods, and safety was monitored by clinical and laboratory evaluations throughout the study.

Results

To-be-marketed (FMC) capsule formulation: fed vs. fasted

Mean plasma aprepitant concentration-time profiles under fasted and fed conditions are presented in Figure 1. Mean pharmacokinetic parameters for aprepitant are summarized in Table 1. Individual AUC ratios, GMR, and its confidence interval are displayed graphically in Figure 2. The geometric mean ratio of AUC0-inf (40 mg FMC capsule fed/ 40 mg FMC capsule fasted) was 1.03, with a 90% confidence interval of (0.94, 1.13). The geometric mean ratio of Cmax (40 mg FMC capsule fed/ 40 mg FMC capsule fasted) was 0.82, with a 90% confidence interval of (0.69, 0.97).

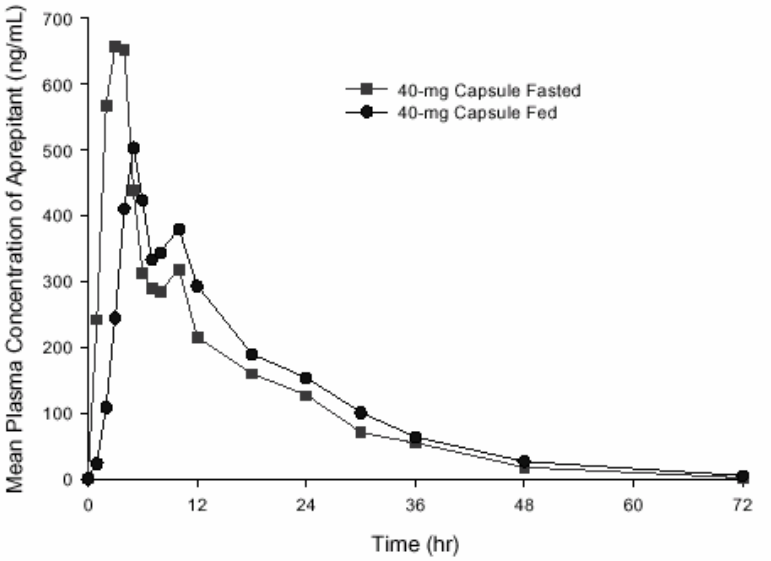


Figure 1. Mean Plasma Concentration versus Time Profiles of Aprepitant Following 40 mg Single Oral Capsule Dose Given Fasted (Treatment A) and Fed (Treatment B)

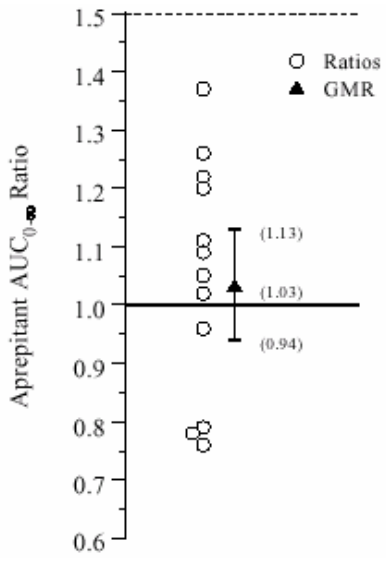


Figure 2. Individual Ratios (Treatment B/ Treatment A), Geometric Mean Ratio (GMR), and 90% CI for GMR of AUC0-inf

<u>To-be-marketed formulation (Treatment A) vs. colloidal suspension (Treatment C): fasted conditions</u>

Arithmetic mean plasma concentration profiles in healthy young subjects receiving a single, oral dose of a 40 mg aprepitant FMC capsule administered in a fasted state and the same subjects receiving a single, 40 mg oral dose of the aprepitant colloidal dispersion (25 mg/mL) administered in a fasted state are shown in Figure 3. Mean PK parameters for these two treatments are listed in Table 1. Individual AUC ratios, GMR, and its confidence interval are displayed graphically in Figure 4. The geometric mean ratio of AUC0-inf (40 mg FMC capsule fasted/ 40 mg colloidal dispersion fasted) was 0.96, with a 90% confidence interval of (0.88, 1.05). The geometric mean ratio of Cmax (40 mg FMC capsule fasted/ 40 mg colloidal dispersion fasted) was 0.99, with a 90% confidence interval of (0.84, 1.16).

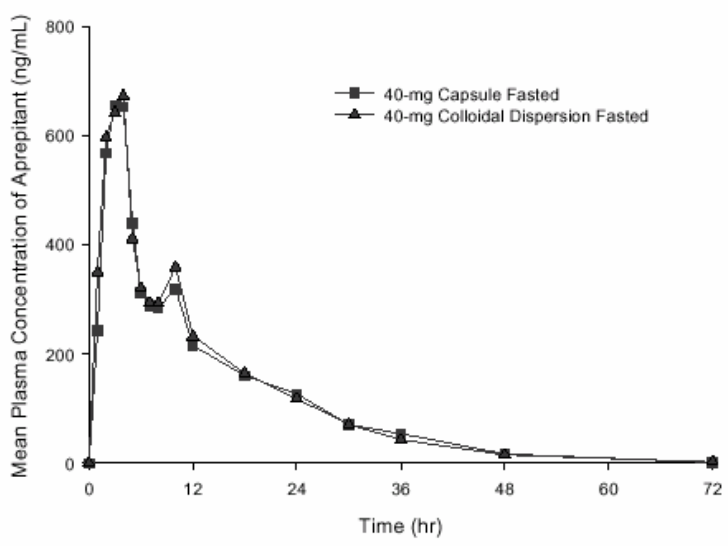


Figure 3. Mean Plasma Concentration versus Time Profiles of Aprepitant Following 40 mg Single Capsule Dose Given Fasted and 40 mg Single Colloidal Dispersion Dose Given Fasted

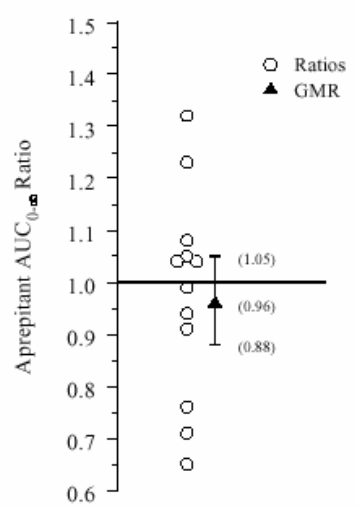


Figure 4. Individual Ratios (Treatment A/ Treatment C), Geometric Mean Ratio (GMR), and 90% CI for GMR of AUC0-inf

Table 1: Summary of Plasma PK Parameters of Aprepitant for the Three Treatments

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	B/A	A/C	B/A	A/C	B/A	A/C
$AUC_{0-\infty}$ (ng•hr/mL)	7751	7999	8092	1.03	0.96	(0.94, 1.13)	(0.88, 1.05)	> 0.250	> 0.250
C_{max} (ng/mL)	675	552	684	0.82	0.99	(0.69, 0.97)	(0.84, 1.16)	0.049	> 0.250
Tmax (hr)	3.0	5.0	4.0	-	-	-	-	-	-
Half-life (hr)	9.0	10.0	9.7	-	-	-	-	-	-

† 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 Tmax 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.

Treatment A: A single, oral dose of a 40 mg aprepitant FMC capsule administered in a fasted state.
Treatment B: A single, oral dose of a 40 mg aprepitant FMC capsule administered following a standard breakfast.
Treatment C: A single, 40 mg oral dose of the aprepitant colloidal dispersion 25 mg/mL administered in a fasted state.

Safety:

Thirteen (13) subjects were included in the assessment of safety and tolerability. Six (6) of the 13 subjects reported at least 1 nonserious clinical adverse experience. A total of 15 nonserious clinical adverse experiences were reported among the 6 subjects. There was 1 serious clinical adverse experience. The investigator determined that the serious adverse experience was definitely not related to aprepitant. The subject was followed until resolution, and she was not discontinued from the study.

Conclusions:

1. Following oral administration of aprepitant 40 mg Final Market Composition (FMC) capsule in the fasted state, the geometric mean AUC0-inf is 7751 ng•hr/mL, the Cmax is 675 ng/mL, the Tmax is 3.0 hours, and the half-life is 9.0 hours. Food (a high fat breakfast) decreased the rate of absorption of aprepitant (Cmax: ↓18%; Tmax: ↑2 hrs) but did not affect the extent of absorption.

2. The aprepitant 40 mg FMC capsule was bioequivalent to the aprepitant colloidal dispersion formulation tested.

Comment:
The plasma aprepitant concentration-time profiles showed a second, lower peak at approximately 10 hrs postdose. The sponsor did not explain why. It could be due to enterohepatic recycling as there was evidence of it in animal studies.

Protocol 108:
An Open-Label, Randomized, 2-Period, Crossover, Single-Center Study to Evaluate the Effect of a Single 125-mg Oral Dose of Aprepitant (MK-0869) on the Pharmacokinetics of Intravenous Midazolam in Healthy Adult Subjects

Objective: To evaluate the effect of a single 125-mg oral dose of aprepitant on CYP3A4 activity in healthy young adult subjects as measured by the pharmacokinetics of midazolam following IV administration.

Study Design:
This was a randomized, open-label, 2-period, crossover study to evaluate the effect of aprepitant after administration of a single 125-mg dose on the pharmacokinetics of midazolam after intravenous administration of a single 2-mg dose. In each treatment period, a 2-mg IV dose of midazolam was administered over 2 minutes either alone (Treatment 1) or 1 hour after a 125-mg dose of aprepitant (Treatment II). The sequence of the treatments was randomly assigned and there was at least 14 days between treatment periods (Period 1 and Period 2). Each treatment was administered after an overnight fast. Thirteen healthy volunteers (10 females & 3 males; age: 27.6 yrs (20-36 yrs) and mean wt: 69.5 kg (54-87.4 kg)) participated and 12 completed the study.

The plasma concentration of midazolam was measured at multiple time points over 24 hours following midazolam administration. Blood samples were also collected for potential measurement of aprepitant at predose and 3 and 24 hours following midazolam administration.

Aprepitant Assay: Blood draws for aprepitant assay were performed pre-aprepitant dose, and at 3 and 24 hours postdose, relative to midazolam administration (Treatment II only).

Midazolam Assay:
Samples were collected at the following time points: predose, end of IV infusion (2 minutes), 15 minutes, 30 minutes, 45 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours following IV administration (start of IV push).

Assay was conducted by (b) (4)

Results
Figure 1 presents mean midazolam plasma concentrations with and without coadministration of aprepitant, while Table 1 lists mean plasma PK parameters for the two treatments. Coadministration with aprepitant increased midazolam plasma concentrations due to decreased midazolam clearance (from 445 mL/min to 302 mL/min). Figure 2 presents individual ratios, geometric mean ratio of aprepitant $AUC_{0-\infty}$ and 90% CI for subjects receiving midazolam administered with aprepitant and the same subjects receiving midazolam alone. The geometric mean ratio (midazolam with aprepitant/ midazolam alone) was 1.47 with a 90% CI of 1.36-1.59.

Figure 1: Mean Midazolam Plasma Profiles in Healthy Young Subjects (N=12) Who Received 2.0 mg IV Midazolam With and Without 125 mg Oral Aprepitant

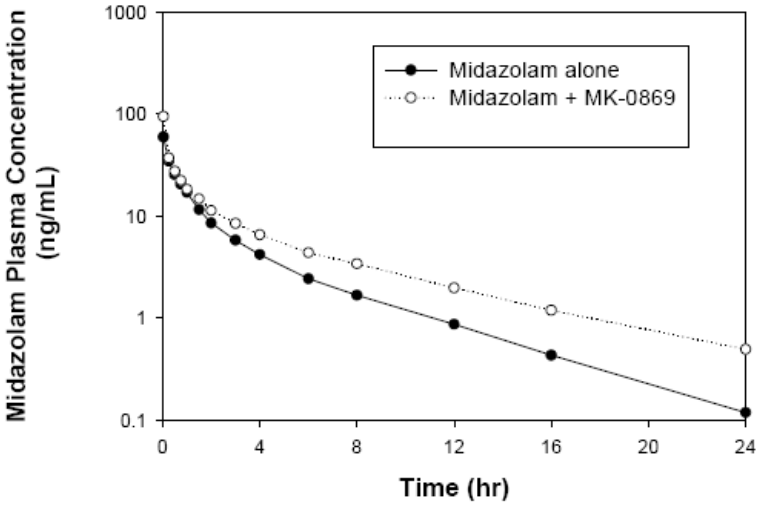
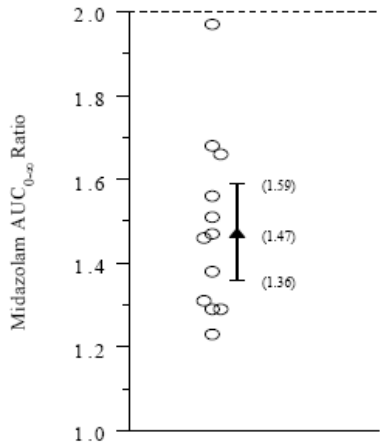


Table 1: Plasma Midazolam PK Parameters With and Without Coadministration of Aprepitant

Variable (units)	Geometric Means†‡ Midazolam With Aprepitant	Geometric Means†‡ Midazolam Alone	Geometric Mean Ratio† (Midazolam With Aprepitant/ Midazolam Alone) and 90% CI	p-Value§	MSE‖
$AUC_{0-\infty}$ (ng•hr/mL)	110.3	75.0	1.47 (1.36, 1.59)	< 0.001	0.0103
Cl_p (mL/min)	302.1	444.5	0.68 (0.63, 0.73)	< 0.001	0.0103
C_{max} (ng/mL)	71.8	59.7			
T_{max} (hr)	0.14	0.15			
$t_{½}$ (hr)	5.2	3.7			

† Geometric means, geometric mean ratios, and CIs back-transformed from least-squares means from ANOVA.
‡ Median for T_{max}, harmonic mean for $t_{½}$.
§ Tests null hypothesis of no between-treatment difference versus two-sided alternative.
‖ Mean square error on natural log scale.

Figure 2: Individual Ratios (Midazolam With Aprepitant/ Midazolam Alone) With Geometric Mean Ratio and 90% CI for Midazolam AUC0-∞



Conclusion:
Aprepitant administered as a single oral dose of 125 mg has no clinically meaningful effect on the pharmacokinetics of midazolam co-administered as a single intravenous dose of 2 mg.

Note: A previous study indicated that the modified low dose regimen of aprepitant (Day 1: 40 mg; Days 2-5: 25 mg) did not significantly affect midazolam plasma levels with an AUC ratio of 1.02.

Effects on Midazolam $AUC_{0-\infty}$ (ng-h/mL)						
Day	Treatment Regimen Midazolam $AUC_{0-\infty}$†	Reference Regimen Midazolam $AUC_{0-\infty}$†	Ratio†	p-Value	95% CI	Hypothesized Interval
Midazolam Evaluation (Amendment 041-01)						
1	Low-dose MK-0869 with oral midazolam (I) 52.1	Oral midazolam alone (prestudy) 23.0	I/Prestudy 2.27	< 0.01	(1.64, 3.14)	N/A
5	Low-dose MK-0869 with oral midazolam (I) 75.7	Oral midazolam alone (prestudy) 23.0	I/Prestudy 3.30	< 0.01	(2.39, 4.56)	N/A
1	Modified low-dose MK-0869 with oral midazolam (J) 37.7	Oral midazolam alone (prestudy) 30.8	J/Prestudy 1.22	0.143	(0.93, 1.61)	N/A
5	Modified low-dose MK-0869 with oral midazolam (J) 31.4	Oral midazolam alone (prestudy) 30.8	J/Prestudy 1.02	> 0.25	(0.77, 1.35)	N/A

† Least squares geometric mean. For the amendment, estimates for treatment ratios were based on both paired and unpaired observations for those treatments.
CI = Confidence interval.
N/A = Not applicable. No hypothesis specified; estimation only.

*N= 8 per treatment.

Appendix 2: Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-549**	**Brand Name**	**Emend**
OCP Division (I, II, III)	**III**	**Generic Name**	**Aprepitant**
Medical Division	**Division of Gastroenterology Products**	**Drug Class**	**NK1-receptor antagonist**
OCP Reviewer	**Sue-Chih Lee, Ph.D.**	**Indication(s)**	**Prevention of postoperative nausea and vomiting**
OCP Team Leader	**Dennis Bashaw, Pharm.D.**	**Dosage Form**	**Capsules**
Date of Submission	**8/29/05**	**Proposed Dosing Regimen**	**Single 40 mg dose within 3 hours prior to induction of anesthesia**
Estimated Due Date of OCP Review	**May 15, 2006**	**Route of Administration**	**Oral**
Medical Division Due Date	**May 31, 2006**	**Sponsor**	**Merck**
PDUFA Due Date	**June 30, 2006**	**Priority Classification**	**Standard**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**	**1**	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**	**1**	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	**X**	**1**	**1**	
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	**X**	**1**	**1**	
solution as reference:				
alternate formulation as reference:	**X**	**1**	**1**	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	**X**	**1**	**1**	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
QT study				
Simulations				
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	**x**	**Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?**
Comments sent to firm		**Comments have been sent to firm (or attachment included). FDA letter date if applicable.**
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	**Sue-Chih Lee, Ph.D. /06**	
Secondary reviewer Signature and Date	**Dennis Bashaw, Pharm.D.**	

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/s/

Sue Chih Lee
6/5/2006 10:38:43 AM
BIOPHARMACEUTICS

Dennis Bashaw
6/5/2006 01:25:35 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21549Orig1s010

OTHER REVIEW(S)

MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology WO 22, Mailstop 4447, HFD-420 Center for Drug Evaluation and Research

To: Brian Harvey, MD
Director, Division of Gastroenterology Products
HFD-180

From: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Through: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

Date: May 18, 2006

Subject: OSE Review 00-0298-4, Emend (Aprepitant Capsules) 40 mg; NDA 21-549/S-010

This memorandum is in response to a May 11, 2006 request from your Division for a review of the container label, carton and package insert labeling for Emend 40 mg. Emend was approved March 26, 2003 with product strengths of 80 mg and 125 mg. The current supplement, submitted January 30, 2006 provides for a 40 mg strength.

A. Adverse Event Reporting System

Since Emend was initially approved in 2003, DMETS conducted a search of the Agency's Adverse Event Reporting System for medication errors associated with Emend 80 mg and 125 mg capsules. The search was conducted using the high group level term "medication errors," and the preferred terms "medication error", "pharmaceutical product complaint", "accidental overdose", and "overdose," and "circumstance or information capable of leading to medication error," as well as the active ingredient "aprepitant," the tradename "Emend," and the verbatim terms "aprepitant%" and "Emend%." The search identified ten (n=10) medication errors associated with the use of Emend capsules, which can be divided in to similar/incomplete labeling, wrong drug, and dosing errors.

1. Similar Label Appearance and Poor Packaging Design (n=3)

Three medication error cases can be attributed to the design of the labels and labeling of Emend capsules. Two cases (n=2) involved healthcare practitioners with concerns about the similar appearance of the 80 mg and 125 mg strength labels. Of the two cases, one case stated that their facility has placed the product on an internal alert list for potential mix-ups in strength. The other case stated that the different geometric shapes around the product strengths do not adequately differentiate the two strengths. The remaining one case involves the 3-day kit for Emend capsules which contains one 125 mg capsule to be taken on day 1 and two 80 mg capsules to be taken on days 2 and 3. The report states that the blister packaging in which the capsules are supplied does not provide "the name of the drug, capsule strength, expiration date, or lot # if the capsules are removed and/or separated from the kit." Upon investigation of these errors and review of the labels and labeling involved we determined there is a similarity in the product labels and labeling, and the kit should be revised. We refer you to section B for label and labeling recommendations.

2. Wrong Drug (n=5)

There were five cases involving confusion between Emend and other drug products. The first case involved a patient undergoing chemotherapy who was prescribed "Emend tripack" and the pharmacy filled the prescription with a Zithromax Z-Pak in error. The patient took the medication with her to her chemotherapy appointment, but did not take the medication. The patient's physician provided the correct medication from sample supplies. The second case involved a verbal prescription for Emend 80 mg. The prescription was called in to a pharmacist. The drug name was spelled to the pharmacist, and the dose, indication for use, and instructions were discussed as well. The pharmacist transcribed and dispensed the prescription order as Amen, the branded generic of medroxyprogesterone 8 x 10 mg tablets in error However, the patient brought the misfilled prescription to the doctor's office before taking any of the medication. The name pair, Emend and Amen is one of which DMETS anticipated the potential for confusion in our proprietary name review of Emend (OSE Consult 02-0073-1).

The final three cases involve complaints that the drug names, Emend and M-End (an anti-tussive combination product) could potentially be confused due to similarities of the names. Two cases were reported by pharmacists, and one case was reported by a pharmaceutical sales representative. In all three cases, the reporter stated concern with regard to the sound-alike similarity between Emend and M-End. DMETS does not believe that any regulatory action is required at this time. However, we will continue to monitor errors due to confusion between Emend and Zithromax, Amen, and M-End.

3. Dosing Errors (n=2)

There were two cases involving errors with regard to Emend dosing. The first case involved a female patient who took an overdose of three capsules (dose unknown) daily for approximately two weeks. The overdose was caused by the patient having Emend prescriptions from both her general practitioner and the hospital physician. The second case involved a female patient who accidentally took one Emend capsule at night and then another capsule in the morning. Patient outcome was not reported for either of these cases. DMETS does not believe that any regulatory action is required at this time. However, we will continue to monitor dosing errors associated with Emend.

B. Labeling, Packaging, and Safety Related Issues

In the review of the container labels, carton and insert labeling of Emend, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error. Furthermore, in light of the medication errors identified through the AERS search for Emend 80 mg and 125 mg, the following recommendations encompass safety issues for all three strengths (i.e. 40 mg, 80 mg, and 125 mg). The recommendations pertaining to the 80 mg and 125 mg blister labels and carton labeling have been made after review of the labeling submitted to the Agency Decmeber 7, 2005 for Supplement 008.

1. General Comments

   The color scheme used for each strength (40 mg, 80 mg, and 125 mg) is almost identical to each other. Each strength is utilizing a different shade of blue containing white text and a banner. Although each strength is boxed using slightly different geometric shapes (i.e. hexagon for 40 mg, rectangle for 80 mg, and parallelogram for 125 mg), at a glance the geometric shapes do not offer adequate differentiation of the product strengths. Postmarketing evidence demonstrates that a lack of **distinct** differentiation between the product strengths may lead to selection errors. Therefore, DMETS recommends that each strength be readily differentiated by using different color schemes (i.e., not using different shades of the same color) and increase the size of the strength to give it more prominence.

2. Blister Label (1 capsule and 5 capsules – trade, 40 mg, 80 mg, and 125)

   See General Comment.

3. Blister Label (1 capsule and 5 capsules – sample, 80 mg and 125 mg)

   a. See General Comment.

   b. Revise the "Complimentary" statement to read, "Physician Sample – Not for Sale," and increase the prominence of this statement.

4. Carton Labeling (1 capsule and 5 capsules – trade, 40 mg, 80 mg, and 125 mg)

   a. See General Comment and comment 3-c.

   b. DMETS recognizes that the drawing of the capsule on the principal display panel is not intended to be the statement of product strength, however, the product strength is presented in the representation of the capsule. Postmarketing evidence demonstrates that the presentation of the net quantity in close proximity to the product strength may lead to medication errors. Relocate the net quantity so that it is not presented in close proximity to the product strength.

5. Carton Labeling (1 capsule – sample, 80 mg and 125 mg)

   a. See General Comment and comments 3-b and 3-c.

   b. Relocate the word "capsules" from inside the text box containing the product strength to outside the text box immediately following the established name. Additionally, the statement "capsules" should be revised to read "capsule" as the sample package only contains one capsule. For example:

      Emend
      (Aprepitant) Capsule

6. Tri-Fold Label (125 mg and 80 mg capsules – trade 3 day kit)

   a. See General Comment.

   b. Relocate the word "capsules" from directly under the text box containing the product strength to immediately following the established name. Additionally increase the prominence so that it is the same size font as the active ingredient, aprepitant. As presented it does not appear that capsules is part of the established name, which is incorrect.

c. DMETS recommends that *each blister label* at a minimum contain the established name, proprietary name, strength, lot number, expiration date, and the manufacturer. Thus, each blister should be labeled so that if torn from the outer carton, the drug will be appropriately labeled. For example:

Emend
(Aprepitant Capsules)
XX mg
Lot#: _____ Exp:_____

7. Tri-Fold Label (125 mg and 80 mg capsules – sample 3 day kit)

   a. See General Comment and comments 3-b, 6-b, and 6-c.

In summary, DMETS recommends implementation of the above label and labeling comments. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Diane Smith at 301-796-0538.

FDA Receipt Date ISR #	Type of Error	Abbreviated Narrative
Similar Labeling		
7/9/2003 4144137-3	Similar Labeling	On 26-Jun-2003 at the FDA public meeting, "Minimizing Medication Errors – Methods for Evaluating Proprietary Names for the Confsuion Potential," held at the Renaissance Washington, D.C. Hotel, information has been received from a pharmacist concerning the packaging of aprepitant. The pharmacist stated that the labeling was "awful" in that the packaging is virtually identical in appearance for the two strengths of the product. The pharmacist stated that the expression of strength appears in rather small print. Further, he reported that he wasn't sure whether there was an attempt to "color code" the strengths differently or if the slight variation is shade was simply a function of different batches of the same ink. The reporter stated that the Pharmacy Department immediately put the product on an internal "alert list" for potential mix-ups in strength because of the similarity of the two packages.
6/6/2005 4683321-7	Similar Labeling	As with all Merck unit-dose packages, it is difficult to tell the different between the different strengths of a medication. With Emend (aprepitant) the 80 mg and 125 mg strengths appear within different geometric forms that are intended to help differentiate the strengths. However this distinction is hard to notice.
Incomplete Labeling		
4/27/2006 4984886-8	Incomplete Labeling	Emend – aprepitant – is an antiemetic manufactured by Merck and is available as a kit and as unit-dose capsules – 5 capsules/box. The kit NDC 0006-3862-32 is designed to promote the ease of the approved 3-day therapy, 125 mg on day 1, then 80 mg on day 2 and 3, but the blister packaging it comes in does not provide labeling that indicated the name of the drug, capsule strength, expiration date, or lot # if the capsules are removed/separated from the kit. This can lead to incorrect dispensing in a hospital setting where medications are typically sent for a 24-hour period. While we are aware of the availability of the unit dose product it is not the product stocked by our wholesaler.
Emend and Zithromax Z Pak Confusion		
5/16/2003 4110601-6	Wrong Drug	Patient undergoing chemotherapy nos who was placed on therapy with aprepitant, capsule (dose, duration and indication not reported). Subsequently the physician wrote a prescription for Emend tripack and the pharmacy filled the prescription for a Z-Pack (Zithromax). It was reported that the patient took the product (Zithromax) with her to chemotherapy but did not take the medication. The patient's physician provided the correct medication from sample supplies.
Emend and M-End Confusion		
5/8/2003 4106160-4	Potential Error	Information has been received from a pharmacist reporting a concern that "Emend sounds too much like M-End." The pharmacist stated that Emend could be confused with a "regional" product he dispenses, M-End, which is a cough suppressant, nasal decongestant and antihistamine. The pharmacist added that he is reporting a potential medication error and that no actual errors have occurred.
5/9/2003 4106596-1	Potential Error	Information has been received from a company representative reporting that she observed another product in a physician's sample closet whose name sounded like "Emend." The product is called "M-End," an anti-congestant, antihistamine, and anti-tussive. It is made by (b) (4) for R.A. McNeil Inc. The company representative added that no medication errors have occurred, but that she is reporting the potential for a medication error.
5/16/2003 4110599-0	Potential Error	Information has been received from a pharmacist reporting a concern that "Emend looks like M-End." The pharmacist reported that he had "received a letter from Merck cautioning against confusing Emend with the products Amen and V Fend." He stated that he realized that it was even more likely that there could be confusion with a cough medicine they dispense, M-End. The pharmacist added that he is reporting a potential medication error and that no actual errors have occurred… He stated that the drug M-End, distributed by R.A. McNeil in Chattanooga, TN, is often prescribed in his area. The pharmacist added that he has not seen any prescriptions for Emend yet.

Emend and Amen Confusion		
1/20/2006 4887947-7	Wrong Drug	Rx was called to pharmacist for Emend 80 mg Drug name was spelled to pharmacist. Dose, indication, and instructions for use were discussed. Pharmacist transcribed Rx as Amen, and Rx was subsequently filled as Amen – branded generic of medroxyprogesterone 8 x 10 mg tablets. Fortunately, patient brought filled prescription to doctor's office before taking any of the medication. This report is to notify the FDA of potentially dangerous similarity of product names.
Overdose		
12/30/2005 4869936-1	Overdose	39 year-old female patient with metastatic breast cancer treated with chemotherapy who, at the beginning of September 2005, was placed on therapy with aprepitant for the treatment of prophylaxis against chemotherapy induced vomiting. It was reported that the patient took an overdose of three capsules aprepitant (dose unknown) daily for the duration of approximately two weeks. The overdose was caused by a double prescription of aprepitant by the general practitioner and the hospital physician.
Extra Dose		
1/3/2004 4289087-7	Extra Dose	Female undergoing chemotherapy who on 10-Nov-2003 accidentally took one aprepitant capsule at night and also another capsule in the morning on 11-Nov-2003 for the treatment of prophylaxis against chemotherapy induced vomiting (dose and duration not reported).

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/s/

Linda Kim-Jung
6/15/2006 11:43:36 AM
DRUG SAFETY OFFICE REVIEWER
Also signing for Kristina Arnwine in her absence on June 15, 2006.

Carol Holquist
6/15/2006 04:32:27 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: March 29, 2006

TO: Brian Harvey, M.D., Ph.D., Director
Division of Gastrointestinal Products

VIA: Betsy Scroggs, Pharm. D., Regulatory Project Manager
Division of Gastrointestinal Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Acting Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review of Patient Labeling for Emend® (aprepitant) Capsules, NDA 21-549/S-010

Summary
The sponsor submitted and Efficacy Supplement August 29, 2005, to provide a new capsule strength (40 mg) and to expand the INDICATION to include prevention of post-operative nausea and vomiting.

The product has an approved PPI and the proposed revisions in this supplement reflect the new capsule strength and indication.

Comments and Recommendations

1. We have recommended revisions to the proposed new language to enhance consumer comprehension (see attached).

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.

We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please let us know if you have any questions.

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/s/

Jeanine Best
3/29/2006 11:05:17 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
3/29/2006 05:45:14 PM
DRUG SAFETY OFFICE REVIEWER