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APPROVAL PACKAGE FOR:

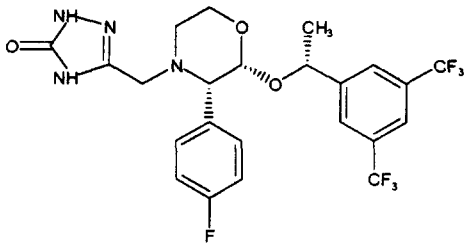
APPLICATION NUMBER

21-549

Medical Review(s)

CLINICAL REVIEW

NDA 21-549
Aprepitant



NDA:	21-549
Serial Number:	000
Chemical Name:	Aprepitant
Date Received:	September 27, 2002
Indication:	Prevention of Acute and Delayed Nausea and Vomiting Associated with Initial and Repeated courses of Highly Emetogenic Cancer Chemotherapy
Dose:	125/80mg capsules
Applicant:	Merck & Co., Inc.
Documents Reviewed:	Electronic Submitted NDA and Data Sets Proposed Package Insert: Safety Update Report, January 7, 2003
Division Director:	Robert Justice M.D. M.S.
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Clinical Review for NDA 21-549

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The submitted trials support the approval of the aprepitant regimen for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of chemotherapy that include highly emetogenic doses of cisplatin with or without concomitant chemotherapy.

The Applicant submitted two identical pivotal studies to support the approval of the aprepitant regimen. Both studies (Study 052 and 054) were successful in demonstrating superior efficacy over standard therapy for the primary endpoint, Complete Response, in the overall phase and several of the supporting secondary endpoints.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

In agreement with the Advisory Committee members and the Agency's concerns, the following Phase IV Studies are recommended:

1) Complete the pending docetaxel drug interaction study

2) Conduct *in vitro* metabolism interaction studies of aprepitant with various chemotherapy agents metabolized by CYP450 enzyme system.

3) Conduct *in vivo* studies to investigate the effect of the aprepitant regimen on the safety, tolerability and pharmacokinetics of chemotherapy agents metabolized by CYP3A4:
   a. irinotecan
   b. vinblastine
   c. imatinib
   d. vinorelbine
   e. etoposide

4) Conduct *in vivo* drug interaction study to investigate the effect of aprepitant on the safety, tolerability and pharmacokinetics of dolasetron (include patients who are poor metabolizers for CYP2D6 isozyme).

5) Conduct post marketing risk assessment for drug errors due to name similarity with the trade name EMEND® IE: AMEND®, VFEND®

APPEARS THIS WAY
ON ORIGINAL

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Aprepitant (previously known as MK-0869 and L-754030), is a New Molecular Entity (NME) that is the first in a new therapeutic class: a nonpeptide, selective NK_1 -receptor antagonist. Preclinical studies indicated that a highly selective NK_1-receptor antagonists could inhibit emesis induced by cytotoxic chemotherapeutic agents. Substance P is the preferred agonist for the NK_1 receptor. The Applicant has demonstrated that administration of substance P into the region of the nucleus tractus solitarius produces vomiting in animal models. NK_1 receptors are found in brain regions that are critical for the regulation of the vomiting reflex in the brain stem nuclei of the dorsal vagal complex.

Four different formulations of aprepitant were used during the clinical development of the aprepitant treatment regimen. The proposed commercial formulation is a nanoparticle capsule (Formulation D) which was used in CINV Phase IIb dose-finding studies and in the pivotal Phase III studies.

The CINV Phase IIb studies (Protocol 040/042) evaluated an antiemetic regimen similar to the Phase III studies, however, aprepitant was administered for 5 days rather than 3 days as in the Phase III studies.

One of the arms of these Phase IIb studies (aprepitant 375-mg regimen) was terminated when a drug-drug interaction with dexamethasone was identified. The aprepitant regimen resulted in a 2-fold increase in plasma concentrations of dexamethasone. During the Phase IIb studies the incidence of febrile neutropenia and serious infections was higher in the aprepitant groups than the standard therapy group. The sponsor proposes that the increased exposure to dexamethasone when coadministered with aprepitant played a role in the increased incidence of immunosuppression-related adverse experiences. The sponsor modified the aprepitant treatment regimen based on the results of the Phase IIb studies. Patients in the aprepitant arm received half the dose of dexamethasone compared to the control arm.

Table 1
Treatment Regimens (Phase III Studies)

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

B. Definitions

Complete Response:	No emesis, no rescue therapy
No Emesis:	No vomiting or retching or dry heaves (includes patients who received rescue therapy)
No Nausea:	Maximum nausea VAS <5 mm
No Significant Nausea:	Maximum nausea VAS <25 mm
Complete Protection:	No emesis, no rescue therapy, no significant nausea (maximum nausea <25 mm on VAS)
Total Control:	No emesis, no rescue therapy, and no nausea (maximum nausea <5 mm on VAS)
Acute Phase:	0-24 Hours
Delayed Phase:	25-120 Hour
Overall Phase:	0-120 Hour

C. Efficacy

In both pivotal studies (052 and 054) the primary endpoint was *Overall Complete Response* (0 to 120 hours post cisplatin). Complete Response for the acute (0 to 24 hours) and delayed phase (25 to 120 hours) were secondary endpoints.

The sponsor defined multiple secondary endpoints which included: complete response (acute and delayed phases), no emesis (overall, acute, and delayed phases), no nausea (overall and delayed phases), no significant nausea (overall and delayed phases), complete protection (overall, acute and delayed phases), and time to first emesis (overall phase). Analyses were also completed for total score for the Functional Living Index-Emesis (FLIE) for the overall phase. The FLIE questionnaire was a VAS-based, validated patient-reported measure of the impact of CINV on daily life.

A summary table of the efficacy results was created using the sponsor's data.

Table 2
Summary of Efficacy

	Aprepitant Regimen n/m (%)	Standard Therapy n/m (%)
[redacted]		
Study 052		
Overall Phase	202 / 260 (77.7)**	143 / 260 (55.0)
Acute Phase	234 / 260 (90.0)**	207 / 261 (79.3)
Delayed Phase	210 / 260 (80.8)**	153 / 260 (58.8)
Study 054		
Overall Phase	172 / 260 (66.2)**	117 / 263 (44.5)
Acute Phase	218 / 261 (83.5)**	181 / 263 (68.8)
Delayed Phase	186 / 260 (71.5)**	127 / 263 (48.3)
[redacted]		
Study 052		
Overall Phase	189/260 (72.7)**	136/260 (52.3)
Acute Phase	231/259 (89.2)**	203/260 (78.1)
Delayed Phase	196 / 260 (75.4)**	145/260 (55.8)
Study 054		
Overall Phase	163 / 260 (62.7)**	114/263 (43.3)
Acute Phase	216 / 261 (82.8)**	180/263 (68.4)
Delayed Phase	176 / 260 (67.7)**	123/263 (46.8)
[redacted]		
Study 052		
Overall Phase	163 / 257 (63.4)**	128 / 260 (49.2)
Acute Phase	217 / 256 (84.8)**	194 / 260 (74.6)
Delayed Phase	172 / 259 (66.4)**	134 / 260 (51.5)
Study 054		
Overall Phase	145 / 261 (55.6)**	107 / 263 (40.7)
Acute Phase	208 / 260 (80.0)**	170 / 263 (64.6)
Delayed Phase	159 / 261 (60.9)**	116 / 263 (44.1)

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

Table 3
Summary of Efficacy

	Aprepitant Regimen n/m (%)	Standard Therapy n/m (%)
[redacted]		
Overall Phase	117/257 (45.5)	104/260 (40.0)
Acute Phase	181/256 (70.7)	167/260 (64.2)
Delayed Phase	127/259 (49.0)	111/260 (42.7)
[redacted]		
Overall Phase	116/261 (44.4)**	84/263 (31.9)
Acute Phase	166/261 (63.6)	149/263 (56.7)
Delayed Phase	130/261 (49.8)**	89/263 (33.8)
[redacted]		
Study 052		
Overall Phase	210/260 (80.8)**	184/260 (70.8)
Acute Phase	244/259 (94.2)*	231/260 (88.8)
Delayed Phase	211/260 (81.2)*	191/260 (73.5)
Study 054		
Overall Phase	214/260 (82.3)**	191/263 (72.6)
Acute Phase	251/261 (96.2)**	236/263 (89.7)
Delayed Phase	216/260 (83.1)*	195/263 (74.1)
[redacted]		
Study 052		
Overall Phase	188/257 (73.2)	171/259 (66.0)
Delayed Phase	195/259 (75.3)	178/260 (68.5)
Study 054		
Overall Phase	185/260 (71.2)	168/263 (63.9)
Delayed Phase	189/260 (72.7)	172/263 (65.4)
[redacted]		
Study 052		
Overall Phase	122 / 257 (47.5)	115 / 260 (44.2)
Delayed Phase	132 / 259 (51.0)	124 / 260 (47.7)
[redacted]		
Overall Phase	127 / 260 (48.8)*	102 / 263 (38.8)
Delayed Phase	137 / 260 (52.7)**	105 / 263 (39.9)

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

Both studies demonstrated that the aprepitant regimen was more effective than standard therapy in the prevention of CINV for the overall, acute and delayed phases.

The sponsor successfully demonstrated the aprepitant regimen was superior to standard therapy for the primary endpoint, complete response in the overall phase, as well as the secondary endpoints of complete response in the acute and delayed phases. The aprepitant regimen showed a consistent statistically significant advantage for the no vomiting endpoint in the overall, acute and delayed phases.

The results of the no nausea endpoints, however, were not as robust. The aprepitant regimen did not reach statical significance for the no nausea endpoint in the acute phase of Study 054 or any of the three phases in Study 052. The results of the secondary endpoint no significant nausea was only statistically significant in the acute phase of Study 054 with a unadjusted p-value of 0.01.

The data demonstrates the aprepitant regimen was more effective than standard therapy for the prevention of CINV in the overall, acute and delayed phases of Cycle 1 and continued to be more effective than standard therapy with subsequent cycles of chemotherapy.

Study 052 allowed enrollment of adolescent patients at a single study site in the U.S. A total of 4 adolescents were enrolled. The number of adolescents was too small to draw an conclusions.

D. Safety

All patients who received cisplatin and at least one dose of study drug were included in the safety analyses. The Integrated Summary of Safety (ISS) included data on 1094 patient and utilized pooled data from the two Phase III studies (Protocols 052 and 054). The Sponsor supplemented this safety data with a Safety Update Report received on January 7, 2003.

Aprepitant has a complex metabolic pathway. It is a substrate, a moderate inhibitor, as well as an inducer of CYP3A4. In addition to this aprepitant is also an inducer of CYP2C9.

In general, the incidences of clinical and laboratory adverse events were similar between treatment groups. Adverse experiences that occurred more frequently (>2% difference) in the aprepitant group compared with the standard therapy group include asthenia/fatigue (17.8% and 11.8%), dizziness (6.6% and 4.4%), diarrhea (10.3% and 7.3%), cough (2.4% and 0.5%), and hiccups (10.8% and 5.6%). Serious adverse events were also balanced, occurring in approximately 13% of the patients. Overall, the aprepitant regimen was well tolerated and did not appear to significantly alter the toxicity of concomitant chemotherapy.

There was limited data available for chemotherapy metabolized via the CYP3A4 pathways. There were small differences noted in serious hematologic and infection-related serious adverse events during cycle 1. Some of these differences were not appreciated during the multi-cycle extension so the significance of this can not be ascertained. The differences noted during cycle 1 and the theoretical risks of CPY3A4 drug-drug interactions warrant post marketing studies.

E. Dosing

Dose: 125 mg capsule orally 1 hour prior to chemotherapy (Day 1) and 80 mg once daily in the morning on days 2 and 3.

Indication: Prevention of Acute and Delayed Nausea and Vomiting Associated with Initial and Repeated courses of Highly Emetogenic Cancer Chemotherapy in Adults

The proposed treatment regimen is a three-drug therapy that includes aprepitant in combination with a 5-HT_3 antagonists and a corticosteroid. Due to the CYP3A4 inhibitory effect of aprepitant, a dose adjustment in the standard corticosteroid dose is recommended in the proposed label.

F. Special Populations

Pediatric

Study 052 allowed enrollment of adolescent patients at a single U.S. study site. A total of 4 adolescents were enrolled. The number of adolescents were too small to draw an conclusions. The efficacy and safety results were similar to the adult population.

Analysis by Gender

During the Phase III trials a treatment by gender interaction was identified in one of the 2 pivotal studies, Study 052. The efficacy of the aprepitant regimen was statistically superior to standard therapy in all three phases for female patients however, was only numerically better for male patients in Study 052. No treatment interaction by gender was demonstrated in Study 054. Overall, the aprepitant regimen was effective in both male and female patients.

Analysis by Age

A total of 311 patients 65 years or older were evaluated in this NDA. The aprepitant regimen was more efficacious than the standard therapy for all age groups. There did not appear to be a significant treatment-by-age interaction.

Analysis by Race

The majority of patients recruited were Caucasian (White). A treatment by race interaction was tested individually by the applicant at a 10% significance level using logistic models. A treatment by race interaction was not identified, however the number of Asian, Black and Hispanic patients were too small to permit meaningful analysis.

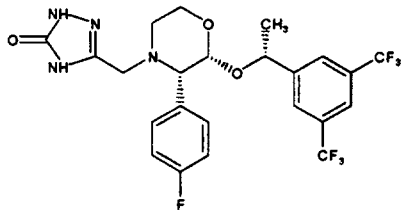
Pregnancy Use

Pregnancy was part of the exclusion criteria for all the studies. The proposed label classifies it as a Pregnancy Category B. No adequate or well-controlled studies in pregnant women have been performed.

Clinical Review

I. Introduction and Background

A. Drug: EMEND (aprepitant)



C23H21F7N4O3

Class:	Substance P Neurokinin 1 (NK_1) receptor antagonist
Proposed Indication(s):	Prevention of Acute and Delayed Nausea and Vomiting Associated with Initial and Repeated courses of Highly Emetogenic Cancer Chemotherapy in Adults
Dose:	125/80mg capsules

B. State of Armamentarium for Indication(s)

Aprepitant is the first in a new class of drug that augments the antiemetic activity of 5-HT_3-receptor antagonists and corticosteroids against chemotherapy induced nausea and vomiting.

C. Important Milestones in Product Development

Merck Research Laboratories (MRL) submitted IND [redacted] on April 9, 1996 to evaluate a new molecular entity (NME) initially described as L-754,030. Since the original IND the study medication has undergone name changes as well as formulation changes. In medical literature aprepitant may be referred to as L-754,030, MK-0869, aprepitant, or EMEND®.

An injectable, water soluble pro-drug of the aprepitant compound, L-758298, was evaluated through an IND [redacted] previously submitted to the Division on September 28, 1995.

On September 16, 1997 the Agency recommended additional toxicokinetic studies to document whether a plateau in systemic exposure to the parent compound was limited by saturation of absorption or was due to enhanced metabolism. These studies were based on the Executive Carcinogenicity Assessment Committee's review of dose selection. On November 3, 1998, MRL submitted data to support dose selection based on the recommended studies.

In subsequent communications, dated January 20, 1999 and February 9, 1999 the Agency agreed that MRL had adequately demonstrated saturation of exposure to aprepitant and the seven metabolites with Formulation M (particle size approximately [redacted]. The Agency, however, noted that the smaller drug particle size [redacted] of an aprepitant submicron formulation under evaluation resulted in a doubling of systemic exposure and that exposure did not appear to saturate over the tested dose ranges.

On April 5, 1999, a teleconference regarding the outstanding dose selection issues occurred. From this discussion, a proposal was made for additional 2 two-week bridging studies in mice and rats that would link the [redacted] aprepitant formulation and [redacted] aprepitant particle size formulation in terms of systemic exposure to both parent drug and metabolites..

During the April 14, 1999 End-of-Phase 2 meeting the Agency made the following recommendations:

1) Use the [redacted] formulation in all subsequent clinical pharmacology studies.
2) Describe the non-linearity of aprepitant for multidose pharmacokinetics
3) Characterize the aprepitant metabolic profile in humans.

In November 1999 the Sponsor reported on dose-ranging studies and revise the treatment regimen. These dose changes were necessary because a drug-drug interaction with aprepitant and dexamethasone resulted in higher than predicted plasma concentrations when aprepitant was administered.

Based on new findings available from the Phase II and IIB studies, MRL requested a second End-of-Phase 2 meeting. This meeting was held on September 21, 2000. During this meeting, agreements were reached regarding dose selection, primary efficacy endpoints and a deferral of submitting pediatric data in the original NDA.

D. Other Relevant Information

As of March 27, 2003, aprepitant is not approved in any other country and has no pending applications in any other countries. Aprepitant has not been withdrawn from any market.

Aprepitant is in Phase III trials as a treatment for major depression. The Applicant also has non-CINV studies in progress for [redacted] as well as in healthy subjects with [redacted]

On October 9, 2000 Merck notified the FDA that the trade name EMEND™ had been accepted for registration with the U.S. Trademark and Patent Office and was adopted as the global trademark designation for aprepitant. Merck requested that the trademark be reviewed by the Agency. Following a review, the Agency expressed concerns to the Sponsor regarding possible drug errors due to a similarity in name with AMEND™ On October 17, 2002, the Applicant requested a formal dispute resolution. After a formal review of the Applicants appeal and supporting documentation, the Office of Drug Evaluation III approved the use of the trade name EMEND™ on October 30, 2002 with the stipulation that a post-marketing risk management program be implemented. On February 27, 2003 the Applicant reported the trade mark designation EMEND™ was changed to EMEND®.

E. Important Issues with Pharmacologically Related Agents

Aprepitant is the first in a new class of drugs termed (Neurokinin 1) NK_1 receptor antagonist. Substance P is the preferred agonist for the NK_1 receptor. Substance P is the most abundant and widely distributed tachykinin in the mammalian central nervous system.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Animal Studies

Aprepitant was generally well tolerated in animals following subacute and chronic administration at doses equal to and in excess of the intended therapeutic dose based on systemic exposures. Preclinical toxicity studies of aprepitant were conducted in rats, mice, and dogs.

The exposure levels obtained in animals were modest when compared to the exposure levels in humans. The findings included increased liver and thyroid weights, hepatocellular centrilobular hypertrophy, thyroid follicular cell hyperplasia, pituitary cell vacuolation, and slight increases in serum cholesterol and decreases in serum triglycerides.

In dogs, the treatment-related changes in serum chemistry parameters occurred at systemic exposures in excess of those in humans (13 times the recommended human dose based on systemic exposure). Significant decreased body weight gain, testicular degeneration, and prostatic atrophy were seen in dogs at systemic exposures 32 times the systemic exposure of the recommended human dose.

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 thyroid 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. A through review and discussion of the aprepitant toxicology studies will be outlined by the Agency's Pharmacology division.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Aprepitant is a substrate and inhibitor of CYP3A4 and may affect the pharmacokinetics of drugs that are metabolized through 3A4 pathways. Administration of aprepitant for 28 days or longer has demonstrated that

aprepitant is also an inducer of CYP3A4 during chronic administration and can auto induce its own metabolism.

The potential for aprepitant to act as a CYP3A4 inhibitor has been characterized using orally administered midazolam, a CYP3A4 substrate that is highly sensitive to modulation of CYP3A4 activity. The Aprepitant regimen increased the AUC of midazolam 2.3-fold on Day 1 and 3.3-fold by Day 5. Based on the effect on midazolam, aprepitant is considered a moderate inhibitor of CYP3A4.

Aprepitant was also demonstrated to be an inducer of CYP2C9, as characterized by a drug interaction study with S-warfarin. Consequently, aprepitant might affect the pharmacokinetics of drugs that are CYP2C9 substrates

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, and an inhibitor of P-gp-mediated transport of vinblastine, with a potency probably 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.

Relevant Findings:

Corticosteroids: The metabolism of both dexamethasone and methylprednisolone is mediated by CYP3A4. When aprepitant (125 mg) was administered with IV methylprednisolone or oral dexamethasone (both CYP3A4 substrates), aprepitant increased the AUC of methylprednisolone 1.3-fold, compared with a 2.3-fold increase in the AUC of dexamethasone.

5-H_{T3} Antagonists: The Applicant has exposure and pharmacokinetic data for only ondansetron and granisetron. In these drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of the specific drug in the formulations studied. The Applicant does not have data for the intravenous formulation of granisetron or the oral formulation of ondansetron. Because of first pass metabolism, the inhibitory effect is greatest with the oral formulation, therefore one cannot extrapolate PK results from the intravenous ondansetron studies to its oral formulation. The Applicant presently has no data on the use of the aprepitant regimen with dolasetron.

Chemotherapeutic Agents:

Cyclophosphamide: Clinical data indicate that cyclophosphamide induces its own metabolism (autoinduction) during successive cycles of therapy. There are no data to indicate that cyclophosphamide induces the metabolism of other drugs. Current data suggest that CYP3A4 does not play a major role in cyclophosphamide metabolism.

Ifosfamide: Metabolic activation of ifosfamide is mediated by CYP3A4; as is the metabolism of several ifosfamide metabolites. A clinical study in which patients receiving ifosfamide therapy were treated with either ketoconazole (a strong CYP3A4 inhibitor) or rifampin (a relatively non-specific inducer of multiple pathways) showed that ketoconazole produced relatively minor changes in the plasma AUC of ifosfamide (14% increase) and had variable effects on its active metabolites. Rifampin produced a 49% decrease in the AUC of ifosfamide and had variable effects on its active metabolites.

Doxorubicin: There is no evidence that cytochrome P-450 enzymes are involved in doxorubicin metabolism. Clinical drug interaction studies with doxorubicin indicate that it is a P-glycoprotein (P-gp) substrate as evidenced by interactions with other drugs that are P-gp substrates including cyclosporine A, verapamil, paclitaxel.

Etoposide: Clinical data indicate that clearance of etoposide is increased by anticonvulsants (CYP3A4 inducers) in children (2- to 3-fold) and adults (37% by phenytoin).

Taxanes: Both paclitaxel and docetaxel are metabolized by CYP3A4 and clinical interactions with drugs that modulate CYP3A4 activities are possible. The Applicant has a drug interaction study with docetaxel in progress.

Vinca Alkaloids: The sponsor reports that data on the pharmacokinetics and metabolism of vinca alkaloids (vinblastine, vincristine, vinorelbine) are relatively sparse. However, it is assumed that clearance of vinca alkaloids might be affected by drugs that alter CYP3A4 activity.

Irinotecan (also known as CPT-11): The pharmacokinetics, metabolism and elimination of CPT-11 are complex. The sponsor acknowledges that it is possible that the pharmacokinetics of irinotecan can be altered by drugs that affect CYP3A4 activity.

B. Pharmacodynamics

Because of first pass metabolism, the inhibitory effect of aprepitant is greatest when CYP3A4 substrates are administered orally. When the same dose of aprepitant (125 mg) was administered prior to IV methylprednisolone or oral dexamethasone (both CYP3A4 substrates), aprepitant increased the AUC of methylprednisolone 1.3-fold compared with a 2.3-fold increase in the AUC of dexamethasone.

IV. Description of Clinical Data and Sources

A. Overall Data

Clinical and Pre-Clinical Sections of the NDA
Proposed Package Insert
Electronic Submitted Data Sets
On-line Literature Search
Safety Update Report

B. Tables Listing the Clinical Trials

Table 4
Clinical Trials Phase II and III

Study	Phase	Number of Patients	Formulation and Dose
004	IIa	53	L- 758298 100 mg IV
CN007	IIa	177	L- 758298100 mg IV
007	IIa	161	aprepitant 400 mg PO
012	IIa	354	aprepitant 400 mg PO
044	IIa	55	aprepitant 125 mg PO
040/042	IIb	583	aprepitant Dose Range
052	III	534	aprepitant 125/80 mg PO
055	III	569	aprepitant 125/80 mg PO

C. Post-marketing Experience

At the time of this NDA submission, aprepitant has not been approved for use in any country.

D. Literature Review

The sponsor submitted several articles to support the findings and study design of the pivotal Phase III studies. Additional literature search was performed utilizing the Agency's on-line databases and resources. The Agency accepts the study design and the Applicant's definition for acute and delayed chemotherapy induced nausea and vomiting.

V. Clinical Review Methods

A. How the Review was Conducted

A multi-specialty review of the pivotal studies and PK studies was performed utilizing applicant-submitted data. The review included physicians, statisticians, biopharmaceutical specialists and a project manager. Each study was reviewed individually and compared to the results reported in the Applicant's integrated summary of safety and efficacy.

B. Overview of Materials Consulted in Review

Proposed Package Insert
Clinical and Pre-Clinical Sections of the NDA
Safety Update Report
Electronic Submitted Data Sets
MEDLINE

C. Overview of Methods Used to Evaluate Data Quality and Integrity

A comprehensive review of the preclinical and clinical studies submitted with NDA 21-549 was performed with periodic sampling of the case report forms (CRF). Randomly CRFs were reviewed and compared with SAS transport files utilizing the JMP program. The quality and results of the data were discussed in consultation with the Agency's Biostatistical division.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The Applicant states all studies were conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

E. Evaluation of Financial Disclosure

The sponsor has submitted a signed certification stating that they did not enter into any financial agreement with the clinical investigators whereby the value of compensation could be affected by outcome of studies. The sponsor also certifies that none of the clinical investigators held a proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 54.2(b).

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The submitted pivotal trials, Study 052 and 054, support the approval of the aprepitant regimen for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of chemotherapy that include highly emetogenic doses of cisplatin with or without concomitant chemotherapy.

B. General Approach to Review of the Efficacy of the Drug

Utilizing applicant-submitted data, the pivotal studies of NDA 21-549 were reviewed independently and compared to the Applicant's Integrated Summary of Efficacy. The Phase IIa and IIb studies were also reviewed in regard to the development of the present aprepitant regimen. CRFs were selected randomly and compared with the data base provided and with the integrated summary of efficacy. Efficacy results from each study were reviewed and compared to one another. Statistical analyses were reviewed in consultation with the biometrics review team.

C. Detailed Review of Trials by Indication

<u>Demographics</u>

Patients were stratified according to gender and then according to use of concomitant emetogenic chemotherapy ≥ Hesketh level 3. In Cycle 1, the baseline characteristics were generally similar between treatment groups with respect to gender, age, race, alcohol consumption, and use of concomitant emetogenic chemotherapy. The incidence of the specific secondary diagnoses (past medical histories) was generally similar between treatment groups.

The mean dose of cisplatin was similar between treatment groups. Eighty-nine percent (89%) of the patients in the aprepitant group and 88% of the standard therapy groups were chemotherapy naïve.

The primary cancer diagnoses were generally similar between treatment groups during both Cycle 1 and the multi-cycle extension. Non-small cell lung cancer was the most prevalent diagnosis in both treatment groups (32.4% and 31.7% in the aprepitant group and the standard therapy group, respectively) with ovarian malignancy the second most frequent diagnosis (9.5% and 11.1% in the aprepitant group and the standard therapy group, respectively).

Concomitant Chemotherapeutic Agents

The chemotherapy most commonly used in conjunction with cisplatin was etoposide (19.4% and 16.7% in the aprepitant and standard therapy groups, respectively). Other frequently used chemotherapies were fluorouracil, gemcitabine, and vinorelbine tartrate. Antineoplastic agents used during the multiple-cycle extension were generally similar to those in Cycle 1.

Table 5

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

	Aprepitant Regimen (N=547)		Standard Therapy (N=552)	
	n	(%)	n	(%)
Patients with one or more concomitant antineoplastic agents	520	(95.1)	530	(96.0)
Patients with no concomitant antineoplastic agent	27	(4.9)	22	(4.0)
Antineoplastic and Immunomodulating Agents				
Antineoplastic Agent	**520**	**(95.1)**	**530**	**(96.0)**
Bleomycin	21	(3.8)	23	(4.2)
Capecitabine	1	(0.2)	1	(0.2)
Carboplatin	0	(0.0)	1	(0.2)
Cyclophosphamide	50	(9.1)	43	(7.8)
Cytarabine	1	(0.2)	0	(0.0)
Dacarbazine	4	(0.7)	4	(0.7)
Docetaxel	11	(2.0)	14	(2.5)
Doxorubicin	38	(6.9)	44	(8.0)
Epirubicin	4	(0.7)	7	(1.3)
Etoposide	106	(19.4)	92	(16.7)
Fluorouracil	100	(18.3)	93	(16.8)
Gemcitabine	89	(16.3)	101	(18.3)
Ifosfamide	2	(0.4)	1	(0.2)
Irinotecan hydrochloride	0	(0.0)	1	(0.2)
Melphalan	0	(0.0)	1	(0.2)
Methotrexate	5	(0.9)	4	(0.7)
Mitomycin	14	(2.6)	5	(0.9)
Paclitaxel	52	(9.5)	58	(10.5)
Raltitrexed	2	(0.4)	3	(0.5)
Trastuzumab	1	(0.2)	3	(0.5)
Vinblastine	11	(2.0)	12	(2.2)
Vincristine	2	(0.4)	0	(0.0)
Vinorelbine tartrate	84	(15.4)	80	(14.5)

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

Aprepitant Regimen = Aprepitant 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.

Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.

CINV = Chemotherapy-induced nausea and vomiting.
P.O. = By mouth.
IV = Intravenous.
N = Number of adult patients.

(Ref. Table E-60 ISS.pdf)

Table 6
Efficacy Summary

	Aprepitant Regimen n/m (%)	Standard Therapy n/m (%)
Study 052		
Overall Phase	202 / 260 (77.7)**	143 / 260 (55.0)
Acute Phase	234 / 260 (90.0)**	207 / 261 (79.3)
Delayed Phase	210 / 260 (80.8)**	153 / 260 (58.8)
Study 054		
Overall Phase	172 / 260 (66.2)**	117 / 263 (44.5)
Acute Phase	218 / 261 (83.5)**	181 / 263 (68.8)
Delayed Phase	186 / 260 (71.5)**	127 / 263 (48.3)
Study 052		
Overall Phase	189/260 (72.7)**	136/260 (52.3)
Acute Phase	231/259 (89.2)**	203/260 (78.1)
Delayed Phase	196 / 260 (75.4)**	145/260 (55.8)
Study 054		
Overall Phase	163 / 260 (62.7)**	114/263 (43.3)
Acute Phase	216 / 261 (82.8)**	180/263 (68.4)
Delayed Phase	176 / 260 (67.7)**	123/263 (46.8)
Study 052		
Overall Phase	163 / 257 (63.4)**	128 / 260 (49.2)
Acute Phase	217 / 256 (84.8)**	194 / 260 (74.6)
Delayed Phase	172 / 259 (66.4)**	134 / 260 (51.5)
Study 054		
Overall Phase	145 / 261 (55.6)**	107 / 263 (40.7)
Acute Phase	208 / 260 (80.0)**	170 / 263 (64.6)
Delayed Phase	159 / 261 (60.9)**	116 / 263 (44.1)

Calculated by Sponsor
** $p<0.01$ when compared with Standard Therapy
* $p<0.05$ when compared with Standard Therapy

Table 7
Efficacy Summary

	Aprepitant Regimen n/m (%)	Standard Therapy n/m (%)
Overall Phase	117/257 (45.5)	104/260 (40.0)
Acute Phase	181/256 (70.7)	167/260 (64.2)
Delayed Phase	127/259 (49.0)	111/260 (42.7)
Overall Phase	116/261 (44.4)**	84/263 (31.9)
Acute Phase	166/261 (63.6)	149/263 (56.7)
Delayed Phase	130/261 (49.8)**	89/263 (33.8)
Study 052		
Overall Phase	210/260 (80.8)**	184/260 (70.8)
Acute Phase	244/259 (94.2)*	231/260 (88.8)
Delayed Phase	211/260 (81.2)*	191/260 (73.5)
Study 054		
Overall Phase	214/260 (82.3)**	191/263 (72.6)
Acute Phase	251/261 (96.2)**	236/263 (89.7)
Delayed Phase	216/260 (83.1)*	195/263 (74.1)
Study 052		
Overall Phase	188/257 (73.2)	171/259 (66.0)
Delayed Phase	195/259 (75.3)	178/260 (68.5)
Study 054		
Overall Phase	185/260 (71.2)	168/263 (63.9)
Delayed Phase	189/260 (72.7)	172/263 (65.4)
Study 052		
Overall Phase	122 / 257 (47.5)	115 / 260 (44.2)
Delayed Phase	132 / 259 (51.0)	124 / 260 (47.7)
Study 054		
Overall Phase	127 / 260 (48.8)*	102 / 263 (38.8)
Delayed Phase	137 / 260 (52.7)**	105 / 263 (39.9)

Calculated by Sponsor
** $p<0.01$ when compared with Standard Therapy
* $p<0.05$ when compared with Standard Therapy Calculated by Sponsor

In both pivotal studies (052 and 054) the primary endpoint was Overall Complete Response (0 to 120 hours post cisplatin). Complete Response for the acute (0 to 24 hours) and delayed phase (25 to 120 hours) were secondary endpoints.

The sponsor defined multiple secondary endpoints which included: complete response (overall and delayed phases), no emesis (overall, acute, and delayed

phases), no nausea (overall and delayed phases), no significant nausea (overall and delayed phases), complete protection (overall, acute and delayed phases), and time to first emesis (overall phase). Analyses were also completed for total score for the FLIE (overall phase). Because the Applicant predefined several secondary and exploratory endpoints, any nominally significant results can not be taken at face value due to multiple comparisons.

Complete Response Endpoint:

Complete Response was defined as no emesis and no rescue therapy. For the complete response endpoints in the overall, acute and delayed phase, both studies demonstrated that the aprepitant regimen was statistically significantly superior to standard therapy.

No Emesis Endpoint:

No Emesis was defined as no emetic episodes regardless of use of rescue therapy. For the no vomiting endpoint, the aprepitant regimen was statistically more effective than standard therapy in the overall, acute and delayed phase for both studies.

No Nausea Endpoint (Maximum Nausea VAS <5 mm)

No Nausea was defined as <5mm on a Visual Analog Scale (VAS). The No Nausea endpoints were only statistically significant in the overall and delayed phases of Study 054. The aprepitant regimen did not reach statical significance in the acute phase of Study 054 or any of the three phases in Study 052.

No Significant Nausea Endpoint (Maximum Nausea VAS <25 mm)

The no significant nausea endpoints were only statistically significant in the acute phase of Study 054 with a unadjusted p-value of 0.01. The results of the nausea endpoints will be discussed and interpreted in the efficacy conclusions section.

Complete Protection Endpoint

Complete protection was defined as No Emesis, No Rescue Medication, and No Significant Nausea (VAS< 25mm). For this endpoint the studies reached statistical significance in the overall, acute and delayed phases.

Total Control

Total control was defined as No Emesis, No Rescue Medication, and No Nausea (VAS< 5mm). For the total control endpoint, the aprepitant regimen was only numerically better than standard therapy for the overall, acute and delayed phase in Study 052. In Study 054, the total control endpoint reached statistical significance in the overall and delayed phases, but was only numerically better than standard therapy in the acute phase.

No Rescue Therapy Endpoint

Rescue therapy was permitted for the treatment of established nausea or emesis. No rescue therapy was defined as no use of rescue medication. In both studies the aprepitant group had a statistically significantly higher proportion of patients with no use of rescue medication than the standard therapy group.

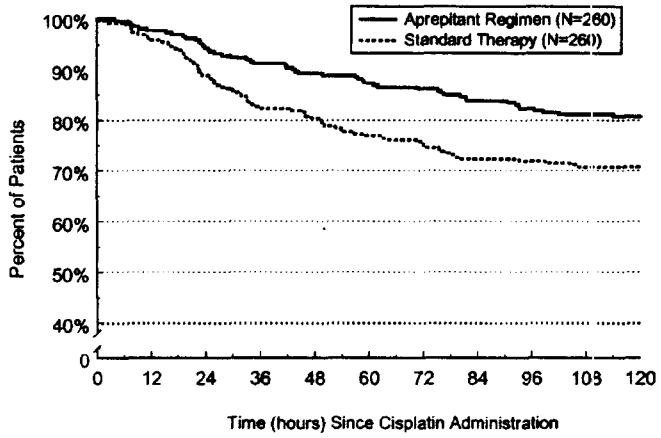
To demonstrate the aprepitant regimen's delayed phase efficacy, the sponsor reports that 79% of the patients in the aprepitant group who did not take rescue medication during the acute phase also had no delayed phase emetic episodes. In contrast, only 59% of the patients in the standard therapy group who did not take rescue medication during the acute phase also had no delayed phase emetic episodes. The results of the no rescue therapy endpoint will be discussed and interpreted in the efficacy conclusions section.

Time to First Rescue Endpoint—Overall Phase (Not Prespecified)

For both studies, the Kaplan-Meier curves show that the time to first use of rescue medication was longer in patients in the aprepitant group compared with the standard therapy group. The timing of the use of first rescue medication was similar in the 2 treatment groups for the first 12 hours post-cisplatin administration. Beyond 12 hours, the first use of rescue medication occurred earlier with standard therapy than with the aprepitant regimen.

Table 8

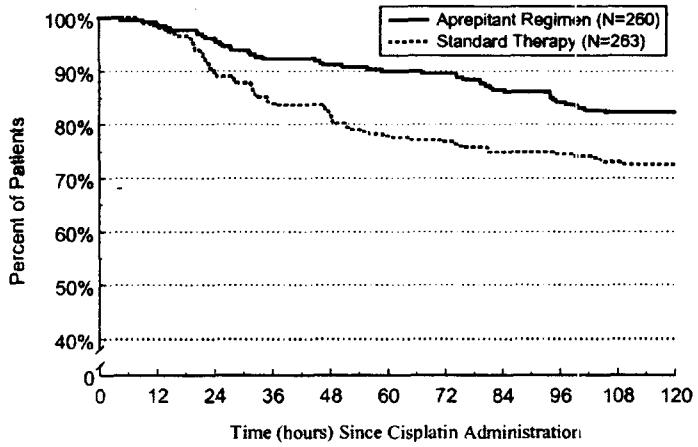
Kaplan-Meier Curves for Time to First Rescue From Start of Cisplatin Administration in the Overall Phase (Cycle 1)—Protocol 052 (Modified-Intention-to-Treat Analysis)



(Ref. Figure D-6 ise.pdf)

Table 9

Kaplan-Meier Curves for Time to First Rescue From Start of Cisplatin Administration in the Overall Phase (Cycle 1)—Protocol 054 (Modified-Intention-to-Treat Analysis)



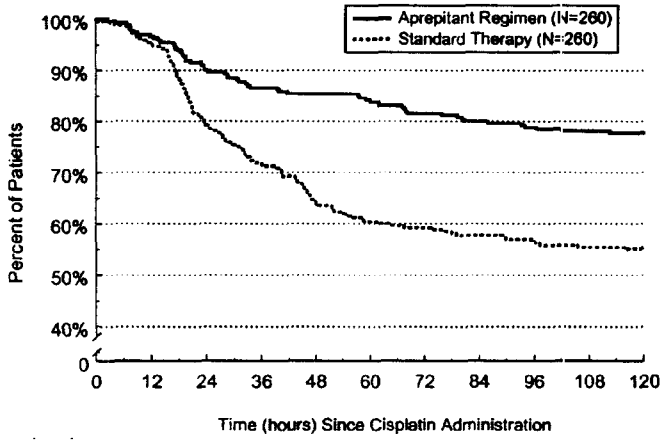
(Ref. Figure D-8 ise.pdf)

Time to First Emesis Endpoint—Overall Phase

For both studies, the Kaplan-Meier curves show that the time to first emesis was longer in patients in the aprepitant group compared with the standard therapy group. For the first 16 hours post-cisplatin administration the Kaplan-Meier curves are similar. Subsequently, the difference between treatment groups becomes evident.

Table 10

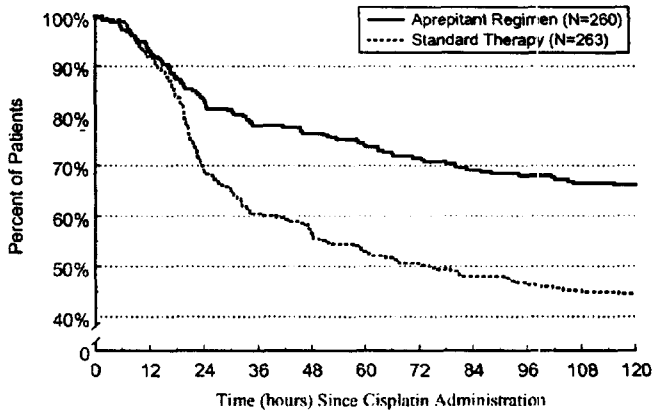
Kaplan-Meier Curves for Time to First Emesis From Start of Cisplatin Administration in the Overall Phase (Cycle 1)—Protocol 052 (Modified-Intention-to-Treat Analysis)



(Ref. Figure D-5 ise.pdf)

Table 11

Kaplan-Meier Curves for Time to First Emesis From Start of Cisplatin Administration in the Overall Phase (Cycle 1)—Protocol 054 (Modified-Intention-to-Treat Analysis)



(Ref. Figure D-7 ise.pdf)

Relationship Between Acute and Delayed Phase Emesis: (Carry-Over Effect)

Effective control of acute symptoms has been proposed to result in reduced symptomatology in the delayed phase (commonly referred to as "carry-over" effect).

In the aprepitant group, 83% of the 451 patients without acute emesis also had no delayed emesis. In contrast, only 67% of the 387 patients in the standard therapy group without acute emesis also had no delayed emetic episodes.

Table 12

Categorization of Delayed Phase Emesis in Subset of Patients With No Acute Phase Emesis by Treatment Group Regardless of Rescue Therapy (Delayed Phase)— Protocols 052 and 054 Combined (Modified-Intention-to-Treat Analysis)

	Aprepitant Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Protocol 052				
No emesis in delayed phase	202/234	(86.3)	143/206[†]	(69.4)
≥1 emetic episode in delayed phase	32/234	(13.7)	63/206	(30.6)
Protocol 054				
No emesis in delayed phase	172/217[‡]	(79.3)	117/181	(64.6)
≥1 emetic episode in delayed phase	45/217	(20.7)	64/181	(35.4)
Combined Protocols 052 and 054				
No emesis in delayed phase	374/451[‡]	(82.9)	260/387[†]	(67.2)
≥1 emetic episode in delayed phase	77/451	(17.1)	127/387	(32.8)

[†] One (1) Standard Therapy patient (AN 8517) in Protocol 052 who had no emesis in acute phase and no delayed phase data was excluded.
[‡] One (1) aprepitant patient (AN 6267) in Protocol 054 who had no emesis in acute phase and no delayed phase data was excluded.

(Ref. Figure D-65 ise.pdf)

In the aprepitant group, 32% of the 69 patients with acute emetic episodes had no delayed emetic episodes. In contrast, only 15% of the 136 patients in the standard therapy group with acute emesis had no delayed emetic episodes.

Table 13

Categorization of Delayed Phase Emesis in Subset of Patients With Acute Phase Emesis by Treatment Group Regardless of Rescue Therapy (Delayed Phase)— Protocols 052 and 054 Combined (Modified-Intention-to-Treat Analysis)

	Aprepitant Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Protocol 052				
No emesis in delayed phase	8/26	(30.8)	10/54	(18.5)
≥1 emetic episode in delayed phase	18/26	(69.2)	44/54	(81.5)
Protocol 054				
No emesis in delayed phase	14/43	(32.6)	10/82	(12.2)
≥1 emetic episode in delayed phase	29/43	(67.4)	72/82	(87.8)
Combined Protocols 052 and 054				
No emesis in delayed phase	22/69	(31.9)	20/136	(14.7)
≥1 emetic episode in delayed phase	47/69	(68.1)	116/136	(85.3)

(Ref. Figure D-66 ise.pdf)

Although the analysis was not pre-specified, the data show that regardless of the presence or absence of acute emesis, the aprepitant regimen produced superior control of delayed emesis than standard therapy. The prevention of delayed emesis with the aprepitant regimen cannot be solely a consequence of a primary prevention of acute emesis ("carry-over effect").

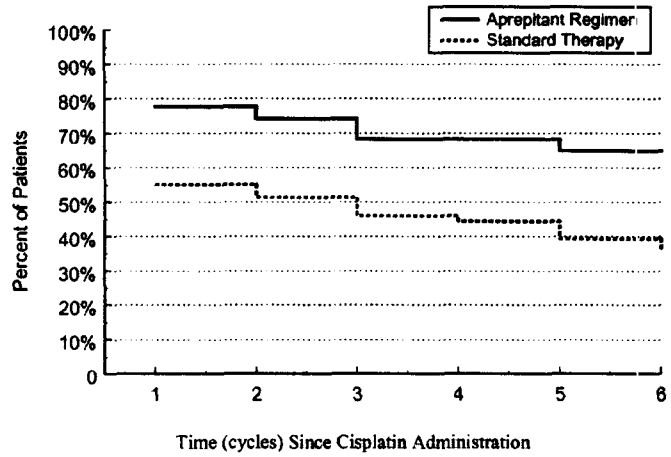
Multiple-Cycle extension (Cycles 2 to a maximum of Cycle 6)

In both Phase III studies the multiple-cycle extension (Cycles 2 to a maximum of Cycle 6) was optional. During the multiple-cycle extension, efficacy data were collected for the no emesis endpoint and for no significant nausea ("absence of nausea that interfered with normal activities."). During the multiple cycles, these data were captured as a binary response (Yes, No) for the 2 endpoints of interest.

In pre specified analysis of time to first emesis during the multiple-cycle extension, the Kaplan-Meier curves demonstrate that efficacy was better maintained with the aprepitant regimen than with standard therapy. Additionally, the time to first emesis was longer in patients in the aprepitant group compared with the standard therapy group.

Table 14

Kaplan-Meier Curves of Continued Success Rate for
Time (Cycle) to First Emesis in Protocol 052—Cycles 1 to 6
(Modified-Intention-to-Treat Analysis)

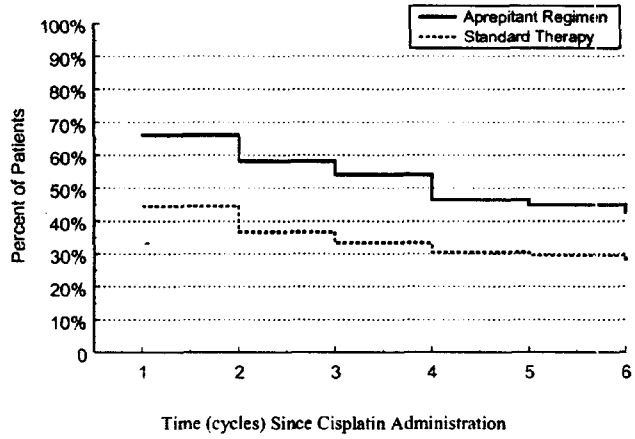


Patients in Each Cycle						
Aprepitant Regimen:	N = 260	N = 132	N = 101	N = 61	N = 42	N = 31
Standard Therapy:	N = 260	N = 104	N = 68	N = 32	N = 17	N = 12

(Ref. Figure D-10 ise.pdf)

Table 15

Kaplan-Meier Curves of Continued Success Rate for
Time (Cycle) to First Emesis in Protocol 054—Cycles 1 to 6
(Modified-Intention-to-Treat Analysis)



Patients in Each Cycle						
Aprepitant Regimen:	N = 260	N = 124	N = 84	N = 58	N = 28	N = 20
Standard Therapy:	N = 263	N = 97	N = 65	N = 48	N = 29	N = 17

(Ref. Figure D-13 ise.pdf)

D. Efficacy Conclusions

The sponsor successfully demonstrated the aprepitant regimen was superior to standard therapy for the primary endpoint, complete response in the overall phase as well as the secondary endpoints of complete response in the acute and delayed phases. The no vomiting endpoint was also superior to standard therapy in the overall, acute and delayed phases.

The aprepitant regimen was less effective for the secondary endpoints that were specifically related to nausea alone. The more frequent use of rescue medication in the standard therapy group may have affected efficacy outcome in regard to endpoints that were specifically related to nausea. Twenty-eight percent (28%) of the patients in the standard therapy group required rescue therapy compared to 18% in the aprepitant group.

Chemotherapy induced nausea and vomiting is a clinical syndrome. It is difficult to analyze and separate nausea from vomiting since the progression of nausea leads to vomiting. When taking into consideration that a higher proportion of patients in the Standard Therapy group used rescue therapy, the analyses are supportive for the composite endpoint of nausea and vomiting.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Overall, the incidence of clinical and laboratory adverse events was similar between treatment groups. Serious adverse events were also balanced, occurring in approximately 13% of the patients. In general, the aprepitant regimen was well tolerated and did not appear to significantly alter the toxicity of concomitant chemotherapy.

Aprepitant has a complex metabolic pathway. It is a substrate, a moderate inhibitor, as well as an inducer of CYP3A4. In addition to this, aprepitant is also an inducer of CYP2C9.

There was limited data available for chemotherapy that is metabolized via the CYP3A4 pathways. There were differences noted in serious hematologic and infection related serious adverse events during cycle 1. Some of these differences were not appreciated during the multi-cycle extension so the significance of these differences can not be ascertained. The differences noted during Cycle 1 and the theoretical risks of CPY3A4 drug-drug interactions warrant close post marketing observation and additional safety studies.

B. Description of Patient Exposure

Table 16

Total Number of Patients/Subjects on Aprepitant or L-758298 in the Development Program

	Aprepitant Capsules (Formulation D) FMI	Aprepitant Tablets (Formulations A, B, and C)	L-758298	Total
Clinical Pharmacology	356[†]	229[‡]	114	699
CINV Phase IIa	29	369	149[§]	547
CINV Phase IIb	368	0	0	368
CINV Phase III	549[‖]	0	0	549[‖]
Total CINV	946	369	149	**1464**
Non-CINV Studies	180	926	66	1172
Total	**1482**	**1524**	**329**	**3335**

[†] Eight (8) of these patients are incorrectly recorded in the SAS transport files as having received tablets; 11 of these patients also received gel capsules in addition to the regular capsules.
[‡] Sixty (60) additional patients received tablets but also received capsules and are represented only in the capsule column.
[§] Sixty-two (62) of these patients also received aprepitant tablets (300 mg) on Days 2 to 5 but are not counted in the tablets column.
[‖] Includes 2 adolescent patients in Protocol 052.
CINV = Chemotherapy-induced nausea and vomiting.
FMI = Final Market Image (nanoparticle capsule formulation).

(Ref Table E-3 iss.pdf)

Overall, 3335 patients were evaluated during development of aprepitant. One thousand one hundred three patients (549 in the aprepitant group and 554 in the standard therapy group) were enrolled in the 2 Phase III CINV studies, Protocol 052 and Protocol 054. Four of these patients were adolescents (Protocol 052).

C. Methods and Specific Findings of Safety Review

Safety data from the Phase II and Phase III studies were reviewed independently. The safety data was not merged because of differences between the aprepitant formulations and treatment regimens.

Combined safety analyses were performed on the Phase III data pooled from Protocols 052 and 054. The Integrated Summary of Safety included all adverse experiences that occurred in Cycle 1 and any adverse experiences that occurred in the multiple-cycle extension period that were considered serious, drug related, or caused study discontinuation.

D. Adequacy of Safety Testing

Appropriate safety monitoring for patients receiving the aprepitant regimen was performed. The Applicant was very through in performing safety analysis.

E. Safety Conclusions

The Phase III studies evaluated a broad age range of patients. The majority of the patients ranged between 35-74 years of age. There were an inadequate number of Asian and Black patients to evaluate for possible interaction with race.

Aprepitant has a complex metabolic pathway. It has been identified as a substrate, a moderate inhibitor, as well as an inducer of CYP3A4. The potential for serious drug-drug interactions with chemotherapeutic agents has not been thoroughly evaluated. During the Phase III trials, approximately 95% of the patients received a concomitant chemotherapeutic agent in addition to the protocol cisplatin. Of these patients, 517 were treated with a concomitant chemotherapy metabolized through 3A4 pathways. In spite of this, there is only limited safety data for most CYP3A4 metabolized oncologic agents.

Adverse Events

During Cycle 1, 69% of the patients in the aprepitant group and 67% in the standard therapy group experienced an adverse event. Overall, the incidence of most adverse events were similar between treatment groups.

The most common adverse experiences that occurred more frequently (>2% difference) in the aprepitant group compared with the standard therapy group include: asthenia/fatigue (17.8% and 11.8%), dizziness (6.6% and 4.4%), diarrhea (10.3% and 7.3%), cough (2.4% and 0.5%), and hiccups (10.8% and 5.6%).

Severe Adverse Events (Cycle 1)

Serious adverse experiences occurred in 73 out of 544 patients (13.4%) in the aprepitant group and 74 out of 550 patients (13.5%) in the standard therapy group during Cycle 1. The incidence of infection-related serious adverse events was higher in the aprepitant group during Cycle 1, with 3.7% of the aprepitant group developing a infection-related serious adverse event compared to 2.4% in the standard therapy group.

Table 17

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

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Patients with one or more serious adverse experiences	73	(13.4)	74	(13.5)
Patients with no serious adverse experience	471	(86.6)	476	(86.5)
Body as a Whole/Site Unspecified	**27**	**(5.0)**	**21**	**(3.8)**
Abdominal pain	2	(0.4)	0	(0.0)
Abnormal consciousness	0	(0.0)	1	(0.2)
Asthenia/fatigue	0	(0.0)	1	(0.2)
Cardiopulmonary failure	1	(0.2)	3	(0.5)
Chills	0	(0.0)	1	(0.2)
Collapse	0	(0.0)	1	(0.2)
Dehydration	10	(1.8)	5	(0.9)
Dizziness	1	(0.2)	1	(0.2)
Drug overdose	0	(0.0)	1	(0.2)
Fever	3	(0.6)	2	(0.4)
Fistula	1	(0.2)	0	(0.0)
Infection	2	(0.4)	1	(0.2)
Malignant neoplasm	2	(0.4)	0	(0.0)
Metastatic neoplasm of known primary	2	(0.4)	1	(0.2)
Sepsis	2	(0.4)	0	(0.0)
Septic shock	3	(0.6)	2	(0.4)
Syncope	2	(0.4)	2	(0.4)
Unknown cause of death	1	(0.2)	1	(0.2)
Upper respiratory infection	1	(0.2)	0	(0.0)
Cardiovascular System	**17**	**(3.1)**	**17**	**(3.1)**
Acute myocardial infarction	0	(0.0)	1	(0.2)
Angina pectoris	1	(0.2)	1	(0.2)
Arrhythmia	1	(0.2)	1	(0.2)
Arterial thrombosis	0	(0.0)	1	(0.2)
Atrial fibrillation	2	(0.4)	1	(0.2)
Cardiac arrest	2	(0.4)	3	(0.5)
Cardiogenic shock	0	(0.0)	1	(0.2)
Cerebral infarction	0	(0.0)	1	(0.2)
Cerebrovascular accident	1	(0.2)	1	(0.2)
Deep venous thrombosis	3	(0.6)	2	(0.4)
Hemorrhage	0	(0.0)	1	(0.2)
Hypovolemic shock	0	(0.0)	1	(0.2)

(Ref. Table E-69 ISS.pdf)

Table 17 (cont)

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

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Myocardial infarction	3	(0.6)	0	(0.0)
Orthostatic hypotension	0	(0.0)	1	(0.2)
Pulmonary edema	1	(0.2)	0	(0.0)
Pulmonary embolism	4	(0.7)	3	(0.5)
Vascular stenosis	0	(0.0)	1	(0.2)
Venous infusion infection	1	(0.2)	0	(0.0)
Venous thrombosis	1	(0.2)	1	(0.2)
Digestive System	**10**	**(1.8)**	**16**	**(2.9)**
Candida esophagitis	1	(0.2)	0	(0.0)
Constipation	0	(0.0)	1	(0.2)
Diarrhea	3	(0.6)	2	(0.4)
Duodenitis	1	(0.2)	0	(0.0)
Erosive esophagitis	1	(0.2)	0	(0.0)
Esophageal malignant neoplasm	0	(0.0)	1	(0.2)
Esophageal tear	1	(0.2)	0	(0.0)
Esophagitis	0	(0.0)	1	(0.2)
Gastritis	1	(0.2)	0	(0.0)
Gastrointestinal perforation	1	(0.2)	2	(0.4)
Hiatal hernia	1	(0.2)	0	(0.0)
Intestinal obstruction	0	(0.0)	1	(0.2)
Nausea	1	(0.2)	1	(0.2)
Necrotizing enterocolitis	1	(0.2)	0	(0.0)
Oral candidiasis	0	(0.0)	1	(0.2)
Pancreatitis	0	(0.0)	1	(0.2)
Paralytic ileus	1	(0.2)	0	(0.0)
Perforating duodenal ulcer	1	(0.2)	0	(0.0)
Pseudomembranous enterocolitis	0	(0.0)	1	(0.2)
Stomatitis	0	(0.0)	2	(0.4)
Upper gastrointestinal hemorrhage	0	(0.0)	2	(0.4)
Vomiting	1	(0.2)	3	(0.5)
Endocrine System	**2**	**(0.4)**	**3**	**(0.5)**
Carcinoid syndrome	0	(0.0)	1	(0.2)
Diabetes mellitus	1	(0.2)	1	(0.2)
Diabetic ketoacidosis	0	(0.0)	1	(0.2)
Syndrome of inappropriate antidiuretic hormone	1	(0.2)	0	(0.0)

(Ref. Table E-69 ISS.pdf)

Table 17 (cont)

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

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Hemic and Lymphatic System	**22**	**(4.0)**	**16**	**(2.9)**
Anemia	2	(0.4)	0	(0.0)
Febrile neutropenia	7	(1.3)	7	(1.3)
Leukopenia	1	(0.2)	4	(0.7)
Neutropenia	12	(2.2)	6	(1.1)
Pancytopenia	1	(0.2)	3	(0.5)
Thrombocytopenia	4	(0.7)	1	(0.2)
Immune System	**0**	**(0.0)**	**1**	**(0.2)**
Hypersensitivity reaction	0	(0.0)	1	(0.2)
Metabolism and Nutrition	**3**	**(0.6)**	**6**	**(1.1)**
Hyperglycemia	0	(0.0)	1	(0.2)
Hypoglycemia	0	(0.0)	1	(0.2)
Hypokalemia	2	(0.4)	2	(0.4)
Hyponatremia	1	(0.2)	3	(0.5)
Musculoskeletal System	**1**	**(0.2)**	**4**	**(0.7)**
Bone malignant neoplasm	0	(0.0)	1	(0.2)
Bone pain	0	(0.0)	1	(0.2)
Leg pain	0	(0.0)	2	(0.4)
Muscular weakness	1	(0.2)	1	(0.2)
Nervous System	**0**	**(0.0)**	**3**	**(0.5)**
Encephalopathy	0	(0.0)	1	(0.2)
Head trauma	0	(0.0)	1	(0.2)
Spinal cord compression	0	(0.0)	1	(0.2)
Psychiatric Disorder	**2**	**(0.4)**	**0**	**(0.0)**
Confusion	1	(0.2)	0	(0.0)
Disorientation	1	(0.2)	0	(0.0)
Respiratory System	**14**	**(2.6)**	**14**	**(2.5)**
Airway obstruction	0	(0.0)	1	(0.2)
Aspiration pneumonia	1	(0.2)	0	(0.0)
Bacterial pneumonia	0	(0.0)	1	(0.2)
Chronic obstructive pulmonary disease	1	(0.2)	0	(0.0)
Dyspnea	3	(0.6)	2	(0.4)
Hemoptysis	0	(0.0)	1	(0.2)

(Ref. Table E-69 ISS.pdf)

Table 17 (cont)

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

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Hypoxia	0	(0.0)	1	(0.2)
Lower respiratory infection	0	(0.0)	1	(0.2)
Lung carcinoma	0	(0.0)	1	(0.2)
Lung malignant neoplasm	2	(0.4)	0	(0.0)
Non-small cell lung carcinoma	2	(0.4)	1	(0.2)
Pleural effusion	0	(0.0)	2	(0.4)
Pneumonia	4	(0.7)	3	(0.5)
Pneumonitis	0	(0.0)	1	(0.2)
Pneumothorax	1	(0.2)	0	(0.0)
Pulmonary hemorrhage	0	(0.0)	1	(0.2)
Respiratory insufficiency	5	(0.9)	1	(0.2)
Skin and Skin Appendages	**2**	**(0.4)**	**0**	**(0.0)**
Catheter site infection	1	(0.2)	0	(0.0)
Herpes zoster	1	(0.2)	0	(0.0)
Urogenital System	**9**	**(1.7)**	**8**	**(1.5)**
Acute renal failure	1	(0.2)	0	(0.0)
Breast cellulitis	1	(0.2)	0	(0.0)
Cystitis	0	(0.0)	1	(0.2)
Hematuria	0	(0.0)	1	(0.2)
Nephrotoxicity	1	(0.2)	1	(0.2)
Renal failure	1	(0.2)	1	(0.2)
Renal insufficiency	3	(0.6)	0	(0.0)
Testicular malignant neoplasm	0	(0.0)	1	(0.2)
Uremia	0	(0.0)	1	(0.2)
Urinary retention	1	(0.2)	0	(0.0)
Urinary tract infection	1	(0.2)	2	(0.4)

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

Aprepitant Regimen = Aprepitant 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.

Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.

CINV = Chemotherapy-induced nausea and vomiting.

P.O. = By mouth.

IV = Intravenous.

N = Number of adult patients who received at least one dose of study therapy.

(Ref. Table E-69 ISS.pdf)

Severe Adverse Events (Cycle 1)

By analyzing serious adverse events by body system, the most common serious adverse events were within the Body as a Whole/Site Unspecified body system. Twenty-seven (27) patients in the aprepitant group and 21 patients in the standard therapy group reported a serious adverse event in this category. The most frequently reported serious adverse event in this category was dehydration, occurring in 1.8% of the patients in the aprepitant group compared to 0.9% in standard therapy. This difference was not seen during the multi-cycle analysis, therefore the significance of this is uncertain.

The second most common serious adverse events were in the Hematologic and Lymphatic System. The most frequently reported serious adverse event in this category was neutropenia, which occurred more frequently in the aprepitant group (2.2%) than the standard therapy group (1.1%). By analyzing the data according to the NCI toxicity criteria, the severity of neutropenia was comparable across both treatment groups. The incidence of Grade 3 (severely abnormal) neutropenia was 5.6% and 5.9% in the aprepitant group and standard therapy group, respectively. The incidence of neutropenia categorized as Grade 4 (life threatening) was 1.5% in both treatment groups.

The incidence of febrile neutropenia was similar in the two treatment groups, and the incidence of leukopenia was higher in the standard therapy group.

The third most common serious adverse experiences were in the Cardiovascular System. The pattern of serious adverse experiences in the Cardiovascular System was generally similar in the two treatment groups with 17 patients in the aprepitant group and 17 patients in the standard therapy group.

Serious adverse events of respiratory insufficiency occurred more frequently in the aprepitant group (0.9%) compared with the standard therapy group (0.2%). The significance of this is uncertain since this trend did not continue during the multiple-cycle extension period.

Severe Adverse Events (Multiple-Cycle)

During the multiple-cycle extension, only adverse events that were serious, caused discontinuation of study therapy or were determined by the investigators to be drug-related were reported. Sixty-two (62) out of 394 patients (15.7%) in the aprepitant group and 72 out of 428 patients (16.8%) in the standard therapy group reported a serious adverse event during the multi-cycle extension.

Table 18

Number (%) of Patients With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System— CINV Phase III Studies (Cycles 2 to 6)

	Aprepitant Regimen (N=394)		Standard Therapy (N=428)	
	n	(%)	n	(%)
Patients with one or more serious adverse experiences	62	(15.7)	72	(16.8)
Patients with no serious adverse experience	332	(84.3)	356	(83.2)
Body as a Whole/Site Unspecified	**25**	**(6.3)**	**23**	**(5.4)**
Abdominal pain	1	(0.3)	1	(0.2)
Asthenia/fatigue	2	(0.5)	2	(0.5)
Bacteremia	1	(0.3)	0	(0.0)
Burn	0	(0.0)	1	(0.2)
Cardiopulmonary failure	1	(0.3)	0	(0.0)
Chest pain	0	(0.0)	1	(0.2)
Dehydration	5	(1.3)	6	(1.4)
Fever	5	(1.3)	4	(0.9)
Fistula	0	(0.0)	1	(0.2)
Flank Pain	1	(0.3)	0	(0.0)
Infection	2	(0.5)	1	(0.2)
Malignant neoplasm	1	(0.3)	1	(0.2)
Metastatic neoplasm of known primary	1	(0.3)	0	(0.0)
Metastatic neoplasm of unknown primary	1	(0.3)	1	(0.2)
Mucous membrane disorder	2	(0.5)	0	(0.0)
Peritonitis	0	(0.0)	1	(0.2)
Sarcoma	1	(0.3)	0	(0.0)
Sepsis	2	(0.5)	1	(0.2)
Septic shock	3	(0.8)	2	(0.5)
Syncope	0	(0.0)	1	(0.2)
Tumor lysis syndrome	0	(0.0)	1	(0.2)
Unknown cause of death	1	(0.3)	1	(0.2)
Cardiovascular System	**8**	**(2.0)**	**15**	**(3.5)**
Acute myocardial infarction	0	(0.0)	1	(0.2)
Bradycardia	1	(0.3)	0	(0.0)
Cardiac arrest	0	(0.0)	1	(0.2)
Cardiovascular anomaly	1	(0.3)	0	(0.0)
Cerebrovascular accident	0	(0.0)	2	(0.5)
Congestive heart failure	0	(0.0)	1	(0.2)
Deep venous thrombosis	3	(0.8)	1	(0.2)
Hypertension	1	(0.3)	0	(0.0)
Hypotension	0	(0.0)	1	(0.2)

(Ref. Table E-70 ISS.pdf)

Table 18 (cont)

Number (%) of Patients With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System— CINV Phase III Studies (Cycles 2 to 6)

	Aprepitant Regimen (N=394)		Standard Therapy (N=428)	
	n	(%)	n	(%)
Pericardial effusion	0	(0.0)	2	(0.5)
Phlebitis	0	(0.0)	1	(0.2)
Pulmonary embolism	2	(0.5)	4	(0.9)
Supraventricular tachycardia	1	(0.3)	0	(0.0)
Venous infusion infection	0	(0.0)	1	(0.2)
Venous thrombosis	1	(0.3)	2	(0.5)
Digestive System	**15**	**(3.8)**	**10**	**(2.3)**
Anorectal hemorrhage	1	(0.3)	1	(0.2)
Appendicitis	0	(0.0)	1	(0.2)
Constipation	0	(0.0)	1	(0.2)
Diarrhea	9	(2.3)	1	(0.2)
Gastrointestinal bleeding	1	(0.3)	0	(0.0)
Gastrointestinal perforation	0	(0.0)	1	(0.2)
Intestinal amebiasis	0	(0.0)	1	(0.2)
Intestinal obstruction	2	(0.5)	0	(0.0)
Melena	0	(0.0)	1	(0.2)
Nausea	0	(0.0)	1	(0.2)
Oral cavity malignant neoplasm	1	(0.3)	0	(0.0)
Perforating duodenal ulcer	1	(0.3)	0	(0.0)
Stomatitis	1	(0.3)	1	(0.2)
Tongue malignant neoplasm	1	(0.3)	0	(0.0)
Upper gastrointestinal hemorrhage	0	(0.0)	1	(0.2)
Vomiting	2	(0.5)	2	(0.5)
Endocrine System	**0**	**(0.0)**	**2**	**(0.5)**
Diabetes mellitus	0	(0.0)	1	(0.2)
Diabetic ketoacidosis	0	(0.0)	1	(0.2)
Hemic and Lymphatic System	**18**	**(4.6)**	**11**	**(2.6)**
Anemia	5	(1.3)	2	(0.5)
Febrile neutropenia	3	(0.8)	5	(1.2)
Leukopenia	0	(0.0)	1	(0.2)
Neutropenia	8	(2.0)	5	(1.2)
Pancytopenia	2	(0.5)	0	(0.0)
Thrombocytopenia	4	(1.0)	0	(0.0)

(Ref. Table E-70 ISS.pdf)

Table 18 (cont)

Number (%) of Patients With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System— CINV Phase III Studies (Cycles 2 to 6)

	Aprepitant Regimen (N=394)		Standard Therapy (N=428)	
	n	(%)	n	(%)
Metabolism and Nutrition	**4**	**(1.0)**	**4**	**(0.9)**
Anorexia	1	(0.3)	1	(0.2)
Electrolyte imbalance	1	(0.3)	0	(0.0)
Hypercalcemia	0	(0.0)	1	(0.2)
Hyperglycemia	2	(0.5)	0	(0.0)
Hypoglycemia	0	(0.0)	1	(0.2)
Hypokalemia	1	(0.3)	0	(0.0)
Malnutrition	0	(0.0)	1	(0.2)
Musculoskeletal System	**2**	**(0.5)**	**1**	**(0.2)**
Back pain	1	(0.3)	0	(0.0)
Bone malignant neoplasm	1	(0.3)	0	(0.0)
Muscular weakness	0	(0.0)	1	(0.2)
Nervous System	**3**	**(0.8)**	**4**	**(0.9)**
Aphasia	0	(0.0)	1	(0.2)
Encephalopathy	0	(0.0)	1	(0.2)
Paresis	0	(0.0)	1	(0.2)
Seizure	2	(0.5)	0	(0.0)
Seizure Disorder	1	(0.3)	0	(0.0)
Vertigo	0	(0.0)	1	(0.2)
Psychiatric Disorder	**1**	**(0.3)**	**0**	**(0.0)**
Confusion	1	(0.3)	0	(0.0)
Respiratory System	**21**	**(5.3)**	**21**	**(4.9)**
Aspiration pneumonia	0	(0.0)	1	(0.2)
Bacterial pneumonia	0	(0.0)	1	(0.2)
Bronchitis	2	(0.5)	0	(0.0)
Chronic obstructive pulmonary disease	0	(0.0)	1	(0.2)
Dyspnea	1	(0.3)	1	(0.2)
Hemoptysis	0	(0.0)	1	(0.2)
Lower respiratory infection	1	(0.3)	0	(0.0)
Lung carcinoma	0	(0.0)	1	(0.2)
Lung malignant neoplasm	0	(0.0)	1	(0.2)
Non-small cell lung carcinoma	2	(0.5)	3	(0.7)
Pleural effusion	3	(0.8)	2	(0.5)
Pleural malignant neoplasm	1	(0.3)	0	(0.0)

(Ref. Table E-70 ISS.pdf)

Table 18 (cont)

Number (%) of Patients With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System— CINV Phase III Studies (Cycles 2 to 6)

	Aprepitant Regimen (N=394)		Standard Therapy (N=428)	
	n	(%)	n	(%)
Pneumonia	8	(2.0)	4	(0.9)
Pulmonary aspergillosis	1	(0.3)	0	(0.0)
Respiratory failure	0	(0.0)	1	(0.2)
Respiratory infection	1	(0.3)	0	(0.0)
Respiratory insufficiency	2	(0.5)	3	(0.7)
Small cell lung carcinoma	1	(0.3)	1	(0.2)
Thoracic empyema	1	(0.3)	1	(0.2)
Skin and Skin Appendages	**1**	**(0.3)**	**1**	**(0.2)**
Catheter site infection	1	(0.3)	0	(0.0)
Cellulitis	0	(0.0)	1	(0.2)
Urogenital System	**5**	**(1.3)**	**8**	**(1.9)**
Bladder malignant neoplasm	0	(0.0)	1	(0.2)
Cystitis	0	(0.0)	1	(0.2)
Epididymitis	0	(0.0)	1	(0.2)
Nephrotoxicity	0	(0.0)	1	(0.2)
Ovarian malignant neoplasm	1	(0.3)	0	(0.0)
Pyelonephritis	1	(0.3)	0	(0.0)
Renal failure	1	(0.3)	2	(0.5)
Urinary tract infection	1	(0.3)	3	(0.7)
Urinary tract obstruction	1	(0.3)	1	(0.2)

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

Aprepitant Regimen = Aprepitant 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.

Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.

CINV = Chemotherapy-induced nausea and vomiting.
P.O. = By mouth.
IV = Intravenous.
N = Number of adult patients who entered the extension.

(Ref. Table E-70 ISS.pdf)

Severe Adverse Events (Multiple-Cycle)

By analyzing serious adverse events by body system during the *multi-cycle* extension, the most common serious adverse events were within the Body as a Whole/Site Unspecified body system. The most frequently reported serious adverse event in this body system was dehydration, which occurred in 1.3% and

1.4% of the patients in the aprepitant group and standard therapy groups, respectively.

The second most common serious adverse events were those within the Respiratory System. In the Respiratory System, serious adverse experiences of pneumonia occurred more frequently in the aprepitant group (8 patients, 2.0%), compared to the standard therapy group (4 patients, 0.9%).

The third most common serious adverse events were in the Hematologic and Lymphatic System. The most frequently reported serious adverse event in this category was neutropenia, which occurred in 2.0% and 1.2% of the patients in the aprepitant group and the standard therapy group, respectively. The incidence of thrombocytopenia was higher in the aprepitant group than the standard therapy group. Four patients (1%) in the aprepitant group developed thrombocytopenia compared to no patients in the standard therapy group. The incidence of febrile neutropenia and leukopenia, however, was slightly more common in the standard therapy group. The significance of these hematologic findings is uncertain.

Laboratory Adverse Experiences

In the aprepitant group 22% of the patients reported at least one laboratory adverse event compared to 20% in the standard therapy group. Laboratory adverse experiences that occurred more frequently in the aprepitant group compared with the standard therapy group include: alkaline phosphatase increased (2.1% and 0.2%) and aspartate aminotransferase increased (3.0% and 1.3%). The majority of these abnormalities were graded as 1 (mildly abnormal) or 2 (moderately abnormal), according to the NCI toxicity criteria.

Serious laboratory adverse experiences were infrequent during Cycle 1, occurring in 1 patient in each group. During the multiple-cycle extension, serious laboratory adverse experiences were infrequent and occurred in 4 out of 375 patients (1.1%) in the aprepitant group and 2 out of 412 patients (0.5%) in the standard therapy group.

Table 19

Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence ≥2% in One or More Treatment Groups) by Laboratory Test Category—CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n/m	(%)	n/m	(%)
Patients with one or more laboratory adverse experiences	119/539	(22.1)	106/543	(19.5)
Patients with no laboratory adverse experience	420/539	(77.9)	437/543	(80.5)
Blood Chemistry	**76/537**	**(14.2)**	**64/542**	**(11.8)**
Alanine aminotransferase increased	31/536	(5.8)	23/537	(4.3)
Alkaline phosphatase increased	11/536	(2.1)	1/538	(0.2)
Aspartate aminotransferase increased	16/535	(3.0)	7/537	(1.3)
Blood urea nitrogen increased	25/537	(4.7)	19/540	(3.5)
C-reactive protein increased	0/†		1/2	(50.0)
Carbon dioxide partial pressure increased	0/2	(0.0)	1/3	(33.3)
Hypocalcemia	0/4	(0.0)	1/6	(16.7)
Hypomagnesemia	2/4	(50.0)	0/2	(0.0)
Hypophosphatemia	1/1	(100)	0/1	(0.0)
Lactate dehydrogenase increased	0/†		1/1	(100)
Serum creatinine increased	20/537	(3.7)	23/540	(4.3)
Total serum protein decreased	0/4	(0.0)	1/3	(33.3)
Troponin I increased	0/1	(0.0)	1/1	(100)
Uric acid increased	1/4	(25.0)	0/3	(0.0)
Hematology	**29/537**	**(5.4)**	**35/538**	**(6.5)**
Granulocytes decreased	1/2	(50.0)	0/6	(0.0)
Neutrophils decreased	9/536	(1.7)	16/534	(3.0)
Platelets decreased	12/523	(2.3)	14/528	(2.7)
Prothrombin time decreased	0/3	(0.0)	1/5	(20.0)
Urinalysis	**42/528**	**(8.0)**	**33/527**	**(6.3)**
Proteinuria	35/528	(6.6)	28/526	(5.3)

† Indicates there was no associated laboratory test or there were no patients for whom the laboratory test was recorded.

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

Aprepitant Regimen = Aprepitant 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.

Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.

CINV = Chemotherapy-induced nausea and vomiting.
P.O. = By mouth.
IV = Intravenous.
n/m = Number of randomized Cycle 1 patients with laboratory adverse experiences/number of randomized Cycle 1 patients for whom the laboratory test was recorded.

(Ref. Table E-75 ISS.pdf)

Laboratory Adverse Experiences

The data presented as laboratory adverse experiences were dependent on the investigator's judgment that the abnormality fulfilled the criteria of an adverse experience. The Agency requested additional analysis for ALT and AST using the criteria > 2.5 x upper limit of normal. No statistically significant difference was found between the treatment groups with respect to the proportion of patients reporting elevated AST or ALT at either the of the two protocol specified time points.

Table 20

TABLE 1: Protocol 052
Number (and Percent) of Patients with
ALT > 2.5 ULN

	Aprepitant	Standard Therapy	Comparison: Aprepitant vs Standard Therapy
Day 6 - 8	18/236 (7.6%)	16/237 (6.8%)	p=0.72
Day 19 - 29	0/228 (0%)	2/228 (0.9%)	p=0.50

Number (and Percent) of Patients with
AST > 2.5 ULN

	Aprepitant	Standard Therapy	Comparison: Aprepitant vs Standard Therapy
Day 6 - 8	2/233 (0.9%)	2/233(0.9%)	p=0.99
Day 19 - 29	1/224 (0.5%)	0/227 (0%)	p=0.50

(Ref. Table 1 response.pdf date: 01-08-2003)

Table 21

TABLE 2: Protocol 054
Number (and Percent) of Patients with
ALT > 2.5 ULN

	Aprepitant	Standard Therapy	Comparison: Aprepitant vs Standard Therapy
Day 6 - 8	14/256 (5.5%)	18/254 (7.1%)	p=0.47
Day 19 - 29	5/245 (2.0%)	9/255 (3.5%)	p=0.42

Number (and Percent) of Patients with
AST > 2.5 ULN

	Aprepitant	Standard Therapy	Comparison: Aprepitant vs Standard Therapy
Day 6 - 8	5/251 (2.0%)	4/251 (1.6%)	p=0.99
Day 19 - 29	1/243 (0.4%)	5/253 (2.0%)	p=0.22

(Ref. Table 2 response.pdf date: 01-08-2003)

In general, the pattern of abnormal laboratory findings was similar between treatment groups during Cycle 1. The incidences of decreased neutrophil counts categorized as NCI Grade 3 (<1000/mm 3) were 5.6% and 5.9% in the aprepitant group and standard therapy group, respectively. The incidence of decreased neutrophil counts categorized as Grade 4 (<500/mm 3) was 1.5% in both treatment groups. The pattern of abnormal hematological toxicity (Grades 3 and 4) was comparable across both treatment groups for Cycles 2 to 6.

Deaths - Cycle 1

The incidence of fatal adverse experiences was balanced between treatment groups, with 20 patients in each group (total 40 deaths).

The incidence of fatal hematologic adverse experiences was small, but higher in the aprepitant group (0.7%) compared with the standard therapy group (0.2%).

Deaths attributed to respiratory adverse events occurred in 7 patients in each group. However, the specific adverse experience of respiratory insufficiency resulting in death was more common in the aprepitant group (5 patients [0.9%]) compared with the standard therapy group (1 patient [0.2%]).

The applicant states a temporal relationship to the aprepitant regimen could not be identified, however, four of these five patients received vinorelbine as a concomitant chemotherapy. The aprepitant regimen may have affected the pulmonary toxicity of vinorelbine. The significance of this finding is uncertain since this trend did not continue into the multi-cycle extension. During the multiple-cycle extension the number of patients who died due to respiratory failure or respiratory insufficiency was the same in the aprepitant group as the standard therapy group (n=2 in each group)

Table 22

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

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Patients with one or more adverse experiences resulting in death	20	(3.7)	20	(3.6)
Patients with no adverse experience resulting in death	524	(96.3)	530	(96.4)
Body as a Whole/Site Unspecified	**8**	**(1.5)**	**7**	**(1.3)**
Cardiopulmonary failure	1	(0.2)	3	(0.5)
Malignant neoplasm	2	(0.4)	0	(0.0)
Metastatic neoplasm of known primary	0	(0.0)	1	(0.2)
Sepsis	1	(0.2)	0	(0.0)
Septic shock	3	(0.6)	2	(0.4)
Unknown cause of death	1	(0.2)	1	(0.2)
Cardiovascular System	**6**	**(1.1)**	**6**	**(1.1)**
Arrhythmia	1	(0.2)	1	(0.2)
Cardiac arrest	2	(0.4)	3	(0.5)
Cardiogenic shock	0	(0.0)	1	(0.2)
Cerebrovascular accident	0	(0.0)	1	(0.2)
Hemorrhage	0	(0.0)	1	(0.2)
Myocardial infarction	1	(0.2)	0	(0.0)
Pulmonary embolism	2	(0.4)	2	(0.4)
Digestive System	**1**	**(0.2)**	**3**	**(0.5)**
Esophageal malignant neoplasm	0	(0.0)	1	(0.2)
Gastrointestinal perforation	0	(0.0)	1	(0.2)
Necrotizing enterocolitis	1	(0.2)	0	(0.0)

(Ref. Table E-105 ISS.pdf)

Table 22 (cont)

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

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Stomatitis	0	(0.0)	1	(0.2)
Upper gastrointestinal hemorrhage	0	(0.0)	1	(0.2)
Hemic and Lymphatic System	**4**	**(0.7)**	**1**	**(0.2)**
Febrile neutropenia	1	(0.2)	0	(0.0)
Leukopenia	0	(0.0)	1	(0.2)
Neutropenia	2	(0.4)	1	(0.2)
Pancytopenia	1	(0.2)	0	(0.0)
Thrombocytopenia	1	(0.2)	0	(0.0)
Metabolism and Nutrition	**1**	**(0.2)**	**0**	**(0.0)**
Hypokalemia	1	(0.2)	0	(0.0)
Respiratory System	**7**	**(1.3)**	**7**	**(1.3)**
Airway obstruction	0	(0.0)	1	(0.2)
Aspiration pneumonia	1	(0.2)	0	(0.0)
Chronic obstructive pulmonary disease	1	(0.2)	0	(0.0)
Dyspnea	1	(0.2)	2	(0.4)
Hemoptysis	0	(0.0)	1	(0.2)
Lung carcinoma	0	(0.0)	1	(0.2)
Lung malignant neoplasm	1	(0.2)	0	(0.0)
Non-small cell lung carcinoma	1	(0.2)	1	(0.2)
Pulmonary hemorrhage	0	(0.0)	1	(0.2)
Respiratory insufficiency	5	(0.9)	1	(0.2)
Urogenital System	**0**	**(0.0)**	**2**	**(0.4)**
Testicular malignant neoplasm	0	(0.0)	1	(0.2)
Uremia	0	(0.0)	1	(0.2)

Aprepitant Regimen = Aprepitant 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.

Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.

CINV = Chemotherapy-induced nausea and vomiting.
P.O. = By mouth.
IV = Intravenous.
N = Number of adult patients who received at least one dose of study therapy.

(Ref. Table E-105 ISS.pdf)

III. Dosing, Regimen, and Administration Issues

Proposed Indication(s):

In combination with other antiemetic agents, 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.

Dose: 125mg capsule orally 1 hour prior to chemotherapy (Day 1)
80mg capsule orally in the morning on Day 2 and Day 3

Regimen: Aprepitant is taken for 3 days as part of a regimen that includes a corticosteroid administered daily for 4 days and a 5-HT_3 antagonist administered on Day 1, 30 minutes prior to chemotherapy.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

During the Phase III trials a treatment by gender interaction was identified in one of the 2 pivotal studies, Study 052. The efficacy of the aprepitant regimen was statistically superior to standard therapy in all three phases for female patients however, was only numerically better for male patients in Study 052. The treatment by gender interaction seen in Study 052 did not occur in Study 054. For the complete response endpoints, the MK-0869 regimen was statistically superior to standard therapy in all three phases for both male and female patients.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Analysis by Age

A total of 311 patients 65 years or older were evaluated in this NDA. The aprepitant regimen was more efficacious than the standard therapy for all age groups. There did not appear to be a specific treatment-by-age interaction.

Table 24
Protocol 052 and 054
Breakdown by Patient's Age

Age < 65	357	375
Age ≥ 65	163	148
Age < 75	492	500
Age ≥ 75	28	23

(Ref. Modified Table D-74 ise.pdf)

Analysis by Race

Table 25

Protocol 052 and 054
Breakdown by Race

Asian	16	11
Black	25	21
Hispanic	64	70
Multi-Racial	98	104
White	317	317

(Ref. Modified Table D-74 ise.pdf)

The majority of patients recruited were Caucasian (White). The number of Asian, Black and Hispanic patients were too small to permit meaningful analysis.

C.

1)

2)

D. Comments on Data Available or Needed in Other Populations

5-HT3 antagonists

During the development of aprepitant regimen the sponsor only evaluated granisetron and ondansetron. There is presently no safety data on the use on the use of the aprepitant regimen with dolasetron.

Chemotherapy (CYP3A4)

During the Phase III trials, 517 adult patients were treated with a concomitant chemotherapy metabolized through 3A4 pathways. In spite of the number of patients, there is only limited safety data on most CYP3A4 metabolized agents. The applicant has no safety data for irinotecan or imatinib, and has only very limited information on several others.

Table 26
CYP3A4 Metabolized Chemotherapy
Exposure

Chemotherapy	Aprepitant Regimen (N=547)		Standard Therapy (N=552)	
	n	(%)	n	(%)
Any Chemotherapy	520	95%	530	96%
Chemotherapy (CYP3A4)	**266**	**49%**	**251**	**46%**
Imatinib	0	0%	0	0%
Irinotecan	0	0%	1	0.2%
Ifosfamide	2	0.4%	1	0.2%
Vincristine	2	0.4%	0	0%
Vinblastine	11	2%	12	2%
Docetaxel	11	2%	14	3%
Paclitaxel	52	10%	58	11%
Vinorelbine tartrate	84	15%	80	15%
Etoposide	106	19%	92	17%

Amifostine

Amifostine was specifically part of the Exclusion Criteria because of its association with nausea and vomiting. Amifostine is used to decrease the toxicity of chemotherapeutic agents, including cisplatin. There is a high potential for these drugs to be utilized together. Amifostine is not a CYP3A4 substrate or inducer, however the safety of co-administration with aprepitant has not been evaluated and should be considered.

X. Conclusions and Recommendations

A. Conclusions

The sponsor successfully demonstrated the aprepitant regimen was superior to standard therapy for the primary endpoint, complete response in the overall phase as well as the secondary endpoints of complete response in the acute and delayed phases. The no vomiting endpoint was also superior to standard therapy in the overall, acute and delayed phases.

The aprepitant regimen was less effective for the secondary endpoints that were specifically related to nausea alone. Chemotherapy induced nausea and vomiting is a clinical syndrome. It is difficult to analyze and separate nausea from vomiting since the progression of nausea leads to vomiting.

When taking into consideration that a higher proportion of patients in the standard therapy group used rescue therapy, the analyses are supportive for the composite endpoint of chemotherapy induced nausea and vomiting.

In general, the adverse experience profile was comparable in both treatment groups. The overall incidence of serious adverse experiences was similar in the two treatment groups in Cycle 1. Thirteen percent (13%) of the aprepitant group and 14% of the standard therapy group reported a serious adverse event during cycle 1. During the multiple-cycle extension, 16% of the aprepitant group and 17% in the standard therapy group reported a serious adverse event.

There were more infection-related adverse events reported in the aprepitant group compared to the standard therapy group. Serious infection-related adverse events occurred in 3.7% of the patients in the aprepitant group during Cycle 1, compared to 2.4% of the patients in the standard therapy group. The significance of this is uncertain.

Aprepitant is a moderate 3A4 inhibitor. When analysis was performed in patients receiving a 3A4-metabolized chemotherapy, a higher incidence of hematologic and infection related serious adverse events was seen in the aprepitant group during cycle 1. The numbers of patients were small, and the differences between treatment groups were too small to establish a definitive conclusion.

B. Recommendations

The data submitted by the Applicant supports approval of aprepitant for use in the defined treatment regimen for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic chemotherapy.

I am in agreement with the recommendations of the Advisory Committee members. The present data is sufficient to grant approval with appropriate labeling that clearly defines the limitations of the present exposure and safety data with regard to the co-administration of aprepitant with certain chemotherapeutic agents. A definitive safety signal was not identified during this review, however, additional post-marketing studies will be useful for developing a safety profile with a broader range of chemotherapeutic agents.

The label must emphasize that aprepitant acts as a CYP3A4 inhibitor when administered according to the treatment regimen, but can become a CPY3A4 inducer if administered for longer periods of time.

XI. Appendix

A. Study 052 (filed separately in DFS)
B. Study 054 (filed separately in DFS)

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

/s/

Gary DellaZanna
3/14/03 09:17:22 AM
MEDICAL OFFICER

Make sure you only have 1 clinical review to sign off. I got an error bringing it into DFS

Joyce Korvick
3/14/03 10:01:53 AM
MEDICAL OFFICER