

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-023

MEDICAL REVIEW



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

MEMORANDUM

DATE: 1/25/08

FROM: Joyce A Korvick, MD, MPH
DGP/ODE III

SUBJECT: Deputy Division Director Action Recommendations

APPLICANT: Merck

DRUG: NDA 22-023,
Emend® (fosprepitant dimeglumine) for Injection, 115 mg/10mL

DIVISION RECOMMENDATION:

I concur with the medical review team regarding the efficacy evaluation for this product. We recommend the approval of this NDA.

I. Regulatory History:

This new drug application provides for the use of Emend (fosaprepitant dimeglumine) for Injection, 115 mg 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.
- the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

During the original review of this NDA there were several CMC deficiencies recognized which led to an approvable letter 5/3/07 (please refer to letter for details).

In addition there were several issues raised by the clinical pharmacology group and included in the approvable letter:

1. Regarding the drug interaction with diltiazem (Study Protocol 011): For a closer evaluation of the effect of I.V. fosaprepitant on the systolic and diastolic pressures of hypertensive patients receiving oral diltiazem, please provide the following information:

- A table for individual data listing of systolic and diastolic pressures at various time points for baseline, when diltiazem was given alone, and when diltiazem was coadministered with fosaprepitant, respectively. Also include changes from baseline and fosaprepitant concentrations in different columns of the same table. Evaluate the relationship between fosaprepitant concentration and difference in systolic and diastolic pressures between the two treatments (with and without fosaprepitant).
- A table for maximum change from baseline and the time associated with this maximum change for systolic and diastolic pressures for each individual when diltiazem was given alone, and when diltiazem was coadministered with fosaprepitant. Also include summary statistics (mean, SD, max, min) in the table.

The present submission has addressed these issues to the satisfaction of the Chemistry Review Group. The review included final labeling negotiations by the clinical, chemistry and clinical pharmacology groups (see final label).

The approval of this NDA will provide an intravenous, pro-drug formulation of aprepitant for the use on the first day of a 3 day regimen to treat CINV.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

The Trade-name was agreed to by the DDMAC and DMETS.

B. SEALD:

No new comments.

C. Chemistry and Manufacturing:

D. Pre-Clinical Pharmacology/Toxicology:

No new issues.

E. Biopharmaceutics:

The review of clinical pharmacokinetics recommended approval of this formulation based upon recommended labeling changes. These changes were regarding characterization of the IV profile and further characterization of the drug-drug interactions. See final label for details.

F. Clinical/Statistical:

This was reported in this last review. Of interest, and reflected in the label is mild effect on the blood pressure of patients receiving Emend and Diltiazem concomitantly. This study included 9 patients and the reviewers felt, in consultation with the Cardiorenal Division, it was worth more study and should be labeled and used with caution. This is the subject of a Post-marketing Commitment (see below).

Efficacy:

As mentioned in the Clinical Pharmacology review, this is an intravenous formulation of the oral EMEND. As is expected the CMAX is higher but AUCs are similar when comparing IV to oral preparations. As this is the first dose of a 3 day regimen, there were no efficacy studies conducted, however, a study using this regimen was conducted for safety.

Safety:

The interaction of fosprepitant with diltiazem was studied in Study 011. The following are comments from the Medical Review:

“Study 011 was one of 13 studies in the database, and was designed to investigate pharmacokinetics and pharmacodynamics of concurrent administration of diltiazem and fosaprepitant/aprepitant in hypertensive patients. The study showed that a single dose of fosaprepitant (100 mg I.V.) brought about 6.0 mm Hg decreases of the mean systolic blood pressures, as compared with the no-medication control. No clinically meaningful changes were found (heart rate, PR interval, QTc interval and clinical signs were examined). Upon DGP’s request, Merck submitted the detailed individual blood pressure data of Study 011 on July 27, 2007.”

“The detailed data from Study showed that a single dose of fosaprepitant (100 mg I.V.) in combination with diltiazem (120 mg P.O. t.i.d.) decreased the individual systolic pressures by up to 38 mm Hg, and the diastolic pressures by up to 49 mm Hg (July 27, 2007 submission). A blood pressure consult was placed by DGP on November 16, 2007. The response by Division of Cardiovascular and Renal Products (DCRP) was received on December 17, 2007.”

The Cardio-renal Consult made the following comments and recommendations:

“DCRP first reaction is that Study 011 is an inadequately powered trial rather unusually presented. By the study report’s power analysis the study had 90% power of detecting a difference of -10/-8, virtually diltiazem’s entire effect sized at trough. The sponsor’s presentation of the data is unusual in many ways:

- No summaries of baseline vital signs are provided in the original report. No data sets of the vital sign changes were provided in the NDA submission (that DCRP could find).
- The study collected baseline data at multiple timepoints but the analyses adjust using a single timepoint rather than using time-matched changes.
- The later submission summarizes changes only for the first two hours.
- The later submission summarizes changes in blood pressure with I.V. aprepitant (fosaprepitant-DGP reviewer) alone for protocol 009 but does not provide the corresponding data for Study 011.”

“However, within the limitations that the small Study 011 does not provide definitive answers, DCRP interpret the results as suggestive that I.V. fosaprepitant acutely reduces blood pressure slightly and acutely potentiates the effects of diltiazem upon blood pressure. Whether the latter effect is purely a PK interaction as the sponsor concludes cannot be determined from this study. DCRP is not greatly concerned that some of the individual decreases ranged to 49 mm Hg: The use of a single baseline timepoint to adjust as well as the methodology of picking the maximum values can lead to aberrantly high estimates of changes in individual readings.”

“According to DCRP, the point estimates of the mean maximum changes with fosaprepitant, about -6 mg Hg, are not worrisome by themselves. DCRP did not identify any suggestive problems with hypotensive adverse events in the fosaprepitant and apreipitant studies, but they did not review the adverse events thoroughly.”

The medical team and discussed this consult and felt that given the current AE profile where there was not an excessive amount of syncope reported, the further characterization of this drug interaction could be studied as a Post-Marketing Commitment. The sponsor agreed.

G. Pediatric Use:

Merck agrees to study this intravenous formulation (fospreipitant) in pediatric patients 6 months to 17 years. There are insufficient numbers of pediatric cancer patients to study under the age of 6 months.

III. Labeling Recommendations:

Labeling recommendations included CMC, Clinical Pharmacology (especially the drug-drug interaction section), and clinical. Essentially this label was a modification of the original oral EMEND label, where the changes made reflect information specific to the Intravenous formulation. Please refer to approval letter for final label.

IV. Post-Marketing Commitments:

1. Deferred pediatric study under PREA for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly and moderately emetogenic cancer chemotherapy including high dose cisplatin in pediatric patients ages 6 months to 17 years.

Study Start Date: Dec 31, 2008

Study Completion Date: Mar 31, 2011

Final Report Submission: June 30, 2011

2. Further characterize the effects of fosaprepitant on blood pressure.

Statistical Plan Submission: April 30, 2008

Study Start: April 30, 2008

Final Report Submission: by July 31, 2008

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/s/

Joyce Korvick
1/25/2008 06:34:15 PM
MEDICAL OFFICER



Memorandum

**MEDICAL OFFICER REVIEW
DIVISION OF GASTROENTEROLOGY PRODUCTS**

Date: January 14, 2008

From: Wen-Yi Gao, M.D., Ph.D., Medical Officer, DGP (HFD-180), ODE3, CDER

Through: Hugo Gallo-Torres, M.D., Ph.D., Medical Team Leader, DGP, ODE3, CDER

To: NDA 22-023/000 File

Sponsor: Merck Research Laboratories

Product: Fosaprepitant Dimeglumine for injection

Indication: Prevention of acute and delayed nausea and vomiting associated with cancer chemotherapy

Documents: Class II resubmission with 6-month PDUFA goal date (Submission date July 27 2007; Goal date January 27, 2008)

- Safety update (dated July 27, 2007);
- Results of Study 011 investigating the pharmacokinetics and pharmacodynamics of fosaprepitant/aprepitant in combination with diltiazem in hypertensive patients;
Consult review by Dr. Thomas Marciniak (Division of Cardiovascular and Renal Products (DCRP));
- Pediatric studies: The sponsor requested waiving pediatric studies;
- Labeling revisions

Subject: Recommendations for Regulatory Action

Review Completion Date: January 14, 2008

I. EXECUTIVE SUMMARY

The primary components of this Class II resubmission include 1) Results of Study 011 and 2) Labeling revisions. DGP requested additional information (Study 011) and safety update of NDA 22-023/000 on May 3, 2007. Merck Research Laboratories responded to this letter by providing detailed data of fosaprepitant in combination with diltiazem in decreasing blood pressures in hypertensive patients (Study 011) on July 27, 2007. No additional safety issue is identified in the resubmission. The results of Study 011 were reviewed by the consult reviewer Dr. Thomas Marciniak (DCRP) on December 17, 2007 (see Section III and Attachment 1).

Based on these updated results, we recommend:

- 1) **Approval** of NDA 22-023/000;
- 2) A Phase 4 post-marketing commitment to better characterize the effects of fosaprepitant upon blood pressure; and
- 3) The labeling revisions listed in Section V.

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II. BACKGROUND OF STUDY 011

Merck Research Laboratories submitted a set of safety database (13 studies) of fosaprepitant to support NDA 22-023/000 (for the prevention of cancer chemotherapy associated nausea and vomiting). Study 011 was one of 13 studies in the database, and was designed to investigate pharmacokinetics and pharmacodynamics of concurrent administration of diltiazem and fosaprepitant/aprepitant in hypertensive patients. The study showed that a single dose of fosaprepitant (100 mg I.V.) brought about 6.0 mm Hg decreases of the mean systolic blood pressures, as compared with the no-medication control (n=8, see Attachment 1, Table 1). The single dose of fosaprepitant further decreased by 5.5 and 6.3 mm Hg, respectively, of diltiazem-induced reduction of systolic and diastolic blood pressures in these patients (Attachment 1, Table 3). No clinically meaningful changes were found (heart rate, PR interval, QTc interval and clinical signs were examined). Upon DGP request, Merck submitted the detailed individual blood pressure data of Study 011 on July 27, 2007.

The detailed data showed that a single dose of fosaprepitant (100 mg I.V.) in combination with diltiazem (120 mg P.O. t.i.d.) decreased the individual systolic pressures by up to 38 mm Hg, and the diastolic pressures by up to 49 mg Hg (see Tables 5 and 6, Attachment 1, July 27, 2007 submission). A blood pressure consult was placed by DGP on November 16, 2007. The response by Division of Cardiovascular and Renal Products (DCRP) was received on December 17, 2007.

III. COMMENTS AND RECOMMENDATIONS FROM DCRP (Dr. Thomas Marciniak)

DCRP first reaction is that Study 011 is an inadequately powered trial rather unusually presented. By the study report's power analysis the study had 90% power of detecting a difference of -10/-8, virtually diltiazem's entire effect sized at trough. The sponsor's presentation of the data is unusual in many ways:

- No summaries of baseline vital signs are provided in the original report. No data sets of the vital sign changes were provided in the NDA submission (that DCRP could find).
- The study collected baseline data at multiple timepoints but the analyses adjust using a single timepoint rather than using time-matched changes.
- The later submission summarizes changes only for the first two hours.
- The later submission summarizes changes in blood pressure with I.V. aprepitant (fosaprepitant-DGP reviewer) alone for protocol 009 but does not provide the corresponding data for Study 011.

However, within the limitations that the small Study 011 does not provide definitive answers, DCRP interpret the results as suggestive that I.V. fosaprepitant acutely reduces blood pressure slightly and acutely potentiates the effects of diltiazem upon blood pressure. Whether the latter effect is purely a PK interaction as the sponsor concludes cannot be determined from this study. DCRP is not greatly concerned that some of the individual decreases ranged to 49 mm Hg: The use of a single baseline timepoint to adjust as well as the methodology of picking the maximum values can lead to aberrantly high estimates of changes in individual readings.

According to DCRP, the point estimates of the mean maximum changes with fosaprepitant, about -6 mg Hg, are not worrisome by themselves. DCRP did not identify any suggestive problems with hypotensive adverse events in the fosaprepitant and aprepitant studies, but they did not review the adverse events thoroughly.

Recommendations of DCRP

“You need to judge whether your better knowledge of the adverse event profile for fosaprepitant and aprepitant suggests any increase in hypotensive event rates for these drugs. You may consider whether better characterization of the effects of fosaprepitant upon blood pressure should be left to a post-marketing commitment. We recommend starting with better analyses of the data in Study 011 and any other studies in which blood pressure was measured frequently (Protocol 009, others?)”

IV. COMMENTS AND RECOMMENDATIONS OF DGP MEDICAL REVIEWERS

1. DGP Medical Officers' Comments:

Fosaprepitant (four formulations) has been studied in 696 subjects in 13 clinical trials including Study Protocol 009, as mentioned by Dr. Marciniak. The most frequent adverse events in the studies of chemotherapy induced nausea and vomiting were abdominal pain,

constipation, diarrhea, dry mouth, dyspepsia, nausea and stomatitis. In our experience, hypotension has not been reported as a treatment-associated adverse event in the 13 trials.

We the DGP medical reviewers agree that Study 011 is an inadequately powered study and did not provide definitive answers which were pointed out by the DCRP consult reviewers. We did not identify any suggestive hypotensive adverse events of fosaprepitant in Study 011. As shown in Table 1, the mean maximum changes with fosaprepitant were approximately -6 mm Hg. These data suggest that I.V. fosaprepitant may acutely reduce blood pressure slightly and potentiate the effects of diltiazem on blood pressure in hypertensive patients. Since no definite answers can be given, we recommend further characterizing the effects of fosaprepitant on blood pressure in hypertensive patients with anti-cancer chemotherapy as a post-marketing commitment.

2. DGP Medical Officers' Regulatory Recommendations:
NDA 22-023/000 is recommended for approval.

The effects of fosaprepitant on blood pressure in hypertensive patients with anti-cancer chemotherapy should be further characterized as a post-marketing commitment.

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V. LABELING REVISIONS

The Sponsor's Proposed Label and the Reviewers' Proposed Label are as the following:

Sponsor's Proposed Label	Reviewers' Proposed Label
Pages 8-9 PRECAUTIONS ┌	PRECAUTIONS <i>General</i>

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ATTACHMENT 1

Synopsis of Study 011

Protocol Title: A Double-Blind, Randomized, 3-Period Study to Investigate the Effects of I.V. L-758298 (fosaprepitant)/Oral L-754030 (aprepitant) on Diltiazem Pharmacokinetics and Pharmacodynamics in Hypertensive Patients

Clinical Phase: 1

Duration of Treatment: Three 13-day periods

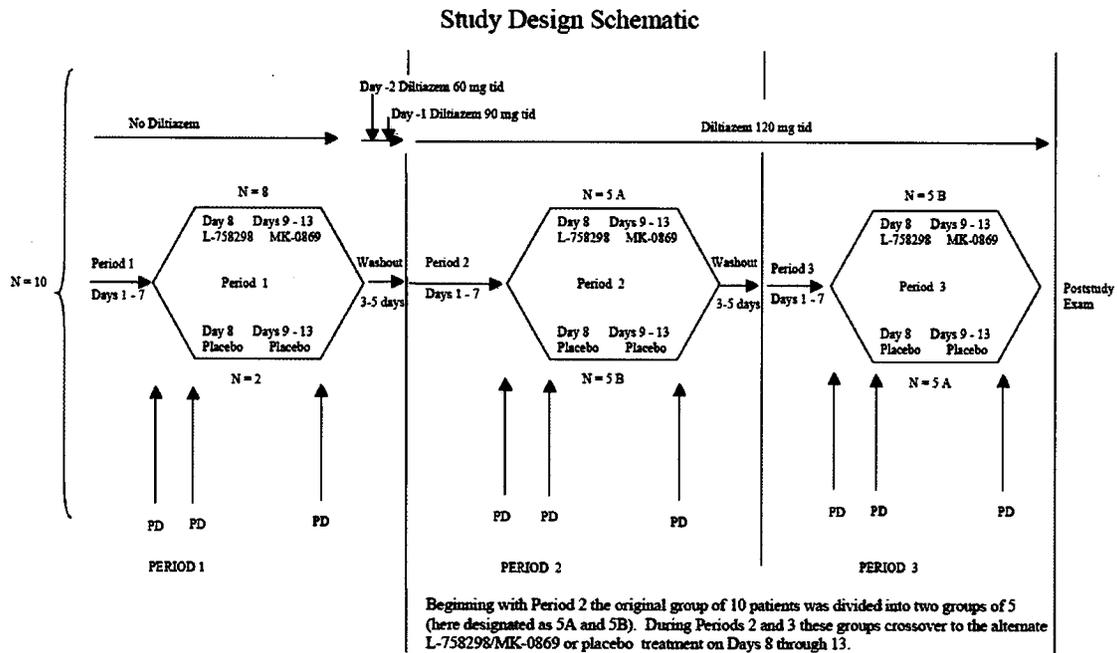
Objectives: (1) To investigate the safety and tolerability of concurrent administration of diltiazem and of fosaprepitant intravenous/aprepitant orally. (2) To determine the effect of concurrent administration of fosaprepitant I.V./aprepitant orally and diltiazem orally on PR interval, blood pressure, and heart rate. (3) To determine the effect of concurrent administration of fosaprepitant I.V./aprepitant orally and diltiazem orally on the plasma profile of diltiazem and its metabolites (desacetyldiltiazem and N-monodesmethyldiltiazem). (4) To confirm the absence of a clinically meaningful effect of fosaprepitant I.V./aprepitant orally on electrocardiogram indices and HR/BP. (5) To investigate the effect of concurrent administration of diltiazem and fosaprepitant I.V./aprepitant orally on the plasma concentrations of aprepitant, if a pharmacodynamic interaction (HR, BP, PR interval) or unanticipated adverse event not clearly attributable to diltiazem is observed.

Study Design: This was a double-blind, randomized, placebo-controlled, 3-period study with 10 hypertensive patients. Patients were to participate in all 3 periods. Period 1: Prior to the start of Period 1, patients had a 1- to 2-week washout from prior hypertensive medication. In Periods 2 and 3, treatments were administered according to a 2-period crossover design.

In Period 1, patients received no medications for 7 days. On Day 8, they were given 100 mg of fosaprepitant or placebo as a 15-minute intravenous infusion followed by 5 days (Days 9 to 13) of single oral 300-mg doses of aprepitant or placebo alone. Frequent ECG and vital signs monitoring was performed on Days 7, 8, and 13.

Diltiazem titration started prior to Period 2; all patients received diltiazem 60 mg orally 3 times daily on Day -2, diltiazem 90 mg orally 3 times daily on Day -1, and diltiazem 120 mg orally 3 times daily beginning on Day 1 of Period 2 and continuing through the end of Period 3 (including the 3- to 5-day washout between periods) and until the poststudy visit. Periods 2 and 3 were identical except: in 1 period, patients on Day 8 were given a 15-minute intravenous administration of 100 mg of fosaprepitant, and on Days 9 to 13 were administered a single 300-mg oral dose of aprepitant; and in the other period, patients were given placebo to match the fosaprepitant intravenous administration and placebo to match aprepitant. Frequent ECG and vital signs monitoring was performed on Days 8 (diltiazem 120 mg 3 times daily plus fosaprepitant or placebo) and 13 (diltiazem 120 mg 3 times daily plus aprepitant or placebo) of Periods 2 and 3, and on Day 7 of Period 2 only (after 7 days of diltiazem 120 mg 3 times daily).

Figure 1: Study Design Flow Chart



Diagnosis/Inclusion Criteria: This study was conducted in nonsmoking mildly to moderately hypertensive patients 18 to 55 years old, who were within 25% of their ideal body weight.

Results:

The sponsor reported changes of blood pressure, heart rate and ECG interval from baseline, as shown in Table 1 through Table 4.

Table 1: BP Results of Fosaprepitant vs. No Medication Control (Study 011 Period 1)

	Mean Maximum Change From Baseline		Geometric Mean Ratio (L-758298/No Medication) or Least Square Mean Difference (L-758298/No Medication)	90% Confidence Interval	p-Value
	L-758298 (N=8) [†]	No Medication (N=8) [†]			
PR interval (msec) [‡]	1.05	1.01	1.04	(0.99, 1.09)	0.172
QTc interval (msec) [‡]	1.01	1.02	0.99	(0.94, 1.03)	0.534
Systolic BP (mm Hg) [§]	-11.83	-5.88	-5.96	(-11.40, -0.52)	0.077
Diastolic BP (mm Hg) [§]	-8.25	-5.65	-2.60	(-6.91, 1.70)	0.289
Heart rate (beats/min) [§]	-8.33	-9.19	-0.85	(-2.58, 4.29)	0.652

[†] ECG data were not available for AN 1707.
[‡] Geometric mean maximum relative change from baseline and geometric mean ratio.
[§] Least square mean maximum moving average change from baseline and least square mean difference.
 BP = blood pressure

From the sponsor's submission on June 10, 2002

Table 2: BP Results of Aprepitant vs. No Medication Control (Study 011 Period 1)

	Mean Maximum Change From Baseline		Geometric Mean Ratio (MK-0869/ No Medication) or Least Square Mean Difference (MK-0869/No Medication)	90% Confidence Interval	p-Value
	MK-0869 (N=8) †	No Medication (N=8) †			
PR interval (msec)‡	1.06	1.01	1.05	(0.99, 1.10)	0.146
QTc interval (msec)‡	1.00	1.02	0.98	(0.94, 1.02)	0.397
Systolic BP (mm Hg)§	-13.33	-5.87	-7.46	(-18.06, 3.14)	0.224
Diastolic BP (mm Hg)§	-6.46	-5.65	-0.81	(-9.09, 7.46)	0.858
Heart rate (beats/min)§	-7.71	-9.19	1.48	(-2.04, 5.00)	0.452

† ECG data were not available for AN 1707.
‡ Geometric mean maximum relative change from baseline and geometric mean ratio.
§ Least square mean maximum moving average change from baseline and least square mean difference.
BP = blood pressure

From the sponsor's submission on June 10, 2002

Table 3: BP Results of Fosaprepitant vs. Diltiazem (Study 011 Periods 2 & 3)

	Geometric Mean MRCB† or Least Square Mean MMACB‡		Geometric Mean Ratio (With/ Without) or Least Square Mean Difference (With/Without)	90% Confidence Interval	p-Value
	Diltiazem With L-758298 (N=9)	Diltiazem Without L-758298 (N=9)			
PR interval (msec)†	1.19	1.13	1.05	(0.99, 1.12)	0.161
QTc interval (msec)†	1.01	1.00	1.01	(0.99, 1.04)	0.339
Systolic BP (mm Hg)‡	-24.37	-18.83	-5.54	(-10.88, -0.21)	0.090
Diastolic BP (mm Hg)‡	-16.84	-10.53	-6.32	(-10.39, -2.24)	0.022
Heart rate (beats/min)‡	-10.11	-6.18	-3.93	(-7.63, -0.24)	0.084

† Geometric mean maximum relative change from baseline and geometric mean ratio.
‡ Least square mean maximum moving average change from baseline and least square mean difference.
BP = blood pressure

From the sponsor's submission on June 10, 2002

Table 4: BP Results of Aprepitant vs. Diltiazem (Study 011 Periods 2 & 3)

	Geometric Mean MRCB† or Least Square Mean MMACB‡		Geometric Mean Ratio (With/ Without) or Least Square Mean Difference (With - Without)	90% Confidence Interval	p-Value
	Diltiazem With MK-0869 (N=9)	Diltiazem Without MK-0869 (N=9)			
PR interval (msec)†	1.17	1.12	1.04	(1.00, 1.09)	0.102
QTc interval (msec)†	1.00	1.02	0.98	(0.95, 1.01)	0.217
Systolic BP (mm Hg)‡	-12.66	-18.80	6.14	(-3.11, 15.40)	0.249
Diastolic BP (mm Hg)‡	-12.36	-12.72	0.36	(-6.17, 6.89)	0.920
Heart rate (beats/min)†	-5.53	-3.43	-2.09	(-7.43, 3.25)	0.482

† Geometric mean maximum relative change from baseline and geometric mean ratio.
‡ Least square mean maximum moving average change from baseline and least square mean difference.
BP = blood pressure

From the sponsor's submission on June 10, 2002

Upon DGP request, the sponsor submitted the individual BP data on July 27, 2007. The individual decreases of BP are summarized in Tables 5 and 6.

Table 5: Maximum Decrease of BP (mmHg) from Baseline in the Presence of Diltiazem with and without Fosaprepitant (Study 011 Periods 2 & 3, Individual Results)

Parameter	Alloc	Diltiazem With Fosaprepitant		Diltiazem Alone	
		Maximum Change	Hour	Maximum Change	Hour
DIASTOLIC	1601				
	1602				
	1603				
	1604				
	1605				
	1606				
	1608				
	1609				
	1610				
	1703				
	N	10		10	
	Mean	-24.3		-15.6	
	SD	10.2		4.1	
Min					
Max					
SYSTOLIC	1601				
	1602				
	1603				
	1604				
	1605				
	1606				
	1608				
	1609				
	1610				
	1703				
	N	10		10	
	Mean	-29.5		-23.8	
	SD	7.9		4.8	
Min					
Max					

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From the sponsor's submission on July 27, 2007, Table 5

Table 6: Maximum Decrease of BP (mmHg) from Baseline in the Presence of Diltiazem with and without Aprepitant (Study 011 Periods 2 & 3, Individual Results)

Parameter	Alloc	Diltiazem With Aprepitant		Diltiazem Alone		
		Maximum Change	Hour	Maximum Change	Hour	
DIASTOLIC	1601					
	1602					
	1603					
	1604					
	1605					
	1606					
	1608					
	1609					
	1610					
	1703					
	N		10		10	
	Mean		-18.9		-17.3	
	SD		10.0		6.8	
Min						
Max						
SYSTOLIC	1601					
	1602					
	1603					
	1604					
	1605					
	1606					
	1608					
	1609					
	1610					
	1703					
	N		10		10	
	Mean		-19.7		-23.0	
	SD		10.7		10.8	
Min						
Max						

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From the sponsor's submission on July 27, 2007, Table 6

Wen-Yi Gao, M.D., Ph.D.
Medical Officer, DGP (HFD-180), ODE3, CDER

Hugo Gallo-Torres, M.D., Ph.D.
Medical Team Leader, DGP (HFD-180), ODE3, CDER

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this page is the manifestation of the electronic signature.**

/s/

Wen-Yi Gao
1/16/2008 08:40:02 AM
MEDICAL OFFICER

Hugo Gallo Torres
1/16/2008 12:21:20 PM
MEDICAL OFFICER



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 17, 2007

From: Thomas A. Marciniak, M.D.
Medical Team Leader
Division of Cardiovascular and Renal Products (HFD-110)

Subject: Fosaprepitant (NDA 22-023) interaction with diltiazem

Through: Norman Stockbridge, M.D., Ph.D.
Division Director

To: Jagjit Grewal, R.P.M.
Division of Gastroenterology Products (HFD-180)

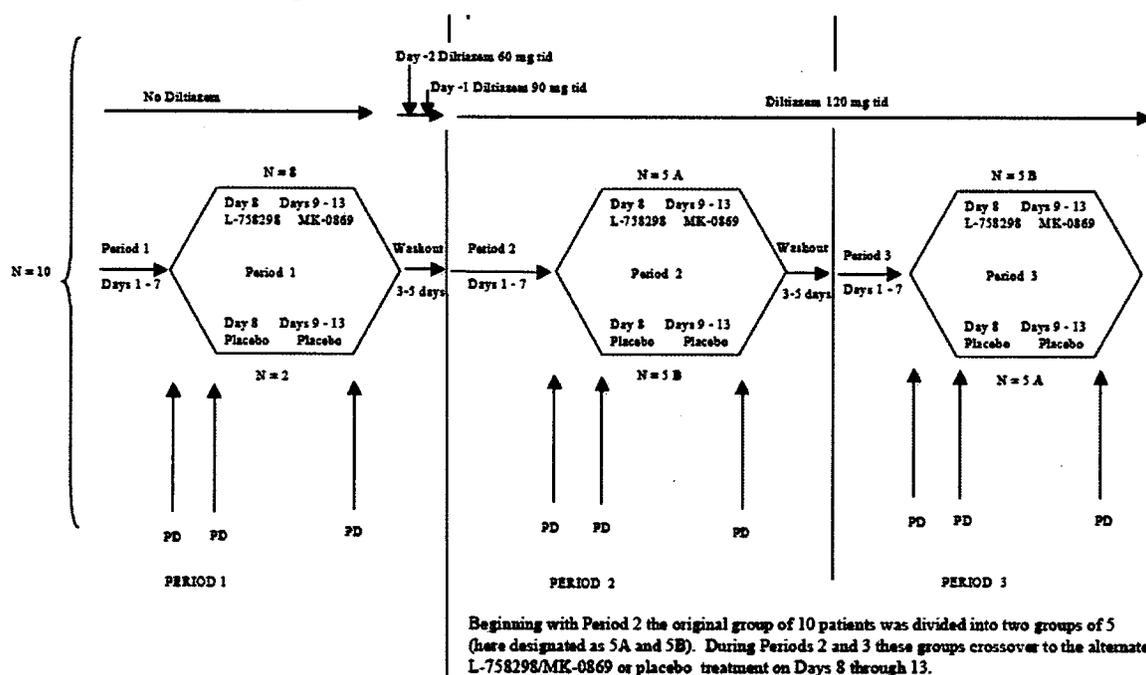
This memo responds to your consult to us dated November 16, 2007, requesting our comments on the blood pressure changes with the combination of fosaprepitant and diltiazem in Study 011. Fosaprepitant is the N-phosphoryl, water-soluble prodrug of aprepitant, an approved oral antiemetic aprepitant (Emend[®]) that is a substance P/neurokinin 1 (NK1) receptor antagonist. Fosaprepitant is the subject of an NDA submission dated July 27, 2007 that is approvable pending resolution of CMC issues. As your consult notes, you found during the NDA review that fosaprepitant potentiated diltiazem effects on the reduction of blood pressure in hypertensive patients in Study 011. In some patients, the individual systolic pressures were decreased by up to 49 mg Hg; in others, the diastolic pressures decreased by up to 28 mg Hg. We have included below our observations regarding the Study 011 results followed by our comments and recommendations. We judge this small study to be underpowered but suggestive that fosaprepitant acutely decreases blood pressure modestly.

Study 011 Findings

Study 011 was a double-blind, randomized, placebo-controlled, three-period study in hypertensive patients (planned 10) with background diltiazem. Study 011 was done because pre-clinical studies show an affinity of aprepitant for the L-type calcium channel, including possible enhancement of the depressor response to diltiazem in dogs. Prior to the start of period 1, patients had a 1- to 2-week washout from prior hypertensive medication, with DBP 96-114 at the end for eligibility. In period 1, patients received no medications for seven days. On day 8 they were given 100 mg of fosaprepitant (L-758298) or placebo as a 15- minute intravenous infusion followed by five days (days 9 to 13) of single oral 300-mg doses of aprepitant (MK-0869) or placebo alone. There was a 1-week interval between periods 1 and 2.

In periods 2 and 3, treatments were administered according to a two-period crossover design. Diltiazem titration started prior to period 2; all patients received diltiazem 60 mg orally 3 times daily on day -2, diltiazem 90 mg orally three times daily on day -1, and diltiazem 120 mg orally three times daily beginning on day 1 of period 2 and continuing through the end of period 3 (including the 3- to 5-day washout between periods) and until the poststudy visit. Periods 2 and 3 were identical except in one period, patients were given a 15-minute intravenous administration of 100 mg of fosaprepitant on day 8 and single 300-mg oral doses of aprepitant on days 9 to 13; and in the other period, patients were given placebo to match the fosaprepitant intravenous administration and placebo to match aprepitant. The study design is shown schematically in the Figure.

Figure: Study 011 Design



On the days on which “PD” was done as indicated in the Figure, automated HR/BP measurements (device not described) were done every 10 minutes initiated 20 minutes prior to dosing and continued to 6 hours postdose, then every 2 hours to 14 hours postdose. An orthostatic measurement was made 2 and 4 hours postdose. The primary analyses used mean maximum changes from baseline of three-point moving averages of measurements during successive 10-minute periods. For day 7 the report defines the baseline as the measurement taken at the time of day corresponding to predose on day 8; for days 8 and 13 the report defines baseline as the predose measurement on day 8.

The estimate of the power of the study was based on a SD of 12.8 mm Hg for SBP and 7.6 mm Hg for DBP at trough with diltiazem 360 mg QD. The protocol estimated the SD for the mean maximum changes as 9.1 mm Hg for SBP and 5.4 mm Hg for DBP. With ten subjects the

protocol estimated 80% power of detecting a difference of ≥ 7.9 mm Hg in SBP and ≥ 4.7 mm Hg in DBP. The protocol defined a “clinically significant” decrease as the lower 90% confidence limit less than -10/-8.

The study enrolled 11 black subjects, 9 men and 2 women, aged 37 to 56. No summary of baseline vital signs is provided in the report. Two subjects did not complete the study and another subject missed diltiazem doses based on the PK data.

The pharmacokinetic results were that aprepitant AUC increased about 2-fold and C_{max} increased 1.2-fold with background diltiazem. However, the mean C_{max} reported, about 1.7 mcg/mL, is substantially lower than the C_{max} reported (3.25 mcg/mL) for dosing with 115 mg of the to-be-marketed formulation. Diltiazem AUC and C_{max} increased 1.4-1.6 with fosaprepitant and aprepitant dosing, while the metabolite desacetyldiltiazem AUC increased about 2-fold with repeated aprepitant dosing.

The sponsor’s summaries of the study results for blood pressure, as well as heart rate and ECG interval, are shown in Table 1 through Table 4.

Table 1: Study 011 Period 1 IV Fosaprepitant BP Results

	Mean Maximum Change From Baseline		Geometric Mean Ratio (L-758298/No Medication) or Least Square Mean Difference (L-758298/No Medication)	90% Confidence Interval	p-Value
	L-758298 (N=8) [†]	No Medication (N=8) [†]			
PR interval (msec) [‡]	1.05	1.01	1.04	(0.99, 1.09)	0.172
QTc interval (msec) [‡]	1.01	1.02	0.99	(0.94, 1.03)	0.534
Systolic BP (mm Hg) [§]	-11.83	-5.88	-5.96	(-11.40, -0.52)	0.077
Diastolic BP (mm Hg) [§]	-8.25	-5.65	-2.60	(-6.91, 1.70)	0.289
Heart rate (beats/min) [§]	-8.33	-9.19	-0.85	(-2.58, 4.29)	0.652

[†] ECG data were not available for AN 1707.
[‡] Geometric mean maximum relative change from baseline and geometric mean ratio.
[§] Least square mean maximum moving average change from baseline and least square mean difference.
 BP = blood pressure

Table 2: Study 011 Period 1 Oral Aprepitant BP Results

	Mean Maximum Change From Baseline		Geometric Mean Ratio (MK-0869/ No Medication) or Least Square Mean Difference (MK-0869/No Medication)	90% Confidence Interval	p-Value
	MK-0869 (N=8) [†]	No Medication (N=8) [†]			
PR interval (msec) [‡]	1.06	1.01	1.05	(0.99, 1.10)	0.146
QTc interval (msec) [‡]	1.00	1.02	0.98	(0.94, 1.02)	0.397
Systolic BP (mm Hg) [§]	-13.33	-5.87	-7.46	(-18.06, 3.14)	0.224
Diastolic BP (mm Hg) [§]	-6.46	-5.65	-0.81	(-9.09, 7.46)	0.858
Heart rate (beats/min) [§]	-7.71	-9.19	1.48	(-2.04, 5.00)	0.452

[†] ECG data were not available for AN 1707.
[‡] Geometric mean maximum relative change from baseline and geometric mean ratio.
[§] Least square mean maximum moving average change from baseline and least square mean difference.
 BP = blood pressure

Table 3: Study 011 Periods 2 & 3 IV Fosaprepitant/Diltiazem BP Results

	Geometric Mean MRCB [†] or Least Square Mean MMACB [‡]		Geometric Mean Ratio (With/ Without) or Least Square Mean Difference (With/Without)	90% Confidence Interval	p-Value
	Diltiazem With L-758298 (N=9)	Diltiazem Without L-758298 (N=9)			
PR interval (msec) [†]	1.19	1.13	1.05	(0.99, 1.12)	0.161
QTc interval (msec) [†]	1.01	1.00	1.01	(0.99, 1.04)	0.339
Systolic BP (mm Hg) [‡]	-24.37	-18.83	-5.54	(-10.88, -0.21)	0.090
Diastolic BP (mm Hg) [‡]	-16.84	-10.53	-6.32	(-10.39, -2.24)	0.022
Heart rate (beats/min) [‡]	-10.11	-6.18	-3.93	(-7.63, -0.24)	0.084

[†] Geometric mean maximum relative change from baseline and geometric mean ratio.
[‡] Least square mean maximum moving average change from baseline and least square mean difference.
 BP = blood pressure

Table 4: Study 011 Periods 2 & 3 Oral Aprepitant/Diltiazem BP Results

	Geometric Mean MRCB [†] or Least Square Mean MMACB [‡]		Geometric Mean Ratio (With/ Without) or Least Square Mean Difference (With - Without)	90% Confidence Interval	p-Value
	Diltiazem With MK-0869 (N=9)	Diltiazem Without MK-0869 (N=9)			
PR interval (msec) [†]	1.17	1.12	1.04	(1.00, 1.09)	0.102
QTc interval (msec) [†]	1.00	1.02	0.98	(0.95, 1.01)	0.217
Systolic BP (mm Hg) [‡]	-12.66	-18.80	6.14	(-3.11, 15.40)	0.249
Diastolic BP (mm Hg) [‡]	-12.36	-12.72	0.36	(-6.17, 6.89)	0.920
Heart rate (beats/min) [‡]	-5.53	-3.43	-2.09	(-7.43, 3.25)	0.482

[†] Geometric mean maximum relative change from baseline and geometric mean ratio.
[‡] Least square mean maximum moving average change from baseline and least square mean difference.
 BP = blood pressure

Because of the blood pressure changes noted in the Study 011 report you requested that the sponsor provide the following information: “Regarding the drug interaction with diltiazem

Table 6: Study 011 Changes from Baseline in DBP for Diltiazem with and without Fosaprepitant

Time (hr)	Change from Baseline Diltiazem with Fosaprepitant			Change from Baseline Diltiazem Alone			P-Value
	N	Mean	SD	N	Mean	SD	
Baseline Value	9	87.14	8.23	10	87.87	5.91	
0.17	9	-1.81	6.33	10	-2.57	7.99	> 0.25
0.33	9	-5.59	5.18	10	-2.17	8.66	0.178
0.5	9	-2.37	5.31	10	-4.17	6.41	> 0.25
0.67	9	-7.93	3.79	10	-2.67	4.70	0.046
0.83	9	-1.48	5.82	10	-1.27	4.98	> 0.25
1.0	9	-3.70	5.21	10	2.43	4.88	0.022
1.17	8	-1.08	5.55	10	0.03	6.18	> 0.25
1.33	9	-3.48	7.71	10	-0.47	9.89	0.229
1.5	9	-8.26	8.28	10	-2.37	8.96	0.027
1.67	9	-7.15	7.46	10	-0.87	9.29	0.019
1.83	9	-5.93	8.59	10	-4.47	7.77	> 0.25
2.0	9	-8.15	9.03	9	2.48	4.93	< 0.01

P-value for test of no between-treatment difference, based on linear mixed effects model.

In addition, to document that IV aprepitant alone does not affect blood pressure, this later submission also included tables of data from Protocol 009. Data from period 1 of Study 011 were not included.

No adverse events (AEs) related to hypotension were reported in Study 011. We did not do a comprehensive review of possible hypotensive AEs in the other fosaprepitant and aprepitant studies. We do note in some studies that AE rates of dizziness and flushing were more common with aprepitant than placebo but not with fosaprepitant. We did not find reported AEs of hypotension or low blood pressure. More serious events (cardiac arrest, renal failure) were rare and distributed between fosaprepitant and active control and hence difficult to interpret.

Comments

Our first reaction is that Study 011 is an inadequately powered study rather unusually presented. **By the study report's power analysis the study had 90% power of detecting a difference of -10/-8, virtually diltiazem's entire effect size at trough. The sponsor's presentation of the data is unusual in many ways:**

- No summaries of baseline vital signs are provided in the original report. No data sets of the vital sign changes were provided in the NDA submission (that we could find).
- The study collected baseline data at multiple timepoints but the analyses adjust using a single timepoint rather than using time-matched changes.
- The later submission summarizes changes only for the first two hours.

- The later submission summarizes changes in blood pressure with IV aprepitant alone for Protocol 009 but does not provide the corresponding data for Study 011.

However, within the limitations that the small Study 011 does not provide definitive answers, we interpret the results as suggestive that IV fosaprepitant acutely reduces blood pressure slightly and acutely potentiates the effects of diltiazem upon blood pressure. Whether the latter effect is purely a PK interaction as the sponsor concludes can not be determined from this study. We are not greatly concerned that some of the individual decreases ranged to 49 mm Hg: The use of a single baseline timepoint to adjust as well as the methodology of picking the maximum values can lead to aberrantly high estimates of changes in individual readings.

The point estimates of the mean maximum changes with fosaprepitant, about -6 mm Hg, are not worrisome by themselves. We did not identify any suggestive problems with hypotensive adverse events in the fosaprepitant and aprepitant studies, but we did not review the adverse events thoroughly.

Recommendations

You need to judge whether your better knowledge of the adverse event profile for fosaprepitant and aprepitant suggests any increase in hypotensive event rates for these drugs. You may consider whether better characterization of the effects of fosaprepitant upon blood pressure should be left to a post-marketing commitment. We recommend starting with better analyses of the data in Study 011 and any other studies in which blood pressure was measured frequently (Protocol 009, others?)

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MEMORANDUM

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

DATE: 5/2/07

FROM: Joyce A Korvick, MD, MPH
DGP/ODE III

SUBJECT: Acting Division Director Approvable Comments
NDA 22-023

APPLICANT: Merck

DRUG: Emend® (fosoprepitant dimeglumine) Injection, 115 mg/10mL

DIVISION RECOMMENDATION:

Due to significant CMC deficiencies, I recommend an approvable action for this NDA.

The drug substance manufacturing process, controls are adequate. The Specifications for the drug substance and drug product are adequate as are the reference standards and analytical methods. The Facility Inspections are satisfactory. However, the manufacturing process of the drug product is not adequately established with the supporting data. Therefore, this application is Approvable until the manufacturing process is satisfactorily established. Resolution of the following deficiencies, as outlined in the CMC review, must be addressed as well as labeling negotiations finalized prior to approval:

- 1) The Applicant has informed the Agency that the drug product production process is not considered robust and will require further process improvement changes (Letter to Agency, Dated February 21, 2007). Consequently, the manufacturing process for the drug product has not been finalized. A full description of the final production process to be used for the manufacture of Fosaprepitant Dimeglumine drug product is required for approval.
- 2) To date, only 1 month of stability data on three batches of drug product manufactured with the modified lyophilization process, has been submitted. An additional time point (at 3 months) is needed on these batches as further support for the process changes to date. Furthermore, three months of stability data on three additional batches of drug product manufactured with the final manufacturing process will need to be submitted in support of the final manufacturing process.

BACKGROUND:

Fosaprepitant dimeglumine for injection is a sterile, lyophilized formulation intended for treatment of chemotherapy induced nausea and vomiting (CINV). It is a substance neurokinin 1 (NK1) antagonist. The active pharmaceutical ingredient (API) is the phosphorylated form which is a water soluble prodrug of aprepitant (EMEND® Approved NDA 21549). Following intravenous infusion of the reconstituted product, fosaprepitant is rapidly converted to aprepitant.

Emend for Injection (fosaprepitant) is an addition to the current Emend product line. It is a prodrug of aprepitant and as such it is approved to be used in combination with other anti-emetic 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 and in the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. Emend intravenous is to be administered at a dose of 115 mg given 30 minutes prior to chemotherapy on Day 1 only of the CINV regimen as an intravenous infusion over 15 minutes.

The currently approved aprepitant is used in a 3 day oral regimen to treat Chemotherapy-Induced Nausea and Vomiting (CINV). The sponsor proposed that EMEND-IV (115 mg) may be substituted for EMEND (125 mg), 30 minutes prior to chemotherapy, on Day 1 only of the CINV regimen as an infusion administered over 15 minutes.

This is the proposed labeling for the IV formulation:

DOSAGE AND ADMINISTRATION

TRADENAME (fosaprepitant) for intravenous administration is a lyophilized prodrug of aprepitant containing polysorbate 80 (PS80). Aprepitant is available as capsules (EMEND) for oral administration.

TRADENAME (115 mg) may be substituted for EMEND (125 mg) 30 minutes prior to chemotherapy, on Day 1 only of the CINV regimen as an infusion administered over 15 minutes.

The 3-day CINV regimen includes TRADENAME (115 mg) or EMEND (125 mg) on day 1; EMEND (80 mg) on days 2 and 3; in addition to a corticosteroid and a 5-HT₃ antagonist as specified in the tables below.

In clinical studies with EMEND, 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 chemotherapy treatment on Day 1.

In a clinical study with EMEND, 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.

The sponsor supported this change primarily through pharmacokinetic studies. The efficacy indications that are claimed are the same as those for oral aprepitant.

CMC:

As described above there were significant CMC deficiencies which must be resolved prior to approval.

The site inspection was performed and found satisfactory. The micro review was performed and was found satisfactory.

PRE-CLINICAL:

There were no new safety concerns in animal toxicology or pharmacology studies. The reviewer recommended approval of this new formulation of aprepitant.

CLINICAL PHARMACOLOGY:

The Office of Clinical Pharmacology found the overall Clinical Pharmacology Section acceptable.

They summarized the findings as follows:

There are no adequate, well-controlled clinical trials conducted for fosaprepitant to demonstrate safety and efficacy in the target patient population. To support the safety and efficacy of IV fosaprepitant, the sponsor is relying on the following data:

- (A) Demonstration of efficacy is primarily based on comparative pharmacokinetics between IV fosaprepitant 115 mg and oral aprepitant 125 mg.
- (B) Demonstration of safety related to high aprepitant Cmax following IV administration of fosaprepitant is based on previous clinical data for oral aprepitant at the 375-mg dose level as the latter resulted in even higher Cmax values.
- (C) Demonstration of safety related to fosaprepitant concentration is based on the fosaprepitant safety data in Phase 1 and 2 trials in healthy subjects and patients in studies for various indications.
- (D) Demonstration of safety related to phosphate and meglumine that are released from fosaprepitant upon conversion to aprepitant is based on the information related to the quantity of these two components released following administration of fosaprepitant IV 115 mg, nonclinical findings and clinical experience during the Phase 1 and 2 trials. Upon conversion of 115-mg of fosaprepitant to aprepitant, 18.3 mg of phosphate is

liberated from fosaprepitant. The sponsor considers this amount of phosphate safe. (Note that assuming the amount of phosphate released stays in the plasma, it could increase the plasma concentration of free phosphate by 0.61mg/dL). The sponsor stated that the safety on this aspect is substantiated by the lack of hypocalcemia in the clinical studies. In addition to phosphate, 73 mg of meglumine (1.04 mg/kg for a 70 kg person) is also administered as part of the fosaprepitant salt form. The sponsor indicated that meglumine

b(4)

_____ Dr. Sushanta, pharm/tox reviewer of HFD-180, does not have safety concerns about meglumine in view of the wide safety margins based on nonclinical findings.

They described the pharmacokinetic findings for fosaprepitant and its active metabolite, aprepitant, as follows:

Fosaprepitant: Following IV infusion of fosaprepitant 115 mg over 15 minutes, fosaprepitant plasma levels fell near or below the lower limit of quantitation (10 ng/mL) within 30 minutes after the end of infusion and conversion of fosaprepitant to aprepitant was nearly complete. The exact identity of the enzyme(s) involved in the conversion of fosaprepitant to aprepitant has not been identified but is thought not to involve the CYP family of enzymes. Mean fosaprepitant C_{max} was approximately 5900 ng/mL and mean AUC was 1483 ng.h/mL. The elimination half-life for fosaprepitant was estimated to be 2-3 minutes.

Aprepitant: Following IV infusion of fosaprepitant 115 mg over 15 minutes, peak aprepitant concentrations occurred approximately at the end of the infusion. Mean C_{max} was 3267 (±1159) ng/mL and mean AUC was 31724 (±14287) ng.h/mL. The fosaprepitant AUC was approximately 5% of the aprepitant AUC.

Relative bioavailability: IV fosaprepitant vs. Oral aprepitant (Protocol 012L1)

Following IV infusion of fosaprepitant 115 mg over 15 minutes in healthy subjects, plasma aprepitant concentrations were higher than those observed with oral aprepitant 125 mg for the first 4-5 hours post dose but thereafter the concentrations were similar between the two formulations. The geometric mean ratio was 1.13 (90% CI: 1.06-1.20) for AUC, and 2.47 (90% CI: 2.25-2.71) for C_{max}.

Thus the efficacy of a single dose of IV fosaprepitant (115 mg) and a single dose of 125 mg oral aprepitant should be equally efficacious. The reviewer noted that the high C_{max} was covered by previous data submitted for a single 375 mg dose of aprepitant, however, the medical officer would need to address the peak fosaprepitant levels in their review.

Finally, the reviewers commented on certain aspects of the drug -drug interaction studies.

Regarding drug interaction with **diltiazem** (Study Protocol 011): For a closer evaluation of the effect of IV fosaprepitant on the systolic and diastolic pressures of hypertensive patients receiving oral diltiazem, the sponsor should provide the following information:

- A table for individual data listing of systolic and diastolic pressures at various time points for baseline, when diltiazem was given alone, and when diltiazem was

coadministered with fosaprepitant, respectively. Also include changes from baseline and fosaprepitant concentrations in different columns of the same table. Evaluate the relationship between fosaprepitant concentration and difference in systolic and diastolic pressures between the two treatments (with and without fosaprepitant).

- A table for maximum change from baseline and the time associated with this maximum change for systolic and diastolic pressures for each individual when diltiazem was given alone, and when diltiazem was coadministered with fosaprepitant. Also include summary statistics (mean, SD, max, min) in the table.

A more detailed summary of the effect follows:

1. When fosaprepitant (single 100-mg IV dose) or aprepitant (300mg TID given orally for 5 days) was given alone to hypertensive patient, a small but clinically meaningful decrease in systolic blood pressure was observed (although there was no meaningful change in diastolic blood pressure, heart rate, or PR interval). According to Dr. Yi-Wen Gao, Medical Officer of the Division of Gastroenterology Products, this was not observed with the much larger database for aprepitant or fosaprepitant in cancer patient population.
2. Coadministration of fosaprepitant IV with oral diltiazem may further decrease patients' systolic and diastolic pressure by approximately 6 mm Hg. This was not observed when diltiazem was coadministered with oral aprepitant. Under the study conditions, PK interaction in terms of diltiazem or aprepitant AUC was greater when oral aprepitant PO, as compared to IV fosaprepitant, was coadministered with diltiazem. As such, PK interactions cannot explain the greater effect of IV fosaprepitant (as compared to oral aprepitant) on blood pressure. The reason is unknown but the effect could be due to fosaprepitant itself or a result of higher aprepitant C_{max} for the IV formulation. Caution should be exercised when IV fosaprepitant is coadministered with diltiazem.
3. The sponsor's analysis involves log transformation of the data. To fully evaluate the study, the sponsor should provide the following information:
 - a. Summary statistics (arithmetic mean, SD, min and max) for changes from baseline in systolic and diastolic pressures following each treatment.
 - b. Summary statistics (arithmetic mean, SD, min and max) for differences in systolic and diastolic pressures between treatments using diltiazem as the reference treatment (e.g., [fosaprepitant IV+ diltiazem] vs. diltiazem)

The reviewer suggested this be addressed in the resubmission, but this was not a deficiency.

A thorough QT study was performed and reviewed by the QT review team. The study was considered adequate and demonstrated no QT concerns. The team proposed some wording to describe the study that should be included in the final labeling.

Finally, due to the inhibition of metabolism of dexamethasone by aprepitant, the oral regimen utilized a lower dose than standard of care on the first day (12 mg vs 20 mg dexamethasone). There was concern by the clinical pharmacology reviewer that the exposure of patients to dexamethasone might be slightly lower when 115 mg IV dose was given. In discussion with the clinical review team, this potential decrease was not felt to be significant enough to impact the overall efficacy. Therefore, the overall pK

characteristics of the IV formulation were felt to be similar when compared to the oral dose on the first day and that this new dose recommendation was acceptable from an efficacy point of view.

CLINICAL SAFETY:

The medical officer review did not find any new safety issues with this dose regimen or new formulation. This conclusion was based on 12 pharmacokinetic studies and one phase III study which collected safety data. The data set of 696 subjects were exposed to fosprepitant.

No patient died because of fosprepitant treatment. No serious adverse events that were caused by treatment. The most frequent adverse experiences in fosprepitant CINV studies were abdominal pain, constipation, diarrhea, dry mouth, dyspepsia, nausea and stomatitis.

PHASE 4 commitments:

There were no recommendations at this time from any of the reviewing disciplines.

Labeling:

Labeling will be completed after the sponsor has addresses the CMC deficiencies. No labeling comments were sent this cycle.

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Joyce Korvick
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MEDICAL OFFICER

CLINICAL REVIEW
DIVISION OF GASTROENTEROLOGY PRODUCTS

Application Type NDA
Submission Number 22-023/000

Letter Date March 31, 2006
Stamp Date March 31, 2006
PDUFA Goal Date May 3, 2007

Reviewer Name Wen-Yi Gao, MD, PhD
Medical Officer
HFD-180
Review Completion Date April 25, 2007

Established Name Fosaprepitant Dimeglumine
(Proposed) Trade Name Pending
Therapeutic Class Substance P receptor antagonist
Applicant Merck & Co., Inc.
Priority Designation S

Formulation Fosaprepitant PS80 — 15 mg for I.V. administration

Dosing Regimen 115 mg intravenous infusion in combination with aprepitant and dexamethasone

Indication Prevention of acute and delayed nausea and vomiting associated with cancer chemotherapy

Intended Population 18 years of age or older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

NDA 22-023/000, fosaprepitant PS80 — 115 mg for intravenous administration, is **recommended for approvable** in combination with aprepitant and other antiemetic agents for the prevention of acute and delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in patients aged 18 years or older. b(4)

The recommendation is supported by 1) the demonstrated safety outcomes of fosaprepitant — the prevention of chemotherapy induced nausea and vomiting (Study 007L1); 2) the rapid conversion of fosaprepitant in vivo to aprepitant (Studies 011L1 and 012L1); and 3) the demonstrated bioequivalence to oral aprepitant AUC exposure (Study 012L1). b(4)

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

From the clinical perspective, no risk management activity is recommended.

1.2.2 Required Phase 4 Commitments

b(4)

b(5)

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Fosaprepitant is a phosphoryl prodrug of aprepitant, and belongs to a class of selective, high-affinity antagonist of human substance P/neurokinin 1 (NK₁) receptors. The route of administration is intravenous infusion, and the indication is to prevent chemotherapy induced nausea and vomiting (CINV).

Four types of fosaprepitant formulations were evaluated during the development of this drug. Only one was considered suitable for clinical use, fosaprepitant PS80 — This formulation is the focus of this marketing application. The other formulations were discontinued because of b(4)

_____ to the high concentration (_____) PS80 diluent formulation. A total of 696 subjects were evaluated with the 4 types of fosaprepitant formulations:

b(4)

Table 1. Fosaprepitant formulations and patient populations

Formulation Type	Healthy adult Subjects	Disease Subjects	Total
Fosaprepitant PS80 _____	123	0	123
Fosaprepitant _____	98	149 CINV; 56 migraine; 10 hypertension	313
Fosaprepitant PS80 _____	35	0	35
Fosaprepitant _____	58	167 PONV	225

b(4)

The study populations included chemotherapy induced nausea and vomiting (149 subjects), migraine (56 subjects), hypertension (10 subjects), post-operative nausea and vomiting (PONV, 167 subjects), and healthy adults (314 subjects).

Fosaprepitant was only studied as a single dose I.V. administration, whereas repeated dose of aprepitant was studied. The longest aprepitant treatment duration was 8 weeks (up to 375 mg once daily) in patients with major depressive disorder.

With respect to the dose levels of the proposed market formulation, the level of 90 mg was evaluated in 34 administrations, the 100 mg in 89 administrations, the 115 mg in 66 administrations, and the 150 mg in 10 administrations (Section 2.5 Table 2.5:8 of the submission).

Efficacy of fosaprepitant was studied in 2 primary Phase II trials (Study 004L1 and Study 007L1) using fosaprepitant _____. These efficacy studies enrolled 230 oncology patients prior to administration of cisplatin-based highly-emetogenic chemotherapy (HEC).

b(4)

Safety and tolerability of all formulations of intravenous fosaprepitant were studied in the following 13 studies:

- Phase II HEC CINV studies: Protocols 004L1 and 007L1
- Phase II migraine and motion-induced nausea studies: Protocols 003L1 and 006L1
- Phase III PONV safety study: Protocol 015L1
- Phase I studies: Protocols 001L1, 005L1, 009L1, 011, 011L1, 012L1, 013C1 and 024

The primary safety evaluation was also conducted in patients with CINV in Studies 004L1 and 007L1. The overall number of subjects in the safety database was 696 subjects. The extents of exposure of all formulations were 200 mg (17 administrations), 150 mg (39 administrations), 120 mg (6 administrations), 115 mg (66 administrations), 100 mg (306 administrations), 90 mg (34 administrations), and <90 mg (383 administrations) (Section 2.5 of the submission).

Medical Officer's Comments: The total fosaprepitant administrations of all dose levels were 851 injections in 696 subjects. This submission did not provide the number of subjects who had more than one administration and the study containing such subjects.

1.3.2 Efficacy

The major efficacy trials of fosaprepitant were conducted in Studies 004L1 and 007L1 using fosaprepitant .

Study 004L1 was a multi-center, randomized active controlled (ondansetron) trial to evaluate the efficacy, safety, and tolerability of a single I.V. fosaprepitant dose in prevention of cisplatin-induced emesis. Seven investigators located in 3 countries (Belgium, the United Kingdom, and the Netherlands). All patients (53 subjects) received intravenous infusion of fosaprepitant (60 mg or 100 mg) or ondansetron (32 mg) 1 hour prior to cisplatin (50 to 100 mg/m² I.V. infusion). The primary efficacy endpoint was the proportion of complete responders (no emetic episodes, no rescue therapy) at 24 hours post-cisplatin (acute phase). Emetic episodes were defined as one or more continuous vomits or retches, with distinct episodes being separated by the absence of vomiting or retching for at least 1 minute. The secondary efficacy endpoint was the patient self-assessment of nausea during the acute and delayed phases, using a 4-point scale (0= none, 1= mild, 2= moderate, 3= severe) recorded in a diary every 2 hours while awake during the acute phase and every 8 hours during the delayed phase.

Emesis

All 53 patients were included in the acute phase analysis and 52 patients were included in the delayed phase analysis.

Acute phase (primary efficacy endpoint, 0 to 24 hours post-cisplatin infusion)—The proportions of complete responders in the fosaprepitant and ondansetron treatment groups were 36.7% and 47.8%, respectively (p=0.57). At 8 hours post-cisplatin, the proportions of complete responders were 36.7% in the fosaprepitant treatment group and 73.9% in the ondansetron treatment group (p=0.012). Fourteen (14) patients (46.7%) in the fosaprepitant treatment group were treatment failures; all of these treatment failures occurred during the first 8 hours post-cisplatin infusion.

Delayed phase (24 hours to 168 hours following initiation of cisplatin infusion)—The proportion of complete responders in the fosaprepitant treatment group (48.3%) was significantly higher than in the ondansetron treatment group (17.4%) (p=0.04).

Nausea (Secondary Efficacy Parameter)

The analyses were based on the patient self-assessment of nausea data from 53 patients in the acute phase and 52 patients in the delayed phase.

Acute phase—The overall between-group comparison of the distribution of peak nausea values, as well as the proportion of patients reporting a peak nausea value of 0, significantly favored the ondansetron treatment group ($p=0.013$) and ($p=0.0035$), respectively.

Delayed phase—The overall between-group comparison of the distribution of peak nausea values favored the fosaprepitant treatment group but did not reach statistical significance ($p=0.062$).

Medical Officer's Comments: The formulation of fosaprepitant ~~used in this study~~ was discontinued due to stability issues. The efficacy of proposed market formulation (fosaprepitant PS80 ~~is~~) has not been studied in HEC CINV population.

b(4)

The reviewer's efficacy conclusion of Study 004L1 is that in patients receiving cisplatin chemotherapy (50 to 100 mg/for underlying malignancy, fosaprepitant : ~~is~~ 60 mg or 100 mg I.V. is:

- i) less effective than ondansetron 32 mg I.V. in preventing nausea during the acute phase post-cisplatin;
- ii) less effective than ondansetron 32 mg I.V. in preventing emetic episodes or nausea during the first 8 hours post-cisplatin;
- iii) as effective as ondansetron 32 mg I.V. in preventing emetic episodes and nausea in the delayed phase (Days 2 to 7) post-cisplatin; and
- iv) generally well tolerated, with adverse experience rates comparable to those of ondansetron 32 mg I.V.

Study 007L1 was a multi-center double-blind, randomized, active controlled (ondansetron plus dexamethasone) trial to investigate the safety, tolerability, and efficacy of fosaprepitant ~~and~~ and aprepitant in prevention of cisplatin-induced emesis.

Cisplatin-naïve patients (177 subjects) from 24 clinical centers in the United States and Europe were evaluated for the prevention of both acute (0 to 24 hours) and delayed (Days 2 to 5) emesis after cisplatin I.V. (≥ 70 mg/m²). All patients received dexamethasone 20 mg intravenously before cisplatin. In addition, patients were randomized to 1 of 3 groups to receive: fosaprepitant 100 mg intravenously prior to cisplatin and aprepitant 300 mg once daily on Days 2 to 5 (Group A); fosaprepitant 100 mg intravenously prior to cisplatin and placebo once daily on Days 2 to 5 (Group B); ondansetron 32 mg intravenously prior to cisplatin and placebo once daily on Days 2

to 5 (Group C). Nausea was assessed by means of visual analog scale (VAS) ratings at 24-hour intervals over the treatment period. Emetic episodes were recorded daily in a patient diary. Rescue therapy was permitted on an as-needed basis at any time for all patients but was not to be given prophylactically. Randomization was stratified both for gender and for moderate to highly emetogenic chemotherapy given in addition to cisplatin.

Emesis

Acute Phase (primary) —**During the acute phase, the Standard Therapy group of ondansetron plus dexamethasone (Group C) provided the best control of emesis.** The proportion of patients without emesis regardless of rescue therapy was significantly higher in Group C (84.5%) than either Group A (50.0%) or Group B (45.6%) or in the combined group (Groups A and B) that received fosaprepitant plus dexamethasone (47.9%). The difference between the combined group (Groups A and B) and Group C was -36.6%, with a 90% CI about this difference of -49.6 to -24.2%, which did not include 0. Furthermore, an additional exploratory analysis showed that the proportion of patients without emesis and no use of rescue therapy in Group C (82.8%) was higher than either Group A (45.0%), Group B (35.1%), or the combined group (40.2%; $p < 0.001$ for Group C versus the combined Groups A and B).

Delayed Phase (secondary) —**During the delayed phase, patients who received fosaprepitant and/or aprepitant (Groups A and B) had the best control of emesis.** The prevention of delayed emesis in Groups A and B was significantly higher than that of Group C, which received ondansetron plus dexamethasone on Day 1 and placebo in the delayed phase. The percentages of patients without delayed emesis regardless of use of rescue therapy in Groups A, B, and C were 66.1, 60.7, and 41.4%, respectively. Groups A and C were significantly different based on a 95% CI (5.9 to 43.6%) on the difference (24.7%), which did not include 0. Groups B and C were significantly different based on a 95% CI (0.4 to 38.8%) on the difference (19.3%), which did not include 0.

An exploratory analysis showed a similar advantage in the proportion of patients without emesis and no use of rescue therapy in the delayed phase (59.3, 44.6, and 37.9% in Groups A, B, and C, respectively; Groups A versus C were significantly different, $p < 0.05$). Nausea: Acute Phase: The nausea scores for the combined Groups A and B were significantly higher, meaning more nausea ($p = 0.005$) compared with Group C. The proportion of patients who reported no nausea (VAS = 5) in the acute phase. However, it was not significantly different between Group A and Group C. Delayed Phase (secondary) and Overall Phase (exploratory): The distribution of nausea scores and the proportions of patients who had no nausea (VAS = 5) were similar among treatment groups. However, the proportions of patients who reported no nausea in the delayed and overall phases were not significantly different between Group A and Group C. Global Satisfaction: The distribution of global satisfaction ratings on Day 6 was comparable between Groups A and C.

Medical Officer's Comments: Study 007L1 was the pivotal efficacy study of fosaprepitant, and involved 177 patients with cisplatin chemotherapy (≥ 70 mg/m²). This is a HEC study. The medical reviewer has the following efficacy conclusions:

- i) **Administration of fosaprepitant (100 mg I.V.) plus dexamethasone (20 mg I.V.) was less effective than standard therapy of ondansetron (32 mg I.V.) plus dexamethasone (20 mg I.V.) in preventing emesis during the acute phase (0 to 24 hours) post-cisplatin;**
- ii) **Fosaprepitant plus dexamethasone (Day 1) in combination with aprepitant (300 mg P.O.) once daily (Days 2 to 5) was more effective than the standard therapy in preventing delayed (Days 2 to 5) cisplatin-induced emesis;**
- iii) **A single dose of fosaprepitant was less effective than that of aprepitant once daily on Days 2 to 5 in combination with fosaprepitant and dexamethasone (Day 1) in reducing delayed emesis;**
- iv) **Fosaprepitant plus dexamethasone on Day 1, with or without the addition of aprepitant once daily on Days 2 to 5, was generally well tolerated, with adverse experiences comparable with the standard therapy.**

1.3.3 Safety

Fosaprepitant (all four formulations) as a single intravenous infusion was administered to 696 subjects. The proposed market formulation was administered to 123 healthy adults.

Exposure

The dose levels of fosaprepitant (all formulations) were 200 mg (17 administrations), 150 mg (39 administrations), 120 mg (6 administrations), 115 mg (66 administrations), 100 mg (306 administrations), 90 mg (34 administrations) and <90 mg (382 administrations).

The dose levels of the proposed market formulation were 150 mg (10 administrations), 115 mg (66 administrations), 100 mg (89 administrations), and 90 mg (34 administrations).

The highest single oral dose of aprepitant in human was 375 mg P.O. (Study P043), and the longest exposure was 250 mg P.O. daily for 8 weeks (Study P039).

Fosaprepitant was rapidly converted to aprepitant after intravenous infusion, and was undetectable in serum in 30 minutes. Fosaprepitant (115 mg) had a similar AUC to oral aprepitant 125 mg. However, its plasma level at the end of a 15-minute infusion was significantly higher than that of the oral aprepitant 125 mg (5800 ng/ml vs. 3095 ng/ml).

Deaths

No deaths that caused by the treatment of fosaprepitant were reported in this submission. A total of 10 patients died in fosaprepitant studies: Nine patients died in the Phase II CINV studies. The causes of death were consistent with that of cancer patients receiving high-dose cisplatin chemotherapy. One patient with ovarian cancer died of perforated bowel and abscess post-operation.

Serious adverse events

No serious adverse events due to the treatment with fosaprepitant were reported. The pattern of serious adverse events was typical of patients receiving cisplatin-based highly-emetogenic chemotherapy. For example, gastrointestinal disorders, hematopoietic and lymphoid system disorders, infections, cardiac disorders, general disorders, and metabolism disorders.

Common adverse events

The most frequent adverse experiences in fosaprepitant — CINV studies (004L1 and 007L1) were abdominal pain, constipation, diarrhea, dry mouth, dyspepsia, nausea, and stomatitis.

b(4)

Medical Officer's Comments: The safety and tolerability of fosaprepitant were studied in healthy subjects and patients with CINV, PONV, and motion-induced nausea. The four formulations of fosaprepitant including the proposed market formulation were generally well tolerated.

1.3.4 Drug-Drug Interactions

The effect of fosaprepitant as a CYP3A4 (Cytochrome P450 3A4) inhibitor was evaluated using midazolam, a sensitive CYP3A4 probe. The dose of 100-mg of fosaprepitant (fosaprepitant PS80 : —), used in this midazolam interaction study is comparable to the recommended 115-mg dose as determined by the pharmacokinetics in Protocol 012.

b(4)

Midazolam concentrations were increased 1.6 fold with concomitant fosaprepitant administration. Based on PhARMA guidelines using midazolam as a CYP3A4 probe, fosaprepitant is considered a weak inhibitor of this enzyme system. Oral aprepitant 125 mg is described as a moderate CYP3A4 inhibitor (midazolam AUC increase of 2.3 fold). These results confirm that substitution of intravenous fosaprepitant on Day 1 will have no more of an effect on CYP3A4 substrates than oral aprepitant 125-mg. It is recommended that the same precautions used for the orally administered regimen be carried forward with the Day 1 substitution of fosaprepitant.

Since fosaprepitant is unlikely to be metabolized by the CYP isoenzymes, conversion of fosaprepitant to aprepitant is not expected to be altered by inhibition or induction of CYP isoenzymes. Upon conversion to aprepitant, the extent of induction or inhibition of aprepitant metabolism on the systemic clearance of aprepitant is expected to be similar to that of orally administered aprepitant. Therefore, the effect of co-administered drugs that alter the metabolism of aprepitant would be expected to have a similar effect on aprepitant exposure following intravenous fosaprepitant administration.

1.3.5 Special Populations

The age range of this submission is 18 years old or older. The current labeling for oral aprepitant indicates that no additional dosage adjustment is recommended, including patients with mild to moderate hepatic insufficiency, renal insufficiency, and ESRD undergoing hemodialysis.

Fosaprepitant is metabolized in various extrahepatic tissues; therefore, hepatic insufficiency is not expected to alter the conversion of fosaprepitant to aprepitant.

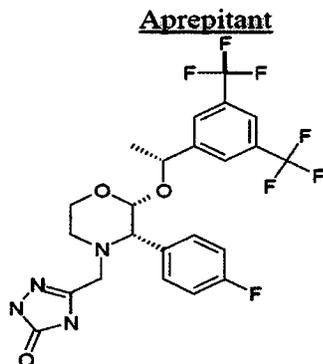
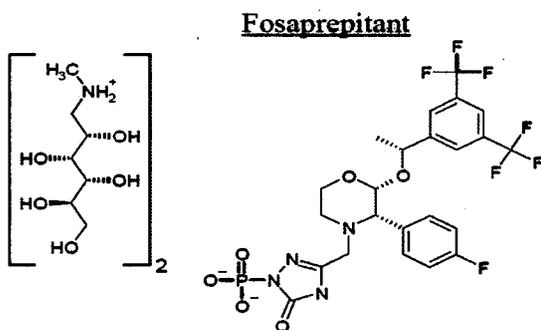
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INTRODUCTION AND BACKGROUND

1.4 Product Information

Trade name: pending. Established name: fosaprepitant dimeglumine

Fosaprepitant is a white amorphous powder with a molecular weight of 1004.83. Its empirical formula is $C_{23}H_{22}F_7N_4O_6P \cdot 2(C_7H_{17}NO_5)$.



Pharmacological class: Fosaprepitant is a prodrug of aprepitant. When administered intravenously, it is rapidly converted to aprepitant. Aprepitant is a selective substance P/neurokinin 1 (NK₁) receptor antagonist. Positron Emission Tomography (PET) studies with aprepitant showed that it crosses the blood brain barrier and occupies brain NK₁ receptors. Animal and human studies showed that aprepitant potentiates the antiemetic activity of the 5-HT₃-receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis.

Proposed Indication: In combination with other antiemetic agents, fosaprepitant 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

Proposed Age Group: ≥18 years of age

Route of Administration and Formulation: Intravenous administration

Dosing Regimen: 115 mg intravenous infusion over 15 minutes

1.5 Currently Available Treatment for Indications

The 3-day CINV regimen includes aprepitant 125 mg on Day 1; and 80 mg on Days 2 and 3; in addition to a 4-day oral dexamethasone regimen, as shown in Table 2 below, and a single intravenous administration of 5-HT₃ antagonist ondansetron on Day 1.

Table 2. Current Treatment Regimens for CINV

	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 I.V.	none	none	none

1.6 Availability of Proposed Active Ingredient in the United States

Aprepitant is currently marketed in the United States for the treatment of

- 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

1.7 Important Issues with Pharmacologically Related Products

There are no important issues with pharmacologically related products.

3.3 Compliance with Good Clinical Practices

According to the sponsor, all studies were conducted under Good Clinical Practice (GCP) guidelines, as documented in the International Conference on Harmonization (ICH) and the Food and Drug Administration (FDA).

3.4 Financial Disclosures

The sponsor has submitted FDA Form 3454 certifying that no investigator of any of the covered clinical studies had any financial interests to disclose.

Medical Officer's Comments:

Merck has adequately disclosed financial arrangements with clinical investigators in this application. The submitted financial disclosures do not bring up any concerns which would possibly jeopardize the integrity of the data.

4 INTEGRATED REVIEW OF EFFICACY

4.1 Indication

The proposed indication for fosaprepitant is for the prevention of acute and delayed nausea and vomiting associated with cancer chemotherapy.

Medical Officer's Comments: The indication makes no distinction between highly emetogenic or moderately emetogenic chemotherapy. In fact, only highly emetogenic chemotherapy was studied in this submission.

4.1.1 Methods

Study 007L1 provided the major efficacy data to support the indication. It was a Phase 2, randomized, active controlled, double-blind design. The efficacy variables were evaluated by the following endpoints:

- (1) Assessment of the efficacy of fosaprepitant plus dexamethasone in the acute phase (first 24 hours) of cisplatin-induced emesis;
- (2) Assessment of a single dose of fosaprepitant plus dexamethasone followed by 4 days of oral aprepitant or placebo in prevention of delayed emesis (Days 2 to 5 post-cisplatin infusion); and

(3) Assessment of a single dose of fosaprepitant plus dexamethasone followed by 4 days of oral aprepitant or placebo in reduction of delayed emesis (Days 1 to 5 post-cisplatin infusion).

4.1.2 General Discussion of Endpoints

Substance P is a neuropeptide that is present in the regions of the brainstem that are believed to mediate the vomiting reflex. The NK1 receptor is the preferred receptor for substance P, and it is also present in the areas of the brainstem implicated in the pathophysiology of vomiting. Available evidence suggests that substance P acting via NK1 receptors may be involved in the pathogenesis of emesis. It has been shown that NK1-receptor antagonists inhibit acute and delayed emesis induced by cytotoxic chemotherapeutic agents such as cisplatin in the ferret, and that central nervous system (CNS) penetration is essential for antiemetic activity.

A pilot study (004L1) was completed with fosaprepitant to preliminarily assess the efficacy of fosaprepitant in the prevention of acute (0 to 24 hours) and delayed (Day 2 to 7) emesis in patients scheduled to receive cisplatin at highly emetogenic doses (50 to 100 mg/m²) (Protocol 004). This double-blind, randomized, active-agent (ondansetron)-controlled study enrolled 53 cisplatin-naïve patients. All patients received I.V. treatment with fosaprepitant (60 or 100 mg) or ondansetron (32 mg) for prophylaxis against emesis following emetogenic chemotherapy (cisplatin at 50 to 100 mg/m²). A 60- to 100-mg I.V. dose of fosaprepitant was found to be generally as effective as ondansetron 32 mg I.V. in preventing emetic episodes during the acute phase post-cisplatin and more effective than ondansetron in preventing emetic episodes and nausea in the delayed phase (Days 2 to 5) post-cisplatin.

The primary purpose of the confirmatory study (007L1) was to determine whether the combination of fosaprepitant and dexamethasone (Groups A and B) would provide a level of antiemetic protection in the acute phase similar to Standard Therapy with the ondansetron-dexamethasone combination (Group C). Secondary objectives were to determine whether fosaprepitant plus dexamethasone on Day 1 (Group B) and fosaprepitant plus dexamethasone on Day 1 followed by oral aprepitant on Days 2 to 5 (Group A) would be more effective than Standard Therapy (Group C) in preventing delayed emesis.

Medical Officer's Comments: The primary and secondary objectives of comparing the antiemetic effects of the combination of fosaprepitant and dexamethasone with the standard therapy are acceptable.

4.1.3 Study Design

Study 007L1 was a double-blind, randomized, multi-center, active-agent (ondansetron plus dexamethasone)-controlled study, which enrolled 177 cisplatin-naïve patients.

In Study 007L1, patients were assigned to their respective treatment groups according to a computer-generated, randomized allocation schedule. Patients were stratified according to gender and moderate to highly emetogenic chemotherapy given in addition to cisplatin. Following prehydration, L-758298 100 mg (Groups A and B) or ondansetron 32 mg (Group C) was infused intravenously in normal saline over 15 minutes beginning 1 hour prior to initiation of the cisplatin infusion. All patients received dexamethasone 20 mg I.V. push 30 minutes prior to initiation of cisplatin. The cisplatin (70 mg/m²) was infused over a period of 3 hours. During Days 2 to 5, patients in Group A received L-754030 (300 mg given orally once daily) and patients in Groups B and C received matching oral placebo in the morning.

Rescue therapy was permitted at any time but was not to be given prophylactically. The recommended rescue medication for Day 1 was metoclopramide (20 to 30 mg P.O. 4 times daily or 1 to 2 mg/kg I.V. 4 times daily), and during Days 2 to 5 was dexamethasone (4 to 8 mg P.O. twice daily). The investigator, however, had the option of prescribing any rescue medication regimen deemed appropriate (except dexamethasone or lorazepam on Day 1). Patients recorded the drug, dosage, and time that they took rescue medication in the patient diary.

Table 3. Summary of Study 007L1 Design

Group (Subjects)	Day 1	Day 2 to 5
A (n=62)	L-758298 (100 mg I.V.) and dexamethasone (20 mg I.V.)	L-754030 (300 mg once daily)
B (n=57)	L-758298 (100 mg I.V.) and dexamethasone (20 mg I.V.)	Placebo matched to L-754030 once daily
C (n=58)	Ondansetron (32 mg I.V.) and dexamethasone (20 mg I.V.)	Placebo matched to L-754030 once daily

Acute Phase (24 Hours Post-Cisplatin)

Emesis (Primary)

The primary efficacy parameter was the proportion of complete responders (regardless of rescue) at 24 hours post-cisplatin infusion. Complete response was defined as the absence of emetic episodes. An emetic episode was defined as a single vomit or retch, or any number of continuous vomits or retches; distinct episodes were separated by at least 1 minute. Efficacy was assessed by the recording of emetic episodes and rescue therapy on the patient diary card.

Nausea (Secondary)

Efficacy was secondarily assessed at 24 hours post-cisplatin by patient self-assessment of nausea using a 100-mm visual analogue scale (VAS) and the patient global satisfaction using a 100-mm VAS. Both assessments were recorded by the patient on a patient diary card.

Delayed Phase (Days 2 to 5)

Emesis (Primary)

The primary efficacy parameter was the proportion of complete responders (regardless of rescue) from Day 2 to Day 5 post-cisplatin. Efficacy was assessed by the recording of emetic episodes and rescue therapy on the patient diary card.

Nausea (Secondary)

Efficacy was secondarily assessed on Days 2 to 5 by the daily patient self-assessment of nausea (VAS) rating. Both assessments were recorded by the patient on the patient diary card.

Patient Global Assessment (Exploratory)

The patient global satisfaction (VAS) rating (on Day 2 and Day 6) reflected the patient's satisfaction with antiemetic treatment over the previous 24 hours.

Table 4. Schedule of Study Assessment and Procedures

Procedure	Pre-study	Time (Hours) Postinitiation of Cisplatin Infusion										Post-Cisplatin Day		
		-1.5	-1	-0.5	0	1	2	3	3.5	4	24	2 to 5	6 to 8	17 to 29
Informed consent/complete history	X													
Physical examination with vital signs (BP, HR, RR, oral temperature)	X	X [†]									X [†]		X [†]	X
Measurement of height and weight	X													X
12-lead ECG (with 1-minute rhythm strip if abnormal)	X									X		X ^{††}	X	
BP/HR monitoring		X	X		X	X	X			X				
Prehydration (1000 mL) [‡]		X	-----	X										
Administered test drug infusion [§]			X											
Administered dexamethasone (20 mg IV)				X										
Administered cisplatin					X	-----	X [†]							
Administered additional chemotherapeutics agents if indicated								X	-----	X ^{¶¶}				
L-754030 (300 mg P.O. once daily)/placebo												X		
Laboratory safety tests	X [†]	X ^{††}										X [†]	X [†]	X
Serum pregnancy test [‡]	X													
Urine pregnancy test [‡]		X												X
Telephone contact ^{††}												X		
Emesis/nausea assessments		X			X	-----	X ^{§§}					X ^{§§}		
Global assessments												X	X	

Medical Officer's Comments: The primary efficacy parameter and the study design are acceptable.

4.1.4 Efficacy Findings

4.1.4.1 Fosaprepitant clinical efficacy in prevention of CINV

Efficacy in the prevention of acute CINV

The proportion (percent) of patients with Complete Response during the acute phase of CINV is as follows:

- 82.8% in patients who received Standard Therapy (ondansetron (32 mg I.V.) plus dexamethasone (20 mg I.V.) (Group C) ($p < 0.001$, for combined Groups A and B versus Group C);
- 45.0% in patients who received fosaprepitant on Day 1 in addition to dexamethasone, and aprepitant once daily on Days 2 to 5 (Group A);
- 35.1% in patients who received fosaprepitant on Day 1 in addition to dexamethasone, and placebo once daily on Days 2 to 5 (Group B).

Efficacy in the prevention of delayed CINV

The proportion (percent) of patients with Complete Response during the delayed phase of CINV is as follows:

- 37.9% in patients who received Standard Therapy (ondansetron 32 mg I.V.) plus dexamethasone (20 mg IV) (Group C);
- 59.3% in patients who received fosaprepitant on Day 1 in addition to dexamethasone, and aprepitant once daily on Days 2 to 5 (Group A) ($p < 0.05$ for Group A versus C);
- 44.6% in patients who received fosaprepitant on Day 1 in addition to dexamethasone, and placebo once daily on Days 2 to 5 (Group B) ($p = 0.57$ for Group B versus C).

These results suggest that the prevention of delayed emesis was better in the combination of fosaprepitant and aprepitant treatment group (Group A), compared with the control group (Group C) ($p < 0.05$) as shown in Table 3. Single dose fosaprepitant (Group B) failed to show statistically significant improvement as compared with the standard ondansetron treatment (Group C).

Table 5. Number of Patients with Complete Response (Study 007L1)

Phase	Treatment Group					
	Fosaprepitant Mannitol/Aprepitant [†] (Group A)		Fosaprepitant Mannitol/Placebo [†] (Group B)		Ondansetron/Placebo [†] (Group C)	
	N	n (%)	N	n (%)	N	n (%)
Acute (Day 1)	60	27 (45.0)	57	20 (35.1)	58	48 (82.8)
Delayed (Days 2 to 5)	59	35 (59.3) [*]	56	25 (44.6)	58	22 (37.9)

^{*} p<0.05 compared with Group C.
[†] All patients received dexamethasone 20 mg IV on Day 1.
N = Number of patients included in ITT analysis.
n = Number of patients with no emesis.
ITT = Intention-to-treat.
IV = Intravenous.
P.O. = By mouth.

4.1.4.2 Overall summary of aprepitant efficacy in prevention of CINV

Aprepitant, administered as a 3-day oral regimen, demonstrated to be effective for prevention of CINV associated with HEC and MEC. Three studies of the 3-day aprepitant regimen were conducted: 2 studies in HEC populations (Study 052 and Study 054) and 1 study in a MEC population (Study 071).

The CINV studies (004L1 and 007L1) showed that the combination of fosaprepitant (Day 1) and aprepitant (Days 2 to 5) was significantly less effective in preventing acute phase emesis post-cisplatin administration as compared with that of the standard ondansetron treatment. In prevention of the delayed phase emesis, the combination of fosaprepitant and aprepitant regimen was more effective than the ondansetron regimen. However, the single dose fosaprepitant regimen failed to show statistically more effective than the standard treatment.

The oral aprepitant dose-finding study showed that no additional benefit was provided by the 375/250-mg dose regimen relative to the 125/80-mg regimen. The sponsor proposed that 125/80 mg was the most appropriate dose regimen for registration. The sponsor proposed that the higher aprepitant C_{max} observed after I.V. fosaprepitant will result in neither additional receptor occupancy nor additional clinical benefit as was demonstrated in pharmacodynamic studies and validated in dose selection clinical studies.

4.1.5 Clinical Microbiology

Not applicable.

4.1.6 Efficacy Conclusions

Based on the available information, the following results supported the proposed indications:

- Fosaprepitant in combination with aprepitant and dexamethasone was significantly less effective in preventing acute phase cisplatin-induced emesis.
- Fosaprepitant combination regimen was more effective in prevention of the delayed (Days 2 to 5) phase emesis than the standard therapy.
- Single dose fosaprepitant regimen did not bring about more effective prevention of delayed phase cisplatin-induced emesis than the standard ondansetron treatment.

Medical Officer's Comments: Preventing the acute phase emesis is essential in evaluating anti-emetic agents. The submission failed to demonstrate the acute phase efficacy of the fosaprepitant regimen.

5 INTEGRATED REVIEW OF SAFETY

5.1 Methods and Findings

The safety data set consisted of 13 clinical studies of all formulations of intravenous fosaprepitant:

- Phase II HEC CINV studies: Protocol 004L1 and 007L1
- Phase II migraine and motion-induced nausea studies: Protocols 003L1 and 006L1
- Phase III PONV safety study: Protocol 015L1
- Phase I studies: Protocols 001L1, 005L1, 009L1, 011, 011L1, 012L1, 013C1 and 024

The data set involved 696 subjects: 149 subjects with CINV, 233 subjects with other symptoms (post-operative nausea and vomiting, migraine, motion-induced nausea, or hypertension), and 314 healthy adults. The proposed market formulation was administered to 123 healthy subjects.

No patient died because of the fosaprepitant treatment. No serious adverse events that caused by the treatment. The most frequent adverse experiences in fosaprepitant CINV studies were abdominal pain, constipation, diarrhea, dry mouth, dyspepsia, nausea, and stomatitis. Fosaprepitant including the proposed market formulation was generally well tolerated.

b(4)

5.1.1 Deaths

No fosaprepitant-related deaths were reported in this submission. A total of 10 patients died in fosaprepitant studies: Nine patients died in the Phase II CINV studies. The causes of death were consistent with that of cancer patients receiving high-dose cisplatin chemotherapy. One patient with ovarian cancer died of perforated bowel and abscess post-operation.

5.1.2 Other Serious Adverse Events

No serious adverse events caused by the treatment of fosaprepitant were reported. The pattern of serious adverse events was typical of patients receiving cisplatin-based highly-emetogenic chemotherapy. For example, gastrointestinal disorders, hematopoietic and lymphoid system disorders, infections, cardiac disorders, general disorders, and metabolism disorders.

5.1.3 Dropouts and Other Significant Adverse Events

No patient of the 696 subjects who were administered fosaprepitant discontinued the therapy due to the test article-related clinical adverse events.

5.1.3.1 Overall profile of dropouts

There were two patients, in Study 007L1, who were discontinued due to a laboratory adverse experience. However, these were not considered the test article-related by the investigator.

Medical Officer's Comments: Patient (#1996) experienced mild increase of serum creatinine (2.53 mg/dL). Patient (#2078) had moderate hypocalcemia (7.70 mg/dL), hypokalemia (4.9 mEq/L), and hypomagnesemia (1.30 mEq/L). The conclusion on causality of not related appeared to be reasonable.

5.1.4 Common Adverse Events

The most frequent adverse experiences in the Phase II fosaprepitant _____ CINV (HEC) studies were diarrhea, headache, asthenia, constipation, abdominal pain, dry mouth, dyspepsia, nausea, and stomatitis consistent with the population studied (Table 4).

b(4)

The increased incidence of diarrhea in the fosaprepitant _____ group relative to the ondansetron control group is most likely a consequence of chemotherapy, as it was not seen in non-CINV studies.

b(4)

Adverse experiences related to the infusion site, such as erythema, inflammation, and pain, were infrequent but more common with fosaprepitant _____. There were no reports of phlebitis in patients who received fosaprepitant _____ in these studies.

b(4)

Table 6. Most frequent adverse events in pooled Phase II CINV studies (Protocols 004L1 and 007L1)

Common Adverse Event	Fosaprepitant (N=30)	Fosaprepitant + Aprepitant + Other Drugs (N=119)	Ondansetron (N=23)
Diarrhea	17 (56.7%)	31 (26.1%)	4 (17.4%)
Headache	15 (50.0%)	18 (15.1%)	9 (39.1%)
Asthenia	12 (40.0%)	20 (16.8%)	8 (34.8%)
Constipation	11 (36.7%)	12 (10.1%)	10 (43.5%)
Abdominal pain	6 (20.0%)	10 (8.4%)	4 (17.4%)
Dry mouth	6 (20.0%)	2 (1.7%)	1 (4.3%)
Dyspepsia	3 (10.0%)	9 (7.6%)	0 (0.0%)
Nausea	3 (10.0%)	23 (19.3%)	3 (13.0%)
Stomatitis	3 (10.0%)	5 (4.2%)	3 (13.0%)

Derived from Table 2.7.4:21

Medical Officer's Comments: The patient populations of the treatment and control groups were imbalanced (Table 6). The numbers between the treatment and control groups are not comparable. However, the profile of common adverse events of fosaprepitant group appeared to be consistent with the known safety profile of aprepitant.

5.1.4.1 Eliciting adverse events data in the development program

Adverse event data was obtained on a fixed schedule as outlined in the study plan (Table 2). General AE assessment was made through 29-day study period on each visit. Laboratory assessment was conducted at screening period, Day 2, Day 8, Day 29.

Medical Officer's Comments: This is an acceptable approach.

5.1.4.2 Incidence of common adverse events

Incidence rates for common adverse events are best estimated from the pooled Phase II CINV Studies: Protocols 004L1 and 007L1. The most common adverse events were diarrhea (56.7%), headache (50.0%), asthenia (40%), constipation (36.7%), abdominal pain (20.0%), and dry mouth (20.0%) as shown in Table 4.

5.1.5 Laboratory Findings

Laboratory findings (chemistry, hematology, and urinalysis) of Studies 004L1 and 007L1 were reviewed. There were no trends of test article-related laboratory abnormalities. There were 4 patients who had drug-related laboratory adverse events (increased creatinine or alanine

aminotransferase). The investigator did not consider as serious laboratory findings (Page 123 of Study 007L1 report).

Medical Officer's Comments: There were 10 oncology patients (5.7%) who had at least one serious laboratory adverse experience, all of which were nonfatal and considered by the investigator to be unrelated to the study drug.

5.1.6 Vital Signs

Systolic and diastolic blood pressure and heart rate were evaluated at prestudy, 1, 2, and 4 hours post-cisplatin, Days 6 to 8 and Days 17 to 29. There were no patterns of vital sign abnormalities in patients over the duration of the two studies.

5.1.7 Electrocardiograms (ECGs)

The PR interval was examined at prestudy, 4 hours post-cisplatin, and on Days 6 to 8. No significant differences among the treatment groups and the control were observed.

In patients with moderate hypertension (N=8, Study P011), a single 100-mg intravenous dose of fosaprepitant and 300-mg oral doses of aprepitant given for 5 days caused a small decrease in systolic blood pressure (-5.96 mm Hg) as compared with the no medication control. No other clinically meaningful changes were identified (diastolic blood pressure, heart rate, or PR interval was examined) (Page 18 of Study P011 report).

5.2 Adequacy of Patient Exposure and Safety Assessments

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

The safety data sources used in conducting the review were:

- Phase II HEC CINV studies (Primary sources): Protocols 004L1 (n=53) and 007L1 (n=177)
- Phase II migraine and motion-induced nausea studies: Protocols 003L1 (n=72) and 006L1 (n=19)
- Phase III PONV safety study: Protocol 015L1 (n=211)

- Phase I studies: Protocols 001L1 (n=36), 005L1 (n=16), 009L1 (n=49), 011 (n=11), 011L1 (n=10), 012L1 (n=150), 013C1 (n=12) and 024 (n=32)

The patients that were selected for Studies 004L1 and 007L1 (primary source of safety) met the following criteria:

- Patient was scheduled to receive first course of cisplatin chemotherapy for malignancy at a dose of ≥ 70 mg/m². These included patients with lung cancers, nonepithelial and epithelial ovarian cancers, head and neck cancer, bladder cancer, cervical cancer, and adenocarcinoma of unknown origin.
- Patient was a male or female ≥ 18 years old.

5.2.1.1 Study type and design/patient enumeration

These were two Phase II, multicenter double-blind, randomized, active agent controlled studies to evaluate safety, tolerability, and efficacy of a single I.V. dose fosaprepitant plus aprepitant in cisplatin-induced emesis.

Study 004L1: fosaprepitant (60 mg or 100 mg, I.V. 1 hour prior to cisplatin), 30 subjects; or ondansetron 32 mg, 23 subjects.

Study 007L1: Group A: fosaprepitant (100 mg I.V. 1 hour prior to cisplatin) plus aprepitant (300 mg P.O. on Days 2 to 5) and dexamethasone (20 mg I.V. 30 minutes prior to cisplatin on Day 1), 62 subjects;

Group B: fosaprepitant (100 mg I.V. 1 hour prior to cisplatin) plus placebo for aprepitant on Days 2 to 5 and dexamethasone (20 mg I.V. 30 minutes prior to cisplatin on Day 1), 57 subjects;

Group C: Ondansetron (32 mg I.V. 1 hour prior to cisplatin) plus placebo for aprepitant on Days 2 to 5 and dexamethasone (20 mg I.V. 30 minutes prior to cisplatin on Day 1), 58 subjects.

5.2.1.2 Demographics

One hundred forty nine (30 treated subjects from Study 004L1 and 119 treated subjects from Study 007L1) CINV patients were included in the safety data set. Of these, 93 were male (22 to 78 years old) and 56 were female (28 to 74 years old). They were scheduled to receive the first course of cisplatin chemotherapy at a dose of ≥ 50 mg/m². As previously noted, the malignancy involved lung cancers, nonepithelial and epithelial ovarian cancers, head and neck cancer, bladder cancer, cervical cancer, and adenocarcinoma of unknown origin.

5.2.1.3 Extent of exposure (dose/duration)

One hundred forty CINV subjects received a single I.V. dose of 100 mg fosaprepitant, and 9 subjects received a dose of 60 mg.

The overall dose levels of all fosaprepitant formulations administered were 200 mg (17 administrations), 150 mg (39 administrations), 120 mg (6 administrations), 115 mg (66 administrations), 100 mg (306 administrations), 90 mg (34 administrations) and <90 mg (382 administrations) in 696 subjects (from Section 2.5 Table 2.5:8 of the submission).

The dose levels of the proposed market formulation were 150 mg (10 administrations), 115 mg (66 administrations), 100 mg (89 administrations), and 90 mg (34 administrations) in 123 healthy adult subjects (Section 2.5 Table 2.5:8 of the submission)

The highest oral dose of aprepitant in humans was 375 mg P.O. once daily for 8 weeks (89 subjects with major depressive disorder, Study P039).

5.2.2 Adequacy of Overall Clinical Experience

Medical Officer's Comments: The safety population consisted of 696 subjects. Of these, 434 subjects received at least an I.V. dose of 100 mg fosaprepitant. The proposed market dose will be 115 mg I.V. The overall clinical experience of fosaprepitant is adequate.

5.2.3 Assessment of Quality and Completeness of Data

Medical Officer's Comments: In general, the quality and completeness of the safety data are acceptable. The safety data set consisted of 13 clinical studies of all formulations of intravenous fosaprepitant:

- Phase II HEC CINV studies: Protocol 004L1 and 007L1
- Phase II migraine and motion-induced nausea studies: Protocols 003L1 and 006L1
- Phase III PONV safety study: Protocol 015L1
- Phase I studies: Protocols 001L1, 005L1, 009L1, 011, 011L1, 012L1, 013C1 and 024

The data set involved 696 subjects: 149 subjects with CINV, 233 subjects with other symptoms (post-operative nausea and vomiting, migraine, motion-induced nausea, or hypertension), and 314 healthy adults. The proposed market formulation was administered to 123 healthy subjects.

The study reports contained investigator comments, serious adverse event analysis, and frequent adverse events summarizations. These explanations helped the safety evaluations by the medical reviewer.

The deficiency in the quality of the data was that only highly-emetogenic chemotherapy was studied (004L1 and 007L1), whereas moderately-emetogenic chemotherapy was not studied.

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

Medical Officer's Comments: In general, the drug-related adverse events of fosaprepitant were consistent with the known safety profile of aprepitant. Diarrhea, headache, asthenia, constipation, and abdominal pain were more frequent observed (Table 4). No serious adverse events caused by the treatment of fosaprepitant were reported.

6 ADDITIONAL CLINICAL ISSUES

6.1 Dosing Regimen and Administration

Fosaprepitant 115 mg is used only in the CINV regimen for substitution of aprepitant (125 mg). Fosaprepitant is administered 30 minutes prior to chemotherapy on Day 1 as an intravenous infusion over 15 minutes.

- The efficacy and safety of the approved oral 3-day aprepitant regimen (125 mg/80 mg) has been established in patients at risk for CINV receiving both HEC and MEC.
- Additional oral Phase II studies using at least 375 mg (resulting in higher peak aprepitant levels than those achieved after administration of fosaprepitant 115 mg) demonstrated a plateau of efficacy at aprepitant 125 mg.

6.2 Drug-Drug Interactions

- **Fosaprepitant as an Inhibitor of CYP3A4**

The effect of fosaprepitant as a CYP3A4 inhibitor was evaluated using midazolam, a sensitive CYP3A4 probe (Study P012 part II). The dose of 100-mg of fosaprepitant (fosaprepitant PS80 — used in this midazolam interaction study is comparable to the recommended 115-mg dose as determined by the pharmacokinetics in Study P012.

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Midazolam concentrations were increased 1.6 fold with concomitant fosaprepitant administration. Oral aprepitant 125 mg was described as a moderate CYP3A4 inhibitor (midazolam AUC increase of 2.3 fold). These results confirm fosaprepitant was no worse of a

CYP3A4 inhibitor than oral aprepitant. Therefore, the investigator concluded that substitution of intravenous fosaprepitant on Day 1 will have no more of an effect on CYP3A4 substrates than oral aprepitant 125 mg.

Medical Officer's Comments: The same precautions regarding interactions with cytochrome P450 system of the aprepitant should be carried forward with the substitution of fosaprepitant.

- **Effect of Other Drugs on Fosaprepitant**

Since fosaprepitant is unlikely to be metabolized by the CYP isoenzymes, the investigator proposed that conversion of fosaprepitant to aprepitant is not expected to be altered by inhibition or induction of CYP isoenzymes. Upon conversion to aprepitant, the extent of induction or inhibition of aprepitant metabolism on the systemic clearance of aprepitant is expected to be similar to that of orally administered aprepitant. Therefore, the effect of coadministered drugs that alter the metabolism of aprepitant would be expected to have a similar effect on aprepitant exposure following intravenous fosaprepitant administration.

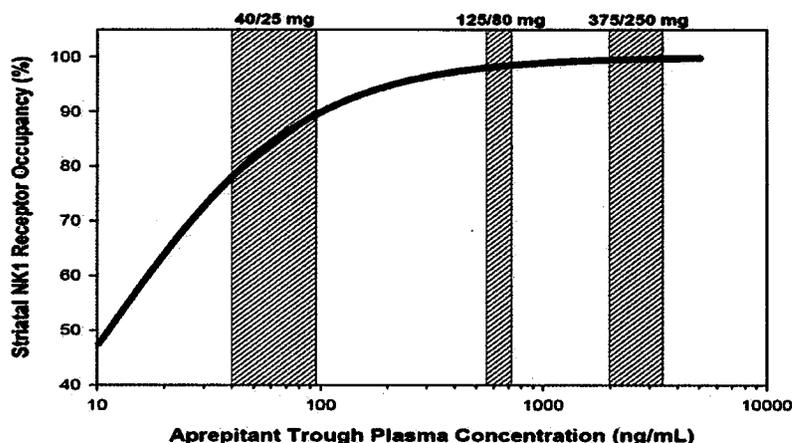
- **Pharmacodynamics and PK/PD Relationships**

Previous study using PET (positron emission tomography) demonstrated that plasma aprepitant concentration and NK1 receptor occupancy in the corpus striatum are well correlated in rhesus monkeys and humans (Reference 16 of this submission). Aprepitant plasma concentrations of ~10 ng/mL and ~100 ng/mL produce NK1 receptor occupancies of ~50% and ~90%, respectively. The aprepitant CINV regimen (125 mg on Day 1; 80 mg on Days 2 and 3) produces mean trough plasma aprepitant concentrations ≥ 500 ng/mL, which would be expected to result in $>95\%$ brain NK1 receptor occupancy. In addition to being equivalent in terms of aprepitant AUC, 115-mg fosaprepitant (fosaprepitant PS80) produced a C_{24hr} (plasma concentration at 24 hour) of 504 ng/mL. Based on the data seen in Figure 1, this trough concentration would result in similar (i.e. $>95\%$) brain NK1 receptor occupancy.

b(4)

Also, previous Phase II studies demonstrated a plateau of efficacy at 125 mg aprepitant. Therefore no additional efficacy is expected from a higher C_{max} with fosaprepitant (Study 041).

Figure 1. NK₁ Receptor occupancy and mean aprepitant trough plasma concentrations



6.3 Pediatrics

There were no pediatric patients included in fosaprepitant studies.

7 OVERALL ASSESSMENT

7.1 Conclusions

Prevention of acute and delayed emesis in highly-emetogenic chemotherapy (cisplatin ≥ 50 mg/m²) by the regimen of fosaprepitant (Day 1) in combination with aprepitant (Days 2 to 5) and dexamethasone (Day 1) was studied. The regimen was significantly more effective than the standard ondansetron (32 mg I.V., Day 1) therapy in preventing the delayed emesis (24 hours to 120 hours) post cisplatin (≥ 70 mg/m²) administration (Study 007L1). However, in preventing the acute phase emesis (0 to 24 hours), this fosaprepitant regimen was significantly less effective than the standard ondansetron therapy. Single dose of fosaprepitant was not statistically more effective than the standard ondansetron therapy in preventing the delayed phase emesis (Study 007L1).

The effects of the fosaprepitant regimen in moderately-emetogenic chemotherapy (e.g., cisplatin < 50 mg/m²) were not studied.

Since fosaprepitant is rapidly converted to aprepitant following intravenous administration, this clinical review believed that the efficacy and safety data obtained from orally administered aprepitant is applicable to I.V. administered fosaprepitant, provided that the Clinical Pharmacology Review supports this substitution.

Nausea and vomiting are common complications of cancer chemotherapy. They have a **significant impact on patients' quality of life** and patients may delay scheduled chemotherapy. There is a medical need for route of administration options (such as intravenous administration) to prevent CINV in patients who cannot easily tolerate orally administered medication prior to initiating chemotherapy. Parenteral administration is frequently more convenient prior to the administration of chemotherapy (which is also commonly given intravenously).

This submission is approvable for intravenously administered fosaprepitant PS80 — 115 mg. It will allow fosaprepitant to be substituted for 125-mg aprepitant on Day 1 of the currently approved 3-day oral aprepitant CINV regimen (aprepitant 125 mg on Day 1 followed by aprepitant 80-mg on Days 2 and 3). The application is based on that the modified CINV regimen on Day 1 will provide comparable efficacy and safety profiles as the all-oral regimen. This premise is supported by the following points:

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- The regimen is significantly more effective than the standard ondansetron (32 mg I.V., Day 1) therapy in preventing the delayed emesis (24 hours to 120 hours) post cisplatin ($\geq 70 \text{ mg/m}^2$) administration.
- Fosaprepitant is rapidly converted to aprepitant (within 30 minutes) in vivo following intravenous administration.
- Fosaprepitant 115 mg administered intravenously provides an equivalent aprepitant AUC to oral aprepitant 125 mg, although the prodrug has a higher C_{max} .
- The efficacy and safety of the approved oral 3-day aprepitant regimen (125 mg/80 mg) has been established in patients at risk for CINV receiving both HEC and MEC.
- Oral Phase II studies using at least 375 mg (resulting in higher peak aprepitant levels than those achieved after administration of fosaprepitant 115 mg) demonstrated a plateau of efficacy at aprepitant 125 mg.
- Based on data with the CYP3A4 probe midazolam, the potential for CYP3A4 drug-drug interactions with intravenously administered fosaprepitant should be similar to or no worse than with the oral marketed aprepitant regimen.

7.2 Recommendation on Regulatory Action

The clinical recommendation is **approvable** for the application of fosaprepitant in combination with other antiemetic agents for the prevention of acute and delayed nausea and vomiting of highly or moderately emetogenic cancer chemotherapy.

7.3 Labeling Review

The Sponsor's Proposed Label and the Reviewer's Proposed Label are as the following:

Sponsor's Proposed Label	Reviewer's Proposed Label

b(4)

b(5)

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this page is the manifestation of the electronic signature.**

/s/

Wen-Yi Gao
4/25/2007 01:09:41 PM
MEDICAL OFFICER

Hugo Gallo Torres
4/25/2007 04:28:17 PM
MEDICAL OFFICER

**Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: QT Study Review**

NDA	22023
Brand Name	NA
Generic Name	Fosaprepitant dimegulmine (MK-0517)
Sponsor	Merck& Co.
Indication	Chemotherapy induced nausea and vomiting
Dosage Form	IV
Therapeutic Dose	115-mg IV infusion on day 1 followed by 80-mg po doses on days 2 and 3 following chemotherapy
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	Not reported
Application Submission Date	31 March 2006
Review Classification	NDA Standard Review
Date Consult Received	17 October 2006
Date Consult Due	15 January 2007
Clinical Division	DGP/HFD 180
PDUFA Date	03 May 2007

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

The effects of a single intravenous 200 mg dose of fosaprepitant (MK-0517) administered over 15 minutes on the QTc were assessed in this "thorough QT study" (TQT). This study assessed the drug effect on QTc for only 8 hours after dosing; effects on the QTc interval after 8 hours can not be excluded.

The mean C_{max} was 6.3 µg/ml which is approximately 2-fold larger than the mean C_{max} obtained from 115 mg MK-0517 dose given over 15 minutes (3.1 µg/ml). Co-administration of MK-0517 with strong inhibitors of CYP3A4 (e.g., ketoconazole) has the potential to increase aprepitant plasma concentrations greater than 2-fold. This drug-drug interaction study with the IV formulation of MK-0517 was not performed by the sponsor.

The FDA statistical reviewer performed an independent analysis of the primary endpoint, the placebo corrected QTcF interval change from baseline for fosaprepitant (i.e., the difference (fosaprepitant - placebo) in QTcF interval change baseline). The agency findings are consistent with those reported by the sponsor.

The statistical reviewer concludes the following:

- Moxifloxacin, a positive control, prolongs QTcF as expected and so the study demonstrated assay sensitivity (Table 9).
- The largest mean difference between MK-0517 and placebo occurred 6 h after dosing and was 3.6 msec with an upper 95% CI of 7.92 msec. This values is less than the

level of 10 msec that is specified as the threshold of regulatory concern in the ICH E14 guideline (Table 8).

1.2 RESPONSES TO QUESTIONS POSED BY THE REVIEW DIVISION

- The review division did not submit any questions.

1.3 REVIEWER'S COMMENTS

- Fosaprepitant is a water-soluble prodrug for aprepitant, which is marketed in an oral formulation Emend®. The pharmacological effect of fosaprepitant is attributed to aprepitant and fosaprepitant was developed as an intravenous substitute for aprepitant. Aprepitant is a substrate for CYP3A4. Plasma concentrations of aprepitant increased 2-fold after co-administration of Emend® with diltiazem and 1.5-fold after co-administration with ketoconazole. The label states Emend®, “: _____”
_____” The suprathreshold dose of 200 mg of MK-0517 infused IV over 15 minutes provides a 2-fold increase in C_{max} over the therapeutic dose.
- ECG collection times were obtained at times corresponding to the peak concentration of both fosaprepitant and aprepitant.
- The sponsor did not perform multiple endpoint adjustment for the moxifloxacin.
- The sponsor's categorical analysis results do not match with our statistical analysis. It seems that the sponsor used the average of five replicates at each timepoint, while FDA calculation is based on the individual measurement.

b(4)

2 PROPOSED LABEL

The sponsor did not include any labeling for the effects of product administration on the QT interval. The following recommendations are suggestions for labeling only. **We defer all final labeling decisions to the review division.**

12.2 Pharmacodynamics

Cardiac Electrophysiology

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b(5)

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3 BACKGROUND

3.1 INDICATION

MK-0517, 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 (HEC) including high-dose cisplatin
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

3.2 DRUG CLASS

Fosaprepitant when administered intravenously is rapidly converted to aprepitant, a substance P/neurokinin 1 (NK1) receptor antagonist.

3.3 MARKET APPROVAL STATUS

Aprepitant (EMEND™) is an approved orally administered neurokinin 1 receptor antagonist.

3.4 PRECLINICAL INFORMATION

The preclinical information in the current submission mostly references studies performed with oral formulations of aprepitant. No mention is made of hERG or other *in vitro* testing. It does mention that no electrocardiographic abnormalities were noted in an Aprepitant repeat dose toxicity study in dogs.

3.5 PREVIOUS CLINICAL EXPERIENCE

The label for Emend® does not include any reference to its effect on the QT interval nor does it mention Torsades de pointe. The clinical reviewer did not perform an independent analysis of the post-marketing safety database.

3.6 CLINICAL PHARMACOLOGY

Fosaprepitant is a prodrug that is rapidly converted into aprepitant after intravenous administration. Since fosaprepitant has a very short half-life (~2-3 minutes), it is believed that the pharmacological activity of fosaprepitant is completely attributable to aprepitant. Plasma levels of fosaprepitant fall below the lower limit of quantitation (LLOQ) within 30 minutes of the end of infusion (Figure 1).

Table 1 summarizes the key features of aprepitant's clinical pharmacology.

Figure 1. Mean Plasma Concentration of Fosaprepitant and Aprepitant Following 115-mg IV Fosaprepitant Administered as a Constant Rate Infusion Over 15 Minutes

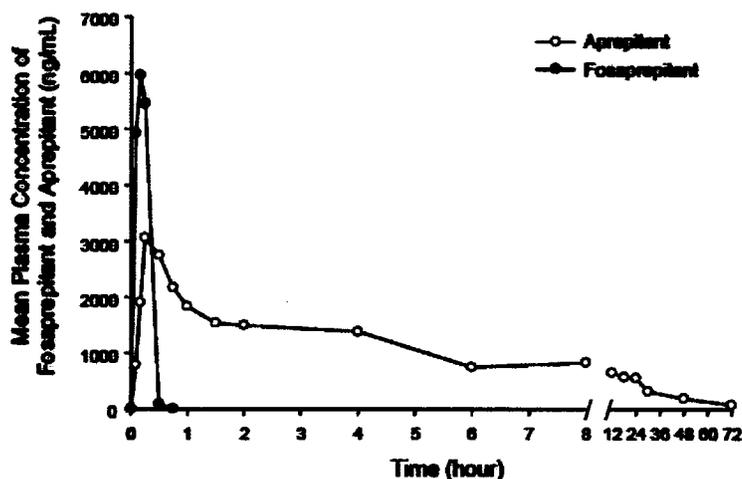


Table 1: Highlights of Clinical Pharmacology (Data Compiled by the Reviewer)

Therapeutic dose	115-mg IV infusion on day 1, and 80-mg po doses on days 2 and 3 following chemotherapy	
Maximum tolerated dose	Not reported	
Principal Adverse Events	The most notable adverse experiences associated with the Emend® administration in the clinical study in highly emetic chemotherapy clinical study were asthenia, nausea, dizziness, diarrhea, cough, and hiccups. In the clinical study in moderate emetic chemotherapy, common adverse events were abdominal pain, dyspepsia, arthralgia, anxiety, cough, rash, and hot flushes	
Maximum dose tested	Healthy Volunteers	150 mg administered over 15 minutes
	Target Population	115 mg administered over 15 minutes
Exposures Achieved	Single Dose of 115 mg	C _{max} : 3.26 mcg/mL AUC: 19.8 mcg•hr/mL
	Steady State	Not applicable
Accumulation	Not applicable	
Range of linear PK	Not applicable	
Absorption	T _{max}	Not applicable
	F	Not applicable
Distribution	V _{ss}	7 L
	Protein binding	> 95%
Elimination	T _{1/2}	9 to 13 hours.
	CL	Not reported
	Route	Aprepitant undergoes extensive

		metabolism primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19
Metabolites	Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma	
Intrinsic Factors	Elderly (> 65y)	21-36% higher AUC 10-24% higher C _{max}
	Gender	16% higher C _{max} in females; 25% lower t _{1/2}
	Race	25-29% higher AUC in Hispanics 22-31% higher C _{max} in Hispanics
	Severe Renal Impairment	AUC _{0-∞} of total aprepitant (unbound and protein bound) decreased by 21% and C _{max} decreased by 32%
	ESRD	AUC _{0-∞} of total aprepitant decreased by 42% and C _{max} decreased by 32%.
Extrinsic Factors	Food Effects	Not applicable
	DDI	<ul style="list-style-type: none"> • Co-administration of Ketoconazole with Emend® resulted in the AUC of aprepitant being increased approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold. • Co-administration of Diltiazem with Emend® resulted in a 2-fold increase in plasma concentrations of aprepitant.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted a 'thorough QT study' for review.

4.2 TQT STUDY

4.2.1 Title

A Double-Blind, Double-Dummy, Randomized, Placebo-Controlled, 3-Period, Single-Dose, Crossover Study to Assess the Effect of MK-0517 on QTc Interval in Healthy Subjects

4.2.2 Protocol Number

Protocol 016

4.2.3 Objectives

Primary

(1) To investigate the safety and tolerability of a 200 mg intravenous dose of MK-0517 in young, healthy subjects.

(2) To evaluate effects of a supra-therapeutic dose of MK-0517 on the QTc.

Secondary

To demonstrate sensitivity of this QTc assay using moxifloxacin as a positive control.'

4.2.4 Design

4.2.4.1 Description

This study was a double-blind, double-dummy, placebo-controlled, randomized 3-period balanced crossover study in healthy young male and female subjects to evaluate the effects of a suprathereapeutic (200 mg) dose of MK-0517 on the QTc. Each period consisted of a single oral dose of either 400 mg moxifloxacin, 200 mg MK-0517 IV, or placebo. There was a 7-day washout between periods.

4.2.4.2 Sponsor's Justification for Design

The sponsor did not provide a justification for the design.

4.2.4.3 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.4.4 Blinding

All study treatments were blinded.

4.2.5 Study Subjects

Healthy, nonsmoking adult males and females between 18 and 45 years of age, within 30% of ideal weight. Female subjects could not be pregnant or breastfeeding, and female subjects of childbearing potential were required to use specified birth control.

4.2.6 Dosing Regimens

4.2.6.1 Treatment Arms

Subjects received an oral dose (moxifloxacin or placebo) and an intravenous (IV) dose (MK-0517 or placebo) in each treatment period.

- Treatment A consisted of a single orally administered 400 mg moxifloxacin tablet and a single intravenously administered dose of placebo (saline) exactly to match 200 mg MK-0517 (200 ml)
- Treatment B consisted of a single orally administered placebo tablet and a single intravenously administered dose of 200 mg MK-0517 (200 mL)
- Treatment C consisted of a single orally administered placebo tablet and a single intravenously administered dose of placebo exactly to match 200 mg MK-0517 (200 mL)

Subjects received the three treatments in a randomized sequence in a crossover design.

4.2.6.2 Sponsor's Justification for Doses

The dose of MK-0517 utilized in this study was 200 mg administered over 15 minutes.

The highest dose tested in the current formulation previously tested was 150 mg administered over 15 minutes. This dose and formulation achieved an MK-0517 AUC and C_{max} of 1987 ng•hr/mL and 7750 ng/mL (Table 2). The previous study of 200 mg MK-0517 in the older formulation administered over 30 minutes achieved an MK-0517 AUC and C_{max} of 2400 ng•hr/mL and 6030 ng/mL, respectively. The 200-mg dose in the current formulation administered over 15 minutes was expected to equal or exceed these concentrations. The pharmacokinetic modeling with data from previous studies of MK-0517 showed that a 200-mg dose over 15 minutes in the current study would be estimated to have mean (90% CI) AUC and C_{max} of ~2790 ng•hr/mL (2430, 3150) and 11,800 ng/mL (10800, 12800). These are ~2 fold higher AUC and C_{max} exposures of MK-0517 than those achieved with the 115-mg dose of MK-0517. Of note, MK-0517 exposures are predicted to fall near or below the limit of quantitation of the assay (20 ng/mL) within 30 minutes post-infusion.

MK-0517 is converted rapidly to aprepitant. The doses of 150 mg over 15 minutes in the current formulation and 200 mg over 30 minutes in the previous formulation reached maximum aprepitant concentrations (C_{max}) of 4569 and 5317 ng/mL and had AUC values of 44,578 and 55,563 ng•hr/mL, respectively. Based on this data and those from previous studies, the 200-mg dose of MK-0517 in the current study would be estimated to produce mean (90% CI) aprepitant AUC of ~61,100 ng•hr/mL (54700, 67400) and C_{max} of ~6040 ng/mL (5520, 6560), which are about 2-fold higher than achieved with the 115-mg MK-0517 dose given over 15 minutes (29611 ng.hr/mL and 3095 ng/mL, respectively).

Table 2: Predicted Exposures of Aprepitant

Dose of MK-0517	MK-0517		Aprepitant	
	AUC (ng•hr/mL)	C _{max} (ng/mL)	AUC (ng•hr/mL)	C _{max} (ng/mL)
115 mg over 15 min				
150 mg over 15 min				
200 mg over 30 min				
Projected Mean† (90% CI) 200 mg over 15 min				

† Projections based on data from previous studies. Please see appendix [16.2.5.1]

Data Source: [16.1.12.3; 16.1.12.4; 16.2.5.1]

(Sponsor's Table 7-1, page 16)

4.2.6.3 Instructions with regard to meals

There were no instructions for timing of meals.

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4.2.6.4 Study Assessments

Table 3: Highlights of Schedule of Interventions

Study Day	1
Intervention	15 min infusion
12-Lead ECGs	Predose, 2 min, 5 min, 10 min, 15 min, 20 min, 30 min, 45 min, 1, 1.5, 2, 3, 4, 6, and 8 hours post initiation of 15 minute infusion
PK Samples for drug	Predose, 2 min, 5 min, 10 min, 15 min, 20 min, 30 min, 45 min, 1, 1.5, 2, 3, 4, 6, and 8 hours post initiation of 15 minute infusion

4.2.6.5 Sponsor's justification for sampling schedule

The sponsor did not provide justification for sampling times.

4.2.6.6 Baseline

The within-day, pre-dose ECG was defined as baseline.

4.2.7 ECG Collection

The QTc interval was assessed by 12-lead ECGs extracted from _____ Holter records by a centralized core ECG laboratory that was blinded to treatments, period, and time.

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4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Thirty-four female and male healthy volunteers (between 18 to 44 years old) were enrolled in the study. Thirty subjects completed all 3 periods.

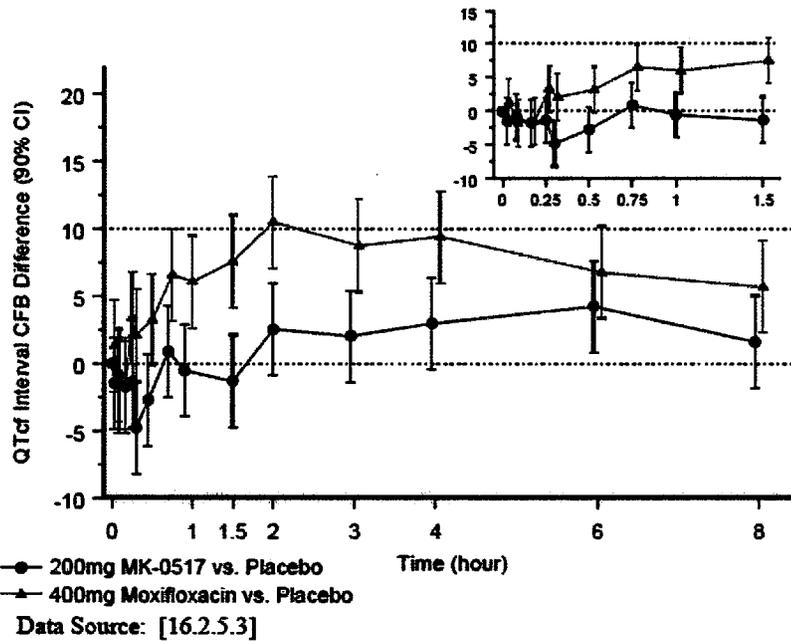
4.2.8.2 Statistical Analyses

4.2.8.2.1 E14 Analysis

Mean between-treatment differences (active - placebo) for QTcf change from baseline over time are indicated in Figure 2. For 200 mg MK-0517 versus placebo, the upper limits of the confidence intervals at all time points were less than 10 msec.

For moxifloxacin versus placebo, the lower limit of the 90% confidence interval for the mean between treatment difference in QTcF change from baseline was greater than zero at all measured time points from 45 minutes onward (The Tmax for moxifloxacin is 2 hours postdose with the range from 30 minutes to 4 hours postdose).

Figure 2: Mean (90% CI) Between-treatment Differences (Active - Placebo) in QTcf Change From Baseline Following Single Doses of 200-mg MK-0517 and Moxifloxacin Over Time in Healthy Male and Female Subjects (N=32)



(Sponsor's Figure 11-1, page 39)

Table 4: Summary Statistics for QTcF, QTcF Change From Baseline and Mean Differences in QTcF Change From Baseline by Treatment and Time Point Following 200-mg MK-0517 and Placebo in Healthy Male and Female Subjects

Treatment	Time	QTcf Value (msec)			QTcf Change from Baseline [†] (CFB) (msec)		CFB Difference (msec) (Active - Placebo)	
		n	Mean	95% CI	Mean	95% CI	Mean	90% CI
200 mg MK-0517	Predose	32	397.82	(391.18,404.47)				
	2 minutes	32	389.90	(383.25,396.55)	-7.87	(-11.09,-4.64)	-1.48	(-4.9,1.94)
	5 minutes	32	399.40	(392.75,406.05)	1.63	(-1.59,4.86)	-0.89	(-4.31,2.52)
	10 minutes	32	398.57	(391.93,405.22)	0.81	(-2.41,4.03)	-1.73	(-5.15,1.68)
	15 minutes	32	396.32	(389.67,402.97)	-1.45	(-4.67,1.77)	-1.37	(-4.78,2.05)
	20 minutes	32	392.34	(385.69,398.99)	-5.43	(-8.65,-2.21)	-4.79	(-8.2,-1.37)
	30 minutes	32	395.39	(388.74,402.04)	-2.37	(-5.6,0.85)	-2.71	(-6.12,0.71)
	45 minutes	32	397.92	(391.27,404.57)	0.15	(-3.07,3.37)	0.88	(-2.54,4.3)
	1 hour	32	398.14	(391.49,404.79)	0.37	(-2.85,3.59)	-0.53	(-3.94,2.89)
	1.5 hours	32	397.19	(390.54,403.84)	-0.58	(-3.8,2.64)	-1.31	(-4.76,2.13)
	2 hours	32	399.51	(392.86,406.16)	1.75	(-1.48,4.97)	2.54	(-0.88,5.96)
	3 hours	32	402.07	(395.43,408.72)	4.31	(1.09,7.53)	2.05	(-1.37,5.46)
	4 hours	32	402.05	(395.4,408.7)	4.28	(1.06,7.51)	2.98	(-0.43,6.4)
	6 hours	32	396.41	(389.76,403.05)	-1.36	(-4.58,1.86)	4.27	(0.85,7.68)
8 hours	32	393.31	(386.66,399.96)	-4.45	(-7.68,-1.23)	1.62	(-1.8,5.04)	

[†] QTcf change from baseline using Fridericia's correction, predose baseline, and average of 5 replicate measurements

Data Source: [16.2.5.3]

(Sponsor's Table 11-2, page 43)

Table 5: Summary Statistics for QTcF, QTcF Change From Baseline and Mean Differences in QTcF Change From Baseline by Treatment and Time Point Following 400-mg Moxifloxacin and Placebo in Healthy Male and Female Subjects

Treatment	Time	QTcF Value (msec)			QTcF Change from Baseline [†] (CFB) (msec)		CFB Difference (msec) (Active - Placebo)	
		n	Mean	95% CI	Mean	95% CI	Mean	90% CI
400 mg Moxi.	Predose	32	397.91	(391.26,404.56)				
	2 minutes	32	392.96	(386.31,399.61)	-5.05	(-8.28,-1.83)	1.33	(-2.08,4.75)
	5 minutes	32	398.82	(392.17,405.47)	0.80	(-2.42,4.02)	-1.72	(-5.14,1.69)
	10 minutes	32	399.10	(392.45,405.75)	1.08	(-2.14,4.31)	-1.46	(-4.87,1.96)
	15 minutes	32	401.31	(394.66,407.96)	3.29	(0.07,6.51)	3.37	(-0.05,6.79)
	20 minutes	32	399.49	(392.85,406.14)	1.48	(-1.75,4.7)	2.12	(-1.3,5.53)
	30 minutes	32	401.59	(394.94,408.24)	3.57	(0.35,6.79)	3.24	(-0.18,6.66)
	45 minutes	32	403.88	(397.23,410.52)	5.86	(2.64,9.08)	6.59	(3.17,10)
	1 hour	32	405.01	(398.36,411.66)	6.99	(3.77,10.21)	6.09	(2.67,9.51)
	1.5 hours	32	406.34	(399.7,412.99)	8.33	(5.1,11.55)	7.59	(4.15,11.04)
	2 hours	32	407.73	(401.08,414.37)	9.71	(6.49,12.93)	10.50	(7.09,13.92)
	3 hours	32	409.03	(402.38,415.67)	11.01	(7.79,14.23)	8.75	(5.33,12.17)
	4 hours	32	408.74	(402.1,415.39)	10.73	(7.5,13.95)	9.43	(6.01,12.84)
	6 hours	32	399.18	(392.53,405.82)	1.16	(-2.06,4.38)	6.79	(3.37,10.2)
8 hours	32	397.64	(390.99,404.29)	-0.38	(-3.6,2.84)	5.69	(2.28,9.11)	

(Sponsor's Table 11-2, page 42)

4.2.8.2.2 Categorical Analyses

No subject had any QTcF values above _____ msec. One subject (AN0017) had QTcF values that ranged between _____ msec following moxifloxacin and placebo administration. No subjects had an increase in QTcF of more than _____ msec. One subject (AN0022) had increases between _____ msec after placebo administration. Two (AN0027 and AN0029) had increases between _____ msec following 200 mg MK-0517, and one (AN0002) had an increase between _____ msec following moxifloxacin.

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4.2.8.2.3 Additional Analyses

The mean difference (MK-0517 - placebo) in QTcF change from baseline was -1.37 msec with corresponding 90% CI of (-4.78, 2.05) msec. The one sided upper 95% confidence interval was below 10 msec.

Table 6: Summary Statistics for the Mean Difference (MK-0517-Placebo) in QTcF Change From Baseline (CFB) at 15 Minutes Postdose (Tmax) Following a Single Dose of 200-mg MK-0517 and Placebo in Healthy Male and Female Subjects

Treatment	Time Point	N [‡]	QTcF Change From Baseline [†] (CFB) (msec)	CFB Difference (msec) (MK-0517 - Placebo)
			Mean (95% CI)	Mean (90% CI)
200-mg MK-0517	15 minutes	32	-1.45 (-4.67,1.77)	-1.37 (-4.78,2.05)
Placebo		30	-0.08 (-3.39,3.23)	

[†] QTcF change from baseline using Fridericia's correction, predose baseline, and average of 5 replicate measurements.
[‡] Some subjects that had incomplete data (AN 0010 and 0013 with only Period 1 data, and AN 0019 with only Periods 1 and 2 data). Therefore, the sample sizes in the two treatment groups were not the same.

Data Source: [16.2.5.3]

(Sponsor's Table 11-1, page 40)

4.2.8.3 Safety Analysis

The sponsor reports "MK-0517 was generally well tolerated in healthy young males and females." No deaths or serious adverse events are reported. No episodes of syncope, ventricular arrhythmias, or seizures were reported. One subject withdrew due to an adverse event, a tooth abscess. No cardiac adverse events are reported. No effects on vital signs are noted.

4.2.8.4 Clinical Pharmacology

Since no detectable effect of MK-0517 on the QTc interval was seen, the sponsor did not assay the archived plasma samples. Therefore, observed exposure to MK-0517 and aprepitant were not reported for this study.

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

The Statistical Reviewer's evaluation is based on the sponsor's data and in accordance with ICH E14 guidelines on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

The Statistical Reviewer used the following data set submitted in the NDA to carry out some of the independent analyses for statistical evaluation of the results:

\\Cdsub1\evsprod\NDA022023\0004\m5\datasets\p01611\listings. This data set is described in the \\Cdsub1\evsprod\NDA022023\0004\m5\datasets\p01611\listings\define.pdf file and it includes individual values of the 5 replicates ECG measurements as well as the other derived ECG parameters and variables.

5.1.1 Inferential Analysis

The raw mean difference of the drug and placebo as well as the positive control and placebo after baseline adjustment was calculated. The results are provided in Table 7.

Table 7: Summary Statistics of QTcF and QTcF Change from Baseline

Treatment	Time	N	QTcF Value (msec)		QTcF Change from Baseline (CFB)(msec)	
			Mean	95% CI	Mean	95% CI
MK-0517	Predose	32	398.14	(390.65, 405.64)	.	
	2 minutes	32	390.22	(383.45, 396.99)	-7.93	(-11.36, -4.49)
	5 minutes	32	399.72	(392.20, 407.24)	1.57	(-1.29, 4.44)
	10 minutes	32	398.89	(391.73, 406.05)	0.75	(-2.29, 3.79)
	15 minutes	32	396.64	(389.69, 403.58)	-1.51	(-5.06, 2.04)
	20 minutes	32	392.66	(386.08, 399.24)	-5.49	(-8.73, -2.24)
	30 minutes	32	395.71	(388.87, 402.55)	-2.43	(-5.70, 0.84)
	45 minutes	32	398.24	(391.07, 405.41)	0.09	(-2.92, 3.11)
	1 hour	32	398.46	(392.00, 404.91)	0.31	(-3.68, 4.30)
	1.5 hours	32	397.51	(390.82, 404.20)	-0.64	(-3.83, 2.55)
	2 hours	32	399.83	(393.38, 406.29)	1.69	(-2.23, 5.61)

	3 hours	32	402.39	(396.03, 408.76)	4.25	(0.00, 8.50)
	4 hours	32	402.37	(395.80, 408.93)	4.23	(-0.26, 8.71)
	6 hours	32	396.73	(390.48, 402.97)	-1.42	(-5.16, 2.32)
	8 hours	32	393.63	(387.22, 400.04)	-4.51	(-8.65, -0.37)
Moxifloxacin	Predose	32	398.84	(392.30, 405.39)	.	
	2 minutes	32	393.90	(387.18, 400.62)	-4.94	(-7.60, -2.29)
	5 minutes	32	399.76	(392.96, 406.55)	0.91	(-1.75, 3.58)
	10 minutes	32	400.04	(393.10, 406.97)	1.19	(-1.83, 4.21)
	15 minutes	32	402.24	(395.03, 409.46)	3.40	(0.66, 6.14)
	20 minutes	32	400.43	(393.14, 407.72)	1.59	(-1.77, 4.95)
	30 minutes	32	402.53	(394.95, 410.10)	3.68	(0.04, 7.32)
	45 minutes	32	404.81	(397.26, 412.36)	5.97	(1.85, 10.09)
	1 hour	32	405.94	(399.15, 412.74)	7.10	(3.87, 10.33)
	1.5 hours	32	407.28	(400.15, 414.42)	8.44	(5.52, 11.36)
	2 hours	32	408.66	(402.16, 415.16)	9.82	(6.74, 12.90)
	3 hours	32	409.96	(402.72, 417.21)	11.12	(7.49, 14.75)
	4 hours	32	409.68	(401.99, 417.37)	10.84	(7.04, 14.64)
	6 hours	32	400.11	(393.65, 406.58)	1.27	(-1.70, 4.24)
	8 hours	32	398.58	(392.26, 404.89)	-0.27	(-2.97, 2.44)
Placebo	Predose	30	397.35	(389.92, 404.79)	.	
	2 minutes	30	391.56	(384.62, 398.50)	-5.79	(-9.41, -2.18)
	5 minutes	30	400.47	(393.63, 407.32)	3.12	(0.35, 5.89)
	10 minutes	30	400.49	(393.33, 407.65)	3.13	(0.12, 6.14)
	15 minutes	30	397.87	(390.29, 405.44)	0.51	(-2.62, 3.64)
	20 minutes	30	397.31	(389.91, 404.70)	-0.05	(-3.81, 3.71)
	30 minutes	30	398.28	(390.58, 405.98)	0.93	(-2.31, 4.17)
	45 minutes	30	397.22	(390.22, 404.22)	-0.13	(-3.49, 3.23)
	1 hour	30	398.85	(391.20, 406.49)	1.49	(-2.06, 5.04)
	1.5 hours	29	398.38	(390.82, 405.94)	1.61	(-1.83, 5.06)
	2 hours	30	397.15	(390.08, 404.23)	-0.20	(-4.04, 3.64)
	3 hours	30	400.21	(393.44, 406.98)	2.85	(-0.99, 6.69)
	4 hours	30	399.25	(392.48, 406.02)	1.89	(-1.73, 5.51)
	6 hours	30	392.32	(386.29, 398.35)	-5.03	(-8.95, -1.12)
	8 hours	30	391.87	(385.73, 398.02)	-5.48	(-9.36, -1.60)

We calculated the mean difference and 1-sided upper 95% confidence bound for QTcF change from baseline between Mk-0517 and placebo at each time point separately. Our results which are presented in Table 8 are very similar to the sponsor's results. All the 1-sided upper 95% confidence bounds are below 10 msec.

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Table 8: Summary Statistics of QTcF Change from Baseline between MK-0517 and Placebo

Treatment	Time	N	Active - Placebo	
			Mean	1-sided 95% UB
MK-0517	2 minutes	30	-2.21	1.74
	5 minutes	30	-1.36	2.34
	10 minutes	30	-2.19	1.38
	15 minutes	30	-1.95	2.57
	20 minutes	30	-5.72	-2.01
	30 minutes	30	-3.17	0.55
	45 minutes	30	0.41	4.07
	1 hour	30	-0.87	3.31
	1.5 hours	29	-1.37	2.88
	2 hours	30	2.21	6.19
	3 hours	30	1.36	6.00
	4 hours	30	1.79	6.43
	6 hours	30	3.63	7.92
	8 hours	30	0.99	5.51

To assess the assay sensitivity, we calculated the mean difference and 1-sided lower 95% confidence bound for QTcF change from baseline between moxifloxacin and placebo. Our results which are presented in Table 9 are very similar to sponsor's results. We did not adjust the multiple timepoints for the assay sensitivity. We examined the moxifloxacin profile, which looks fine.

Table 9: Summary Statistics of QTcF Change from Baseline between moxifloxacin and Placebo

Treatment	Time	N	Active - Placebo	
			Mean	1-sided 95% LB
Moxifloxacin	2 minutes	30	1.08	-2.61
	5 minutes	30	-2.19	-5.39
	10 minutes	30	-1.55	-4.61
	15 minutes	30	2.87	-0.19
	20 minutes	30	1.72	-1.82
	30 minutes	30	2.49	-1.46
	45 minutes	30	6.10	2.21
	1 hour	30	5.39	1.48
	1.5 hours	29	6.77	2.64
	2 hours	30	9.95	6.01
	3 hours	30	7.95	3.54
	4 hours	30	9.27	4.97
	6 hours	30	6.57	3.04
	8 hours	30	5.39	2.06

5.1.2 Categorical Analysis

The results for the categorical analysis are presented in the following tables.

Table 10: Frequency for QTcF > 450 msec

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - MK-0517	32	1	3.13%	160	1	0.63%
Baseline - Moxifloxacin	32	1	3.13%	160	5	3.13%
Baseline - Placebo	30	1	3.33%	150	5	3.33%
MK-0517	32	2	6.25%	2240	12	0.54%
Moxifloxacin	32	2	6.25%	2240	62	2.77%
Placebo	30	1	3.33%	2094	42	2.01%

Table 11: Frequency for QTcF > 480 msec

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - MK-0517	32	0	0.00%	160	0	0.00%
Baseline - Moxifloxacin	32	0	0.00%	160	0	0.00%
Baseline - Placebo	30	0	0.00%	150	0	0.00%
MK-0517	32	0	0.00%	2240	0	0.00%
Moxifloxacin	32	1	3.13%	2240	4	0.18%
Placebo	30	1	3.33%	2094	1	0.05%

Table 12: Frequency for QTcF > 500 msec

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - MK-0517	32	0	0.00%	160	0	0.00%
Baseline - Moxifloxacin	32	0	0.00%	160	0	0.00%
Baseline - Placebo	30	0	0.00%	150	0	0.00%
MK-0517	32	0	0.00%	2240	0	0.00%
Moxifloxacin	32	0	0.00%	2240	0	0.00%
Placebo	30	0	0.00%	2094	0	0.00%

Table 13: Frequency for Δ QTcF between 30 ~ 60 msec

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
MK-0517	32	11	34.38%	2240	36	1.61%
Moxifloxacin	32	14	43.75%	2240	40	1.79%
Placebo	30	8	26.67%	2094	39	1.86%

Table 14: Frequency for Δ QTcF > 60 msec

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
MK-0517	32	0	0.00%	2240	0	0.00%
Moxifloxacin	32	0	0.00%	2240	0	0.00%
Placebo	30	0	0.00%	2094	0	0.00%

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

To determine if the exposure to 200 mg MK-0517, the reviewer computed a C_{max} value for each subject using data provided by the sponsor (\\Cdsesub1\evsprod\NDA022023\0012\m5\datasets\p01611\analysis\qtcfd-mk.xpt). The mean C_{max} was 6299 ng/ml which is approximately 2-fold larger than the mean C_{max} obtained from 115 mg MK-0517 dose given over 15 minutes (3095 ng/mL).

Table 15: Summary of C_{max} (FDA Analysis)

	Total # of Subj.	Mean (CV%)
Aprepitant C _{max} , ng/ml	30	6299 (37%)

5.3 MEDICAL ASSESSMENTS

No cardiac adverse events are reported.

APPEARS THIS WAY ON ORIGINAL

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this page is the manifestation of the electronic signature.**

/s/

Stephen Grant
4/23/2007 01:06:13 PM
MEDICAL OFFICER

Joanne Zhang
4/23/2007 01:16:13 PM
BIOMETRICS

Jinglin Zhong
4/23/2007 02:00:16 PM
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